DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 11 2013

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Re: Docket No. FDA-2007-P-0190

Dear Drs. Parkinson, Park, Wolfe, and Rosendaal:

This letter responds to your citizen petition (Petition) dated February 6, 2007.[1] You request that the Food and Drug Administration (FDA or the Agency) immediately ban third-generation combination oral contraceptives (COCs) containing desogestrel, and you specifically list the following drugs you request be withdrawn and their manufacturers[2]:

- Desogestrel and Ethinyl Estradiol (Duramed/Barr and Watson Pharmaceuticals)
- Desogen (Organon)
- Velivet (Duramed)
- Kariva (Duramed/Barr)
- Reclipsen (Watson)
- Mircette (Duramed/Barr)
- Apri-28 (Duramed/Barr)
- Ortho-cept (Ortho-McNeil)
- Cyclessa (Organon)

[1] This citizen petition was originally assigned docket number 2007P-0044/CP1. The number was changed to FDA-2007-P-0190 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] Petition at 1.

In support of your request that FDA ban all combination oral contraceptives containing desogestrel from the market, you make the following arguments:

1. Desogestrel-containing COC products have an approximately doubled risk of venous thrombosis compared to second-generation contraceptives.
2. Desogestrel-containing COC products lack evidence of clinical benefit as compared to second-generation oral contraceptives.[3]

FDA has carefully considered the information submitted in your Petition, your February 9, 2007, supplement to the Petition, the comments submitted to the docket, and other relevant data identified by the Agency. Based on our review of this information, and for the reasons described below, your requests are denied.[4] However, as with all FDA-

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[3] Id.

[4] We have received other citizen petitions regarding the risks and benefits of oral contraceptives including (1) a petition requesting that FDA revise its draft Guidance for Industry *Labeling for Combined Oral Contraceptives* so that the labels of combined oral contraceptives have warnings relating to the time of the highest risk of thromboembolic disease consistent with those required by the European Medicines Agency (Docket No. FDA-2005-P-0057, formerly 2005P-0501) and (2) a petition requesting that FDA require doctors to have women screened for the blood disorder factor V Leiden before prescribing a desogestrel-containing oral contraceptive (Docket No. FDA-2009-P-0124). This response does not address these citizen petitions, and responses to them will be issued separately.

On two occasions in December 2011, FDA convened a Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee at which the benefits and risks of certain contraceptives were considered. Notices of these meetings were published in the Federal Register (76 FR 59142, September 23, 2011). Desogestrel-containing oral contraceptives or "third-generation oral contraceptives," however, were not the topic of either meeting. The topic at the first meeting was the benefits and risks of drospirenone-containing oral contraceptives, with a focus on the risk of venous thromboembolism. Drospirenone-containing oral contraceptives are often called "fourth-generation combination oral contraceptives." The topic of the second meeting was the benefits and risks of the ORTHO EVRA (norelgestromin/ethinyl estradiol transdermal system) contraceptive patch, with a focus on the risk of venous thromboembolism.

At the end of each meeting, the Advisory Committee concluded that for the drug under consideration the benefits continued to outweigh the risks, but recommended that labeling be revised. FDA has since concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots than COCs that contain other progestins. See FDA Drug Safety Communication "Updated information about the risk of blood clots in women taking birth control pills containing drospirenone" dated April 10, 2012, which states: "The studies reviewed did not provide consistent estimates of the comparative risk of blood clots between birth control pills that contain drospirenone and those that do not. The studies also did not account for important patient characteristics (known and unknown) that may influence prescribing and that likely affect the risk of blood clots. For these reasons, it is unclear whether the increased risk seen for blood clots in some of the epidemiologic studies is actually due to drospirenone-containing birth control pills." (Available at http://www.fda.gov/Drugs/DrugSafety/ucm299305.htm.) FDA also approved revised labeling for the ORTHO EVRA patch to include the results of the FDA-funded study discussed at the Advisory Committee meeting and issued a statement that the results of the study do not change FDA's conclusions about a possible increased risk of blood clots associated with use of ORTHO EVRA. (Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110402.htm.

approved products, we will continue to monitor and review available safety information related to desogestrel-containing COCs.

I. BACKGROUND

A. Combination Oral Contraceptives Containing Desogestrel

COCs containing desogestrel are among a group of COC drug products commonly referred to as "third-generation oral contraceptives." Labeling a COC product as second- (e.g., levonorgestrel) or third- (desogestrel/gestodene) or fourth- (drospirenone or any other new progestin) generation is somewhat imprecise. Frequently, the "generation" label is based on whether a product was approved before or after the approval of levonorgestrel-containing OCs. Whether a particular COC is considered second-generation or third-generation may also depend on whether the original ingredient or the metabolite is considered. We use the terms as we have defined them in this response and because many studies referenced in this response used this terminology. Both second- and third-generation COCs contain estrogen (usually ethinyl estradiol) and various progestins. COCs containing 20, 30 or 35 μg ethinyl estradiol and levonorgestrel are referred to as second-generation COCs.[5] FDA has approved third-generation COCs containing 20, 30 or 25 μg ethinyl estradiol and 100 – 150 μg desogestrel, and this response refers to them as such.[6] Contraceptives that contain both a progestin and an estrogen, regardless of whether they are administered orally or by another route, are referred to as combined hormonal contraceptives.

The first third-generation COC (trade name Desogen) was originally approved in 1992 and marketed by Organon USA, Inc. under new drug application (NDA) 20-071. FDA has approved three other NDAs for third-generation COCs (NDA 20-301, Ortho McNeil Janssen's Ortho-cept; NDA 20-713,Teva Women's Mircette; and NDA 21-090, Organon USA Inc.'s Cyclessa), and eight abbreviated new drug applications (ANDAs 76-915, 76-916, and 77-182 held by Watson Labs; ANDAs 75-256 and 76-455 held by Duramed Pharms Barr (the latter for trade name Velivet); ANDA 75-863 (Kariva) held by Barr); ANDA 76-675 (Emoquette) held by Vintage; and ANDA 91-346 (Viorele) held by Glenmark Generics).

The approved labeling for desogestrel-containing products includes information concerning the potential increased risk of venous thromboembolism (VTE). For example, the approved labeling for Cyclessa includes the following warning:

> *Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives*

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[5] Speroff, L and MA Fritz, 2011, Clinical Gynecologic Endocrinology and Infertility, 8th Edition, Lippincott, Williams, and Wilkins, 966-7; Petition at 2.

[6] Id.

> *[citations omitted]. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1–2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk.*[7]

The Cyclessa labeling also includes a contraindication against the use of oral contraceptives by women who have, or have had a history of, a thromboembolic disorder. The warnings in the Cyclessa labeling are representative of similar warnings in the other FDA-approved desogestrel-containing products.

B. Statutory Framework

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) establishes the circumstances under which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA or ANDA (21 U.S.C. 355(e)). With respect to safety concerns, the Agency will withdraw approval of a drug product if it finds either of the following:

- "that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved" or

- "that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved."[8]

With respect to effectiveness, the Agency will withdraw approval of a drug if it finds "that there is a lack of 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 thereof."[9]

II. DISCUSSION

Your Petition requests the removal of all desogestrel-containing oral contraceptives from the market. In support of this request, you state that (1) the risk of venous thrombosis from use of such COCs is "approximately doubled" relative to that from use of other COCs; and (2) there is a "lack of evidence of clinical benefit as compared to second-generation oral contraceptives" (Petition at 1).

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[7] Labeling for Cyclessa (desogestrel/ethinyl estradiol) Tablets.

[8] Sections 505(e)(1) and (2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)(1) and (2)); see also 21 CFR 314.150(a)(2)(i) and (ii). In addition, approval can be suspended immediately by the Agency if it finds that there is an imminent hazard to the public health (section 505(e) of the FD&C Act).

[9] Section 505(e)(3) of the FD&C Act; see also 21 CFR 314.150 (a)(2)(iii).

In support of your request, you provide your analysis of a number of articles from the medical literature, present what you consider to be a biological explanation for an increased risk, and describe what you consider to be a lack of clinical benefit for desogestrel-containing COCs compared with other COC products. We include in this response our evaluation of the materials submitted in the Petition and other relevant peer-reviewed literature.

For the reasons discussed below, we have determined based on the information available to us at this time that initiating the withdrawal of the marketing approval of the products you list in your petition is not appropriate. It is our opinion that current product labeling for these products, including the warning statement regarding the possibility of an increased risk of VTE in users of third-generation COCs compared to that in users of second-generation COCs, is appropriate to address the risks and is sufficient based on currently available information.

A. The Petition and Other Available Information Do Not Provide Sufficient Evidence to Establish That Desogestrel-Containing COCs Double the Risk of VTEs in the General Population

The Petition asserts that "third generation oral contraceptives essentially double the risk of venous thrombosis when compared to second generation oral contraceptives" (Petition at 3). In particular, you state that there were 30 cases for every 100,000 users per year of third-generation oral contraceptives compared to 15 cases for every 100,000 users of second-generation oral contraceptives (Petition at 1).

We reviewed each of the studies and the other information cited in the Petition, as well as additional studies that we identified in the medical literature about venous thrombosis (and in a few cases, arterial thrombosis) in relation to third-generation COCs. Although some of the studies we identified were published more recently than the date of the Petition, some that were not included in the Petition were available at the time the Petition was submitted. Some of the studies we identified suggest that there are advantages to using third-generation COC products compared to second-generation products.

In the Petition, you certified, as required by regulation[10] "that, to the best of our knowledge and belief, this petition includes . . . representative data and information known to the petitioners which are unfavorable to the petition."[11] Despite your inclusion of this certification, our review of the medical literature revealed numerous studies unfavorable to your position which you did not discuss or disclose in the Petition,[12]

[10] 21 CFR 10.30.

[11] Petition at 6.

[12] See e.g., Suissa S, WO Spitzer, et al., 2000, Recurrent use of newer oral contraceptives and the risk of venous thromboembolism, Hum Reprod, 15:817-821; Lewis MA, KD McCrae, et al., 1999, The differential risk of oral contraceptives: the impact of full exposure history, Hum Reprod, 14:1493-1499; Suissa S, L

including at least two relevant articles authored by, among others, one of the petitioners, Frits Rosendaal, M.D.[13] We discuss our analysis of the literature in more detail below.

1. Studies Reported in the Medical Literature Do Not Demonstrate a Clear and Unbiased Two-Fold Increase in Risk

The studies described in many of the articles cited in the Petition are not specific to the issue of estimating the risk of VTEs with the use of desogestrel-containing COCs. These studies are discussed in Section II.A.1.a. Most of the remaining studies that are cited in the Petition or were identified by FDA are observational studies (not randomized) which provide relevant information, but may be subject to uncontrolled bias, especially if investigators do not suspect a potential bias and do not correct for it. These studies and their limitations are described in Section II.A.1.b.

a. Several Studies Included in the Petition Are Not Relevant Because They Do Not Directly Analyze Differences Between Types of COCs

The Petition includes a total of 31 references, most of which are cited as support for your assertion that the risk of VTEs in users of third-generation COCs is approximately double that of users of second-generation COCs. Approximately half (15) of these references do not provide information relevant to the specific issue of the risk of VTEs associated with desogestrel-containing COCs. These references can be subdivided into the following subject categories, each of which is discussed in more detail below (the remaining references are discussed in subsection II.A.1.b).

- Incidence of venous thromboembolism (one reference)[14]
- Post-thrombotic syndrome (three references)[15]

Blais, et al., 1997, First-time use of newer oral contraceptives and the risk of venous thromboembolism, Contraception, 56:141-6. Koster T, FR Rosendaal, et al., 1995, Protein C deficiency in a controlled series of unselected outpatients: An infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study), Blood, 85:2756-2761; and Liberti G, RM Bertina, et al., 1999, Hormonal state rather than age influences cut-off values of protein S: Reevaluation of the thrombotic risk associated with protein S deficiency, Thromb Haemost, 82:1093-1096.

[13] In both studies (Koster, Rosendaal, et al. 1995 and Liberti, Bertina, et al. 1999), the authors did not find a relationship between protein S levels and thrombosis risk. We discuss this issue in more detail in the section below about your theory of biological plausibility (see Section II.3).

[14] Petition at 1; Anderson, FA, HB Wheeler, et al., 1991, A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism, The Worcester DVT study, Arch Intern Med, 151:933-938.

[15] Petition at 2; Kyrle, PA, and S Eichinger, 2005, Deep vein thrombosis, Lancet, 365:1163-1174; Prandoni P, AWA Lensing et al., 2004, Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial, Ann Intern Med, 141:249-256; and Brandjes, DP, HR Buller et al., 1997, Randomized trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis, Lancet, 349:759-762.

- Recurrent VTEs (one reference)[16]
- Comparing users of third-generation COCs to nonusers (i.e., women who do not use any COC, two references)[17]
- Meta-analyses of epidemiology studies (two references)[18]
- Impact of the "pill scare" of 1995 (five references)[19]
- Review of COCs and risk of venous thrombosis (one reference) [20]

References regarding the incidence of venous thromboembolism, post-thrombotic syndrome, and recurrent VTEs. Five studies are cited in the Petition as general background on the potential seriousness of venous thrombosis.[21] None of them, however, are directly pertinent to the relative seriousness or frequency of VTEs associated with the use of desogestrel-containing COCs, nor to your request to remove desogestrel-containing COC products from the market, because they do not directly discuss differences in risk between second- and third-generation COC products. The first study cited in the Petition (Anderson FA, et al., 1991) did not analyze hormone use at all, much less differences in risk between particular generations of COCs. None of the three articles cited in the Petition (Petition at 2) regarding post-thrombotic syndrome (Kyrle and Eichinger, 2005; Brandjes et al., 1997; and, Christiansen et al., 2005) attempts to correlate post-thrombotic syndrome with thromboses secondary to COC use — indeed, the mean age in the second and third studies was 60 years, which is past the age at which we expect women to use oral contraceptives. In the single article cited in the Petition

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[16] Christiansen, SC, SC Cannegieter, et al., 2005, Thrombophilia, clinical factors, and recurrent venous thrombotic events, JAMA, 293:2352-2361.

[17] Parkin L, DC Skegg, et al., 2000, Oral contraceptives and fatal pulmonary embolism, Lancet, 355:2133-2134; and World Health Organization, 1995, Venous thromboembolic disease and combined oral contraceptives: results of international multicenter case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, Lancet, 346:1575-1582.

[18] Petition at 3; Kemmeren JM, A Algra, et al., 2001, Third generation oral contraceptives and risk of venous thrombosis: meta-analysis, BMJ, 323:131-139; Hennessy S, JA Berlin, et al., 2001, Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis, Contraception, 64:125-133.

[19] Jick, SS, C Vasilakis, et al., 1998, Pregnancies and terminations after 1995 warning about third-generation oral contraceptives, Lancet, 351:1404-14055; Allison C, 1996, Aftermath of the oral contraceptive scare, Br J Sex Med, 23:5-7; Martin RM, SR Hilton, et al., 1997, The impact of the October 1995 'pill scare' on oral contraceptive use in the United Kingdom; analysis of a general practice automated database, Fam Pract, 14:279-284; De Vries, CS, PB Van den Berg, et al., 1998, Oral contraceptive use before and after the latest pill scare in the Netherlands, Contraception, 57:247-9, and De Jong-van den Berg, L, H Tobi, et al., 2003, Influence of the third generation pill controversy on prescriptions for oral contraceptives among first time users: population based study, BMJ, 326:254.

[20] Vandenbroucke, JP, J Rosing, et al., 2001, Oral contraceptives and the risk of venous thrombosis, N Engl J Med, 344:1527-1535.

[21] Anderson, FA, et al., 1991; Kyrle, PA and S Eichinger, 2005; Brandjes, DP, et al., 1997; Prandoni, P, et al., 2004; and Christiansen, SC, et al., 2005.

regarding thrombotic recurrence (Christiansen et al. 2005), the authors did not identify the names of the specific COCs being used by those women using COCs after the initial VTE as reported during their follow-up visits after the initial VTE.[22] We do note that the FDA-approved labeling for COCs contraindicates the use of COCs after a VTE.[23]

Studies comparing users of third-generation COCs to nonusers. These studies[24] do not shed light on the question of the relative safety of different types of COCs because they provide risk estimates for users of third-generation COCs compared to non-COC users, rather than to users of second-generation COCs. The 2000 study of Parkin, et al. involved a small number of subjects with wide confidence intervals (CIs) and variability of results. For these reasons this study is also not informative of absolute risk. Also, you state in the Petition that you performed your own analysis of the WHO 1995 study, but you did not provide any information on how the calculations were performed nor whether you had access to the original data from the study (Petition at 3). Therefore, we cannot confirm the validity of the results of your calculations.

Meta-analyses of epidemiologic studies. Two of the cited studies[25] are meta-analyses of epidemiologic studies. Because the methodologies used in the underlying studies are not comparable, the meta-analyses do not provide helpful information beyond the information provided by the individual underlying studies.

References regarding the "pill scare" of 1995. Five other studies cited in the Petition address the impact of the "pill scare" of 1995,[26] which refers to the decline in use of COCs in reaction to certain epidemiologic studies (Petition at 5). In 1995, the British Committee on Safety of Medicines issued a warning letter to physicians and pharmacists based on three not-then-published studies[27] that indicated an increased risk of VTEs among users of third-generation COCs containing desogestrel or gestodene (a progestin

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[22] Petition at 2.

[23] See, e.g., labeling for Cyclessa: "Oral contraceptives should not be used in women who currently have the following conditions: Thrombophlebitis or thromboembolic disorders [or] A past history of deep vein thrombophlebitis or thromboembolic disorders."

[24] Parkin, Skegg, et al. 2000; and World Health Organization 1995.

[25] Petition at 3; Kemmeren, Algra, et al. 2001; Hennessy, Berlin, et al., 2001.

[26] Jick, SS, et al. 1998; Allison 1996; Martin, et al. 1997; De Vries, et al. 1998; and De Jong-van den Berg, et al. 2003.

[27] Farley TMM, O Meirik, et al., 1995, The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low estrogen oral contraceptives on venous thrombo-embolic disease, Lancet, 346:1582-1588; Jick, H, SS Jick, et al., 1995, Risk of Idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components, Lancet 346:1589-1593; Bloemenkamp KWM FR Rosendaal, et al., 1995, Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen, 346:1593-1596.

never approved in the United States). The warning letter recommended that women using such COCs be advised of the risk and offered the opportunity to change brands, with use of third-generation COCs to be contraindicated in women with other risk factors for VTE. In contrast, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) did not recommend any restrictions on the prescription of third-generation COCs. Use of third-generation products declined following the warnings.

As described in section I.B of this response, the FD&C Act establishes the circumstances under which the Agency will withdraw approval. We base decisions on whether to remove products from the market on safety data and risk-benefit analysis. The studies regarding the "pill scare" cited in the Petition only provide information about the reaction to the announcements and statements made by other regulatory authorities. They do not provide safety information and are not relevant to a decision about whether to remove desogestrel-containing COCs from the U.S. market. The three original 1995 studies that prompted the "pill scare" are further discussed in section II.A.2.

Review of COCs and risk of venous thrombosis. You cited one review article regarding the risk of venous thrombosis from use of oral contraceptives (Petition at 2).[28] As a review article, this article identifies pertinent literature, but does not provide original data. We reviewed the underlying original literature in our review of the issues raised by the Petition, and some of these underlying studies are discussed individually in our response (see, e.g, Jick H, SS Jick, et al., 1995). We note that one of the authors of this review article, Frits Rosendaal, is one of the petitioners for the Petition.

b. More Directly Relevant Studies Provide Only Limited Information About the Relative Risk of Third-Generation COCs

Although the remaining studies cited in the Petition and the additional studies identified by the Agency are in some cases more directly relevant than the studies described above to the question of relative risk of third-generation COCs compared to second-generation COCs, they do not demonstrate that there is a doubling of the risk. These studies include epidemiologic studies comparing VTE occurrence in third-generation COC users to that in second-generation COC users,[29] and each has significant limitations, as we detail

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[28] Vandenbroucke, Rosing, et al. 2001.

[29] Farley, Meirik, et al. 1995; Jick H, Jick SS, et al. 1995; Bloemenkamp, Rosendaal, et al. 1995; Spitzer WO, 1996, Third-generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women, BMJ, 312:83-88; Farmer RD, RA Lawrenson et al., 1997, Population-based study of risk of venous thromboembolism associated with various oral contraceptives, Lancet, 349:83-88; Farmer RD, Todd et al., 1998, The risks of venous thromboembolic disease among German women using oral contraceptives: a database study. Contraception 57:67-70; Lidegaard Ø, B Edstrom, and S Kreiner, 1998, Oral contraceptives and venous thromboembolism. A case-control study, Contraception, 57:291-301; Bloemenkamp KWM, FR Rosendaal, et al., 1999, Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias, Arch Intern Med, 59:65-70; Jick H, JA Kaye, et al., 2000, Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort

below. We also include several studies that looked at both venous and arterial thrombosis in relation to third-generation COCs.[30]

(i) A variety of study design factors limit our ability to draw definitive conclusions about relative risk from available studies.

In general, many studies reported to date cannot reliably measure relative risk because there has been no measurement of or adjustment for the numerous confounders that have been identified as affecting risk for VTE. These confounders include, among others, age, body mass index (BMI), smoking status, duration of use, and personal and family history of thrombotic events.[31] No reported study comparing second- and third-generation COCs has adjusted for all the known confounders. Given that the risk estimates observed when comparing third- to second-generation COCs generally do not exceed 2.0, many investigators believe that the increased risk observed for third-generation COCs could be explained by uncontrolled bias.[32]

Several of the studies cited in the Petition suggest an increased VTE risk from taking third-generation COCs compared with second-generation COCs. The increased risk may not be attributable solely to the products themselves, however, but might be explained, in large part, by study design issues, uncontrolled bias, and evidence of preferential prescribing. Some of these issues were addressed by the investigators who incorporated adjustments into their analyses. No one study, however, adjusts for all identified biases.

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and case control analysis, BMJ, 321:1190-1195; Andersen BS, JS Olsen, et al., 1998, Third generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism, Thromb Haemost, 79:28-31; Heinemann LA, MA Lewis, et al., 2002, Case-control studies on venous thromboembolism: bias due to design? A methodological study on venous thromboembolism and steroid hormone use, Contraception, 65:207-14; Herings RM, J Urquhart, and HG Leufkens, 1999,Venous thromboembolism among new users of different oral contraceptives [published correction appears in Lancet. 1999;354:1478], Lancet, 354:127-128; Farmer RD, RA Lawrensen, et al., 2009, A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives, Br J Clin Pharmacol, 49:580-590; Lidegaard Ø, B Edstrom, and S Kreiner, 2002, Oral contraceptives and venous thromboembolism: a five-year national case-control study, Contraception, 65:187-96.

[30] Suissa, Spitzer, et al. 2000; Lewis, MacRae, et al. 1999; Todd JC, R Lawrenson, et al., 1999, Venous thromboembolic disease and combined oral contraceptives: A re-analysis of the MediPlus database, Hum Reprod, 14:1500-1505; Jick SS, JA Kaye, et al., 2006, Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel, Contraception, 73:566-570.

[31] See, e.g., predictors for VTE identified in Lidegaard, Edstrom, et al. 1998 and in Farmer, Lawrenson, et al. 2000.

[32] Heinemann, Lewis, et al. 2002; Jick, Kaye, et al. 2006; Suissa, Spitzer, et al. 2000; Lewis MA, Heinemann LAJ, et al. with the Transnational Research Group on Oral Contraceptives and the Health of Young Women, 1996, The Increased risk of venous thromboembolism and the use of third generation progestogens: role of bias in observational research, Contraception, 54:5-13.

More significantly, across studies there are notable differences related to case and control selection, exposure criteria, and other study design issues that seriously affect the extent to which we can draw conclusions concerning third-generation COC risks. The epidemiologic studies were either of cohort or case-control design and were based on information from registries or general practitioner databases.[33] Observational studies by their nature do not provide the empirical results that would be provided by properly executed randomized controlled clinical trials. Because the data analyzed in these studies comes from existing registries and databases, the analyses are limited to the information reported in the source.

For example, one of the studies we independently identified showed an adjusted odds ratio (OR) for nonfatal VTE of 1.7 (95% CI, 1.1-2.4).[34] This study utilizes information recorded in a general research database and the authors did not have access to original clinical records to validate the VTE diagnoses. Additionally, the authors could not evaluate potential confounding due to smoking by the patients or BMI, and it was unclear from the report whether there was adjustment for current use of contraceptives.

With respect to control selection, some investigators have expressed concern about bias being introduced into the case-control studies by the type of controls selected.[35] When cases and/or controls are chosen from hospitalized patients, rather than patients from a community, the OR may be biased. You cite one case-control study as having an OR of 1.7 (95% CI, 0.9-3.6).[36] This study also showed, however, that when all controls (community and hospital) were used in the analysis, there was no difference in risk for third-generation users compared to second-generation users (OR 0.9, CI 0.6-1.4). Similarly, you cite only the results using hospital controls (OR 2.2, 95% CI 1.1- 4.2) from a second study (Farley, Meirik, et al. 1995) for which the VTE risk estimate was lower when more appropriate community controls were used (OR 1.4, 95% CI 0.6-3.1).

Studies we identified that were not cited in the Petition show evidence that some women using second-generation COCs may be at increased risk of arterial thromboembolic events (ATEs), particularly myocardial infarction, although the relative risk estimates are

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[33] Farley, Meirik, et al. 1995; Jick H, Jick SS, et al. 1995; Bloemenkamp, Rosendaal, et al. 1995; Spitzer, Lewis, et al. 1996; Farmer, Lawrenson, et al. 1997; Farmer, Todd, et al. 1998; Lidegaard, Edstrom, et al. 1998; Bloemenkamp, Rosendaal, et al. 1999; Jick H, Kaye et al. 2000; Andersen, Olsen, et al. 1998; Heinemann, Lewis, et al. 2002; Herings, Urquhart, et al. 1999; Farmer, Lawrenson, et al. 2000; Lidegaard, Edstrom, et al. 2002; Parkin, Skegg, et al. 2000; and World Health Organization. Lancet 1995; 346:1575-82.

[34] Jick, Kaye, et al. 2006.

[35] Poulter NR, Chang CL, et al. for the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception Investigators, 1995, Venous thromboembolic disease and combined oral contraceptives: results of international multicenter case-control study. Lancet, 346:1575-1582.

[36] Heinemann, Lewis, et al. 2002.

not high and could reflect uncontrolled bias.[37] Other investigators have suggested that differences in risk may be attributable to differences in estrogen dose rather than different progestins.[38] Additional studies suggesting advantages to third-generation COCs when compared to second-generation COCs that were not cited in the Petition are discussed in the section below on clinical benefit.

Our independent review of medical literature identified several epidemiologic studies that were published after your Petition was submitted.[39] Though not designed to directly address differences in second- and third-generation COCs, these studies include comparisons of other COCs/progestins with second- and third-generation COCs/progestins. Because all are non-U.S. studies, they include progestins that are not marketed in the United States. Both a Danish national cohort study[40] and a Dutch population-based case-control study[41]compared fourth-generation drospirenone products with levonorgestrel and desogestrel products, and an Austrian matched case-control study[42] compared the VTE risk of gestodene-containing COCs with those containing any other progestin. Results were contradictory.

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[37] Dunn N, A Arscott, et al., 2001, The relationship between use of oral contraceptives and myocardial infarction in young women with fatal outcome, compared to those who survive: results from the MICA case-control study, Contraception, 63:65-69; Tanis BC, MA van den Bosch, et al., 2001, Oral contraceptives and the risk of myocardial infarction, N Engl J Med, 345:1787-1793; Poulter, et al., 1997, for WHO collaborative study of cardiovascular disease and steroid hormone contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicenter case-control study, Lancet, 349:1202-09; Jick H, SS Jick, et al., 1996, Risk of acute myocardial infarction and low-dose combined oral contraceptives, Lancet, 347:627-628; Lewis MA, LA Heinneman, et al., 1997, The use of oral contraceptives and the occurrence of acute myocardial infarction in young women. Results from the transnational study on oral contraceptives and the health of young women, Contraception,56:129-140; Spitzer WO, JM Faith, et al., 2002, Myocardial infarction and third generation oral contraceptives: aggregation of recent studies, Hum Reprod, 17:2307-2314; Khader YS, J Rice, et al., 2003, Oral contraceptives use and the risk of myocardial infarction: a meta-analysis, Contraception, 68:11-17; Baillargeon JP, DK McClish, et al., 2005, Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: A meta-analysis, J Clin Endocrinol Metab, 90:3863-3870.

[38] Lidegaard O, E Lokkegaard, et al., 2012, Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception, NEJM, 366:2257-66.

[39] Lidegaard O, E Lokkegaard, et al., 2012; Lidegaard O, LH Nielsen, et al., Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9, BMJ 343:d6423; Lidegaard O, E Lokkegaard, et al., 2009, Hormonal contraception and risk of venous thromboembolism: national follow-up study, BMJ, 339:b2890; van Hylckama V, FM Helmerhorst, et al., 2009, The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study, BMJ, 339:b2921; Heinemann LA, JC Dinger JC, et al., Use of oral contraceptives containing gestodene and risk of venous thromboembolism: outlook 10 years after the third-generation "pill scare", Contraception, 81:401-407.

[40] Lidegaard, Lokkegaard, et al. 2009.

[41] van Hylckama, Helmerhorst, et al. 2009.

[42] Heinemann, Dinger, et al. 2010.

The Danish national cohort study[43] was of women aged 15-49 years with no history of cardiovascular or malignant disease, and included 10.4 million woman-years of observation, including 3.3 million woman-years of observation of women who used COCs. Compared with women taking COCs containing levonorgestrel (and the same dose of estrogen after adjustment for duration of use), the VTE rate ratios for women taking COCs containing desogestrel and gestodene were 1.82 (95% CI 1.49-2.22) and 1.86 (95% CI 1.59-2.18), respectively. The authors concluded that for the same dose of estrogen and same length of current use, COCs with desogestrel or gestodene were associated with a greater risk of VTE than COCs with levonorgestrel. Overall, rates adjusted for age were much lower than crude incident rates suggesting (as other studies have) that age is an important factor in absolute risk specifically, and for the relative risk when not adequately adjusted.

The Austrian nested case-control study,[44] on the other hand, reported similar risks of VTE in users of gestodene-containing COCs (adjusted OR = 3.39, 95% CI 2.36-4.87) relative to users of COCs containing progestins other than desogestrel and gestodene (adjusted OR = 3.14, 95% CI 2.1 to 4.47). Although COCs containing gestodene are third-generation products, they are not used in the United States. The adjusted OR (and 95% CI) for a head-to-head comparison of COCs containing gestodene versus those containing other progestins was 1.0 (0.7-1.5) for all cases and 1.0 (0.7-1.5) for confirmed cases. The second-generation COCs used in this study were not limited to levonorgestrel and desogestrel-containing COCs were not included. However, the study had several strengths in that all VTE cases were considered and all were validated with physicians, medical records, and personal interviews. Because the investigators interviewed women directly, they could adjust not only for age, but for information about other potential confounders associated with exposure and outcome (e.g., BMI, parity, and prior use of COCs) was available and adjusted for in the analysis. We are not aware of a reported study that has made all the same adjustments with either all third-generation COCs or with desogestrel-containing COCs alone.[45]

When compared to no use, the Dutch case-control study[46] of women aged <50 years reported a two-fold increased risk of VTE for women who used COCs containing desogestrel compared to levonorgestrel-containing COCs. The study did not adjust for duration of use, however, making comparison across progestin types prone to bias.

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[43] Lidegaard, Lokkegaard, et al. 2009.

[44] Heinemann, Dinger, et al. 2010.

[45] Most of the literature on second- and third-generation COCs is based on research done outside the U.S. where third-generation products such as desogestrel and gestodene were usually combined. Gestodene-containing COCs are not approved for use in the U.S.

[46] van Hylckama, Helmerhorst, et al. 2009.

Based on a request from the European Medicines Agency, Lidegaard et al[47] conducted additional analyses of the Danish registry data originally published in 2009[48] with a focus on the VTE risk for drospirenone-containing COCs compared to levonorgestrel-containing COCs. The analysis also evaluated the risk of VTE with desogestrel-containing COCs. For COCs that contain 30-40 μg of ethinyl estradiol, when compared to levonorgestrel-containing COCs, desogestrel-containing COCs had an adjusted (for five-year age group and duration of use) rate ratio of 2.24 (95% CI 1.65 – 3.02). Like the original 2009 publication, the analysis did not control for family history, smoking, or body mass index, and not all VTEs were confirmed.

A recent Danish historical cohort study[49] looked at the absolute risk of thrombotic stroke and myocardial infarction (but not VTE) for a variety of COCs and other types of combined hormonal contraceptives (e.g., transdermal patches) compared to the risk for nonusers and found that the absolute risk of thrombotic stroke and myocardial infarction associated with each product was low. The difference in risk between COCs based on progestin type was relatively small, but an association between increased risk and the dose of ethinyl estrogen in the particular COC was suggested although residual effects of inadequate adjustment for age may explain some of the increased risk observed. Older published studies included all progestins of a certain generation together without considering differing estrogen levels. More recent studies continue to include all progestins, but some also analyze results separately taking into consideration estrogen levels. The level of estrogen in a particular COC may be implicated in differences that have been previously theorized to be related to differences in progestin type.

Other studies have suggested that women with particular characteristics that may affect risk for VTE are more likely to be prescribed particular COCs for medical reasons other than contraception and these unmeasured differences among users may further confound study results.[50]

(ii) The results of several studies cited in the Petition did not reach statistical significance when appropriately adjusted.

For several cited studies[51] that suggested an increase in risk when comparing use of third-generation to second-generation COCs, the results did not reach statistical significance.

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[47] Lidegaard O, Nielsen LH, et al. 2011.

[48] See fn. 43, supra.

[49] Lidegaard O, E Lokkegaard, et al. 2012.

[50] The American College of Obstetricians and Gynecologists, 2010, Noncontraceptive Uses of Hormonal Contraceptives Clinical Management Guidelines for Obstetrician-Gynecologists, Obstet Gynecol, 115(1): 206-218; SOGC Clinical Practice Guidelines, 2011, Oral contraceptives and the risk of venous thromboembolism: An update No. 252, 2011, Int'l J Gynecol Obstet112 252–256.

[51] See note 29, supra.

In some cases,[52] the results are not considered statistically significant because the CI for the point estimate of relative risk estimates in each study included 1.0 and other studies were not informative because the CI was very wide. Inclusion of 1.0 in the CI for point estimate of relative risk indicates that the increase in risk is not statistically significant. A very wide CI signifies that the results are imprecise.

One study you cited (Farley, Meirik, et al. 1995; Petition at 3) showed an OR > 2.0 with a CI that excluded 1.0 when comparing desogestrel-containing studies to second-generation products. However, the difference in risk was not statistically significant when more appropriate community controls were used, and the study has additional methodological limitations. It did not adjust for duration of use, a factor that has been shown to affect the risk of VTE, and the authors stated that controlling for BMI may have been incomplete because height and weight were self-reported. There also have been criticisms in journal articles and texts that the unadjusted risk estimate does not appear to be biologically plausible because the pills studied contained relatively low levels of estrogen.[53] Finally, in a separate study,[54] it was noted that even in 1995 before the regulatory warnings, COCs containing 20 μg ethinyl estradiol were prescribed more often to women over 35 years of age and to more obese women, a population that may be at greater risk for VTE.

The results in another study you cite (Spitzer, Lewis, et al. 1996; Petition at 3) also were not statistically significant when community controls (generally considered a more appropriate comparison group) were used in the analyses. The Spitzer 1996 study also demonstrated a greater risk of VTE when using hospital controls compared with community controls suggesting that VTE risk differs by the comparator group used. This study did not analyze duration of use of COCs which has been identified as a very important factor in VTE risk.[55]

The results of another study cited in the Petition (Herings, RMC, J Urquhart, et al. 1999; Petition at 2) varied depending on the length of use of the OC. For new users, the relative risk reflected in the OR exceeded 2, but the 95% CI (1.9-106.4) was very wide indicating uncertainty about the exact magnitude of the increased risk. The results for longer term use were not statistically significant and the 95% CI (0.9-3.1) included 1.

You state in the Petition that you performed your own calculations on one of the cited studies (Lidegaard, Edstrom, et al. 1998; Petition at 3), but you did not provide any information on how the calculations were performed or whether you had access to the

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[52] Jick H, SS Jick, et al. 1995; Bloemenkamp, Rosendaal, et al. 1995; Farmer, Lawrenson, et al. 1997; Farmer, Todd, et al. 1998; Lidegaard, Edstrom, et al. 1998; Bloemenkamp, Rosendaal, et al. 1999; Andersen, Olsen, et al. 1998; Heinemann, Lewis, et al. 2002; Farmer, Lawrenson, et al. 2000; Lidegaard, Edstrom, et al. 2002.

[53] See, e.g., Speroff, supra, note 5.

[54] Farmer, Lawrenson, et al. 1997.

[55] See, e.g., Herings, Urquhart, et al. 1999.

original data (Petition at 3). We cannot, therefore, confirm the validity of the results of your calculations.

(iii) The limited information provided by the reported studies does not lead us to conclude that clear and unbiased support exists for the Petition's statement that the relative risk associated with third-generation COCs is double that of second-generation COCs.

In the earlier studies comparing the VTE risk of second- and third-generation COCs, potential confounders such as duration of use had not yet been identified and other, known confounders were not recorded and therefore not controlled for or not adequately controlled in the early studies. Consequently, although the earlier epidemiologic studies suggest an increase in risk for third-generation COCs, these early studies identified a potential problem, but were of limited use in defining the exact magnitude of any difference in VTE risk between second- and third-generation COCs or in determining the significance of any difference.[56] More recently reported studies have been useful in identifying some of the confounding factors, but it is still not clear whether results that show an increased risk of VTE in women who use third-generation COCs indicate a causal relationship, are due to the presence of uncontrolled confounding factors, or are related to channeling (prescribing practices related to a woman's baseline risk of VTE and ATE in which a woman is prescribed a particular COC based on those risks).[57]

Recent studies have also suggested that there are unmeasured differences across users of COCs, particularly women with certain gynecological conditions who may use COCs for reasons other than contraception. Thus far, reported studies have not taken into consideration unmeasured differences across users.[58] Preliminary and as yet not fully developed evidence exists that suggests prescribers steer women with certain conditions such as polycystic ovarian disease to certain COCs resulting in overrepresentation of women with the condition in a treatment group compared with the comparator group. It is not known in some cases whether the particular condition itself is associated with a higher risk of VTEs which may be confounding study results.

Based on our review of the studies cited in your Petition and the additional studies we identified, we have concluded that the epidemiologic studies are not conclusive but are suggestive that an increased VTE risk might exist. The magnitude of the risk is difficult to ascertain when comparing COCs because of the known but unmeasured confounders and also because of unmeasured differences across users and across products (e.g., with differing levels of ethinyl estradiol, with bi- and tri-phasic products). We do not know if the differences observed are explained by differences in the population of users, uncontrolled bias, or real product differences. Consequently, although there may be a

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[56] See note 29, supra.

[57] See note 32, supra.

[58] See note 48 and related text, supra.

slight increase in VTE risk associated with the use of third-generation COCs, the reported studies do not support the overall conclusion that third-generation COCs place all users at increased risk. Overall, the magnitude of differences in risk observed between third- and second-generation COCs does not approach the magnitude of differences observed between any COC use vs. non-use, and much of the difference across different generations of COCs disappears in appropriately designed studies. We have also concluded that none of the epidemiologic studies reported to date provide a clear and unbiased comparison of the risk of VTE associated with desogestrel-containing COCs compared to second-generation COCs. Specific to your request to withdraw the approval of desogestrel-containing COC products based on an elevated risk of VTEs compared with other COC products, we have concluded that the studies cited in your Petition and other information we identified do not provide sufficient evidence to warrant such a withdrawal. Thus, we conclude that the standard for withdrawal in Section 505(e) of the Act has not been met.

As discussed in more detail in Section II.C., to the extent that the studies suggest an increased risk of VTE associated with the use of desogestrel-containing COCs, we believe that existing product labeling appropriately informs of the risk.

2. *FDA's Statement in 1995 Regarding Relative Risk of VTEs Was Based on the Limited Data Available at the Time of the "Pill Scare"*

You also say in the Petition that "FDA acknowledged a doubling of the risk of VTEs in November 1995 when it stated that 'new studies indicate about a two-fold increase in the risk of venous blood clots associated with products containing desogestrel'" (Petition at 3). As explained above, the decline in use of third-generation COCs in reaction to initial epidemiologic studies in 1995 is referred to in the Petition as the "pill scare." FDA's statement was in response to the preliminary data that became available in 1995.

In response to these and subsequent epidemiologic studies, FDA requested that the labeling for desogestrel-containing products include information concerning the potential increased risk of VTE. The approved labeling for one such product currently includes the following warning, which is similar to other warnings in desogestrel-containing products:

> *Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives [citations omitted]. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1–2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk.*[59]

[59] Package Insert (PI) for Cyclessa (desogestrel/ethinyl estradiol) Tablets

Current patient labeling of approved products also contains a warning that the risk of blood clots and blockage of blood vessels may be greater with desogestrel-containing contraceptives.[60] One such warning states:

> *Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the leg can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blockage of the vessel carrying blood to the lungs.* ***The risks of these side effects may be greater with desogestrel-containing oral contraceptives such as Desogen® (desogestrel and ethinyl estradiol) Tablets than with certain other lowdose pills.***
>
> (Emphasis added.)[61]

As outlined in the previous sections of this response, additional data have become available since 1995 that explain some of the results from these initial studies. Consequently, the FDA statement made in 1995 described only the results from the preliminary studies. It does not reflect information provided by later studies that attenuates the risk in part and does not reflect the contradictory results and lack of firm conclusions on this issue. However, labeling of desogestrel-containing COCs does reflect the current state of scientific knowledge on this topic.

3. *The Petition's Proposed Theory of Biological Plausibility of an Increased Risk Associated with Third-Generation COCs*

The Petition posits a biological theory to support its position that there is an increased risk of VTE with third-generation COCs compared to the risk associated with second-generation COCs.[62] Specifically, you state that blood coagulation is a complex process of procoagulant proteins that stimulate the formulation of a clot and anticoagulant

proteins that inhibit these proteins, as well as proteins that break down a clot once it has formed; that normal blood clotting depends upon a specific, delicately balanced interaction between these classes of proteins; and, if one class of proteins has more activity than the other class, an abnormal state exists and a person becomes at risk of either excessive clotting (thrombosis) or excessive bleeding. The Petition goes on to state that it has long been known that changes in female hormonal status seen in pregnancy, hormone replacement therapy, or oral contraceptive usage increase procoagulant activity in the coagulation process, and oral contraceptives affect levels of almost all of the proteins involved in the coagulation process. You assert that the progestin found in desogestrel-containing OCs appears to cause resistance to one of the anticoagulant

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[60] See PI for Desogen (desogestrel and ethinyl estradiol) Tablets and PI for Cyclessa (desogestrel/ethinyl estradiol) Tablets.

[61] PI for Desogen (desogestrel and ethinyl estradiol) Tablets.

[62] Petition at 4.

proteins, activated Protein C (APC), and that as compared to second-generation oral contraceptives, third-generation oral contraceptives significantly decrease total and free Protein S and cause a more pronounced APC resistance. You theorize that when APC and Protein S are not allowed to perform their natural function of inhibiting coagulation, clots tend to form more easily, thereby increasing the risk of venous thrombosis. To support this theory, you cite coagulation studies that purport to explain a difference in VTE risk by showing differences in the effects of second- and third-generation COCs on certain coagulation tests. These tests include an APC resistance test that quantifies the intensity of the plasma anticoagulant response by quantifying the effect of APC on thrombin generation Protein S determinations.[63]

Although your references and other studies we identified independently suggest that there are differences in the results of certain coagulation tests when comparing third-generation and second-generation COCs, you do not cite an adequate study that demonstrates that COC-dependent differences in the laboratory tests are directly linked to an increased risk of VTEs in women taking third-generation COCs compared with those taking second-generation COCs. Additionally, the mechanism of action that affects coagulation and causes differences in coagulation has not been fully evaluated.[64]

In summary, although you provide information that indicates that some coagulation laboratory test results are affected more by third-generation products than second-generation products, you do not provide evidence that directly links these test results to an increased VTE risk in users of third-generation COCs compared with second-generation COCs, and we were not able to independently identify any such studies.

B. The Petitioner's View that Desogestrel-Containing Drugs Do Not Provide a Clinical Benefit Compared to Second-Generation COCs

In the Petition you state that third-generation COCs show no clinical benefit compared to second-generation COCs (Petition at 4). In support of your argument, you cite a letter from FDA to Organon and also state that in an extensive literature review, you did not find any non-industry-sponsored randomized controlled trials comparing supposed clinical benefits of third-generation oral contraceptives to second-generation contraceptives (Petition at 4-5).

We disagree with your statement that it is impossible to recommend that third-generation COC products remain on the market on the basis that there is no evidence of any superior clinical benefit over second-generation COCs, and because second-generation oral contraceptives are equally effective and do not cause an increased risk of blood clots.

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[63] Rosing, Curvers, et al. 2001; Tans G, J Curvers, et al., 2000, A randomized cross-over study on the effects of levonorgestrel- and desogestrel-containing oral contraceptives on the anticoagulant pathways, Thromb Haemost, 84:15-21.

[64] Winkler, UH, 2000, Hemostatic effects of third- and second-generation oral contraceptives: absence of a causal mechanism for a difference in risk of venous thromboembolism, Contraception, 62:11S-20S.

Under section 505(c)[65] of the Act, which pertains to NDAs, FDA shall approve a drug unless any of the specified grounds for denying approval in 505(d) applies. The NDAs for COC products are approved based on the safety data and their effectiveness in preventing pregnancy as supported by data submitted for approval in their respective NDAs. No additional clinical benefit aside from contraceptive efficacy is required for approval of second-generation products over first-generation products. Similarly, no additional clinical benefit is required of third-generation products over second-generation products. When approving desogestrel-containing COCs, the Agency determined that these products were safe and effective when used in accordance with labeling, thereby acknowledging the clinical benefit of an efficacious contraceptive product. With regard to whether to withdraw approval of these products, we have determined that their risk-benefit profile — which includes consideration of any safety risks — does not warrant removal of the products from the market.

You state in the Petition that FDA acknowledged the lack of clinical benefit of third-generation COCs compared to second-generation COCs in a 1999 [sic] letter to Organon (Petition at 4). In particular, you state that FDA's letter stated, "no clinically significant differences between Desogen and other oral contraceptives have been demonstrated in adequate and well-controlled comparative studies" and "furthermore, there are no adequate and well-controlled studies that have demonstrated that the body can sense a difference between oral contraceptives" (Petition at 4). Your interpretation of FDA's letter is not accurate. As stated in the untitled letter,[66] the specific comparative claim "My body knows the difference," was false and misleading promotion because of the lack of adequate and well-controlled comparative studies. Similarly, as further stated in FDA's letter, comparative claims that the Organon product was superior to other COCs because it had fewer side effects were false and misleading because of a lack of appropriate comparative studies. The untitled letter concerned the sponsor's promotional superiority claims that were not supported by comparative clinical trials.

The Petition also fails to mention or include any of the scientific references supporting an opposing viewpoint that there may be potential benefits of third-generation COCs compared to second-generation COCs, including references that suggest that there is less risk of myocardial infarction and that there is an improved lipid profile with the use of third-generation COCs. In fact, the Petition does not even mention the studies (one authored by one of the petitioners) that have tried to analyze potential benefits of third-generation COCs in regard to ATEs, namely myocardial infarction.[67] Although, like the VTE studies discussed above, these studies varied in their results, the World Health Organization included them in their 1998 technical report.[68] Overall, these studies (one

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[65] 21 U.S.C. 355(c).

[66] Untitled Letter to Organon dated July 29, 1998.

[67] See note 37, *supra.*

[68] World Health Organization. WHO Technical Report Series #877. Cardiovascular Disease and Steroid Hormone Contraception 1998.

of which reported statistically significant differences) suggest a tendency for users of third-generation COCs to have less risk of myocardial infarction than users of second-generation COCs.[69]

In addition, you did not mention nor include any of the studies that showed that third-generation COCs are associated with more favorable lipid alterations than second-generation COCs. In particular, one such study found that compared with levonorgestrel, desogestrel-containing COCs caused significant generally beneficial changes in high-density lipoprotein (HDL), low-density lipoprotein, total/HDL cholesterol ratio, and triglycerides in women without the factor V Leiden mutation.[70]

In summary, the arguments in the Petition regarding clinical benefit do not support your position that third-generation COCs are "impossible to recommend" over second-generation COCs and that their approval should be withdrawn. Evidence of superior clinical benefit is not required for approval and you have not provided sufficient evidence that the conditions required by the Act for withdrawal of approval exist. Further, studies not cited in the Petition suggest that third-generation COCs may have some benefits over second-generation products. You did not include those studies in the Petition, and you did not address how these studies support or do not support your assertion that third-generation COCs do not have "superior" clinical benefit.

C. Existing Product Labeling Adequately Informs of the the Risk of Thromboembolism

Review of a drug product's labeling, which includes a description of the risks associated with use of a drug, is part of FDA's assessment of whether the benefits of the drug outweigh the existing or potential risks and is part of FDA's decision whether to approve the drug.[71] As described in Section I.A., current product labeling for desogestrel-containing COCs includes a specific warning related to thromboembolism. The warning statements specific to labeling for third-generation COCs (i.e., desogestrel-containing products) describe the same numeric increase in VTEs as does the Petition, although expressed per 10,000 users rather than per 100,000 as in the Petition. The present warning statements also reflect that there are conflicting views about VTE risk.[72] Current product labeling, including the warning statement regarding the possibility of an increased risk of venous thromboembolism in users of third-generation COCs compared to that in users of second-generation COCs, is appropriate based on currently available information. Because the different results obtained from epidemiologic studies have not

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[69] Lewis et al. 1997.

[70] Kemmeren JM, A Algra, and DE Grobbe, 2001, Effect of second and third generation oral contraceptives on lipid metabolism in the absence or presence of the factor V Leiden mutation, J Intern Med, 250:441-448.

[71] 21 USC 355(d) and 21 CFR 201.100. In addition, if FDA becomes aware of new safety information that it believes should be included in the labeling, FDA could require a sponsor to change their labeling to include the new information. See section 505(o)(3) of the Act.

[72] See representative Warning in Section II.A.2.

been resolved, it is appropriate to continue to alert prescribers and the public about potential risk, while acknowledging that the data are conflicting. In our view, the existing labeling appropriately describes the risks and the uncertainty of the available data on increased risk of thromboembolism.

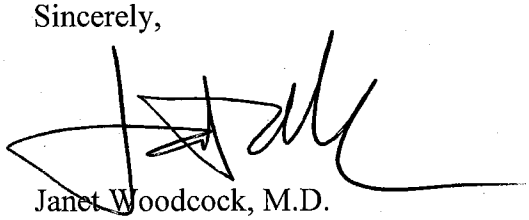
III. CONCLUSION

In summary, the epidemiologic studies that you cited to support an increased risk of VTE with the use of desogestrel-containing COC products for contraception have provided conflicting results, and many have methodological limitations that call into question the validity of their findings and conclusions. More recent studies that more carefully adjusted for duration of use have not shown the magnitude of increased risk of VTE reported in earlier studies. The studies reviewed did not provide consistent estimates of the comparative risk of VTE nor did they fully account for important known and unknown patient characteristics and other biases that may influence prescribing and likely affect the risks. For these reasons, it is unclear whether the increased risk seen in some of the epidemiologic studies is actually due to use of third-generation oral contraceptives. In the Petition, you theorize that use of third-generation oral contraceptives may be associated with changes in the results of coagulation tests, but these alterations have not been shown to be directly responsible for an increase in VTEs. We believe that the present labeling that discusses the epidemiologic findings with respect to these risks is appropriate and adequate for risk management and accurately reflects the medical information currently available.

Additionally, although their results were not statistically significant, some studies of the risk of myocardial infarction have suggested a clinical benefit from use of third-generation products compared to second-generation products.

For the reasons described above, the Petition is denied. FDA will continue to monitor and review available safety information related to desogestrel-containing oral contraceptives and take any further action as appropriate.

Sincerely,



Janet Woodcock, M.D.
Director
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