



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Andrew M. Kaunitz, MD, FACOG
Department of Obstetrics and Gynecology
University of Florida College of Medicine-Jacksonville
653-1 W. 8th Street
Jacksonville, FL 32209

David A. Grimes, MD, FACOG, FACPM, FRCOG (Hon)
Department of Obstetrics and Gynecology
UNC School of Medicine
CB #7570
Chapel Hill, NC 27599-7570

RE: FDA-2013-P-0380

Dear Dr. Kaunitz and Dr. Grimes:

This letter responds to your citizen petition (Petition) received on April 2, 2013. You state that the “black box warning” currently on the labeling for the injectable contraceptive depot medroxyprogesterone acetate (DMPA) should be removed (Petition at 1). The boxed warning states as follows:

WARNING: LOSS OF BONE MINERAL DENSITY

- Women who use Depo-Provera Contraceptive Injection (Depo-Provera CI) may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. (5.1)
- It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. (5.1)
- Depo-Provera Contraceptive Injection should not be used as a long-term birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate. (5.1)

You state that this clinical recommendation was not based on published clinical evidence showing harm with extended use of this drug but instead on an invalid surrogate endpoint, bone mineral density (BMD), that is “known not to predict bone fracture” (Petition at 1).

We have carefully considered your Petition. For the reasons described below, your Petition is denied.

I. BACKGROUND

A. Depot Medroxyprogesterone Acetate

Depo-Provera, an intramuscular (IM) injection of DMPA, sponsored by Pfizer, was approved in 1992 under new drug application (NDA) 20-246 for the prevention of pregnancy. DMPA is a long-acting progestin-only contraceptive injection given once every 3 months. DMPA prevents pregnancy by inhibiting gonadotropin secretion, thereby suppressing ovulation, and altering cervical mucus and the endometrium. The resulting hypoestrogenism is associated with a decrease in BMD. When Depo-Provera was approved, due to concerns about the impact on BMD, the sponsor agreed to conduct a postmarketing commitment study of adult women to evaluate BMD loss during the first 5 years of DMPA use and reversal of BMD loss after discontinuation of treatment.

Subsequently, Pfizer submitted NDA 21-583 on June 30, 2003, seeking approval for depo-subQ Provera 104, a lower dose product administered subcutaneously over the same 3-month intervals as the original IM product. This NDA¹ included the results of the Pfizer-sponsored postmarketing commitment study of adult women noted above, as well as preliminary data from an ongoing Pfizer-sponsored study of BMD in adolescents conducted using the IM formulation of DMPA. Based on review of these data, FDA required that a boxed warning be added to the labeling of Depo-Provera and depo-subQ Provera 104 as part of its approval of depo-subQ Provera 104 for prevention of pregnancy in 2004.²

The following NDAs and abbreviated new drug applications (ANDAs) for injectable contraceptive DMPA drug products are implicated by your request:

- NDA 20-246, Depo-Provera CI, which is indicated for the prevention of pregnancy.
- ANDA 78-711 and ANDA 76-553, two ANDAs for which NDA 20-246 is the reference listed drug.
- NDA 21-583 and NDA 21-584, depo-subQ Provera 104, which is indicated for the prevention of pregnancy in women of child bearing potential and for the management of endometriosis-associated pain, respectively.

For purposes of this response, Depo-Provera, depo-subQ Provera 104, and their generics are referred to collectively as DMPA.

¹ Depo-SubQ Provera 104 (Medroxyprogesterone Acetate) Injectable Suspension, Drug Approval Package, Medical Reviews – Part 1. Available at:

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021583s000_MedR_P1.pdf.

² Depo-SubQ Provera 104 (Medroxyprogesterone Acetate) Injectable Suspension, Drug Approval Package, Printed Labeling. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021583s000_PRNTLBL.pdf.

B. Warnings in Prescription Drug Labeling

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug and biological product labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by those significant adverse reactions and potential safety hazards, and the steps that should be taken if these safety issues occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f)). As described in 21 CFR 201.56(b) and 21 CFR 201.57(c)(6)(i), products that were either approved between June 30, 2001, and June 30, 2006; pending on June 30, 2006; or submitted at any time on or after June 30, 2006, which include the products at issue in this response, must contain this WARNINGS AND PRECAUTIONS section. In addition, a summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) for the product (§§ 201.57(a)(10), 201.57(c)(6)).

Under § 201.57(c)(1), a boxed warning (which is sometimes referred to, as in your Petition, as a "black box 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 other words that convey the general focus of 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)). This warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS section in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

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* (Warnings Guidance) states on page 11 that a boxed warning ordinarily is used to highlight one of the following situations:³

- 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 a 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

³ Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>

21 CFR 314.520 and 601.42 “Approval with restrictions to assure safe use” or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) “Risk Evaluation and Mitigation Strategies” Elements to assure safe use).

The Warnings Guidance (at 11-12) also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.

II. DISCUSSION

Your petition requests that FDA remove the boxed warning found on DMPA products (Petition at 1). In support of your request, you state that the clinical recommendation found on the boxed warning is not based on published clinical evidence showing harm associated with extended use of DMPA but is instead based on an invalid surrogate endpoint, BMD, “known not to predict bone fracture” (Petition at 1). Additionally, you state that inclusion of this boxed warning has deprived women of long-term use of a safe, effective product and has thereby harmed the public health in the United States and around the world (Petition at 2). You further state that the boxed warning has “hurt the public health, contrary to the mission of the Agency,” thereby causing “clinicians and women to reduce use of this effective method of contraception” (Petition at 3).

As explained in detail below, your request to remove the boxed warning from DMPA products is denied because the available data indicate that BMD loss is related to duration of DMPA use, that this loss is not fully reversible following extended DMPA use (> 2 years), and that low BMD is known to be associated with increased risk of osteoporotic fractures.

1. *Clinical Evidence Shows Increased Harm Associated With Extended Use of DMPA*

You state that the clinical recommendation against use for greater than 2 years is based not on published clinical evidence showing harm associated with extended use of DMPA, but on an invalid surrogate endpoint, BMD, “known not to predict bone fracture” (Petition at 1). In support of this assertion, you cite several studies (Petition at 1).⁴ Furthermore, you state the apparent correlation shown in certain studies between DMPA use and fracture risk in reproductive-age women more likely represents bias than cause and effect (Petition at 2).

⁴ David A. Grimes, MD, and Kenneth F. Schulz. Surrogate End Points in Clinical Research: Hazardous to Your Health. *Obstet Gynecol* 2005;105:1114 ; Grimes DA, et al. Surrogate end points in women's health research: science, protoscience, and pseudoscience. *Fertility and Sterility* (2010); 93:1114-8; Shulman LP, Bateman LH, Creinin MD, Cullins VE, Doyle LL, Godfrey E, et al. Surrogate markers, emboldened and boxed warnings, and an expanding culture of misinformation: evidence-based clinical science should guide FDA decision making about product labeling. *Contraception* 2006;73:440-442.

The basis of the initial boxed warning approved in November 2004 as well as the subsequent revision of the boxed warning in October 2010 is clinical data submitted by the sponsor and reviewed by FDA, including the postmarketing commitment study of adult women (Kaunitz, et al.)⁵ and the study of adolescent users (Harel, et al.)⁶ mentioned in Section I.A above, both of which addressed BMD loss and BMD recovery after discontinuation of DMPA. In reviewing the supplements that culminated in the labeling revisions pertaining to BMD, FDA conducted an independent analysis of the data from both studies and found that these studies show that BMD declined in DMPA users, that the decline increased with greater duration of exposure to DMPA, and that full recovery of BMD is not observed in adolescents who used DMPA for greater than 2 years, even when they are followed for 2 to 5 years after discontinuing DMPA. In the adult study, BMD values did not return to baseline for the DMPA user group in the two year follow-up after discontinuation of treatment, as shown in Table 4 of the labeling. In contrast, non-users in both the adult and adolescent studies evaluated over the same time periods showed small but steady increases in BMD at the lumbar spine and total hip compared with their baseline values.

The adolescent study was intended to evaluate the effect of 240 weeks of treatment with DMPA followed by a recovery phase of 120 weeks off-treatment. During the course of the study, the Data Safety and Monitoring Board (DSMB) recommended that the treatment phase be terminated because the accumulated data on BMD was judged to be sufficient and “the risk of continued loss of BMD outweighed the benefits of continued use.” Thus, all users were advised to discontinue DMPA and use another method of contraception until Week 240. FDA’s independent analysis of the data from this study categorized adolescents according to DMPA use ≤ 2 years versus > 2 years. Although few subjects completed the planned 5 years of treatment due to the DSMB decision, FDA’s analysis showed that adolescents who used DMPA for more than 2 years did not experience recovery to baseline levels of total hip BMD or femoral neck BMD even by 5 years post-treatment. In contrast, adolescents who used DMPA for 2 years or less experienced recovery to baseline of total hip and femoral neck BMD by 2 years post-treatment. BMD at the lumbar spine increased to baseline levels or above by 2 years post-treatment, regardless of duration of use. These data are displayed in Table 6 of the labeling.

The decline in BMD observed at the total hip and femoral neck and lack of full recovery to baseline even up to 5 years off-treatment in longer-term users (> 2 years) was of particular concern to FDA. FDA was also concerned about the fact that adolescent users were losing bone density at a time in life when they should be experiencing significant increases. Up to 90 percent

⁵ Kaunitz AM, et al. Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. Contraception (2006); 74:90-99.

⁶ Harel Z, et al. Recovery of bone mineral density in adolescents following use of depot medroxyprogesterone acetate contraceptive injections. Contraception (2010); 81:281-91.

of peak bone mass is acquired by age 18 in girls.⁷ After peak bone mass is achieved, there is a slow but progressive decline in bone mass until a theoretical fracture threshold is reached. Therefore, any factor that reduces bone mass accrual can increase fracture risk later in life.⁸ You specifically contend that the evidence on which the boxed warning is based was not “published” (Petition at 1). First, FDA appropriately considers all relevant material, published or otherwise, in assessing product safety. Second, both studies just discussed were in fact published (see footnotes 1 and 2 above), although the publications did not contain all the analyses conducted or reviewed by FDA. In particular, the authors of those publications did not stratify for duration of use as FDA did⁹ and, for these reasons, reached different conclusions about the data.¹⁰

You cite two recently published case-control studies, Vestergaard, et al. and Meier, et al., which suggest that use of DMPA is associated with an elevated risk of fractures in reproductive age women (Petition at 2).¹¹ You note, however, that both studies have odds ratios of 1.5 (Petition at 2), and you cite an article to support your contention that odds ratios of less than 3-4 in case-control studies more likely represent bias rather than cause and effect (Petition at 2).¹² Although smaller odds ratios (for example, less than 3-4) obtained in case-control studies may sometimes be explained by biases, results from these studies should not be summarily dismissed solely because of the numerical value of the odds ratio.

The Vestergaard study you cite showed an increased fracture risk in reproductive-aged women (aged < 50 years), but the risk was not statistically significant. The study did show a statistically significant increased risk for fracture in women older than 50 years of age, but the investigators did not indicate at what age or for how long the DMPA exposure occurred in these older women.

⁷ National Institute of Arthritis and Musculoskeletal and Skin Diseases. Osteoporosis peak bone mass in women. http://www.niams.nih.gov/Health_info/bone/Osteoporosis/bone_mass.asp.

⁸ Golden NH, Abrams SA; Committee on Nutrition. Optimizing bone health in children and adolescents. Pediatrics. 2014 Oct;134(4):e1229-43. doi: 10.1542/peds.2014-2173.

⁹ The FDA’s analysis is based on comparison of subjects treated for up to 2 years compared to subjects treated for longer than 2 years.

¹⁰ Depo-SubQ Provera 104 (Medroxyprogesterone Acetate) Injectable Suspension, Drug Approval Package, Medical Reviews – Part 1. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021583s000_MedR_P1.pdf

¹¹ Vestergaard P, et al. The effects of depot medroxyprogesterone acetate and intrauterine device use on fracture risk in Danish women. Contraception (2008); 78:459-64; Meier C, et al. Use of depot medroxyprogesterone acetate and fracture risk. J Clin Endocrinol Metab. (2010); 95:4909-16.

¹² Grimes DA, et al. False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol. (2012); 120(4):920-7. Opining that weak associations, or case-control studies with odds ratios of less than 4, are more likely attributable to bias than to causal association and should not be considered credible.

The Meier et al. study that you cite and three other studies we reviewed in preparing this response¹³ suggest a possible association between DMPA use and slightly elevated fracture risk in reproductive-age women. The totality of the evidence relevant to safety has to be carefully considered, and despite the limitations of the studies reviewed, the totality of the evidence suggests an elevated risk for fracture with DMPA use.

More importantly, DMPA has not been marketed long enough for a large number of users to have completed menopause, the time of life when osteoporotic fractures most often occur. In the absence of sufficient data demonstrating a direct link between osteoporotic fractures and DMPA use, it is appropriate to base our analysis primarily on the known links between DMPA use and BMD decline and between BMD decline and osteoporotic fracture risk.

Current data indicate that the actual BMD value is strongly related to osteoporotic fracture risk.¹⁴ The World Health Organization (WHO) definition of osteoporosis is based on the relationship between low BMD and the consequent increase in bone fragility and susceptibility to fracture.¹⁵ Many studies have demonstrated that low BMD measured by dual x-ray absorptiometry (DXA) at any skeletal site (spine, hip, or forearm) can predict osteoporotic fracture and that total hip BMD provides a good prediction for hip fracture.¹⁶ Overall, there is an approximately two-fold increase in risk of such fractures for each standard deviation (SD) decrease in BMD. In a prospective study of 9,704 older women, 2,680 of whom were followed for an average of 14.9 years, the risk of vertebral fracture was inversely related to BMD at all measurement sites.¹⁷ The age-adjusted odds ratio of vertebral fracture for each SD decrease in DXA-measured BMD of the lumbar spine and total hip was 2.1 (95% confidence interval [CI], 1.8-2.3) and 1.8 (95% CI, 1.6-2.0), respectively (i.e., for each SD decrease from the mean BMD, the risk of vertebral fracture about doubled). In a historical cohort study (mean observation 3.2 +/- 1.5 years) of 16,505 Canadian women, total hip BMD measurements were found to be superior to spine BMD

¹³ See Watson KC, et al. Associations between fracture incidence and use of depot medroxyprogesterone acetate and anti-epileptic drugs in women with developmental disabilities. *Womens Health Issues* (2006); 16:346-52; Lappe JM, et al. The impact of lifestyle factors on stress fractures in female Army recruits. *Osteoporos Int.* (2001); 12:35-42; Lanza LL, et al. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. *Obstet Gynecol.* (2013); 121:593-600.

¹⁴ Li Z, et al. Statistical validation of surrogate endpoints: is bone density a valid surrogate for fracture? *J Musculoskeletal Neuronal Interact.* (2004) Mar; 4(1):64-74.

¹⁵ World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser.* (1994); 843:1-129. WHO defines osteoporosis as a BMD that lies 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of <-2.5 SD).

¹⁶ Johnell O, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res.* (2005); 20(7):1185.

¹⁷ Cauley JA, et al. Long-term risk of incident vertebral fractures. *JAMA* (2007); 298(23): 2761.

measurements in predicting overall osteoporotic fracture.¹⁸ Each SD decrease in DXA-measured BMD of the total hip or lumbar spine was associated with an increased risk of osteoporotic fracture at any site (hazard ratio 1.8 [95% CI, 1.7-2.0] for total hip and 1.5 [95% CI, 1.4-1.6] for spine).

You have raised questions about using BMD as a surrogate endpoint due to the observation that treatment with fluoride has been shown to increase spinal bone density while vertebral fracture risk remained unchanged.¹⁹ In fact, this lack of decrease in fracture risk was explained by the observation that some women developed osteomalacia (another risk factor for vertebral fracture) due to exposure to high doses of fluoride.²⁰ Further, the fact that there may be only a weak association or no association at all between increased BMD from fluoride treatment and osteoporotic fracture risk does not invalidate the strong evidence discussed above for the existence of a meaningful association between decreased BMD and increased fracture risk.²¹ As additional support, you cite to an article²² which notes that “validation of a surrogate endpoint for one treatment does not imply that it is valid for another treatment.” Arguably the same holds for findings that a surrogate is *not* valid for one treatment—a finding that a given surrogate is *not* valid as a marker for a particular treatment effect does not necessarily render it an invalid measure for all outcomes.

BMD is an appropriate surrogate endpoint for a clinical outcome of osteoporotic fractures. Decreased BMD has been shown to be correlated with increased osteoporotic fracture risk in a number of studies, as described above. The clinical endpoint of osteoporotic fractures in the population of DMPA users cannot yet be evaluated because DMPA users have not yet aged to the stage of life in which osteoporotic fractures are most often observed. DMPA has not been marketed long enough to have sufficient data on the risk of osteoporotic fractures in former DMPA users. Depo-Provera was approved in 1992, so it has only been marketed in the United States for 23 years (it became available in the United Kingdom in 1987). Therefore, in general, women who took DMPA in adolescence and early adulthood have not yet become postmenopausal.

¹⁸ Leslie WD, et al. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. *J Clin Endocrinol Metab.* (2007); 92(1):77.

¹⁹ Grimes DA, et al. (2010).

²⁰ Riggs BL, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med.* (1990); 322(12):802-809.

²¹ Cefalu CA. Is Bone Mineral Density predictive of fracture reduction? *Curr Med Res Opin.* (2004); 20(3).

²² Grimes DA, et al. 2010.

At this time, given that sufficient data on the risk of osteoporotic fracture in women who used DMPA during their childbearing years are not yet available, BMD data provide the best evidence available to FDA on which to base decisions about the impact of long-term DMPA exposure on bone health.

After considering the totality of the evidence, FDA continues to believe that the boxed warning is appropriate, as described in Part I.B, above.

2. *Boxed Warning Advising Against Long-Term Use of DMPA Has Not Harmed the Public Health*

In your petition, you state that the boxed warning has “hurt the public health” by causing clinicians and women to reduce use of DMPA, which could lead to more unintended pregnancies and induced abortions (Petition at 3). You cite a 2008 National Survey of Family Growth²³ and a survey of Florida Obstetrician-Gynecologists²⁴, which show that DMPA use declined from 3.3% in 2002 to 2.0% for the years 2006-2008 and duration of DMPA use was limited based on the boxed warning, respectively (Petition at 3).

We disagree that the inclusion of the boxed warning on DMPA products has “hurt the public health.” First and foremost, to the extent that use of DMPA may have decreased following inclusion of the boxed warning, we believe lower prevalence of prolonged DMPA use is a public health *benefit*. As discussed above, prolonged DMPA use leads to BMD loss that may not be reversible after drug discontinuation, and low BMD is associated with an increased risk of osteoporotic fracture. Second, the labeling clearly recommends limiting duration of use “unless other birth control methods are considered inadequate.” Therefore, prolonged use of DMPA could be considered for a woman who does not have other contraceptive options. However, there are a variety of birth control options available (such as intrauterine devices that remain effective for 5 to 10 years, implants that last for 3 years, vaginal rings that are placed monthly) for women who cannot maintain compliance with a method that requires daily adherence. These long-acting reversible contraceptive options are highly effective for pregnancy prevention.

You state that in the Florida survey, more than 5% of respondents indicated that they prescribe bisphosphonates (indicated for prevention or treatment of osteoporosis) in reproductive-aged DMPA users, “a practice that is costly, irrational, and potentially dangerous” (Petition at 3). FDA has conducted an independent retrospective data analysis using patient-level commercial claims data. We compared users of combined oral contraceptives (COCs, n=3,019,782) to those

²³ Mosher WD, et al. Use of contraception in the United States: 1982-2008. National Center for Health Statistics. Vital Health Stat (2010); 23(29), available at http://www.cdc.gov/nchs/data/series/sr_23/sr23_029.pdf.

²⁴ Paschall S and Kaunitz AM. Depo-Provera and skeletal health: a survey of Florida obstetrics and gynecologist physicians. Contraception. 2008 Nov;78(5):370-6.

receiving DMPA (n=659,783) over the period from 2001-2013. We have determined that in the period after the boxed warning was added (2003-2005), the proportion of DMPA users who received a BMD test increased in comparison to the proportion of COC users who received a BMD test. However, by 2010, the rate of BMD testing among DMPA users declined, and testing in both groups occurred at a similar rate. Our analysis found that compared to COC users, DMPA users were less likely to receive a bisphosphonate. Furthermore, concurrent use of bisphosphonates was very low among DMPA users (less than 0.05%) and compared to COC users, concurrent bisphosphonate therapy was received for a shorter period of time.

Lastly, the public health issues of unintended pregnancies and induced abortions are complex and involve many other factors beyond the extent and duration of DMPA use. In sum, none of the evidence you provided changes FDA's conclusion that a boxed warning is appropriate.

3. Declines in BMD Associated with Breastfeeding Mothers Are Not Analogous to BMD Declines Associated with Use of DMPA

You state that BMD declines associated with the use of DMPA appear analogous to BMD declines associated with breastfeeding and that “[i]f the FDA truly believes that transient lowering of bone mineral density threatens the bone health of women, then the Agency should warn women not to breast feed.” (Petition at 2). Additionally, you state that although BMD declines in nursing mothers are similar to those in women who used DMPA, nursing one or more infants is not known to increase the risk of subsequent osteoporotic fractures (Petition at 2). Thus, you state that the inconsistency in public health recommendations regarding DMPA and breastfeeding indicates that the boxed warning on DMPA is “incongruous at best” (Petition at 2).

We acknowledge that BMD loss is also seen following lactation. However, unlike the hormonal changes produced by lactation, the hormonal changes produced by DMPA can persist for many years if DMPA is used for an unrestricted duration.

Women often lose 3-5% of their BMD during breastfeeding, although they recover it rapidly after weaning.²⁵ The mechanism of this bone loss in lactation is different from that associated with DMPA use. Parathyroid hormone-related protein (PTHrP), which is secreted by the lactating mammary gland, plays a role in the control of calcium mobilization from bone during lactation in humans.²⁶ In addition, elevated prolactin levels and lower estrogen levels play a role. Bone loss reverses after weaning in 6-18 months,²⁷ and most studies show

²⁵ Pregnancy, Breastfeeding, and Bone Health (Jan. 2012), available at:
http://www.niams.nih.gov/Health_Info/Bone/Bone_Health/Pregnancy/default.asp#b

²⁶ Sowers MF, et al. Elevated parathyroid hormone-related peptide associated with lactation and bone density loss. JAMA (1996); 276(7):549.

²⁷ Kolthoff N, et al. Bone mineral changes during pregnancy and lactation: a longitudinal cohort study. Clin Sci (Lond). (1998); 94(4):405.

no association between either parity (number of births) or duration of lactation and osteoporosis (increased fracture risk) in postmenopausal women.^{28, 29} Thus, transient lowering of BMD in a lactating woman is not a serious concern. The lack of full recovery even after 5 years off-treatment seen with women who used DMPA for more than 2 years, however, is a serious concern.

Accordingly, FDA does not view the decrease of BMD seen in nursing mothers as analogous to the decrease of BMD seen in women using DMPA.

4. *There are Insufficient Data to Know Whether DMPA Use Increases the Risk of Osteoporosis*

You cite three studies which, according to you, suggest that prior use of DMPA does not increase the risk of osteoporosis (Petition at 2). We have reviewed these studies, and we do not believe they alter our reasoning, detailed above, that BMD loss is related to duration of DMPA use, that this loss is not fully reversible following extended DMPA use (> 2 years), and that low BMD is known to be associated with increased risk of osteoporotic fractures.

The study by Cundy, et al. evaluated BMD at the lumbar spine and femoral neck prospectively over 3 years in 15 women who had never used DMPA, reached natural menopause, and did not undergo hormone replacement therapy, and in 16 long-term (at least 5 years) users of DMPA who discontinued DMPA only upon reaching menopause.³⁰ DMPA users, with a median use of 12 years, had mean BMD at the spine and hip that was 10% and 15% lower, respectively, than that of non-users at study entry. The results showed that compared with the non-users, women who used DMPA until menopause had attenuated rates of BMD loss at the lumbar spine and femoral neck, possibly because they had already lost the estrogen-sensitive component of bone due to their long-term use of DMPA. This study had several limitations. The primary limitation is the low number of participants, only 15 controls and 16 DMPA users, which results in a lack of statistical power to determine the risk for low BMD associated with DMPA use. Secondly, both users and non-users were recruited from practitioners who had referred women for BMD testing, which may introduce selection bias. The DMPA users were women who had been referred prior to menopause, while the non-users had been referred shortly after reaching menopause. There is no routine clinical indication to check BMD prior to or once a woman reaches menopause, so these women might have had issues related to bone health prompting the BMD test. These women may not represent normal healthy menopausal women. Additionally,

²⁸ Nichaélsson K, et al. Influence of parity and lactation on hip fracture risk. Am J Epidemiol. (2001); 153(12):1166.

²⁹ Karlsson C, et al. Pregnancy and lactation confer reversible bone loss in humans. Osteoporos Int. (2001); 12:828-34.

³⁰ Cundy T, et al. Menopausal bone loss in long-term users of depot medroxyprogesterone acetate contraception. Am J Obstet Gynecol (2002); 186:978-83.

the women who had used DMPA were similar in mean age and body mass index to the control subjects, but were significantly shorter in height. This may represent random variation due to the small number of subjects or it is conceivable that the DMPA users lost height due to silent vertebral fractures (there was no x-ray or vertebral fracture assessment scan done). It is well known that osteoporosis-related silent vertebral fractures lead to height loss.³¹ If that were the case, BMD measurements in the DMPA group may be spuriously high because collapsed vertebrae appear dense on a DXA scan. Lastly, the authors only compare percent change from baseline, but because the baseline BMD values were lower in DMPA users, this is not a valid comparison. It would be more informative to discuss the absolute BMD values in each group of women.

The study by Orr-Walker, et al. also had several limitations. This study was a cross-sectional study (N = 346) with a low number of DMPA users (N = 34) with a mean age at initiation of use of 41 years (range 28-50 years) and an average duration of DMPA use of 3 years (range 0.2-18.1 years).³² The authors report that there were no significant differences in bone density at any site between the women who had previously used DMPA and the others in the cohort. However, in those who had used DMPA for more than 2 years, there was a trend towards BMD being lower compared with non-users. There are other limitations to this study. First, DMPA use was determined by subject recall, which could be subject to recall bias. Secondly, the cross-sectional nature of this study precludes any firm conclusions about the extent of change in BMD attributable either to use of DMPA or to discontinuation of DMPA use. The researchers of this article also did not provide information on the risk of fractures in the postmenopausal age among long-term users of DMPA.

The study by Viola, et al. is a study of 24 former DMPA users and 55 former copper intrauterine device (IUD) users that evaluated forearm BMD up to 5 years after menopause.³³ The authors report that there were no significant differences between the former DMPA and IUD users with respect to BMD measurements either at the distal radius or at the ultra-distal radius. Again, this study had several limitations. First, women in this study were between the ages of 46-61 years old. The mean duration of contraceptive use was 10.1 ± 1.1 years for the women in the DMPA group and 17.8 ± 0.8 years for the women in the IUD group. Thus, it is possible that a majority of DMPA users might have started DMPA later in their reproductive years, most likely

³¹ Lyles KW. Management of patients with vertebral compression fractures. *Pharmacotherapy*. 1999 Jan;19(1 Pt 2):21S-24S. Review, available at:
https://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/osteoporosis.asp

³² Orr-Walker BJ, et al. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal post-menopausal women. *Clinical Endocrinology* (1998); 49:615-618.

³³ Viola AS, et al. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. *Contraception* 84 (2011); 122-127.

after attainment of peak bone mass. Secondly, women who experienced adverse effects associated with DMPA might have discontinued DMPA use earlier, so this study evaluated a select group of women who were able to continue DMPA for an average of 10 years. Therefore, results do not apply to all DMPA users. In addition, forearm BMD may be less sensitive to the effect of DMPA than hip or spine BMD.³⁴ Another issue to consider is that 86% of DMPA users were white, in contrast to what has been observed in other studies. Also, there is no information about use of DMPA in the control group earlier in their life. Finally, this study provides no information about use of DMPA and risk of fractures beyond age 65. The risk of fractures increases with age, especially after age 65.³⁵

With regard to women who began using DMPA during adolescence, given the lack of full BMD recovery 5 years after discontinuation of DMPA, it remains to be seen whether these women will achieve peak bone mass similar to that of women who did not use DMPA. Ultimately, the BMD with which a former DMPA user enters menopause and her fracture risk later in life (> 65 years, the age at which screening for osteoporosis is recommended) are important concerns.³⁶ As more time passes since the 1992 approval of DMPA, we will know more about the answers to these questions. There may be useful data on the impact of DMPA use on perimenopausal BMD levels and on future fracture risk in another 10-20 years.

FDA continues to believe that long-term use of DMPA results in decreases in BMD, which may be associated with increased osteoporotic fracture risk. Due to the limitations of the studies cited in your petition, FDA does not agree that they undermine this conclusion.

5. FDA Relies on Its Independent Review of Data to Make Regulatory Decisions

The Petition states that FDA's boxed warning is inconsistent with the assessment of major public health organizations, including the World Health Organization, the American College of Obstetricians and Gynecologists, the Society for Adolescent Medicine, and the Society of Obstetrics and Gynecology of Canada, that have indicated that skeletal health concerns should not restrict use, including duration of use, of DMPA (Petition at 3). FDA acknowledges that the groups cited have published opinions at variance with FDA's determination on the need for a boxed warning. Although FDA considers the opinions and analyses of other reputable public

³⁴ Beksinska, et al. also evaluated forearm BMD and found that there was no significant difference in BMD between the DMPA group and a non-user control group. See Beksinska ME, et al. Bone mineral density in adolescents using norethisterone enanthate, depot-medroxyprogesterone acetate or combined oral contraceptives for contraception. Contraception (2007); 75:438–43.

³⁵ <https://www.aace.com/files/osteo-guidelines-2010.pdf>

³⁶ <http://www.uspreventiveservicestaskforce.org/uspstf10/osteoporosis/osteors.htm>, accessed October 23, 2013.

health bodies, in the end FDA relies on its own independent review of the available data to make regulatory decisions.

The opinions of the professional societies may be based solely on the published literature, as they often do not have access to the full data submitted to FDA. FDA's own review of the data did not corroborate the sponsor-funded publications' conclusions regarding BMD recovery after discontinuation. As mentioned earlier, FDA's independent review of the full data from the studies published by Kaunitz, et al. (the study in adult women) and Harel, et al. (the adolescent study) led us to a different conclusion than those reached by the authors of those studies. Although those two studies purported to show full recovery of BMD after discontinuation of DMPA, FDA's review found that women who received more than 2 years of DMPA did not fully recover BMD, especially at the hip.

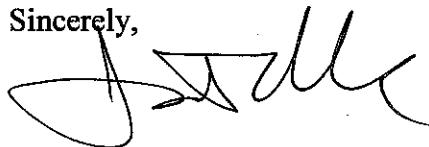
Based on our independent review of the available data related to DMPA use and loss of BMD and the relationship between low BMD and osteoporotic fracture risk, FDA continues to believe that the boxed warning is warranted and appropriate.

III. Conclusion

For the reasons discussed above, and in accordance with the regulations and guidance discussed in Section B, FDA continues to believe that the boxed warning on the labeling of DMPA products is warranted and appropriate.

Therefore, your petition is denied. As with all drug products, we will continue to monitor the safety of DMPA products and take further action as appropriate.

Sincerely,



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