

March 28, 2013

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Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

**RE: Depot Medroxyprogesterone Acetate (DMPA) Black Box Warning**

### **CITIZEN PETITION**

Dear Sir or Madam:

The undersigned submit this petition under 21 C.F.R. 10.30 to request the Commissioner of Food and Drugs to amend the package labeling for the injectable contraceptive depot medroxyprogesterone acetate (DMPA) by removing the current black box warning, instituted in 2004, regarding loss of bone mineral density and limiting use of the drug to two years.

#### **A. Action Requested**

The petitioners are requesting that black box warning on package labeling for the injectable contraceptive depot medroxyprogesterone acetate (DMPA) be removed. Exact wording of black box warning:

#### ***WARNING: LOSS OF BONE MINERAL DENSITY***

***See full prescribing information for complete boxed warning.***

- ***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 bone 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)***

#### **B. Statement of Grounds**

This clinical recommendation was based on no published clinical evidence showing harm associated with extended use of this drug. Instead, the black box warning was based on an invalid surrogate endpoint (**Grimes and Schulz 2005; Grimes, Schulz and Raymond 2010; Shulman, et al**) (bone mineral density, BMD) known not to predict bone fracture. The

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published evidence indicates that these severe restrictions are medically inappropriate. By depriving women of long-term use of this safe, effective product, this black box warning paradoxically has harmed public health in the United States and around the world.

Recommendations concerning safe drug use should be based on rigorous published evidence, and the black box warning regarding DMPA violated this fundamental principle of responsible science. To put the safety of DMPA in a public health perspective, to our knowledge no woman anywhere in the world has ever died as a result of use of this contraceptive. This observation is unique in the history of modern contraception. Regrettably, the black box warning has unjustly stigmatized this safe and effective method.

Although the lower serum estrogen levels associated with current use of DMPA decrease bone mineral density (BMD), full recovery of BMD occurs one to four years after discontinuation in adolescent girls (Scholes et al 2005; Harel et al) and within three years after discontinuation in adult women (Scholes et al 2002; Kaunitz et al 2006). The BMD trends associated with use of DMPA appear analogous to similar trends associated with another common hypoestrogenic state--breastfeeding. Although the BMD declines in nursing mothers are similar to those with use of DMPA, nursing one or more infants is not known to increase the risk of subsequent osteoporotic fractures (Schnatz et al). If 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. This inconsistency in public health recommendations regarding DMPA and breastfeeding indicates that the black box warning on DMPA is incongruous at best.

Few studies have addressed the association between bone mineral density and fracture risk in young women (WHO), indicating that bone density should not be considered a surrogate end point for fracture in this age group. Basing clinical recommendations on invalid surrogate endpoints can harm patients (Grimes and Schulz 2005; Grimes, Schulz and Raymond 2010; Shulman, et al). FDA recommendations should be based on sound clinical studies, not on misleading surrogate end points.

Studies of menopausal women have not suggested that prior use of DMPA has increased the risk of osteoporosis. (Cundy et al; Orr-Walker et al, Viola et al) Two recently published case-control studies, one using a national Danish National Patient Registry (Vestergaard et al) and one based on the United Kingdom Family Practice Research database (Meier et al) have suggested that use of DMPA is associated with an elevated risk of fractures (odds ratios approximately 1.5 in both studies) in reproductive age women. However, odds ratios less than 3-4 in case-control studies are more likely to represent bias than cause and effect (Grimes and Schulz 2012). Furthermore, a cohort analysis using the same British Family Practice database clarifies that the elevated fracture risk observed in women using DMPA occurs prior to initiation of injectable contraception and therefore cannot be caused by use of DMPA (Lanza, et al 2013). If the effect precedes the putative cause, any claim of causality evaporates (Hill; Grimes and Schulz 2002; Susser).

Tragically, the black box warning imposed by the FDA has hurt the public health, contrary to the mission of the Agency. This inappropriate warning has caused clinicians and women to reduce use of this effective method of contraception. The 2008 National Survey of Family Growth indicates that the overall percentage of US women 15-44 years of age who currently use DMPA has declined from 3.3% in 2002 to 2.0% for the years 2006-2008 (**Mosher et al. Table 4**). A survey of Florida Obstetrician-Gynecologists likewise indicated that almost half of respondents place a time limit on duration of DMPA and two thirds of these respondents indicated this restriction was based on the black box warning (**Paschall and Kaunitz**).

Restricting use of DMPA can lead to more unintended pregnancies and induced abortions. Although the risk of death from pregnancy is low, the risk of morbidity from pregnancy, planned or unplanned, remains large in the U.S. According to the CDC, the morbidity rate of pregnancy and childbearing is about 50% (**Bruce et al**) with over 1% of pregnancies associated with severe complications (**Callaghan et al**).

The Florida survey found that two thirds of respondents ordered BMD tests in women using DMPA, with 58% of those physicians doing so attributing this decision to the FDA's black box warning. Indeed, more than 5% of respondents in this Florida survey reported they selectively prescribe bisphosphonates to reproductive age women using DMPA, a practice that is costly, irrational, and potentially dangerous. We are confident that in 2004 the FDA never anticipated this bizarre response to the black box warning.

Importantly, the FDA's black box warning is inconsistent with the assessment of major medical and public health organizations around the world. The World Health Organization (**WHO**), the American College of Obstetricians and Gynecologists (**ACOG**), the Society for Adolescent Medicine (**Cromer et al**), and the Society of Obstetrics and Gynecology of Canada (**Black**) have indicated that skeletal health concerns should not restrict use (including duration of use) of DMPA. In their Medical Eligibility Criteria for contraceptive use, the Centers for Disease Controls have indicated that use of DMPA is category 1 (no restriction of use) in women 18-45 years of age and category 2 (the advantages of the method generally outweigh the theoretical or proven risks) in younger women (**CDC**).

The FDA is appropriately concerned when pharmaceutical companies mislabel their products in ways that are not based on sound science. A dual standard cannot exist. The same evidence-based scientific standards must apply to the FDA itself. FDA's guidance included in DMPA's black box is not evidence-based. It has reduced use of a safe and effective contraceptive method by US women, with the potential for causing harm. Removing this black box would result in greater access to and use of this contraceptive, thereby improving the health of women and their families.

We would be glad to provide you with background references or to meet with you or your advisory committee to discuss removing this unwarranted and unscientific restriction. Thank you for your consideration of this urgent problem of FDA-generated mislabeling. We look forward to your response within 180 days.

**C. Environmental Impact**

Petitioners claim a categorical exclusion under 21 C.F.R. 25.30 and 25.31.

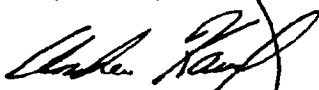
**D. Economic Impact**

Petitioners will submit information on economic impact of this petition upon request of the Commissioner of Food and Drugs.

**E. Certification**

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



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**Disclosures:**

Dr. Kaunitz consults for Teva (which markets generic depot medroxyprogesterone acetate) regarding oral and intrauterine contraception. His Department has received financial support from Teva for oral contraceptive and menopausal vaginal estrogen clinical trials.

Dr. Grimes reports no disclosures relevant to depot medroxyprogesterone acetate.