May 17, 2022

William V. Williams, M.D.
Contraceptive Study Group
620 South Eagle Road
Havertown, PA 19083

Re: Docket No. FDA-2019-P-2289

Dear Dr. Williams:

This letter responds to part of your citizen petition (Petition) received on May 9, 2019 and supplemented and amended on June 23, 2019. In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take several actions with respect to combined hormonal contraceptives (CHCs)[1] that are "combined estrogen-progestogen contraceptive formulations," as well as all "progestin-only contraceptive formulations" (POCs), "regardless of the route of administration".[2] (Petition at 6). This partial response addresses only your request that a boxed warning[3] should be added to prescribing information and "patient-related materials" for all CHCs regarding your claims that these drugs increase the risk of breast cancer. (Petition at 4)[4] The remaining requests in your Petition will be addressed at a later date.

We have carefully considered the evidence and arguments you present in the Petition, comments submitted to the Petition docket, and other pertinent information in the medical literature with respect to the issue of breast cancer risk associated with the use of CHCs. We do not agree, for the reasons described below, that a boxed warning regarding breast cancer risk is appropriate for the CHC product class. Your request for a boxed warning is, therefore, denied. However, based

[1] In the Petition, you refer to COCs as "all combined estrogen-progestogen contraceptive formulations," however, the abbreviation COC is commonly used to refer to combination oral contraceptives. In your Petition, you state that the entire class of estrogen-progestogen contraceptives is implicated, regardless of route of administration. Accordingly, we will refer to this class as combined hormonal contraceptives (CHCs). When referring to combination oral contraceptives only, we will use the COC abbreviation.

[2] You also request that the Agency withdraw injectable Depot Medroxyprogesterone Acetate (DMPA) from the market. (Petition at 4). We defer discussion of the requested action on DMPA (which is not a CHC), as well as discussion of your requested actions regarding other warnings on CHC products, for a subsequent response or responses. We similarly defer discussion of the risk of breast cancer associated with POCs for a subsequent response.

[3] Your Petition requests a "black box warning" for breast cancer. We note that the term "black box warning" is no longer used when referencing warnings on pharmaceutical product labeling. We interpret your request for a "black box warning" as a request for a boxed warning (see 21 CFR 201.57(c)(1)) and use that term in this response.

[4] We interpret your request for changes to the "patient-related materials" for CHC products to refer to the "Patient Package Insert" (PPI) for CHC products. See 21 CFR 310.501. We note that corresponding changes to the PPI would be made in line with any changes to the approved prescribing information (prescription drug labeling).

on the Agency's review of relevant scientific literature, FDA approved a safety labeling change (SLC) for CHCs on April 29, 2022, to better reflect the Agency's current assessment of breast cancer risk associated with the use of these products.

I. BACKGROUND

A. CHC Products and Breast Cancer Risk

CHCs contain a progestin which suppresses ovulation and an estrogen, typically ethinyl estradiol, which contributes to ovulation suppression and helps prevent irregular bleeding.[5] Current FDA-approved CHCs have oral, transdermal, and vaginal routes of delivery and include 40 branded CHC products and approximately 150 generic equivalents. Combined oral contraceptives (COCs) are the most used reversible contraceptive method in the United States. In 2017 to 2019, an estimated 14% of women aged 15 to 49 using contraception in the U.S. used COCs.[6]

In May 1960, the Agency approved the first CHC. Enovid-10 was a COC containing 9.85 milligrams (mg) norethynodrel and 0.15 mg mestranol. Although highly effective for the prevention of pregnancy, early COC formulations were associated with significant adverse effects including cardiovascular and thromboembolic risk. Since the approval of Enovid-10, decreases in hormone dosage and development of new synthetic hormones have improved the safety and tolerability of COCs. By the 1980's, the most prescribed COCs contained < 0.035 mg ethinyl estradiol. Further adjustments in biphasic and triphasic COCs, with different doses of progestins, also allowed for a lower overall dose of progestin during the 28-day cycle. In the following three decades, COCs were developed with even lower doses of ethinyl estradiol (down to 0.010 mg ethinyl estradiol) and new synthetic progestins. There are also CHC products with continuous and extended dosing regimens. The goals of these changes were to decrease side effects and improve safety, while maintaining efficacy, and to reduce the frequency of or eliminate scheduled bleeding episodes.[7] Alternative routes for delivery of combined contraceptive hormones (e.g., transdermal, vaginal) have been approved since 2001.

The relationship between use of CHCs and the risk for breast cancer has been the subject of many studies since the introduction of hormonal contraception in 1960. Characterizing the relationship between breast cancer and use of CHCs is complicated for many reasons, as discussed later in this response.

Breast cancer is the most common cancer diagnosed among women in the U.S. (excluding skin cancers) and is the second leading cause of cancer death among women.[8,9] In 2018, there were

[5] Hatcher RA, Nelson AL, Trussell J, et al. eds. Contraceptive technology. 21st Edition. New York, NY: Ayer Company Publishers, Inc., 2018. Chapter 8 Combined Oral Contraceptives.
[6] See https://www.cdc.gov/nchs/products/databriefs/db388.htm (visited 4/18/22).
[7] Burkman R, Bell C, Serfaty D. The evolution of combined oral contraception: improving the risk-to-benefit ratio. Contraception. 2011;84(1):19-34.
[8] https://www.cdc.gov/cancer/breast/statistics/index.htm. Accessed April 27, 2022.
[9] https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/ Accessed May 10, 2022.

254,744 new female breast cancer cases reported with an incidence of 126.8/100,000 women.[10] The number of deaths from female breast cancer was 42,465 with a death rate of 19.8/100,000 women.[11] The lifetime risk of developing breast cancer in U.S. women is 12.9%. At age 30 years, the risk of being diagnosed with breast cancer in the next 10 years is 0.49% (1 in 204), while at age 70 years, the risk increases to 4.09% (1 in 24).[12] Women aged 65 to 74 years are most frequently diagnosed with breast cancer; the percent of female breast cancer deaths is also highest in that age group. The median age of diagnosis is 63 years and the median age for death is 69 years. Between 2009 and 2018, age-adjusted rates for new female breast cancer cases rose on average 0.3% each year and age-adjusted death rates fell on average 1.3% each year.[13]

Breast cancer is a heterogenous disease. Breast cancers are categorized by cell type and gene expression subtype. The most common type is ductal carcinoma, making up about 80% of all invasive breast cancer.[14] The four main female breast cancer molecular subtypes are based on cancer gene expression, and the distribution of these subtypes varies by age, race, ethnicity, and stage at time of diagnosis. The most common subtype, Luminal A (68% of breast cancer cases), has receptors for estrogen or progesterone (HR+) and low levels of protein HER2/neu (HER2-). The other three subtypes are more likely to be diagnosed in women who are younger, belong to minority groups, and who have cancer diagnosed at a later stage.[15]

Breast cancer detection and diagnosis have improved since 1985 when screening mammograms became widely used. Digital mammography replaced film mammography, improving the accuracy of imaging in younger women and women with dense breasts. The development of breast ultrasonography in the 1990s and breast magnetic resonance imaging (MRI) in the late 1990's has further improved accuracy of imaging, particularly in women at high risk. Most recently, digital breast tomosynthesis, which uses computer reconstruction to create three-dimensional images of the breast, has been shown to improve cancer detection rates.[16]

The main risk factors for breast cancer are female sex (99% of all breast cancers) and advancing age. Other characteristics have been associated with an increased risk of breast cancer, although most women diagnosed with breast cancer do not have identifiable risk factors.[17] Breast cancer risk factors include:

- Known deleterious gene mutation (e.g., BRCA 1)
- Personal history of breast cancer, carcinoma in situ, benign breast disease, dense breast tissue on postmenopausal mammogram

[10] See https://gis.cdc.gov/Cancer/USCS/#/Trends/ Accessed April 22, 2022.
[11] Ibid.
[12] See https://www.cancer.gov/types/breast/risk-fact-sheet, Accessed April 22, 2022
[13] See https://seer.cancer.gov/statfacts/html/breast.html, Accessed April 22, 2022
[14] See https://www.cancer.org/cancer/breast-cancer/about/types-of-breast-cancer/invasive-breast-cancer.html. Accessed April 22, 2022.
[15] See https://seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed April 22, 2022. See https://www.komen.org/breast-cancer/diagnosis/molecular-subtypes/ Accessed April 22,2022
[16] Joe BN and Sickles EA. The evolution of Breast Imaging: Past to Present. Radiology. 2014; 273(2): S23.
[17] ACOG Committee on Practice Bulletin Number 179. July 2017, reaffirmed 2019. Breast Cancer Risk Assessment and Screening in Average-Risk Women.

- Family history of breast cancer or other hereditary breast and ovarian syndrome-associated cancer (also includes pancreatic cancer and melanoma, among others)
- History of high-dose radiation to chest
- Early menarche (< 12 years of age), late menopause (> 55 years of age), age at first full-term pregnancy (≥ 30 years of age), nulliparity, and not breastfeeding
- Menopausal hormone therapy with estrogen and progestin
- Obesity
- Alcohol consumption
- Race[18]

The relationship between CHC use and the risk for breast cancer has been the subject of many studies since the introduction of hormonal contraception in 1960. The difficulty in both identifying studies that have sufficient quality and then determining whether there is a relationship between use of CHCs and breast cancer is complicated by the fact that not all breast cancers are hormonally sensitive. In addition to issues related to study design and quality, there have been many iterations of CHCs over time as well as changes in diagnostic technologies for detecting breast cancer that likely result in differing risk estimates over time.

CHCs containing an estrogen and progestin for the prevention of pregnancy may be expected to carry the same risk of breast cancer regardless of route of administration, and therefore may be considered as a class for labeling purposes.[19] All CHC labeling states that breast cancer is a contraindication for use. This contraindication is in the "CONTRAINDICATIONS" section and in some labeling is repeated in the "WARNINGS AND PRECAUTIONS" section.

B. Boxed Warnings in Prescription Drug Labeling

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (§ 201.57(c)(6)(i); see also §§ 201.80(e) and (f)).[20] A boxed warning is the most serious warning placed in the labeling of a prescription drug.

Under § 201.57(c)(1), a boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and that conveys the general focus of the information in the box (§ 201.57(c)(1)). A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words that are appropriate to identify the subject of the warning) must be included in the HIGHLIGHTS in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

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[18] Ibid.

[19] See Draft Guidance, "Labeling for Combined Hormonal Contraceptives Guidance for Industry." (December 2017).

[20] While many CHC products are subject to the labeling requirements in 21 CFR § 201.57, some older CHC products are subject to the labeling requirements in 21 CFR § 201.80.

As described in FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format*[21] (Warnings and Precautions Guidance), a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug, or

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under section 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1(f)(3)).[22]

There may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.[23]

II. DISCUSSION

A. Studies Relied Upon in the Petition Do Not Support the Request for Breast Cancer Boxed Warning

The Petition asserts that CHC products are "acknowledged by [the International Agency for Research on Cancer][24] as Group 1 carcinogens" and that "[s]ubstantial data supports an increased risk of breast cancer with the use of [CHCs]." The Petition requests that FDA require the addition of a boxed warning to the labeling of all CHC products regarding the risk of breast cancer and that patient-related materials convey this risk also. (Petition at 4). Given the breadth of your requested boxed warning and the fact that, per your request, it would apply to all CHC products, we interpret it as applying to the general contraceptive user population overall.

[21] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.
[22] See Guidance for Industry on *"Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format"* (October 2011) at p. 11.
[23] Ibid.
[24] The International Agency for Research in Cancer, or IARC, is the specialized cancer agency of the World Health Organization.

FDA has reviewed the information you provided in the Petition, and we do not agree that it supports adding a boxed warning to the labeling of all CHC drug products stating that they have been shown to increase the risk of breast cancer. The Petition cites primarily those studies from the published literature that it believes support its claims regarding increased risks. However, overall, epidemiology studies have not found a consistent association between use of CHCs and breast cancer risk. Although there is a substantial amount of data on the use of CHCs and the risk of breast cancer, studies have reported a range of results, including no association, positive association, and negative association between CHC use and the risk of breast cancer. The divergent findings may be due in part to different populations studied and the inconsistent control of confounding variables within each study. Other factors such as the measure of exposure used in the studies (i.e., ever having used CHCs, currently using CHCs, and duration of use of CHCs), many different formulations of CHCs over time, as well as changes in diagnostic technologies for detecting breast cancer, may also contribute to conflicting and inconsistent data generated in studies of breast cancer potentially related to CHC use.

The Petition cites many studies as supportive of an increased risk of breast cancer associated with CHC use when comparing ever users with never users of CHC drugs. We have reviewed these studies and do not agree with your characterization of their findings.[25] When we considered the confidence interval along with the stated relative risk in each of your cited studies, we found that **13 studies showed no significant association with breast cancer.**[26]

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[25] Although many of the studies discussed in this response use the term "oral contraceptive (OC)", the discussions and conclusions in the studies reflect that COCs were used in the studies. Because most OC use consists of COCs, we use COCs when referring to the studies unless otherwise indicated.

[26] Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, and Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev 2010; 19:2496–2502.; Jernström H, Loman N, Johannsson OT, Borg A, and Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur J Cancer 2005; 41:2312–2320.; Lund E, Bakken K, Dumeaux V, Andersen V, and Kumle M. Hormone replacement therapy and breast cancer in former users of oral contraceptives--The Norwegian Women and Cancer study. Int J Cancer 2007; 121:645–648.; Ma H, Bernstein L, Ross RK, and Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res 2006; 8: R39.; Sweeney C, Giuliano AR, Baumgartner KB, Byers T, Herrick JS, Edwards SL, and Slattery ML. Oral, injected and implanted contraceptives and breast cancer risk among U.S. Hispanic and non-Hispanic white women. Int J Cancer 2007; 121:2517–2523.; Folger SG, Marchbanks PA, McDonald JA, Bernstein L, Ursin G, Berlin JA, Daling JR, Norman SA, Strom BL, Weiss LK, Simon MS, Burkman RT, Malone KE, and Spirtas R. Risk of breast cancer associated with short-term use of oral contraceptives. Cancer Causes Control 2007; 18:189–198.; Lee E, Ma H, McKean-Cowdin R, Van Den Berg D, Bernstein L, Henderson BE, and Ursin G. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiol Biomarkers Prev 2008; 17:3170–3178.; Figueiredo JC, Haile RW, Bernstein L, Malone KE, Largent J, Langholz B, Lynch CF, Bertelsen L, Capanu M, Concannon P, Borg A, Børresen-Dale AL, Diep A, Teraoka S, Torngren T, Xue S, and Bernstein JL. Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and noncarriers: the WECARE Study. Breast Cancer Res Treat 2010; 120:175–183.; Poosari A, Promthet S, Kamsa-ard S, Suwanrungruang K, Longkul J, and Wiangnon S. Hormonal contraceptive use and breast cancer in Thai women. J Epidemiol 2014; 24:216–220.; Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, and Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Res 2014a; 74:4078–4089.; Ichida M, Kataoka A, Tsushima R, and Taguchi T. No increase in breast cancer risk in Japanese women taking oral contraceptives: a case-control study investigating reproductive, menstrual and familial risk factors for breast cancer. Asian Pac J Cancer Prev 2015; 16:3685–3690.;

Three additional studies cited in the Petition found **a decrease in the risk of breast cancer** with CHC use.[27]

Of the studies that were statistically significant, most contained issues which made the study results less reliable than the relative risk number alone suggests.[28] For example, the study by Heikkinen does not provide a relative risk number for CHC products separately.[29] The studies by Lumachi, Tehranian, Veisy, and Beaber did not adjust for confounding factors such as age at first menarche, parity, or family history.[30] The study by Beji contained a relatively small number of ever use breast cancer cases relative to the study findings.[31] We discuss some of these studies in detail in the discussion section below.[32]

Amadou A, Fabre A, Torres-Mejía G, Ortega-Olvera C, Angeles-Llerenas A, McKenzie F, Biessy C, Hainaut P, and Romieu I. Hormonal therapy and risk of breast cancer in Mexican women. PLoS One 2013; 8:e79695; Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, and Malone KE. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev 2009; 18:1157–1166.

[27] Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, Giles GG, McCredie MR, Hopper JL, and Whittemore AS. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005; 14:350– 356. Ozmen V, Ozcinar B, Karanlik H, Cabioglu N, Tukenmez M, Disci R, Ozmen T, Igci A, Muslumanoglu M, Kecer M, and Soran A. Breast cancer risk factors in Turkish women—a University Hospital based nested case control study. World J Surg Oncol 2009; 7:37. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, Li CI. Reproductive History and Oral Contraceptive Use in Relation to Risk of Triple-Negative Breast Cancer. J Natl Cancer Inst 2011; 103:470-477.

[28] We note that in Rosenberg (2008) the odds ratio is 1.5 (1.2, 1.8). 1.5 is considered to be a weak association in observational studies with many unknown variables. The study has many limitations, and the results may also not be generalizable. See Rosenberg L, Zhang Y, Coogan PF, Strom BL, and Palmer JR. A case-control study of oral contraceptive use and incident breast cancer. Am J Epidemiol 2008; 169:473–479. We also note that Li (2012) evaluated DMPA which is not a CHC product and not appropriately included as a study supporting the claim of increase breast cancer risk due to CHC use. See Li Cl, Beaber EF, Tang MT, Porter PL, Daling JR, and Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res 2012; 72:2028-2035.

[29] Heikkinen S, Koskenvuo M, Malila N, Sarkeala T, Pukkala E, and Pitkäniemi J. Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment. Cancer Causes Control 2016; 27:249–258.

[30] Lumachi F, Frigo AC, Basso U, Tombolan V, and Ermani M. Estrogen therapy and risk of breast cancer in postmenopausal women: a case-control study and results of a multivariate analysis. Menopause 2010; 17:524–528.; Tehranian N, Shobeiri F, Pour FH, Hagizadeh E. Risk factors for breast cancer in Iranian women aged less than 40 years. Asian Pacific J Cancer Prev. 2010; 11:1723-1725.; Veisy A, Lotfinejad S, Salehi K, and Zhian F. Risk of breast cancer in relation to reproductive factors in North- West of Iran, 2013-2014. Asian Pac J Cancer Prev 2015; 16:451–455.; Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, and Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Res 2014a; 74:4078–4089.

[31] Beji NK and Reis N. Risk factors for breast cancer in Turkish women: a hospital-based case-control study. Eur J Cancer Care (Engl). 2007; 16:178–184.

[32] We note that in Ma (2010) the findings are for triple negative breast cancer which is a small subset of breast cancers, and the findings are of limited usefulness when determining overall risk for breast cancer. See Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, Press MF, and Bernstein L. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer Res 2010; 70:575–587.

Taken as a whole, the weight of the evidence based on the studies cited in the Petition does not support the Petition's claim that CHC use is associated with a significant risk of breast cancer.[33] We have also considered, as discussed further below, whether there are findings in the studies cited in the Petition that would support a boxed warning in a more narrowed context of use, such as age at first use. However, we do not find that the studies cited in the Petition, or the related data cited in the Petition, supports a boxed warning on CHC drugs for the risk of breast cancer in any of these contexts.

a. The meta-analysis studies

The Petition's primary claim with respect to the risk of breast cancer is that "substantial data supports an increased risk of breast cancer with the use of [CHCs]." (Petition at 4). One of the primary types of studies cited in the Petition in support of this claim are meta-analyses,[34] which are included on Table 5 of the Petition. (Petition at 27). The five meta-analyses submitted with the Petition each have limitations, as discussed below.

The meta-analysis by Kahlenborn reviewed only case control studies and included all studies in the literature without applying any quality assessment criteria.[35] Many of these studies date back to the 1980's and the last publication included was published in 2002. As such, the data are outdated. In addition, since the 1980s, CHCs have continued to be developed with much lower doses of estrogen, lower doses of progestins, with newer synthetic progestins, and with differing dosing regimens, so data in older studies are unlikely to be applicable to the current risk characterization. Recent studies are more likely to reflect the risk of currently prescribed CHCs.

The meta-analysis by Bethea focused on African American women in North Carolina, in addition to breast cancer subgroups, and therefore may not be generalizable to the overall U.S. population of CHC users.[36] The meta-analyses by Friebel and Moorman evaluated cancer risk in women

[33] The Petition references IARC's consideration of the carcinogenicity of COCs over a number of years. (Petition at 20). While IARC has classified COCs as carcinogens, from the epidemiologic perspective, classification in and of itself is not sufficient to conclude that use of COCs inevitably produces disease. For the majority of diseases, most, and sometimes all, of the factors that combine (or how they combine) to cause a disease in an individual are unknown. Individual susceptibility and other factors (e.g., age, lifestyle, reproductive history) may increase an individual's risk of developing cancer. Additionally, the IARC classification does not rely on any apparent risk-benefit analysis when it adds an agent to the known carcinogen list. See discussion of IARC classification process at https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf

[34] "The term meta-analysis, as used in FDA Guidance, "refers to the combining of evidence from relevant studies using appropriate statistical methods to allow inference to be made to the population of interest. The most common reason for performing a meta-analysis is to provide an estimate of a treatment effect or measure of relative risk associated with an intervention and to quantify the uncertainty about the estimated effect or risk, when data from a single existing study are insufficient for this purpose, and the conduct of a new, large study would be impractical, take too long or be unethical." See FDA's draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018) at p. 1. When final, this guidance will represent FDA's current thinking on this topic.

[35] Kahlenborn C, Modugno F, Potter DM, and Severs WB. Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis. Mayo Clin Proc 2006; 81:1290–1302.

[36] Bethea TN, Rosenberg L, Hong CC, Troester MA, Lunetta KL, Bandera EV, Schedin P, Kolonel LN, Olshan AF, Ambrosone CB, and Palmer JR. A case-control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. Breast Cancer Res 2015; 17:22. Doi: 10.1186/s13058-015-0535-x.

with BRCA 1, BRCA 2, and a strong family history of breast cancer.[37] The populations in these meta-analyses are at an increased risk of developing breast cancer and are also not generalizable to the overall contraceptive user population.

The Zhu article is a meta-analysis that included 13 prospective cohort studies.[38] The authors do conclude that there is evidence of a non-significant increase in breast cancer risk associated with ever OC use[39] and that this risk for long-term OC users is significantly greater. However, only 5 of the 13 studies provided data on long term use and the authors specifically noted that "the latter finding [regarding long term use] is based on only a limited number of studies." This conclusion is consistent with the Agency's SLC, discussed below in section II.B, and does not support a boxed warning for breast cancer risk in the labeling of CHC drugs (see discussion in section I.B, above).

b. The observational studies

As support for the labeling changes requested, the Petition also cites a number of observational studies.[40] While some of the observational studies referenced in the Petition report a modestly increased relative risk (RR)[41] of breast cancer in current COC users, observational studies are susceptible to confounding and this greatly increases the difficulty of interpreting the association between exposure (e.g., COCs) and outcome (e.g., breast cancer). Significantly, many of the studies cited in the Petition have a RR of 1.5 or less. A RR of 1.5 or less is generally considered

[37] Friebel TM, Domchek SM, and Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst 2014; 106(6): dju091. Doi: 10.1093/jnci/dju091.; Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, and Myers ER. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol 2013;31(33): 4188–4198. Doi: 10.1200/JCO.2013.48.9021.

[38] Zhu H, Lei X, Feng J, and Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. Eur J Contracept Reprod Health Care 2012; 17:402–414. A prospective cohort study is a type of observational study where the study participant is exposed or not and then followed to determine if the disease of interest develops. P59/511 Principles of Epidemiology in Public Health Practice. An Introduction to Applied Epidemiology and Biostatistics. Third Edition. October 2006, Updated May 2012. US Department of Health and Human Service, Center for Disease Control and Prevention, Office of Workforce and Career Development, Atlanta, GA 30333.

[39] For purposes of this response, "ever use" refers to current or prior use of CHCs.

[40] An observational study "is a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol." See FDA's draft guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (December 2021) at p. 2. When final, this guidance will represent FDA's current thinking on this topic. Observational studies include cohort studies, case-control studies, and cross-sectional studies. P 50/511 Principles of Epidemiology in Public Health Practice. An Introduction to Applied Epidemiology and Biostatistics. Third Edition. October 2006, Updated May 2012. US Department of Health and Human Service, Center for Disease Control and Prevention, Office of Workforce and Career Development, Atlanta, GA 30333.

[41] A relative risk is "[a] measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group . . . . A relative risk of one means there is no difference between two groups. . . . A relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk …." See the National Cancer Institute's web page "Dictionary of Cancer Terms" at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/relative-risk, accessed February 25, 2022.

by many epidemiologists to be a weak association;[42] and when interpreting studies with weak associations, the potential impact of bias and residual confounding needs to be considered as this may wholly or in part explain the study findings. FDA consideration of the appropriateness of a boxed warning may be based on, among other things, the totality of the evidence regarding a safety concern and an evaluation of the overall risk-benefit assessment. Here, the rarity of the risk of breast cancer attributable to CHCs must be considered in the context of the multiple known benefits of CHCs, most notably the prevention of pregnancy. The benefits of CHCs vastly, proportionally outweigh the small risk of breast cancer and therefore a boxed warning is not warranted here.

The Petition claims that "recent data confirms an increased risk of breast cancer with the use of [CHCs]". (Petition at 20). We interpret this claim, and the statement noted previously that "[s]ubstantial data supports an increased risk of breast cancer with the use of [CHCs]" as asserting that there is an increased risk of breast cancer with ever use of CHCs (past or current) when compared with never use of CHCs. (Petition at 4).

We have thoroughly reviewed the observational studies cited in the Petition in support of this assertion. In a number of instances, we disagree with the Petition's characterization of the data. In fact, a considerable number of the observational studies cited in the Petition as supportive of an increased risk of breast cancer, due to ever use of CHCs as compared to never use of CHCs, showed no association (either positive or negative) between CHC use and breast cancer.[43] Other cited studies showed a negative association, i.e., a decreased risk of breast cancer.[44] In addition, the Petition did not correctly represent the risks reported in some of the studies. For example, the Petition reported risk estimates for current use or duration of use as risk estimates for past use, which is incorrect (Mørch[45], Ma[46]) and reported ever use risk estimates in BRCA+ cohort only (Brohet[47]) which is not generalizable to a general CHC user population.

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[42] See Rosenthal, James A., Qualitative Descriptors of Strength of Association and Effect Size, Journal of Social Service Research, (1996) 21:4, 37-59, DOI: 10.1300/J079v21n04_02.

[43] Supra at footnote 25.

[44] Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, Giles GG, McCredie MR, Hopper JL, and Whittemore AS. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005; 14:350– 356.; Ozmen V, Ozcinar B, Karanlik H, Cabioglu N, Tukenmez M, Disci R, Ozmen T, Igci A, Muslumanoglu M, Kecer M, and Soran A. Breast cancer risk factors in Turkish women—a University Hospital based nested case control study. World J Surg Oncol 2009; 7:37. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, Li CI. Reproductive History and Oral Contraceptive Use in Relation to Risk of Triple-Negative Breast Cancer. J Natl Cancer Inst 2011; 103:470-477.

[45] Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, and Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017; 377:2228–2239.

[46] Ma H, Bernstein L, Ross RK, and Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res 2006; 8: R39.

[47] Brohet RM, Goldgar DE, Easton DF, Antoniou AC, Andrieu N, Chang-Claude J, Peock S, Eeles RA, Cook M, Chu C, Noguès C, Lasset C, Berthet P, Meijers-Heijboer H, Gerdes AM, Olsson H, Caldes T, van Leeuwen FE, and Rookus MA. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol 2007; 25:3831–3836.

In the Petition you state, "The studies that looked at recent use (within 1–5 years) or current use of [CHCs] in premenopausal women showed the most dramatic increased risk for breast cancer". (Petition at 20). Based on Tables 3-5 of the Petition, you are relying on five studies for this conclusion: Dolle, Trivers, Ichida, Beaber, and Hunter.[48] We also evaluated Mørch which you cite on page 21 of the Petition; Mørch provides the most recent findings regarding recent or current use.

Dolle is a case-control study that investigated the risk factors for triple-negative breast cancer in women under 45 years of age. The authors reported risk of all breast cancers, triple negative and non-triple negative breast cancers. The study did not show an increased risk of all breast cancers (Odds Ratio (OR) 1.0 [95% CI 0.6, 1.8]) in current COC users. The OR of 4.2 (1.9, 9.3) reported in Table 4 of the Petition as risk of breast cancer for current use is the OR for triple-negative breast cancer among women under 40 years of age using COCs >1 to < 5 years compared to never use (use less than 1 year).[49] Thus, Dolle does not support the claim of increased risk of breast cancer with current CHC use in the general contraceptive user population.[50] Trivers is a cohort study that examined the relationship between OC use before breast cancer diagnosis and survival in a population-based sample of women aged 20 to 54 years with a first primary invasive breast cancer during 1990-1992 and followed for up to 8 to 10 years. The study reported all-cause mortality estimates, not risk of developing cancer, among women who were using OCs at diagnosis or stopped use in the previous years compared with nonusers. The study did not evaluate the current use of CHCs and the risk of breast cancer in the general contraceptive user population and, therefore, cannot support the Petition's claim.[51] Ichida is a case-control study of Japanese women investigating COC use and breast cancer risk. It found a lower risk of breast cancer in premenopausal women currently taking COCs compared to never users (OR 0.45 [95% CI 0.22, 0.90]) after adjusting for age, parity, breast feeding, and a family history of breast cancer. Thus, the finding from Ichida actually refutes your claim of increased risk of breast cancer with current CHC use.[52]

[48] We have identified these five studies because, as reflected on Tables 3-5, they looked at recent use or current use. In the Petition, you also cite the studies by Bethea and Lund as part of your discussion regarding recent or current use. The findings from Bethea are discussed on page 8 of this response and the findings from Lund are discussed on page 14 of this response.

[49] We note that definitions of "never use" vary between several of these studies. For example, some studies define "never use" as use of one year of less while others define it as no use at all.

[50] We note that the OR for ever use cited in Table 4 of the Petition is not found in the Dolle study. See Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, and Malone KE. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev 2009; 18:1157–1166.

[51] Trivers KF, Gammon MD, Abrahamson PE, Lund MJ, Flagg EW, Moorman PG, Kaufman JS, Cai J, Porter PL, Brinton LA, Eley JW, and Coates RJ. Oral contraceptives and survival in breast cancer patients aged 20 to 54 years. Cancer Epidemiol Biomarkers Prev 2007; 16:1822–1827.

[52] Ichida M, Kataoka A, Tsushima R, and Taguchi T. No increase in breast cancer risk in Japanese women taking oral contraceptives: a case-control study investigating reproductive, menstrual and familial risk factors for breast cancer. Asian Pac J Cancer Prev 2015; 16:3685–3690. Furthermore, as noted above in footnote 41, contrary to your overall assertions with respect to the risk of breast cancer, Ichida did not show an increased risk of breast cancer associated with CHC use when comparing ever users with never users of CHC drugs.

Of the observational studies cited in the Petition, only three (Beaber[53], Hunter[54], and Mørch[55]) found an increased risk of breast cancer with current/recent COC use compared with never/past users. However, a closer review of these studies also reveals more nuanced results and considerations. Beaber is a case-control study that found recent COC use was associated with a 50% increase in breast cancer risk (OR 1.5 [95% CI 1.3, 1.9]) compared with never/past users. Residual confounding must be carefully considered in the interpretation and application of the findings. It is, however, difficult to assess the reliability of the study's findings (and the degree of such confounding) because, for most women in the study, data regarding the study subjects' risk factors for breast cancer, such as age at menarche, parity (number of births), history of breast feeding, smoking, and family history of breast cancer, were not available. The reported risk estimate compared with other similar studies suggests that these other confounding risk factors likely affected the outcome, but further assessment is not possible given the absence of data.

Hunter is a cohort study that found that "[c]urrent use of any oral contraceptives was related to a marginally significant higher risk" compared with never users (RR 1.33; 95% confidence interval (CI) 1.03, 1.73).[56] The authors note that the attributable risk associated with current use was less than two percent, emphasizing that there is not a major association between current oral contraceptive use and breast cancer.[57] Mørch is a cohort study that compared never users of COCs with current/recent (discontinuation within 6 months) COC users. The RR was 1.19 (95% CI 1.13, 1.26).[58] This finding is consistent with the risk found in Hunter and further supports the determination that there is not a major association between current or recent COC and breast cancer that would support adding a boxed warning to the labeling for CHC products.[59]

Based on our review of the observational studies submitted with the Petition, we conclude there is no consistent association between an increased risk of breast cancer and ever use of CHCs in the general contraceptive user population. As noted above, a considerable number of observational studies submitted in the Petition showed no association between the use of CHCs and risk of breast cancer, and others actually showed a decreased risk. Although there were several studies that did show a modest increased risk of breast cancer in current COC users as compared to never users, as noted above, observational studies are susceptible to confounding, which greatly increases the difficulty of interpretation of the association between exposure (e.g., COCs) and outcomes (e.g., breast cancer). Significantly, many of the studies cited in the Petition have a RR of 1.5 or less. A RR of 1.5 or less is generally considered by many epidemiologists to

[53] Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, and Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Res 2014a; 74:4078–4089.
[54] Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, and Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev 2010; 19:2496–2502.
[55] Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, and Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017; 377:2228–2239.
[56] The marginally significant higher risk was quantified as a multivariate relative risk, [RR] 1.33; 95 %CI 1.03,1.73.
[57] Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, and Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev 2010; 19:2496–2502.
[58] Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, and Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017; 377:2228–2239.
[59] Both the Hunter and Mørch studies were found to be of high quality and are included as supportive of the safety labeling change for breast cancer risk, discussed later in this response.

be a weak association; and when interpreting studies with weak associations, the potential impact of bias and residual confounding needs to be considered as this may wholly or in part explain the study findings. FDA's consideration of the appropriateness of a boxed warning may be based on, among other things, the totality of the evidence regarding a safety concern and an evaluation of the overall risk-benefit assessment. As discussed above, the benefits of CHCs vastly, proportionally outweigh the small risk of breast cancer and therefore a boxed warning is not warranted here.

In light of the inconsistent association in studies between an increased risk of breast cancer and ever use of CHCs in the general contraceptive user population, as well as the potential limitations of observational studies, we conclude the available evidence does not support the addition of a boxed warning as requested by the Petition. However, as discussed below in section II.B, based on our review of the relevant literature, FDA approved a safety labeling change (SLC), on April 29, 2022, to better reflect the Agency's current assessment of breast cancer risk associated with the use of these products.

c. No increased risk of breast cancer in women on hormone replacement therapy with a prior history of COC use

Hormone therapy (HT), previously known as hormone replacement therapy (HRT),[60] is the use of FDA-approved, hormone-containing drugs used to help relieve the symptoms of menopause. Different types of hormone drugs used during and after menopause include estrogen-only drugs, progestin-only drugs, combination estrogen and progestin drugs, and combination estrogen and other drugs.[61] The types of estrogens and progestins in these drugs commonly differ from those in CHCs and the doses are very different from those in CHCs.

Two of the studies relied upon in the Petition relate to risk of developing breast cancer in women using HT who were past users of COCs. In citing these two studies, the Petition appears to suggest that there is a significant association between using HT and developing breast cancer if the woman is a past user of COCs. We disagree. One of the two studies (Thorbjarnardottir) concluded that, "[a]fter taking HRT regimen, duration and currency of use into account, the results of our population-based cohort study do not support the notion that former [oral contraceptive] use increases breast cancer risk among HRT users, on the contrary there was an indication of a slightly lower risk in former OC users, restricted to current, long-term [combined estrogen and progestin]-HRT users."[62] Accordingly, Thorbjarnardottir's study does not support a conclusion that there is a significant increase in the incidence of breast cancer among HT users with a prior history of CHC use.

[60] For purposes of this response, we continue to use the term "HRT" when quoting directly from a study that uses that term.
[61] See FDA's web page "Menopause: Medicines to Help You" at https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you, accessed February 25, 2022.
[62] Thorbjarnardottir T, Olafsdottir EJ, Valdimarsdottir UA, Olafsson O, and Tryggvadottir L. Oral contraceptives, hormone replacement therapy and breast cancer risk: a cohort study of 16,928 women 48 years and older. Acta Oncol 2014; 53:752–758.

The other study cited in the Petition that addresses this population (Lund) has several limitations, which introduces significant bias.[63] The study population of women born from 1927 through 1957 spans decades where COCs were not available (before 1960), as well as decades where the COCs that were available were high dose estrogen COCs that are no longer in use. Without further analysis for contemporary COC use (i.e., at levels currently found in marketed products), the applicability of the findings is limited. The authors noted significant limitations to their study, including the lack of regularly updated information on HT in the follow up period that could lead to misclassification of HT exposure status. Additionally, the reproducibility of hormonal contraceptive histories and validity of hormone composition obtained by self-administered questionnaires was not tested.

Given the limitations of the Lund study and the fact that the Thorbjardardottir study reaches the opposite conclusion regarding the risk of breast cancer in the population of women using HT who previously used CHCs, these two studies do not support a conclusion that there is an increased risk of breast cancer in this population that would justify the addition of a boxed warning to the labeling for CHC products.

d. Breast cancer incidence among CHC users who are younger at the time of initial use

The Petition suggests with respect to several studies that there is an increased incidence of breast cancer among CHC users who are younger at the time of initial use. (Petition at 20-21). After reviewing the studies submitted in support of the Petition that considered age at first CHC use, we conclude that they do not support a conclusion that breast cancer incidence is higher among CHC users in the general contraceptive user population (the population relevant for the broad boxed warning being requested in the Petition) who are younger at the time of initial use. While several of the studies looked at the issue of age at the time of initial CHC use, the findings were varied, and some studies had significant limitations.

Three studies (Milne,[64] Veneroso,[65] Beaber[66]) conclude that age at first COC use was not associated with an increased risk of breast cancer.[67] The Mørch study also looked at women who reported initiating COCs before age 20 and concluded there was a suggestion that initiating COC before age 20 may be associated with higher risks of breast cancer among current users with long duration of use, although the risk estimates were imprecise and the risk estimate was

[63] Lund E, Bakken K, Dumeaux V, Andersen V, and Kumle M. Hormone replacement therapy and breast cancer in former users of oral contraceptives--The Norwegian Women and Cancer study. Int J Cancer 2007; 121:645–648.

[64] Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, Giles GG, McCredie MR, Hopper JL, and Whittemore AS. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005; 14:350– 356.

[65] Veneroso C, Siegel R, and Levine PH. Early age at first childbirth associated with advanced tumor grade in breast cancer. Cancer Detect Prev 2008; 32:215–223.

[66] Beaber EF, Malone KE, Tang MT, Barlow WE, Porter PL, Daling JR, and Li CI. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiol Biomarkers Prev 2014b; 23:755–764.

[67] We note, as discussed on page 12 above, that the Beaber study did not adjust for confounding factors which limits the conclusions about that study in this context.

only statistically significant for users with more than 10 years of current CHC use.[68] Two studies (Haile[69] and Kotsopoulos[70]) evaluated BRCA genetic mutation carrier populations only and therefore are not generalizable to the broader contraceptive user population. Jernström's study found that, among women with breast cancer who had BRCA 1 or BRCA 2 genetic mutation carrier testing, there were three times as many mutation carriers among women who started COC use before age 20 than among those who started COCs at age 20 or older or who had never used COCs.[71] As with Haile and Kotsopoulos, the BRCA genetic mutation carrier populations are not generalizable to the general contraceptive user population. Further, the study did not report the risk of breast cancer in women without mutation carrier status who started OC use prior to age 20, the population that would be pertinent to the suggestion in the Petition that there is an increased incidence of breast cancer in CHC users who are younger at the time of initial use.

Lastly, the Petition asserts that in the Delort study, initiating COCs after age 23 reduced the risk of development of breast cancer at a younger age. (Petition at 21). We agree that Delort concluded that use of COCs at an earlier age increased the risk of breast cancer development earlier in life and that, among other factors, the age at first OC use appeared to be a risk factor.[72] However, although the study states that this cohort had non-hereditary breast cancer, it does not describe how this was determined, thereby limiting interpretability. The study has several other limitations as well. It compares age groups based on date of birth with the earliest age group born between 1910 and 1920 (a group unlikely to be exposed to OCs), defines early breast cancer as that occurring at an age less than the median age for each age bracket, and does not provide the number of cases or the number of controls, thus not allowing interpretation of the findings presented.

Given the findings and/or limitations of these studies, we conclude that they do not support a conclusion that there is an increased incidence of breast cancer among CHC users who are younger at the time of initial use that would justify the addition of a boxed warning to the labeling for CHC products.

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[68] Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017;377(23):2228-2239.

[69] Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne RL, Hopper JL, Jenkins MA, Levine AJ, Daly MM, Buys SS, Senie RT, Andrulis IL, Knight JA, Godwin AK, Southey M, McCredie MR, Giles GG, Andrews L, Tucker K, Miron A, Apicella C, Tesoriero A, Bane A, Pike MC; kConFab Investigators; Ontario Cancer Genetics Network Investigators, and Whittemore AS. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006; 15:1863–1870.

[70] Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C, Neuhausen SL, Karlan B, Kim-Sing C, Huzarski T, Gronwald J, McCuaig J, Senter L, Tung N, Ghadirian P, Eisen A, Gilchrist D, Blum JL, Zakalik D, Pal T, Sun P, and Narod SA; Hereditary Breast Cancer Clinical Study Group. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Breast Cancer Res Treat 2014; 143:579–586.

[71] Jernström H, Loman N, Johannsson OT, Borg A, and Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur J Cancer 2005; 41:2312–2320.

[72] Delort L, Kwiatkowski F, Chalabi N, Satih S, Bignon YJ, and Bernard-Gallon DJ. Risk factors for early age at breast cancer onset—the "COSA program" population-based study. Anticancer Res 2007; 27:1087–1094.

e. Boxed warning regarding the risk of breast cancer is not warranted for CHC products

As stated previously, based on our review of the information provided in the Petition and other relevant data, the Agency does not agree that there are data to support your claim of a significant increase in the risk of breast cancer in CHC users, or that a boxed warning regarding breast cancer is warranted in CHC product labeling, which we interpret to include PPI. Overall, the published literature is inconsistent as to whether there is an association between CHCs and breast cancer. As such, based upon our review of the studies cited in your Petition and other relevant information, the weight of the evidence does not support a significant increase in breast cancer associated with CHC use. Additionally, from the epidemiologic perspective, IARC classification in and of itself is not sufficient to conclude that use of COCs inevitably produces disease. We found no association between CHCs and breast cancer risk when comparing ever use versus never use of CHCs; however, as reflected in the safety labeling change approved on April 29, 2022, and as set forth below in section II.B, there are some studies reporting a small increased risk of breast cancer with current or recent use and current use with increasing duration of use when compared to never use.

As stated in FDA's Warnings and Precautions Guidance, in relevant part, a boxed warning is ordinarily used when "[t]here is an adverse reaction so serious in proportion to the potential benefit from the drug . . . that it is essential that it be considered in assessing the risks and benefits of using [the] drug."[73] Based on our conclusions regarding the inconsistency in the published literature and the weight of the available evidence, we conclude that this standard is not met here. While breast cancer is a serious disease, the benefit of CHCs in preventing pregnancy, is clearly established and must be considered when assessing both the benefits and risks of CHC use. We believe the breast cancer risk from the use of CHCs is appropriately addressed by the labeling revisions further described below. Whether to require a boxed warning is within FDA's discretion, and the agency exercises this discretion judiciously to preserve the impact and significance of boxed warnings. In short, the petitioners have not shown that a boxed warning is necessary under these circumstances.

B. FDA's Safety Labeling Change Regarding Breast Cancer Warnings

Prior to submission of the Petition, FDA had become aware of new safety information through its review of medical literature regarding the risk of breast cancer with CHC product use. Some, but not all, of this information overlaps with the studies submitted with the Petition. The Agency conducted a re-analysis of available data and an analysis of new data. Based on this updated analysis, we concluded that the labeling, including patient prescribing information, for CHC products should be updated to reflect the most up-to-date and high-quality evidence regarding breast cancer risk for this drug class. The Agency believes it is in the best interest of the public health that providers and patients receive a consistent, clear message with the most recent, high-quality information, across the labeling for this product class.

[73] FDA's guidance for industry on "Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format" at p. 11.

We consider this updated analysis to be "new safety information" as defined in section 505-1(b)(3) of the FD&C Act. Therefore, in accordance with section 505(o)(4) of the FD&C Act, on November 18, 2021, we issued SLC notification letters to all application holders for CHC products. These letters notified the applicants that based on the new safety information described above, we believe that the new safety information should be included in the labeling for CHC products. The applicants submitted supplements proposing changes to the approved labeling in accordance with the Agency's SLC notification letters; those supplements were approved on April 29, 2022.

Based on the Agency's review and assessment of the literature, six studies were selected for inclusion in the updated labeling and are shown in the figure below.[74] The studies represent the most recent and best epidemiologic evidence on the risk of breast cancer in COC users. Of these studies, two were conducted in the United States, and five were cohort studies. All six studies matched or adjusted for age, as well as age at first full term pregnancy. Additionally, most also adjusted for body mass index (BMI), age at menarche, family history of breast cancer, parity (number of births), and menopausal status. Although we selected these six studies for inclusion in the labeling, they do have limitations, including heterogenous study populations, the risk estimates for long-term use used different cut points (8 versus 10 years), did not evaluate effect modification by age, and may be impacted by residual confounding. The conflicting data and these limitations were taken into account in the labeling revisions regarding breast cancer, to ensure a measured, accurate message that best reflects the data.

The labeling revisions for the CHC drug class are presented below.

Warnings and Precautions

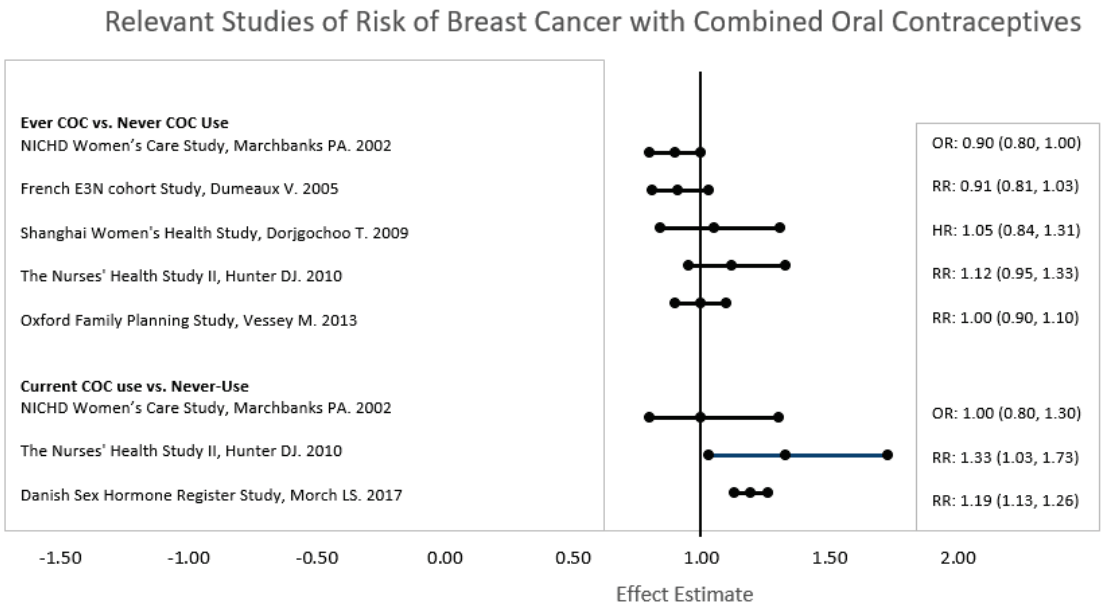
Malignant Neoplasms
Breast Cancer
DRUG is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive [see Contraindications (4)].
Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use [see cross

[74] Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002;346(26):2025-2032.; Dumeaux V, Fournier A, Lund E, Clavel-Chapelon F. Previous oral contraceptive use and breast cancer risk according to hormone replacement therapy use among postmenopausal women. Cancer Causes Control. 2005;16(5):537-544.; Hunter DJ, Colditz GA, Hankinson SE, et al. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(10):2496-2502.; Dorjgochoo T, Shu XO, Li HL, et al. Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006. Int J Cancer. 2009;124(10):2442-2449.; Vessey M, Yeates D. Oral contraceptive use and cancer. Final report from the Oxford-Family Planning Association contraceptive study. Contraception. 2013; 88(6): 678-683.; Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017;377(23):2228-2239.

reference to appropriate section in Adverse Reactions, e.g., Postmarketing Experience (6.2)].

Adverse Reactions

Postmarketing Experience
Five studies that compared breast cancer risk between ever users (current or past use) of COCs and never users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure X).
Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure X). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.



RR = relative risk; OR = odds ratio; HR = hazard ratio; "ever COC" are females with current or prior COC use; "never COC use" are females that never used COCs

Patient Package Insert (PPI)

Do birth control pills cause cancer?
It is not known if hormonal birth control pills cause breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.

In summary, the Agency has approved the new safety labeling changes to prescription labeling for CHCs, including changes to the patient package insert, to align class labeling of CHCs so that it incorporates recent, quality studies and presents data in a clinically meaningful way. The Agency also finds that it is in the best interest of the public health that providers and patients receive a consistent, clear message that reflects this updated safety information across CHC drug labeling. As such, these labeling revisions will permit medical providers and CHC users to appropriately assess the risk of breast cancer with CHC use. We have also determined that no additional risk mitigation actions are necessary at this time.

III. CONCLUSION

For the reasons described above, we are denying the Petition's request for a boxed warning regarding breast cancer on all CHC products, including patient labeling. The approvals for labeling changes on CHC products regarding breast cancer, as discussed above, issued on April 29, 2022. We will respond to the remaining issues in your Petition at a later date.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.05.17 10:57:58 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research