CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020246Orig1s060s062

Trade Name:	DEPO-PROVERA Contraceptive Injection (CI)
Generic or Proper Name:	medroxyprogesterone acetate
Sponsor:	Pharmacia & Upjohn Company LLC, a subsidiary of Pfizer Inc.
Approval Date:	December 4, 2020
Indication:	DEPO-PROVERA CI is a progestin indicated for use by females of reproductive potential to prevent pregnancy. Limitations of Use: The use of Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 020246/S-060 & 062

SUPPLEMENT APPROVAL

Pharmacia & Upjohn Company LLC, a subsidiary of Pfizer Inc.
Attention: Michelle Patel, R.Ph.
Manager, Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-7555

Dear Ms. Patel:

Please refer to your supplemental new drug applications (sNDAs) dated and received October 6, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Depo-Provera (medroxyprogesterone acetate) Contraceptive Injection (CI).

We acknowledge receipt of your amendments dated June 5, 2020, which constituted a complete response to our October 6, 2017, action letter.

These Prior Approval supplemental new drug applications provide for updates to the Warnings and Precautions Section, Subsection Loss of Bone Mineral Density and Clinical Studies Section, Subsection 14.3 Bone Mineral Density Changes in Adolescent Females Treated with Depo-Provera CI.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Christine Nguyen, M.D.
Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AUDREY L GASSMAN
12/04/2020 02:44:32 PM
Signing for Christine Nguyen, Deputy Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020246/S-060 & S-062

COMPLETE RESPONSE

Pharmacia & Upjohn Company a subsidiary of Pfizer Inc.
Attention: Karen Baker, M.S.
Director, Pfizer Essential Health Global Regulatory Affairs Brands
235 East 42nd Street
New York, NY 10017-7555

Dear Ms. Baker:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 6, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEPO-PROVERA Contraceptive Injection 150 mg/ml.

These "Prior Approval" efficacy supplements to your application provides for (b) (4) [redacted]

We have completed our review of these applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

We cannot approve these applications (b) (4) [redacted]

[redacted]

(b) (4) [redacted]

Note any future submission for this application will need to address the above concerns.

PRESCRIBING INFORMATION

We reserve further comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the supplemental application data.
   - Include tables that compare frequencies of adverse events in the supplemental application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the supplemental application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug/product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the applications under 21 CFR 314. You may also request an extension of time in which to resubmit the applications.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the applications may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Acting Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
10/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEPO-PROVERA CI safely and effectively. See full prescribing information for DEPO-PROVERA CI.

DEPO-PROVERA CI (medroxyprogesterone acetate) injectable suspension, for intramuscular use
Initial U.S. Approval: 1959

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 CI 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 CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. (1, 5.1)**

----------RECENT MAJOR CHANGES ----------
Indications and Usage (1) 12/2020

----------INDICATIONS AND USAGE----------
Depo-Provera CI is a progestin indicated for use by females of reproductive potential to prevent pregnancy. (1)

Limitations of Use:
The use of Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. (1, 5.1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dose is 150 mg of Depo-Provera CI every 3 months (13 weeks) administered by deep, intramuscular (IM) injection in the gluteal or deltoid muscle. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Vials containing sterile aqueous suspension: 150 mg per mL (3)
- Prefilled syringes: prefilled syringes are available packaged with 22-gauge x 1 1/2 inch Terumo® SurGuard™ Needles. (3)

----------CONTRAINDICATIONS----------
- Known or suspected pregnancy or as a diagnostic test for pregnancy. (4)
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease. (4)
- Known or suspected malignancy of breast. (4)
- Known hypersensitivity to Depo-Provera CI (medroxyprogesterone acetate or any of its other ingredients). (4)
- Significant liver disease. (4)
- Undiagnosed vaginal bleeding. (4)

----------WARNINGS AND PRECAUTIONS----------
- Thromboembolic Disorders: Discontinue Depo-Provera CI in patients who develop thrombosis. (5.2)
- Cancer Risks: Monitor women with a strong family history of breast cancer carefully. (5.3)
- Ectopic Pregnancy: Consider ectopic pregnancy if a woman using Depo-Provera CI becomes pregnant or complains of severe abdominal pain. (5.4)
- Anaphylaxis and Anaphylactoid Reactions: Provide emergency medical treatment. (5.5)
- Liver Function: Discontinue Depo-Provera CI if jaundice or disturbances of liver function develop. (5.7)
- Carbohydrate Metabolism: Monitor diabetic patients carefully. (5.12)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >5%) are: menstrual irregularities (bleeding or spotting) 57% at 12 months, 32% at 24 months, abdominal pain/discomfort 11%, weight gain >10 lbs at 24 months 38%, dizziness 6%, headache 17%, nervousness 11%, decreased libido 6%. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of contraceptive drug products. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with Depo-Provera CI. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- *Nursing Mothers*: Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera CI. (8.3)
- *Pediatric Patients*: Depo-Provera CI is not indicated before menarche. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1)]*.**
- **It is unknown if use of Depo-Provera CI 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 *[see Warnings and Precautions (5.1)]*.**
- **Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate *[see Indications and Usage (1) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

Depo-Provera CI is indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use:
The use of Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Pregnancy

Both the 1 mL vial and the 1 mL prefilled syringe of Depo-Provera CI should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of Depo-Provera CI every 3 months (13 weeks) administered by deep intramuscular (IM) injection using strict aseptic technique in the gluteal or deltoid muscle, rotating the sites with every injection. As with any IM injection, to avoid an inadvertent subcutaneous injection, body habitus should be assessed prior to each injection to determine if a longer needle is necessary particularly for gluteal IM injection.

Use for longer than 2 years is not recommended (unless other birth control methods are considered inadequate) due to the impact of long-term Depo-Provera CI treatment on bone mineral density (BMD) *[see Warnings and Precautions (5.1)]*. Dosage does not need to be adjusted for body weight *[see Clinical Studies (14.1)]*.

To ensure the patient is not pregnant at the time of the first injection, the first injection should be given ONLY during the first 5 days of a normal menstrual period; ONLY within the first 5-days postpartum if not breast-feeding; and if exclusively breast-feeding, ONLY at the sixth postpartum week. If the time interval between injections is greater than 13 weeks, the physician should determine that the patient is not pregnant before administering the drug. The efficacy of Depo-Provera CI depends on adherence to the dosage schedule of administration.

2.2 Switching From Other Methods of Contraception

When switching from other contraceptive methods, Depo-Provera CI should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of Depo-Provera CI on the day after the last active tablet or at the latest, on the day following the final inactive tablet).

3 DOSAGE FORMS AND STRENGTHS

Sterile Aqueous suspension: 150mg/ml
Prefilled syringes are available packaged with 22-gauge x 1 1/2 inch Terumo® SurGuard™ Needles.

4 CONTRAINDICATIONS

The use of Depo-Provera CI is contraindicated in the following conditions:

- Known or suspected pregnancy or as a diagnostic test for pregnancy.
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease *[see Warnings and Precautions (5.2)]*.
- Known or suspected malignancy of breast *[see Warnings and Precautions (5.3)]*.
- Known hypersensitivity to Depo-Provera CI (medroxyprogesterone acetate) or any of its other ingredients *[see Warnings and Precautions (5.5)]*.
- Significant liver disease *[see Warnings and Precautions (5.7)]*.
- Undiagnosed vaginal bleeding *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Use of Depo-Provera CI reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

A study to assess the reversibility of loss of BMD in adolescents was conducted with Depo-Provera CI. After discontinuing Depo-Provera CI in these adolescents, mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60 months) post-treatment in the sub-group of adolescents who were treated for more than 2 years *[see Clinical Studies (14.3)]*. Similarly, in adults, there was only partial recovery of mean BMD at the total hip, femoral neck, and lumbar spine towards baseline by 2 years post-treatment *[see Clinical Studies (14.2)]*.

The use of Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. BMD should be evaluated when a woman needs to continue to use Depo-Provera CI long-term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of Depo-Provera CI in women with osteoporosis risk factors. Depo-Provera CI can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids).

5.2 Thromboembolic Disorders

There have been reports of serious thrombotic events in women using Depo-Provera CI (150 mg). However, Depo-Provera CI has not been causally associated with the induction of thrombotic or thromboembolic disorders. Any patient who develops thrombosis while undergoing therapy with Depo-Provera CI should discontinue treatment unless she has no other acceptable options for birth control.

Do not re-administer Depo-Provera CI pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. Do not re-administer if examination reveals papilledema or retinal vascular lesions.

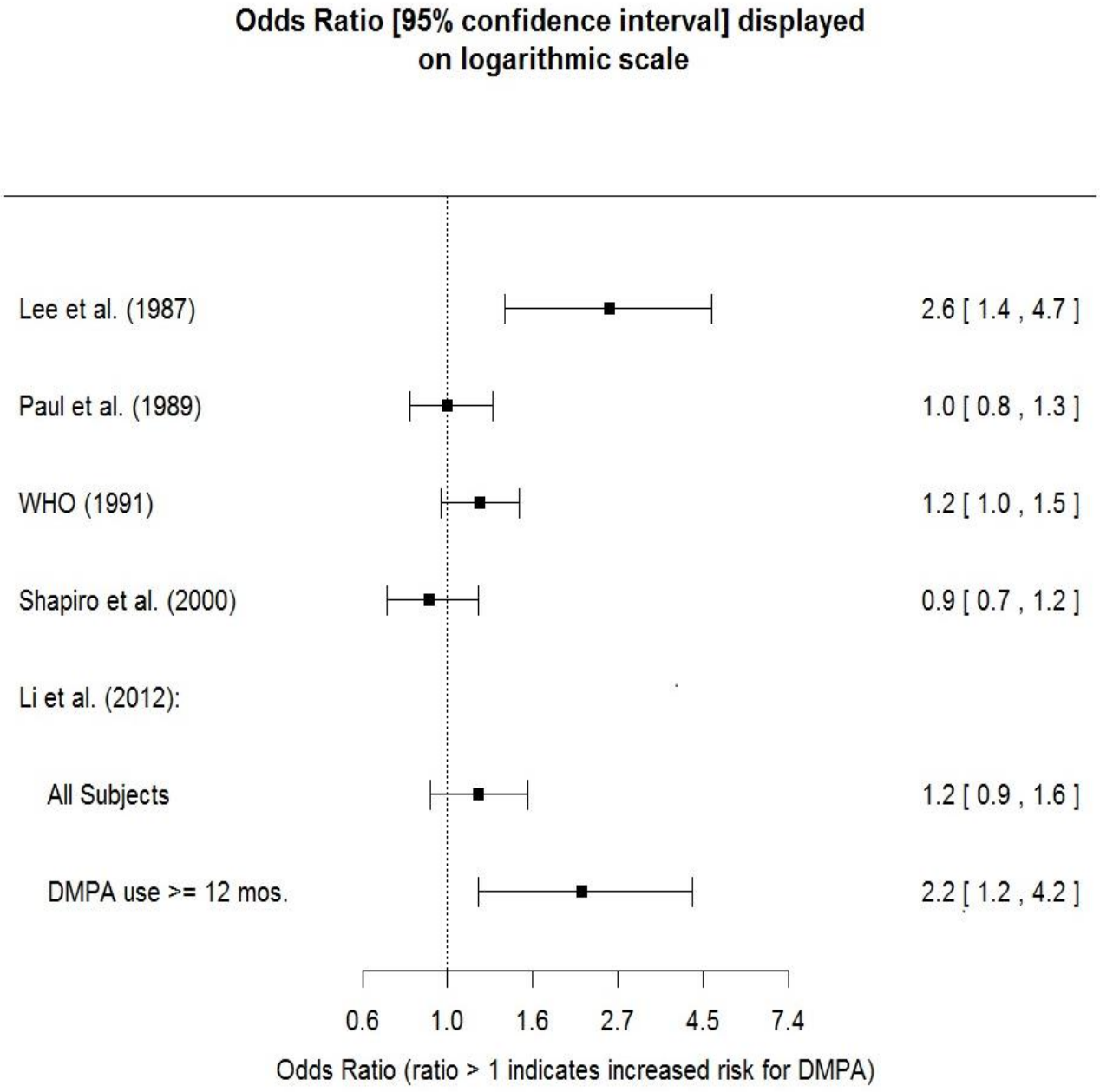
5.3 Cancer Risks

Breast Cancer

Women who have or have had a history of breast cancer should not use hormonal contraceptives, including Depo-Provera CI, because breast cancer may be hormonally sensitive *[see Contraindications (4)]*. Women with a strong family history of breast cancer should be monitored with particular care.

The results of five large case-control studies[1, **Error! Reference source not found.**] assessing the association between depo-medroxyprogesterone acetate (DMPA) use and the risk of breast cancer are summarized in Figure 1. Three of the studies suggest a slightly increased risk of breast cancer in the overall population of users; these increased risks were statistically significant in one study. One recent US study[1] evaluated the recency and duration of use and found a statistically significantly increased risk of breast cancer in recent users (defined as last use within the past five years) who used DMPA for 12 months or longer; this is consistent with results of a previous study.

Figure 1 Risk estimates for breast cancer in DMPA users



Odds ratio estimates were adjusted for the following covariates:
Lee et al. (1987): age, parity, and socioeconomic status.
Paul et al. (1989): age, parity, ethnic group, and year of interview.
WHO (1991): age, center, and age at first live birth.
Shapiro et al. (2000): age, ethnic group, socioeconomic status, and any combined estrogen/progestogen oral contraceptive use.
Li et al. (2012): age, year, BMI, duration of OC use, number of full-term pregnancies, family history of breast cancer, and history of screening mammography.

Based on the published SEER-18 2011 incidence rate (age-adjusted to the 2000 US Standard Population) of breast cancer for US women, all races, age 20 to 49 years, a doubling of risk would increase the incidence of breast cancer in women who use Depo-Provera CI from about 72 to about 144 cases per 100,000 women.

Cervical Cancer
A statistically nonsignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of Depo-Provera CI in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93 to 1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used Depo-Provera CI was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Other Cancers
Long-term case-controlled surveillance of users of Depo-Provera CI found no overall increased risk of ovarian or liver cancer.

5.4 Ectopic Pregnancy
Be alert to the possibility of an ectopic pregnancy among women using Depo-Provera CI who become pregnant or complain of severe abdominal pain.

5.5 Anaphylaxis and Anaphylactoid Reaction
Anaphylaxis and anaphylactoid reaction have been reported with the use of Depo-Provera CI. Institute emergency medical treatment if an anaphylactic reaction occurs.

5.6 Injection Site Reactions
Injection site reactions have been reported with use of Depo-Provera CI *[see Adverse Reactions (6.2)]*. Persistent injection site reactions may occur after administration of Depo-Provera CI due to inadvertent subcutaneous administration or release of the drug into the subcutaneous space while removing the needle *[see Dosage and Administration (2.1)]*.

5.7 Liver Function
Discontinue Depo-Provera CI use if jaundice or acute or chronic disturbances of liver function develop. Do not resume use until markers of liver function return to normal and Depo-Provera CI causation has been excluded.

5.8 Convulsions
There have been a few reported cases of convulsions in patients who were treated with Depo-Provera CI. Association with drug use or pre-existing conditions is not clear.

5.9 Depression
Monitor patients who have a history of depression and do not re-administer Depo-Provera CI if depression recurs.

5.10 Bleeding Irregularities
Most women using Depo-Provera CI experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include amenorrhea, irregular or unpredictable bleeding or spotting, prolonged spotting or bleeding, and heavy bleeding. Rule out the possibility of organic pathology if abnormal bleeding persists or is severe, and institute appropriate treatment.

As women continue using Depo-Provera CI, fewer experience irregular bleeding and more experience amenorrhea. In clinical studies of Depo-Provera CI, by month 12 amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using Depo-Provera CI.

5.11 Weight Gain
Women tend to gain weight while on therapy with Depo-Provera CI. From an initial average body weight of 136 lb, women who completed 1 year of therapy with Depo-Provera CI gained an average of 5.4 lb. Women

who completed 2 years of therapy gained an average of 8.1 lb. Women who completed 4 years gained an average of 13.8 lb. Women who completed 6 years gained an average of 16.5 lb. Two percent of women withdrew from a large-scale clinical trial because of excessive weight gain.

5.12 Carbohydrate Metabolism

A decrease in glucose tolerance has been observed in some patients on Depo-Provera CI treatment. Monitor diabetic patients carefully while receiving Depo-Provera CI.

5.13 Lactation

Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera CI. In nursing mothers treated with Depo-Provera CI, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

5.14 Fluid Retention

Because progestational drugs including Depo-Provera CI may cause some degree of fluid retention, monitor patients with conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction.

5.15 Return of Fertility

Return to ovulation and fertility is likely to be delayed after stopping Depo-Provera CI. In a large US study of women who discontinued use of Depo-Provera CI to become pregnant, data are available for 61% of them. Of the 188 women who discontinued the study to become pregnant, 114 became pregnant. Based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued Depo-Provera CI to become pregnant and who were lost to follow-up or changed their mind.

5.16 Sexually Transmitted Diseases

Patients should be counseled that Depo-Provera CI does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

5.17 Pregnancy

Although Depo-Provera CI should not be used during pregnancy, there appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to medroxyprogesterone acetate injections in early pregnancy. Neonates exposed to medroxyprogesterone acetate in-utero and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

5.18 Monitoring

A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.19 Interference With Laboratory Tests

The use of Depo-Provera CI may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. *[See Drug Interactions (7.2).]*

6 ADVERSE REACTIONS

The following important adverse reactions observed with the use of Depo-Provera CI are discussed in greater detail in the *Warnings and Precautions* section (*5*):

- Loss of Bone Mineral Density *[see Warnings and Precautions (5.1)]*
- Thromboembolic disease *[see Warnings and Precautions (5.2)]*
- Breast Cancer *[see Warnings and Precautions (5.3)]*
- Anaphylaxis and Anaphylactoid Reactions *[see Warnings and Precautions (5.5)]*
- Bleeding Irregularities*[see Warnings and Precautions (5.10)]*
- Weight Gain *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the two clinical trials with Depo-Provera CI, over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of Depo-Provera CI. The population studied ranges in age from 15 to 51 years, of which 46% were White, 50% Non-White, and 4.9% Unknown race. The patients received 150 mg Depo-Provera CI every 3-months (90 days). The median study duration was 13 months with a range of 1-84 months. Fifty eight percent of patients remained in the study after 13 months and 34% after 24 months.

Table 1 Adverse Reactions that Were Reported by More than 5% of Subjects

Body System*	**Adverse Reactions [Incidence (%)]**
Body as a Whole	Headache (16.5%) Abdominal pain/discomfort (11.2%)
Metabolic/Nutritional	Increased weight> 10lbs at 24 months (37.7%)
Nervous	Nervousness (10.8%) Dizziness (5.6%) Libido decreased (5.5%)
Urogenital	Menstrual irregularities: (bleeding (57.3% at 12 months, 32.1% at 24 months) amenorrhea (55% at 12 months, 68% at 24 months)

* Body System represented from COSTART medical dictionary.

Table 2 Adverse Reactions that Were Reported by between 1 and 5% of Subjects

Body System*	Adverse Reactions [Incidence (%)]
Body as a Whole	Asthenia/fatigue (4.2%) Backache (2.2%) Dysmenorrhea (1.7%) Hot flashes (1.0%)
Digestive	Nausea (3.3%) Bloating (2.3%)
Metabolic/Nutritional	Edema (2.2%)
Musculoskeletal	Leg cramps (3.7%) Arthralgia (1.0%)
Nervous	Depression (1.5%) Insomnia (1.0%)
Skin and Appendages	Acne (1.2%) No hair growth/alopecia (1.1%) Rash (1.1%)
Urogenital	Leukorrhea (2.9%) Breast pain (2.8%) Vaginitis (1.2%)

* Body System represented from COSTART medical dictionary.

Adverse reactions leading to study discontinuation in ≥2% of subjects: bleeding (8.2%), amenorrhea (2.1%), weight gain (2.0%)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Depo-Provera CI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been cases of osteoporosis including osteoporotic fractures reported post-marketing in patients taking Depo-Provera CI.

Table 3 Adverse Reactions Reported during Post-Marketing Experience

Body System*	Adverse Reactions
Body as a Whole	Chest pain, Allergic reactions including angioedema, Fever, Injection site abscess†, Injection site infection†, Injection site nodule/lump, Injection site pain/tenderness, Injection site persistent atrophy/indentation/dimpling, Injection-site reaction, Lipodystrophy acquired, Chills, Axillary swelling
Cardiovascular	Syncope, Tachycardia, Thrombophlebitis, Deep vein thrombosis, Pulmonary embolus, Varicose veins
Digestive	Changes in appetite, Gastrointestinal disturbances, Jaundice, Excessive thirst, Rectal bleeding
Hematologic and Lymphatic	Anemia, Blood dyscrasia
Musculoskeletal	Osteoporosis
Neoplasms	Cervical cancer, Breast cancer
Nervous	Paralysis, Facial palsy, Paresthesia, Drowsiness
Respiratory	Dyspnea and asthma, Hoarseness
Skin and Appendages	Hirsutism, Excessive sweating and body odor, Dry skin, Scleroderma
Urogenital	Lack of return to fertility, Unexpected pregnancy, Prevention of lactation, Changes in breast size, Breast lumps or nipple bleeding, Galactorrhea, Melasma, Chloasma, Increased libido, Uterine hyperplasia, Genitourinary infections, Vaginal cysts, Dyspareunia

* Body System represented from COSTART medical dictionary.

† Injection site abscess and injection site infections have been reported; therefore strict aseptic injection technique should be followed when administering Depo Provera CI in order to avoid injection site infections *[see Dosage and Administration (2.1)]*.

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John’s wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration of HIV protease inhibitors. Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Laboratory Test Interactions

The pathologist should be advised of progestin therapy when relevant specimens are submitted.
The following laboratory tests may be affected by progestins including Depo-Provera CI:

(a) Plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol).
(b) Gonadotropin levels are decreased.
(c) Sex-hormone-binding-globulin concentrations are decreased.
(d) Protein-bound iodine and butanol extractable protein-bound iodine may increase. T_3-uptake values may decrease.
(e) Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
(f) Sulfobromophthalein and other liver function test values may be increased.
(g) The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Depo-Provera CI should not be administered during pregnancy. [*See Contraindications and Warnings and Precautions (5.17).]*

8.3 Nursing Mothers

Detectable amounts of drug have been identified in the milk of mothers receiving Depo-Provera CI. [*See Warnings and Precautions (5.13).*]

8.4 Pediatric Use

Depo-Provera CI is not indicated before menarche. Use of Depo-Provera CI is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

8.5 Geriatric Use

This product has not been studied in post-menopausal women and is not indicated in this population.

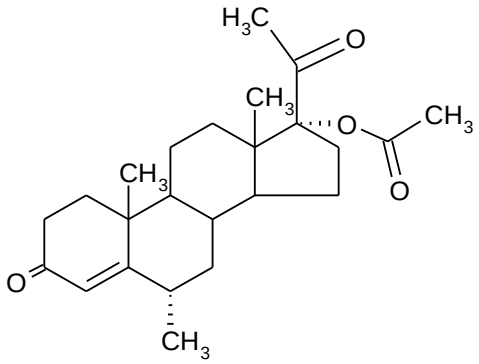
8.6 Renal Impairment
The effect of renal impairment on Depo-Provera CI pharmacokinetics has not been studied.

8.7 Hepatic Impairment
The effect of hepatic impairment on Depo-Provera CI pharmacokinetics has not been studied. Depo-Provera CI should not be used by women with significant liver disease and should be discontinued if jaundice or disturbances of liver function occur. [*See Contraindications (4) and Warnings and Precautions (5.7).*]

11 DESCRIPTION
Depo-Provera CI contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white; odorless crystalline powder that is stable in air and that melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α-).

The structural formula is as follows:



Depo-Provera CI for IM injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

For Depo-Provera CI vials, each mL of sterile aqueous suspension contains:

Medroxyprogesterone acetate	150 mg
Polyethylene glycol 3350	28.9 mg
Polysorbate 80	2.41 mg
Sodium chloride	8.68 mg
Methylparaben	1.37 mg
Propylparaben	0.150 mg
Water for injection	quantity sufficient

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

For Depo-Provera CI prefilled syringes, each mL of sterile aqueous suspension contains:

Medroxyprogesterone acetate	150 mg
Polyethylene glycol 3350	28.5 mg
Polysorbate 80	2.37 mg
Sodium chloride	8.56 mg
Methylparaben	1.35 mg

Propylparaben	0.147 mg
Water for injection	quantity sufficient

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Depo-Provera CI (medroxyprogesterone acetate [MPA]) inhibits the secretion of gonadotropins which primarily prevents follicular maturation and ovulation and causes thickening of cervical mucus. These actions contribute to its contraceptive effect.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Depo-Provera CI.

12.3 Pharmacokinetics

Absorption

Following a single 150 mg IM dose of Depo-Provera CI in eight women between the ages of 28 and 36 years old, medroxyprogesterone acetate concentrations, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

The concentrations of medroxyprogesterone acetate decrease exponentially until they become undetectable (<100 pg/mL) between 120 to 200 days following injection. Using an unextracted radioimmunoassay procedure for the assay of medroxyprogesterone acetate in serum, the apparent half-life for medroxyprogesterone acetate following IM administration of Depo-Provera CI is approximately 50 days. Most medroxyprogesterone acetate metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates.

Specific Populations

The effect of hepatic and/or renal impairment on the pharmacokinetics of Depo-Provera CI is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[*See Warnings and Precautions, (5.3, 5.15, and 5.17).*]

14 CLINICAL STUDIES

14.1 Contraception

In five clinical studies using Depo-Provera CI, the 12-month failure rate for the group of women treated with Depo-Provera CI was zero (no pregnancies reported) to 0.7 by Life-Table method. The effectiveness of Depo-Provera CI is dependent on the patient returning every 3 months (13 weeks) for reinjection.

14.2 Bone Mineral Density Changes in Adult Women Treated with Depo-Provera CI

In a controlled, clinical study, adult women using Depo-Provera CI (150mg) for up to 5 years showed spine and hip bone mineral density (BMD) mean decreases of 5–6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4, and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of Depo-Provera CI, there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. Table 4 shows the change in BMD in women after 5 years of treatment with Depo-Provera CI and in women in a control group, as well as the extent of recovery of BMD for the subset of the women for whom 2-year post treatment data were available.

Table 4. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort (5 Years of Treatment and 2 Years of Follow-Up)

Time in Study	Spine		Total Hip		Femoral Neck	
	Depo-Provera*	Control**	Depo-Provera*	Control**	Depo-Provera*	Control**
5 years	-5.38% n=33	0.43% n=105	-5.16% n=21	0.19% n=65	-6.12% n=34	-0.27% n=106
7 years	-3.13% n=12	0.53% n=60	-1.34% n=7	0.94% n=39	-5.38% n=13	-0.11% n=63

*The treatment group consisted of women who received Depo-Provera CI for 5 years and were then followed for 2 years post-use (total time in study of 7 years).

**The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

14.3 Bone Mineral Density Changes in Adolescent Females (12 to 18 Years of Age) Treated with Depo-Provera CI

The impact of Depo-Provera CI (150 mg) use for up to 240 weeks (4.6 years) was evaluated in an open-label non-randomized clinical study in 389 adolescent females (12 to 18 years of age). Use of Depo-Provera CI was associated with a significant decline from baseline in BMD.

Partway through the trial, drug administration was stopped (at 120 weeks). The mean number of injections per Depo-Provera CI user was 9.3. Table 5 summarizes the study findings. The decline in BMD at total hip and femoral neck was greater with longer duration of use. The mean decrease in BMD at 240 weeks was more pronounced at total hip (-6.4%) and femoral neck (-5.4%) compared to lumbar spine (-2.1%).

Adolescents in the untreated cohort had an increase in BMD during the period of growth following menarche. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of BMD.

Table 5. BMD Mean Percent Change from Baseline in Adolescents Receiving ≥4 Injections per 60-week Period, by Skeletal Site and Cohort

Duration of Treatment	Depo-Provera CI (150 mg IM)		Unmatched, Untreated Cohort	
	N	Mean % Change	N	Mean % Change
Total Hip BMD				
Week 60 (1.2 years)	113	-2.75	166	1.22
Week 120 (2.3 years)	73	-5.40	109	2.19
Week 240 (4.6 years)	28	-6.40	84	1.71
Femoral Neck BMD				
Week 60	113	-2.96	166	1.75
Week 120	73	-5.30	108	2.83
Week 240	28	-5.40	84	1.94
Lumbar Spine BMD				
Week 60	114	-2.47	167	3.39
Week 120	73	-2.74	109	5.28
Week 240	27	-2.11	84	6.40

BMD Recovery Post-Treatment in Adolescents

Longer duration of treatment and smoking were associated with less recovery of BMD following the last injection of Depo-Provera CI. Table 6 shows the extent of recovery of BMD up to 60 months post-treatment for adolescents who received Depo-Provera CI for two years or less compared to more than two years. Post-treatment follow-up showed that, in women treated for more than two years, only lumbar spine BMD recovered to baseline levels after treatment was discontinued. Adolescents treated with Depo-Provera CI for more than two years did not recover to their baseline BMD level at femoral neck and total hip even up to 60 months post-treatment. Adolescents in the untreated cohort gained BMD throughout the trial period (data not shown) *[see Warnings and Precautions (5.1)]*.

Table 6: BMD Recovery (Months Post-Treatment) in Adolescents by Years of Depo Provera CI Use (2 Years or Less vs. More than 2 Years)

Duration of Treatment	2 years or less		More than 2 years	
	N	Mean % Change from baseline	N	Mean % Change from baseline
Total Hip BMD				
End of Treatment	49	-1.5%	49	-6.2%
12 M post-treatment	33	-1.4%	24	-4.6%
24 M post-treatment	18	0.3%	17	-3.6%
36 M post-treatment	12	2.1%	11	-4.6%
48 M post-treatment	10	1.3%	9	-2.5%
60 M post-treatment	3	0.2%	2	-1.0%
Femoral Neck BMD				
End of Treatment	49	-1.6%	49	-5.8%
12 M post-treatment	33	-1.4%	24	-4.3%
24 M post-treatment	18	0.5%	17	-3.8%
36 M post-treatment	12	1.2%	11	-3.8%
48 M post-treatment	10	2.0%	9	-1.7%
60 M post-treatment	3	1.0%	2	-1.9%
Lumbar Spine BMD				
End of Treatment	49	-0.9%	49	-3.5%
12 M post-treatment	33	0.4%	23	-1.1%
24 M post-treatment	18	2.6%	17	1.9%
36 M post-treatment	12	2.4%	11	0.6%
48 M post-treatment	10	6.5%	9	3.5%
60 M post-treatment	3	6.2%	2	5.7%

14.4 Bone Fracture Incidence in Women Treated with Depo-Provera CI

A retrospective cohort study to assess the association between Depo-Provera CI injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between Depo-Provera CI users and contraceptive users who had no recorded use of Depo-Provera CI. The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean=5.5 years) was 1.41 (95% CI 1.35, 1.47). It is not known if this is due to Depo-Provera CI use or to other related lifestyle factors that have a bearing on fracture rate.

In the study, when cumulative exposure to Depo-Provera CI was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.

There were very few osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in Depo-Provera CI users compared to non-users.

Importantly, this study could not determine whether use of Depo-Provera CI has an effect on fracture rate later in life.

15 REFERENCES

1. Li CI, Beaber EF, Tang, MCT et al. Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 years of Age. Cancer Research 2012;72:2028-2035.
2. Paul C, Skegg DCG, Spears GFS. Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. Br Med J 1989; 299:759-62.

16 HOW SUPPLIED/STORAGE AND HANDLING

Depo-Provera CI is supplied in the following strengths and package configurations:

Package Configuration	Strength	NDC
Depo-Provera CI (medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL)		
1 mL vial	150 mg/mL	NDC 0009-0746-30
25 x 1 mL vials	150 mg/mL	NDC 0009-0746-35
Depo-Provera CI prefilled syringes packaged with 22 gauge x 1 1/2 inch Terumo® SurGuard™ Needles		
1 mL prefilled syringe	150 mg/mL	NDC 0009-7376-11

Vials MUST be stored upright at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)."

- Advise patients at the beginning of treatment that their menstrual cycle may be disrupted and that irregular and unpredictable bleeding or spotting results, and that this usually decreases to the point of amenorrhea as treatment with Depo-Provera CI continues, without other therapy being required.
- Counsel patients about the possible increased risk of breast cancer in women who use Depo-Provera CI *[see Warnings and Precautions (5.3)]*.
- Counsel patients that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with use of Depo-Provera CI.
- Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with Depo-Provera CI.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Distributed by

Pharmacia & Upjohn Co

Division of Pfizer Inc, NY, NY 10017

LAB-0149-19.0

Patient Information

Depo-Provera® (*DEP-po pro-VAIR-ah*) CI
(medroxyprogesterone acetate injectable suspension)
Contraceptive Injection

Read this Patient Information carefully before you decide if Depo-Provera CI is right for you. This information does not take the place of talking with your gynecologist or other healthcare provider who specializes in women's health. If you have any questions about Depo-Provera CI, ask your healthcare provider. You should also learn about other birth control methods to choose the one that is best for you.

What is the most important information I should know about Depo-Provera CI?

Depo-Provera CI can cause serious side effects, including:

- **Use of Depo-Provera CI may cause you to lose calcium stored in your bone and decrease your bone mass. The longer you use Depo-Provera CI, the greater your loss of calcium from your bones. Your bones may not recover completely when you stop using Depo-Provera CI.**
- **If you use Depo-Provera CI continuously for a long time (for more than 2 years), it may increase the risk of weak, porous bones (osteoporosis) that could increase the risk of broken bones, especially after menopause.**
- **You should not use Depo-Provera CI for more than two years unless you cannot use other birth control methods.**
- **It is not known if your risk of developing osteoporosis is greater if you are a teenager or young adult when you start to use Depo-Provera CI (see "What are the possible side effects of Depo-Provera CI?").**

Depo-Provera CI is intended to prevent pregnancy. Depo-Provera CI does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

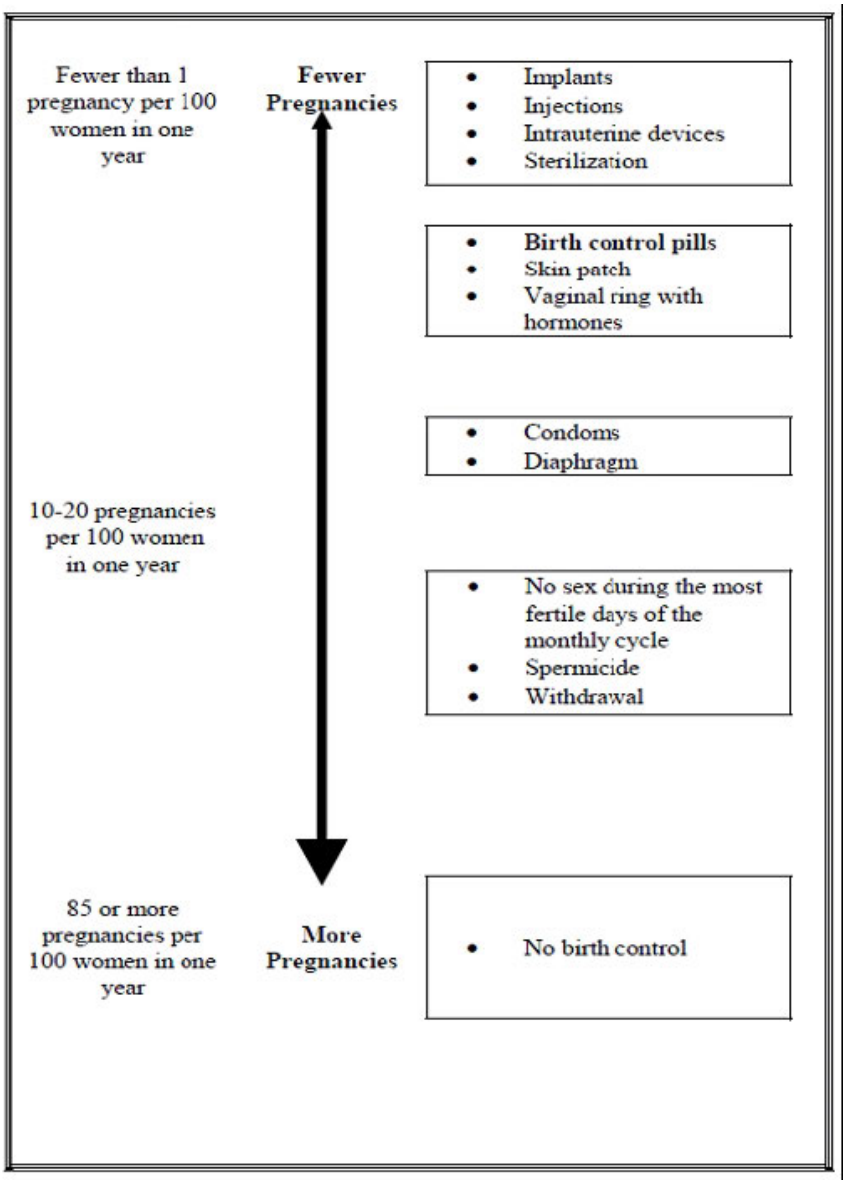
What is Depo-Provera CI?
Depo-Provera CI is a progestin hormone birth control method that is given by injection (a shot) to prevent pregnancy.

How well does Depo-Provera CI work?
Your chance of getting pregnant depends on how well you follow the directions for taking your Depo-Provera CI. The more carefully you follow the directions (such as returning every 3 months for your next injection), the less chance you have of getting pregnant.

In clinical studies, about 1 out of 100 women got pregnant during the first year that they used Depo-Provera CI.

The following chart shows the chance of getting pregnant for women who use different

methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How should I take Depo-Provera CI?

- Depo-Provera CI is given by your healthcare provider as a shot into your muscle (intramuscular injection). The shot is given in your buttock or upper arm 1 time every 3 months. At the end of the 3 months, you will need to return to your healthcare provider for your next injection in order to continue your protection against pregnancy.

- **To make sure that you are not pregnant before you take Depo-Provera CI, the first injection should be given only:**
    - during the first 5 days of a normal menstrual period, or
    - within the first 5 days after giving birth, **if you are not breastfeeding**, or
    - at the 6th week after giving birth, **if you are feeding your baby only breastmilk.**

- Depo-Provera CI may be given at other times than those listed above, but you will likely need to have a pregnancy test first to show that you are not pregnant.
- During treatment with Depo-Provera CI, you should see your healthcare provider every year for a blood pressure check and other healthcare needs.

Who Should Not Use Depo-Provera CI?

Do not use Depo-Provera CI if you:

- are pregnant or think you might be pregnant
- have bleeding from your vagina that has not been explained
- have breast cancer now or in the past, or think you have breast cancer
- have had a stroke
- ever had blood clots in your arms, legs or lungs
- have problems with your liver or liver disease
- are allergic to medroxyprogesterone acetate or any of the other ingredients in Depo-Provera CI. See the end of this leaflet for a complete list of ingredients in Depo-Provera CI.

What should I tell my healthcare provider before taking Depo-Provera CI?

Before taking Depo-Provera CI, tell your healthcare provider if you have:

- risk factors for weak bones (osteoporosis) such as bone disease, use alcohol or smoke regularly, anorexia nervosa, or a strong family history of osteoporosis
- irregular or lighter than usual menstrual periods
- breast cancer now or in the past, or think you have breast cancer
- a family history of breast cancer
- an abnormal mammogram (breast X-ray), lumps in your breasts, or bleeding from your nipples
- kidney problems
- high blood pressure
- had a stroke
- had blood clots in your arms, legs or lungs
- migraine headaches
- asthma
- epilepsy (convulsions or seizures)
- diabetes
- depression or a history of depression
- any other medical conditions

If you are breastfeeding or plan to breastfeed, Depo-Provera CI can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take Depo-Provera CI.

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Depo-Provera CI and certain other medicines may affect each other, causing serious side effects. Sometimes the doses of other medicines may need to be changed while you are taking Depo-Provera CI.

Some medicines may make Depo-Provera CI less effective at preventing pregnancy, including those listed below.

Especially tell your healthcare provider if you take:

- medicine to help you sleep
- bosentan
- medicine for seizures
- griseofulvin
- an antibiotic
- medicine for HIV (AIDS)
- St. John's wort

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider or pharmacist before you first start taking Depo-Provera CI or when you get a new medicine.

Follow your healthcare provider's instructions about using a back-up method of birth control if you are taking medicines that may make Depo-Provera CI less effective.

What are the possible side effects of Depo-Provera CI?

Depo-Provera CI can cause serious side effects, including:

- Effect on the bones: See "What is the most important information I should know about Depo-Provera CI?".
  Teenage years are the most important years to gain bone strength. The decrease in calcium in your bones is of most concern if you are a teenager or have the following problems:
  - bone disease
  - an eating disorder (anorexia nervosa)
  - a strong family history of osteoporosis
  - you take a drug that can lower the amount of calcium in your bones (drugs for epilepsy or steroid drugs)
  - you drink a lot of alcohol (more than 2 drinks a day)

- you smoke

If you need a birth control method for more than 2 years, your healthcare provider may switch you to another birth control method instead of using Depo-Provera CI. If you continue using Depo-Provera CI, your healthcare provider may ask you to have a bone test, especially if you have other risks for weak bones.

When Depo-Provera CI is stopped, your bones may start to regain calcium. However, in a study of teenage girls who used Depo-Provera CI for more than 2 years, their hip bones did not completely recover by 5 years after they stopped using Depo-Provera CI. Taking calcium and Vitamin D and exercising daily may lessen the loss of calcium from your bones.

- possible increased risk of breast cancer. Women who use Depo-Provera CI may have a slightly increased risk of breast cancer compared to non-users.
- blood clots in your arms, legs, lungs, and eyes
- stroke
- a pregnancy outside of your uterus (ectopic pregnancy). Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.
- allergic reactions. Severe allergic reactions have been reported in some women using Depo-Provera CI.
- loss of vision or other eye problems
- migraine headaches
- depression
- convulsions or seizures
- liver problems

Call your healthcare provider right away if you have:

- sharp chest pain, coughing up blood, or sudden shortness of breath (indicating a possible clot in the lung)
- sudden severe headache or vomiting, dizziness or fainting, problems with your eyesight or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- severe pain or swelling in the calf (indicating a possible clot in the leg)
- sudden blindness, partial or complete (indicating a possible clot in the blood vessels of the eye)
- unusually heavy vaginal bleeding
- severe pain or tenderness in the lower abdominal area
- persistent pain, pus, or bleeding at the injection site
- yellowing of the eyes or skin
- hives
- difficulty breathing
- swelling of the face, mouth, tongue or neck

The most common side effects of Depo-Provera CI include:

- irregular vaginal bleeding, such as lighter or heavier menstrual bleeding, or continued spotting
- weight gain. You may experience weight gain while you are using Depo-Provera CI. About two-thirds of the women who used Depo-Provera CI in the clinical trials reported a weight gain of about 5 pounds during the first year of use. You may continue to gain weight after the first year. Women who used Depo-Provera CI for 2 years gained an average of 8 pounds over those 2 years.
- abdominal pain
- headache
- weakness
- tiredness
- nervousness
- dizziness

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of Depo-Provera CI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1- 800-FDA-1088.

What other information should I know before choosing Depo-Provera CI?

- **Pregnancy**. When you take Depo-Provera CI every 3 months, your chance of getting pregnant is very low. You could miss a period or have a light period and not be pregnant. If you miss 1 or 2 periods and think you might be pregnant, see your healthcare provider as soon as possible. You should not use Depo-Provera CI if you are pregnant. However, Depo-Provera CI taken by accident during pregnancy does not seem to cause birth defects.
- **Nursing Mothers**. Although Depo-Provera CI can be passed to the nursing baby in the breast milk, no harmful effects on babies have been found. Depo-Provera CI does not stop the breasts from producing milk, so it can be used by nursing mothers. However, to minimize the amount of Depo-Provera CI that is passed to the baby in the first weeks after birth, you should wait until your baby is 6 weeks old before you start using Depo-Provera CI for birth control.

How will Depo-Provera CI change my periods?

- **Change in normal menstrual cycle**. The side effect reported most frequently by women who use Depo-Provera CI for birth controls is a change in their normal menstrual cycle. During the first year of using Depo-Provera CI, you might have one or more of the following changes:
    - irregular or unpredictable bleeding or spotting
    - an increase or decrease in menstrual bleeding
    - **no bleeding at all**. In clinical studies of Depo-Provera CI, 55% of women

reported no menstrual bleeding (amenorrhea) after one year of use and 68% of women reported no menstrual bleeding after two years of use.

- **Missed period**. During the time you are using Depo-Provera CI for birth controls, you may skip a period, or your periods may stop completely. If you have been receiving your shot of Depo-Provera CI regularly every 3 months, then you are probably not pregnant. However, if you think that you may be pregnant, see your healthcare provider.

Unusually heavy or continuous bleeding is not a usual effect of Depo-Provera CI and if this happens you should see your healthcare provider right away.
With continued use of Depo-Provera CI, bleeding usually decreases and many women stop having periods completely. When you stop using Depo-Provera CI your menstrual period will usually, in time, return to its normal cycle.

What if I want to become pregnant?
Because Depo-Provera CI is a long-acting birth control method, it takes some time after your last shot for its effect to wear off. Most women who try to get pregnant after using Depo-Provera CI get pregnant within 18 months after their last shot. The length of time you use Depo-Provera CI has no effect on how long it takes you to become pregnant after you stop using it.

General Information about Depo-Provera CI
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet summarizes the most important information about Depo-Provera CI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about Depo-Provera CI that is written for healthcare providers.

What are the ingredients in Depo-Provera CI?
Active ingredient: medroxyprogesterone acetate
Inactive ingredients: polyethylene glycol 3350, polysorbate 80, sodium chloride, methylparaben, propylparaben, and water for injection. When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

This Patient Information has been approved by the U.S. Food and Drug Administration.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

LAB-0148-13.0

Revised December 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
NDAs 20246 & 21583
Complete Response Resubmission

Date	November 30, 2020
From	Gerald Willett, M.D.
Subject	Cross-Discipline Team Leader Review
NDAs / Supplement #s	020246 S-060 & S-062 Depo-Provera (medroxyprogesterone acetate) Contraceptive Injection (DMPA CI) 021583 S-033 & S-034 Depo-SubQ Provera 104 (medroxyprogesterone acetate) Injectable Suspension (DMPA SQ)
Applicant	Pfizer Inc
Date of Submission	June 5, 2020
PDUFA Goal Date	December 5, 2020
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy
Dosing	DMPA CI = 150 mg IM once every 3 months DMPA SQ = 104 mg SC once ever 12-14 weeks
Recommendation on Regulatory Action	Approval

These resubmissions are in response to the Complete Response action taken on October 6, 2017, for efficacy supplements 060 and 062 to NDA 20245 (DMPA CI) and efficacy supplements 033 and 034 to NDA 21583 (DMPA SQ) submitted on December 9, 2016.

Background Information for NDA 020246 - S-060 & S-062 Depo-Provera (medroxyprogesterone acetate) Contraceptive Injection

Hereafter in this review this product will be referred to as DMPA CI. S-060 is the supplement that includes proposed labeling changes related to DMPA CI's effect on bone mineral density (BMD) and 2-year limitation of use. S-062 is the supplement that includes proposed labeling changes (b) (4).

DMPA CI is an intramuscular injectable progestin that has been approved since 1992 for female contraception. The 150 mg dose is given in the gluteal or deltoid muscles

every 3 months. Bone mineral density (BMD) loss is a major safety issue for this product. A boxed warning related to BMD was added in 2004 (see verbatim below).

> **"Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.**
>
> **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.**
>
> **Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate. (See WARNINGS.)"**

Study data (Protocol A6791022 – Study 261) related to risk and reversal of decreased BMD in adolescents was submitted by the Applicant in 2009. Product labeling related to this adolescent safety data included tabular results for BMD changes at three locations (total hip, femoral neck and lumbar spine). The WARNINGS AND PRECAUTIONS section stated "After discontinuing Depo-Provevera CI in adolescents, mean BMD loss at total hip and femoral neck did not fully recover by 60 months (240 weeks) post-treatment"

In 2010 the Applicant submitted a report of a fracture study conducted by the General Practice Research Database (GPRD) in the UK (Protocol A6791032). The findings of the GPRD study were labeled and currently appears in Section 14.4 as follows:

> **"Relationship of fracture incidence to use of DMPA 150 mg IM or non-use by women of reproductive age**
>
> A retrospective cohort study to assess the association between DMPA injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between DMPA users and contraceptive users who had no recorded use of DMPA. The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). It is not known if this is due to DMPA use or to other related lifestyle factors that have a bearing on fracture rate.
>
> In the study, when cumulative exposure to DMPA was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.
>
> There were very few osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in DMPA users compared to non-users. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life."

After the submission of data from the GPRD study, the Agency requested the Applicant to conduct additional analyses from the GPRD study data including a more detailed examination of the possible association between the extent of DMPA exposure and

fracture incidence (e.g., with a look-back period of 6-24 months prior to DMPA use) and an examination of fracture rates before and after DMPA treatment in the sub-cohort of women with 6-24 months of pre-index history before any contraceptive use. After the Applicant conducted these analyses, they submitted efficacy supplements 060 and 062 in December 2016. They proposed the following labeling revisions in those supplements (underlined are additions, strikethroughs are deletions):

(b) (4)

Similar changes were made throughout the label to (b) (4) and to state that there (b) (4). The review of this efficacy supplement and literature support was performed by the reproductive and bone team of the Division (DBRUP at that point) and the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI). For more detail regarding the reviews by DBRUP and OSE/DEPI see DARRTS submissions by Dr. Jaffe (August 30, 2017), Dr. Liu (September 27, 2017), Dr. Sewell (October 2, 2017) and Dr. Soule (October 5, 2017).

The Agency reviewers concluded that the prior BMD study data continued to support the current labeling text (b) (4) The Agency reviewers thus recommended no change in the label.

A complete response letter was sent to the Applicant on October 6, 2017 for Suppls 60 & 62. The Agency's reasons for the complete response were as follows:

"We cannot approve these applications (b) (4)

[redacted] (b) (4)

Note any future submission for this application will need to address the above concerns."

In July 2018 the Applicant filed a type C meeting request to further discuss the DMPA bone issues. The Agency's general comments from the October 3, 2018 meeting included the following statement:

"We believe that no new conclusions have been elucidated by the re-analyses of previously evaluated studies in your meeting package submission of July 12, 2018. [redacted] (b) (4) It is likely that you will need robust data from new study(ies) to support important changes to the current labeling on the effect of DEPO-PROVERA CI and Depo SubQ Provera 104 on bone safety."

The agency did offer the Applicant two labeling modifications (additions are underlined):

Addition in Section 5:

After discontinuing Depo-Provera CI in adolescents, mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60 months) post-treatment in the subgroup of adolescents who were treated for more than 2 years [see Clinical Studies (14.3)]. Similarly, in adults, there was only partial recovery of mean BMD at the total hip, femoral neck, and lumbar spine towards baseline by 24 months post-treatment [see Clinical Studies (14.2)].

Addition to Section 14

Clinical studies to date, including the retrospective study described below, have not determined whether use of DMPA has an effect on fracture rate later in life.

Current Submission: Complete Response Resubmission for NDA 020246 - S-060 & S-062 Depo-Provera (medroxyprogesterone acetate) Contraceptive Injection

On June 5, 2020, the Applicant submitted a complete response to the Agency regarding the FDA complete response letter from October 6, 2017. In this resubmission, the

Applicant [redacted] (b) (4) that were included in the December 2016 efficacy supplements and were willing to accept the labeling modifications proposed by the Agency in the Type C meeting on October 3, 2018.

Key Labeling Changes for NDA 020246

The key labeling changes for DMPA CI include labeling modification additions previously suggested by the Agency and harmonization of certain sections to correspond with the DMPA SQ label. Specifically:

The two labeling modifications suggested by the Agency in October, 2018 that specified "mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60) months post-treatment in the sub-group of adolescents who were treated for more than 2 years" (Section 5.1) and the statement "Importantly, this study could not determine whether use of Depo-Provera CI has an effect on fracture rate later in life." (Section 14.4)

The other key change throughout the DMPA CI label is the harmonization with the DMPA SQ label in regard to the duration of use.

The present DMPA SQ label states the following in the boxed warning and limitation of use section:

> "Depo-subQ provera 104 is not recommended as a long-term (i.e., longer than 2 years) birth control method or medical therapy for endometriosis-associated pain unless other options are considered inadequate.

To harmonize the labels, the proposed boxed warning and limitation of use for the DMPA CI label now reads:

> Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate.

For DMPA CI, the present label wording of "should not be used" is being replaced by "is not recommended" in regard to the 2-year limitation. A limitation of use section is being added to the DMPA CI label. The DMPA CI box warning and limitation of use sections will only differ from the SQ label in that endometriosis-associated pain is not included as an indication.

Background Information for NDA 021583 - S-033 & S-034 Depo-SubQ Provera 104 (medroxyprogesterone acetate) Injectable Suspension

Hereafter in this review this product will be referred to as DMPA SQ. S-033 is the supplement that includes proposed labeling changes related to DMPA CI's effect on

bone mineral density (BMD) [redacted]. S-034 is the supplement that includes proposed labeling changes related to [redacted].

DMPA SQ is a subcutaneous injectable progestin that was approved in 2004 for female contraception and subsequently approved for management of endometriosis-associated pain in 2005. Dosing by subcutaneous injection in the anterior thigh or abdomen is performed once every 12 to 14 weeks.

The DMPA SQ label at the time of its approval in 2004 incorporated the same box warning regarding bone loss as the DMPA CI label. The Applicant has [redacted] The boxed warning recommendation against long-term use exceeding 2 years for DMPA SQ was altered with the PLR conversion to include its other indication (endometriosis-associated pain) in 2019.

The background regulatory history for DMPA SQ is essentially the same as for DMPA CI (see above) beginning with the December 2016 efficacy supplements and continuing through the current resubmission of June 5, 2020 (see above).

Current Submissions: Complete Response Resubmissions for NDA 021583 - S-033 & S-034 Depo-SubQ Provera 104 (medroxyprogesterone acetate) Injectable Suspension

On June 5, 2020, the Applicant submitted a complete response to the Agency regarding the FDA complete response letter from October 6, 2017 for NDA 021583. In this resubmission, the Applicant [redacted] that were included in the December 2016 efficacy supplement and were willing to accept the labeling modifications proposed by the Agency in the Type C meeting on October 3, 2018.

Key Labeling Changes for NDA 021583

The key labeling changes (underlined) for DMPA SQ include the following:

The two labeling modifications suggested by the Agency in October, 2018 that specified "mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60) months post-treatment in the sub-group of adolescents who were treated for more than 2 years" (Section 5.1) and the statement "Importantly, this study could not determine whether use of Depo-Provera CI has an effect on fracture rate later in life." (Section 14.4)

Conclusions and Recommendations

This resubmission to address the Agency's complete response letter (October 6, 2017) contains no new data and no issues for other disciplines aside from clinical. The Applicant has accepted the proposed labeling modifications proposed by the Agency at the Type C meeting on October 3, 2018 and (b) (4) in the efficacy supplements from December 2016. Agreed-to labeling with the Applicant was reached on December 3, 2020. I recommend approval of these efficacy supplements.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GERALD D WILLETT
12/03/2020 09:40:17 AM

CHRISTINE P NGUYEN
12/03/2020 09:46:17 AM

Cross-Discipline Team Leader Review

Date	October 4, 2017
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	20-246; SE-8 (Supplements # 060 and 062) 21-583; SE-8 (Supplements # 033 and 034)
Applicant	Pfizer, Inc.
Date of Submission	December 9, 2016
PDUFA Goal Date	October 9, 2017
Proprietary Name / Established (USAN) names	20-246: Depo-Provera Contraceptive Injection; 21-583: depo-subQ provera 104 Medroxyprogesterone acetate
Dosage forms / Strength	20-246: 150 mg every three months by deep intramuscular (IM) injection 21-583: 104 mg every three months by subcutaneous (SQ) injection
Proposed Indication(s)	Prevention of pregnancy (both NDAs) Management of endometriosis-associated pain (21-583)
Recommended:	***Complete Response***

1. Introduction

The Applicant submitted four supplements seeking to revise the labeling regarding (b) (4) bone mineral density (BMD) (S-060 for NDA 20-2426 and S-033 for NDA 21-583) (b) (4) fracture risk (S-062 for NDA 20-2426 and S-034 for NDA 21-583). The specific labeling changes proposed are detailed in Section 12.

The Division has reviewed data on (b) (4) BMD and fracture risk over the past decade, in the context of several supplements as well as a Citizens Petition (see Section 2.2). Much of the information submitted by the Applicant in the current four supplements is material that has been reviewed previously by FDA. The Applicant resubmitted the final study reports for Studies 234 (adults) and 261 (adolescents), along with some new analyses of the General Practice Research Database (GPRD) study of fracture risk in DMPA users that had been requested by the Division following its review of a prior supplement (S-035 for NDA 20-246). The Applicant also submitted a number of publications, some dating back as far as 1929; many of these have been reviewed previously by FDA.

Although the BMD and fracture data to date are based on the DMPA product administered intramuscularly (DMPA-IM, NDA 20-246), the Division has considered the data generalizable to the subcutaneous product as well (depo-subQ provera 104, NDA 21-583), and consistent labeling has been provided for the two products.

2. Background

2.1 DESCRIPTION OF PRODUCT

DMPA-IM contains medroxyprogesterone acetate (MPA), a derivative of progesterone, as its active pharmaceutical ingredient. DMPA-IM was first approved in 1959 for the indication of adjunctive therapy and palliative treatment of inoperable, recurrent and metastatic endometrial carcinoma or renal carcinoma, and was subsequently approved in 1992 for prevention of pregnancy in women. DMPA-IM works by inhibiting gonadotropin secretion, and preventing follicular maturation and ovulation, as well as causing thinning of the endometrium. It is administered as a 150 mg injection given once every three months. MPA has also been marketed for many years in an oral tablet formulation.

A lower dose injectable product containing MPA was approved for contraception in 2004 under NDA 21-583. This product, depo-subQ provera 104, which contains 104 mg of MPA and is injected subcutaneously once every three months, was also approved for treatment of endometriosis in 2005, under NDA 21-584 (this NDA has been subsumed under 21-583).

2.2 REGULATORY HISTORY

When DMPA-IM (NDA 20-246) was approved for contraception in 1992, the primary reviewer recommended that a phase 4 study be conducted to evaluate BMD loss during the first five years of DMPA-IM treatment and reversal of BMD loss after discontinuation of treatment. The Applicant's (then the Upjohn Company) commitment to conduct such a study was acknowledged in the approval letter dated October 29, 1992. It appears that the commitment referred to a study being conducted in adults, as Study 234.

NDA 21-583 for depo-subQ provera 104, submitted in June 2003, included an overview of an adolescent study conducted with DMPA-IM (Study 261), which had begun enrollment in 1998 and completed enrollment in 1999. Completion of the last subject was expected in October 2004. The NDA submission also reported on the postmarketing commitment, Study 234. The final study report for Study 234 was submitted during the review cycle, and informed the labeling developed for depo-subQ provera 104 with respect to BMD effects of treatment with DMPA.

The BMD data were also reviewed by a reviewer from the Division of Metabolic and Endocrine Products (DMEP) and by an academic expert, who reached quite different conclusions. Recommendations by the DMEP reviewer were:

- Limiting use of DMPA-IM to a specific duration is not warranted because the individual risk/benefit profile varies too much
- Periodic monitoring of BMD in adolescent users is not recommended due to the complexities of measuring and interpreting BMD results in premenopausal women
- There is no meaningful threshold level of BMD to guide treatment discontinuation
- While DMPA-IM should not be explicitly labeled as a second line contraceptive, labeling should recommend that prescribers consider other forms of birth control in selected patients.

Recommendations by the academic expert included:

- Treatment should be limited to 12-18 months for adolescents and two years for adults
- BMD should be monitored at baseline and annually
- DMPA-IM should be discontinued if BMD fell by 5% from baseline at any time point
- DMPA-IM should be labeled as a second-line contraceptive agent

Negotiations regarding BMD labeling for DMPA-IM were conducted in the context of reviewing and preparing labeling for the new NDA 21-583. In November 2004, revised labeling for DMPA-IM was approved, and a Dear Healthcare Provider letter was published by the Applicant (now Pfizer), to inform about updated safety information based on postmarketing studies in adults and adolescents regarding the effect of DMPA-IM on BMD. At this time, a Boxed Warning was added to labeling indicating that:

- BMD loss may occur with DMPA-IM use, it is greater with increasing duration of use and may not be fully reversible
- It is unknown whether DMPA-IM use during adolescence will reduce peak bone mass and increase the risk of later osteoporotic fractures
- DMPA-IM should be used long-term (more than two years) only if other birth control methods are inadequate

Similarly, the British National Formulary issued an advisory in 2007 about BMD reduction and rare case reports of osteoporosis and osteoporotic fractures in DMPA users indicating that:

- BMD reduction may be related to duration of use
- Use by adolescents may reduce peak bone mass; other methods should be considered and deemed unsuitable before prescribing DMPA
- Periodic reassessment should be made of contraceptive needs for women of all ages after using DMPA for more than two years

Following completion of Study 261, the Applicant submitted an efficacy supplement (S-036) in December 2009 that addressed the risk and reversal of decreased BMD in adolescent users vs. nonusers of DMPA-IM. The supplement was approved in October 2010, with labeling that differed from that originally proposed by the Applicant. Specifically, the Clinical Studies Section 14.3 was modified to state that, in adolescents, use of DMPA-IM was associated with a significant decline from baseline in BMD, whereas BMD typically increases during adolescence. The section also stated that teenagers who used DMPA-IM for more than two years did not recover to baseline BMD at the femoral neck or total hip, even up to 60 months post-treatment. The Warnings and Precautions and Boxed Warning sections were also slightly modified to reflect the findings of this study. This supplement also provided for conversion of the DMPA-IM labeling to PLR format.

In March, 2009, the Applicant submitted an efficacy supplement (S-035) that addressed the risk of fracture associated with use of DMPA-IM. This supplement was based on an epidemiologic study conducted in the UK's General Practice Research Database (GPRD) of fracture in DMPA users vs. non-users. The supplement was approved on July 28, 2011, with labeling that differed from that originally proposed by the Applicant. Specifically, FDA

deleted the Applicant's proposed [redacted] (b) (4) noted the uncertainty about causality of the higher IRR for fracture observed for DMPA users compared to non-users, discussed the limitation of data based on cumulative (intermittent) exposure to DMPA rather than based on continuous exposure, and noted the inability of the GPRD study to address the question of whether DMPA use affects fracture risk later in life.

On March 28, 2013, two academic physicians submitted a Citizen Petition requesting that FDA remove the Boxed Warning for DMPA regarding loss of BMD and "limiting use of the drug to two years." The Petitioners claimed that BMD is an invalid surrogate endpoint known not to predict bone fracture, that the "severe restrictions are medically inappropriate," and that the Boxed Warning has harmed public health. They further stated that full recovery of BMD has been demonstrated within 1-4 years of DMPA discontinuation in adolescents, and within 3 years in adult women. The Petition was denied on July 7, 2015, with FDA addressing the Petitioners' points as follows:

- The Boxed Warning was based on adolescent and adult data (from Studies 261 and 234, respectively) submitted by the Applicant and independently analyzed by FDA. FDA concluded that the data from both studies showed BMD decreases in DMPA users, that the decline in BMD increased with longer duration of use, and that full recovery of BMD in adolescents who used DMPA for more than two years was not seen, even when follow-up extended for two to five years after discontinuation. Similarly, adult users did not have BMD values restored to baseline during two-year follow-up after discontinuation. In contrast, non-users in both the adult and adolescent studies showed small but steady increases from baseline in BMD in the study period. Regarding the Harel et al. publication[1] of the adolescent study (Study 261) cited by the Petitioners, FDA noted that the authors did not stratify by duration of use, as FDA had, and therefore, reached different conclusions.
- The Petitioners claimed that two case control studies[2, 3] of fracture risk in DMPA users had odds ratios of 1.5, a magnitude that they claimed is more likely to represent bias than association. FDA responded that results from these studies should not be summarily dismissed solely on the basis of the relatively small odds ratios, noting that the totality of the evidence (including three other epidemiologic studies[4, 5, 6] FDA reviewed) suggested an elevated risk of fracture associated with DMPA use.

[1] Harel Z et al. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010; 81: 281-91

[2] Vestergaard P et al. The effects of depot medroxyprogesterone acetate and intrauterine device use on fracture risk in Danish women. Contraception 2008; 78: 459-464.

[3] Meier C et al. Use of depot medroxyprogesterone acetate and fracture risk. J Clin Endocrinol Metab 2010; 95: 4909-4916.

[4] 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: 346-352.

- FDA noted that because DMPA has not been marketed long enough for a large number of users to have completed menopause, the time when osteoporotic fractures most often occur, there are insufficient direct data on the potential association DMPA use with subsequent osteoporotic fractures. Therefore, it is appropriate for the risk analysis to rely upon the known links between DMPA use and BMD decline, and between BMD decline and risk of osteoporotic fractures.
- The Petitioners had claimed that BMD decreases associated with DMPA use were analogous to those seen in breastfeeding women, which are not known to increase the risk of subsequent osteoporotic fractures. FDA noted the differences in these two conditions, including that the mechanism of BMD loss during lactation is different from that associated with DMPA use, and that the BMD decrease observed during lactation is transient and recovers rapidly, in distinction to that seen with DMPA use.

The current submissions were initially submitted to both NDAs as prior approval labeling supplements on October 6, 2016, but following review of the proposed labeling revisions and consultation with the User Fee Office, they were reclassified as SE-8 efficacy supplements requiring payment of a user fee. The Applicant was informed that the submissions were not accepted for filing due to non-payment of user fees on November 7, 2016. The user fee was paid and the applications were submitted as efficacy supplements on December 9, 2016.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Catherine Sewell, stated in her review, dated October 2, 2017:

I recommend a Complete Response for these efficacy supplements (ES) with no changes to the label.

Team Leader Comment:
I concur with Dr. Sewell's recommendation not to approve these supplements.

3. CMC/Device

No new chemistry, manufacturing and controls data were submitted in this applicant; therefore, there was no need for an OPQ review.

[5] Lappe JM, et al. The impact of lifestyle factors on stress fractures in female Army recruits. Osteoporos Int 2001;12:35-42

[6] Lanza LL et al. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. Obstet Gynecol 2013; 121: 593-600.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in this application. The Pharmacology/Toxicology team had planned to review the portions of the labeling that were revised to address the Pregnancy and Lactation Labeling Rule (PLLR), but this will not be addressed in these supplements due to the planned Complete Response action.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted in this application; therefore, there was no need for a review.

6. Clinical Microbiology

Clinical microbiology consultation was not requested for this application, as no changes were made to the approved formulation of the product.

7. Clinical/Statistical - Efficacy

No clinical efficacy data were submitted in this NDA. The efficacy data described in labeling are based on five clinical studies previously submitted to support the contraceptive indication, and two to support the endometriosis indication for NDA 21-583.

8. Safety

This review pertains to four SE8 supplements submitted by the Applicant, (b) (4) Each of the two NDAs contains two submissions, one relating to BMD (S-060 for NDA 20-246 and S-033 for NDA 21-583) and one relating to fracture risk (S-062 for NDA 20-246 and S-034 for NDA 21-583). The contents of the BMD and fracture submissions, respectively, are identical across each NDA. While the original submissions provided a single clinical overview to address both topics, the Division requested the Applicant to distinguish the information intended support changes in BMD labeling from that intended to support changes relating to fracture risk, and to provide separate labeling revisions pertaining to each topic. The clarifying information was submitted on January 18, 2017, and the four distinct labels were submitted on January 31, 2017. Details of these submissions, and the extent to which the material included has been reviewed previously, are discussed in the following sections. A number of the studies and publications discussed in the current submissions have been previously submitted and reviewed. For ease of review, here is a listing of the study/protocol numbers and the nomenclature used to describe them in previous DBRUP reviews:

- M540010234 – **Study 234** (BMD study in adult women)
- A6791022 – **Study 261** (BMD study in adolescents)
- A6791032 – "**GPRD study**" (epidemiologic study of fracture risk in DMPA users)

8.1 Information Addressing Labeling regarding BMD Changes

S-060 and S-033 included the following supportive information:

- Final Study Report (FSR) for Study 261(adolescents), dated September 16, 2008 – this FSR was originally submitted to FDA on September 17, 2008, and was referenced in the S-036 submission (NDA 20-246) of December 17, 2009. The Division reviewed this FSR and its interpretation of the results informed the labeling approved on October 15, 2010. Interim data from this study had also been considered during the review of NDA 21-583 in 2004.
- FSR for Study 234 (adults), dated February 18, 2004 – this FSR was originally submitted to FDA in 2004, and was referenced in the S-036 submission (NDA 20-246) of December 17, 2009. The Division reviewed this FSR and its interpretation of the results informed the labeling approved on October 15, 2004.
- Relevant literature references:
    - Riggs et al. 1998[7] – this study has not been reviewed previously
    - Bauer et al. 1929[8] – this study has not been reviewed previously
    - Karlsson et al. 2001[9] – this study was cited in the FDA response to the Citizen Petition
    - Harel et al. 2010[1] – this is the publication resulting from Study 261, and presents the interpretation upon which the Applicant relies; it was discussed in the Division's response to the Citizen Petition
    - Hui et al. 1988[10] – this study was cited by the Division during review of S-035 (NDA 20-246)
    - Orr-Walker et al. 1998[11] – this study was discussed in the Division's response to the Citizen Petition
    - Johnson et al. 2008[12] – this study has not been reviewed previously, but is a publication describing the methodology of Study 261

8.2 Information Addressing Labeling regarding Fracture risk

S-062 and S-034 included the following supportive information:

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[7] Riggs BL et al. A unitary model for involutional osteoporosis: Estrogen deficiency causes both Type I and Type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res 1998; 13: 763-73

[8] Bauer W et al. Studies of calcium and phosphorous metabolism. J Experimental Med. 1929; 49: 145-61

[9] Karlsson C et al. Pregnancy and lactation confer reversible bone loss in humans. Osteoporosis Int. 2001; 12: 828-34

[10] Hui SL et al. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988; 81: 1804-9

[11] Orr-Walker BJ et al. The effect of past use of injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal post-menopausal women. Clinical Endocrinology 1998; 49: 615-8

[12] Johnson CC et al. Longitudinal study of e depot medroxyprogesterone acetate (Depo-Provera) effects on bone health in adolescents: Study design, population characteristics, and baseline bone mineral density. Contraception 2008; 77: 239-48

- Integrated Summary Report for the GPRD study, dated June 19, 2008 – the original FSR for this study was submitted to FDA on July 21, 2008; additional analyses were included in the submission dated September 28, 2010, and reviewed under S-035 (NDA 20-246). The Division's interpretation of the results from both the original and supplemental analyses informed the labeling approved on July 28, 2011.
- Literature references:
  - GPRD (b) (4) Final Report, 2007
  - GPRD (b) (4) Additional Tables, 2009
  - GPRD (b) (4) Additional Analyses, 2012 – this represents the additional analyses the Division had requested during the review of S-035, and has not been reviewed previously
  - Lanza et al. 2013a[6] – this study is the publication of the GPRD study, and was discussed in the Division's response to the Citizen Petition
  - Lanza et al. 2013b[13] – this reference is a response to a comment on the preceding article
  - Stone et al. 2003[14] – this study has not been reviewed previously
  - Vestergaard et al. 2008[2] – this study was reviewed by DBRUP and DEPI for S-036 and discussed in the Division's response to the Citizen Petition
  - Kanis et al. 2008[15] – this study has not been reviewed previously
  - Hui et al. 1988[10] – also included in S-060/033; this study was briefly mentioned in the review of S-035, because it demonstrated that at the same BMD, the fracture risk is higher in older vs. younger women
  - Kanis et al. 2002[16] – this study has not been reviewed previously
  - Meier et al. 2010[3] – this study was this study was reviewed by DBRUP and DEPI for S-036 and discussed in the Division's response to the Citizen Petition

8.2.1 Applicant's Rationale for Labeling Revisions

The Applicant's original submission dated October 6, 2016, to cover all four supplements, made the following arguments to support its proposed revision to labeling.

- (b) (4)

[13] Lanza 2013 et al. Comment on journal review "Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture." J Fam Plann Reprod Health Care 2013; 39: 306, doi: 10.1136/jfprhc-**2013**-100759

[14] Stone KL et al. BMD at multiple sites and risk of fractures of multiple types: Long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res 2003; 18: 1947-54

[15] Kanis JA et al. Case finding for the management of osteoporosis with FRAX – assessment and intervention thresholds for the UK. Osteopor Int 2008; 19: 1395-1408

[16] Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002; 359: 1929-35

(b) (4)

- [redacted]

Detailed reviews of the Applicant's submissions are described in the primary medical review by Dr. Sewell, the consultative review by Dr. Jaffe (see Section 8.5) and the DEPI review by Dr. Liu (see Section 8.3). My conclusions regarding the Applicant's arguments are provided in Section 8.10.

8.3 Statistical Reviewer's Conclusion:

There were no clinical efficacy data to review, and no statistical review was requested; however, the DEPI review includes input from the Division of Biometrics 7 on the design of the GPRD study.

8.4 OSE Consultation and Recommendation

As noted, during the review of S-035, the Division of Epidemiology (DEPI), OSE, reviewed the original submission of the GPRD results – both the original analysis and the Applicant's modified analysis – and conducted a review of the literature. DEPI's conclusion in its review dated March 4, 2011 was:

> *Although the literature on fracture and DMPA use is limited in quantity, and each study has its own limitations, the results and trends observed are in favor of an association between DMPA-use and fractures, particularly regarding long-term use. One similarity across studies that looked at type of fracture is that, contrary to what was expected, an association was observed between DMPA use and fractures not typically associated with osteoporosis. One hypothesis is that patient age and other unmeasured factors may play a role in the type of fracture experienced if DMPA users are younger than the population at high-risk for osteoporosis. In addition, there are limitations to conducting a post-hoc analysis and deriving conclusions from such an analysis without first confirming them with a more specific study designed to test the hypothesis.*

In light of existing evidence, the labeling change, as proposed, is inappropriate (b) (4) [redacted]

Current labeling language refers only to uncertainty about osteoporotic fractures. (b) (4) [redacted]

For the current efficacy supplements, DBRUP again consulted DEPI, for review of the supplemental GPRD analyses and new literature submitted by the Applicant, and for an updated literature review. DEPI found that in the Applicant's supplementary analysis of the sub-cohort of women with 6-24 months of pre-index history, the fracture risk remained higher in DMPA users than non-users, and appeared to increase slightly by duration of use (dichotomized as ≤ vs. > 1 or 2 years of use).

In the published literature, six studies[17, 18, 19, 20, 21] (including the publication relating to the GPRD study 6) that were published subsequent to the last FDA reviews on DMPA and BMD were considered, along with two new studies identified by DEPI.[22, 23] While acknowledging major limitations of these studies, DEPI determined that the studies were consistent in showing an increased risk of fracture associated with DMPA use.

Wei Liu, Ph.D., M.Sc., the DEPI reviewer, noted that in the new analyses of the GPRD study, the authors evaluated women who had 6-24 months of baseline data in the GPRD database prior to the index date (compared to the sub-cohort with 6 months of pre-index data in the original analysis). While the Division had hoped that this look-back might clarify the extent to which DMPA users and non-users might have had pre-index exposure to DMPA, which could

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[17] Lopez LM, Chen M, Mullins Long S, et al. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Sys Rev 2015; 21(7)

[18] Modesto W, Bahamondes MV, Bahamondes L. Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate. J Women's Health (Larchmt). 2015 Aug;24(8):636-40

[19] Viola AS, Castro S, Bahamondes MV, et al. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011 Nov;84(5):e31-7

[20] Viola AS, Castro S, Marchi NM, et al. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. Contraception. 2011 Aug;84(2):122-7

[21] Pongsatha S, Ekmahachai M, Chaovisitsaree S, et al. Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: a cross sectional study. J Med Assoc Thai. 2009 Oct;92(10):1263-7

[22] Kyvernitakis I, et al. The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK. Osteoporos Int 2017; 28: 291-297

[23] Nieves JW, et al. Eating disorders, menstrual dysfunction, weight change and DMPA use predict bone density change in college-aged women. Bone, 2016. 84: p. 113-9

confound the post-treatment results, the authors used this additional look-back solely to identify additional pre-treatment fractures that occurred prior to the index date in both user groups. Post-treatment fracture risk remained higher for DMPA users than non-users in this new analysis, and there was a small increase in risk by duration of use:

- Non-users: IRR = 1.0 (reference)
- Use ≤ 1 year: IRR 1.35 (95% Confidence interval 1.26, 1.44)
- Use > 1 and ≤ 2 years: IRR 1.28 (1.12, 1.45)
- Use > 2 years: IRR 1.54 (1.36, 1.74)

For exposure defined as the cumulative number of DMPA injections, there was a consistent higher fracture risk in DMPA users vs. non-users, but not a clear dose-response relationship.

The epidemiologic studies reviewed by Dr. Liu included a Cochrane systematic review[17] of four studies previously reviewed by FDA (Kaunitz,[24] Vestergaard,[2] Meier,[3] and Lanza[6]); all but the Kaunitz study (which reported on Study 234) showed a statistically significantly increased risk of fracture for DMPA users. The Kyvernitakis case-control study[22] of reproductive-aged women and fracture risk reported nominally increased adjusted odds ratios for women with either current or past use of 9 months or more of DMPA use compared to non-users, although the confidence intervals included 1 for several of the subsets of duration of use that were evaluated. Highest fracture risk subgroups were women < 30 years of age with ≥ 10 prescriptions (i.e., 2.5 years of use) [odds ratio 3.04 (95% CI 1.36, 6.81)] and women in the late reproductive years with past use of DMPA [odds ratio 1.72 (95% CI 1.13, 2.63)].

The other five studies not previously reviewed addressed the association between DMPA use and BMD. One study in postmenopausal women[20] looking at prior long-term DMPA use vs. non-use found no significant difference in forearm BMD. The remaining studies,[18, 19, 21, 23] using cross-sectional or prospective assessments in reproductive-aged women, found lower BMD in DMPA users.

Dr. Liu concluded the following in his review dated June 30, 2017:

> *In conclusion, the recent epidemiology studies, as well as the 2016 supplementary analyses of the GPRD data, did not provide any new safety information beyond what was known on the association between DMPA use and fracture risk at the time of labeling changes in 2011. Although the epidemiology studies published to date unavoidably have various limitations such as residual confounding, potential misclassification of exposure and outcome, small number of outcome events (e.g., osteoporotic fractures) and inappropriate use of the self-controlled cohort method, the relative consistency of the findings suggest that there is likely an association between DMPA use and fracture risk. Our view remains unchanged; the GPRD study and the published literature suggest a small increased risk for fracture with DMPA use. DEPI disagrees with the sponsor's proposed labeling update* (b) (4) *as we deem the current labeling language appropriate based on the currently available observational data. We do not recommend any additional regulatory action at this point.*

[24] Kaunitz AM et al. Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: Recovery following discontinuation. Contraception 2006; 74: 90-9

8.5 DBRUP Bone Team Consultation and Recommendation

The review team sought input from the DBRUP Bone Team to address some of the Applicant's arguments and rationale for the proposed labeling revisions. The Bone Team was asked to comment on the following four areas; a summary of Dr. Jaffe's comments from her review dated August 30, 2017is included below each topic:

- (b) (4)

  Response: (b) (4)

  Dr. Jaffe also noted that most fractures occur in women with BMD in the osteopenic range, (b) (4) the BMD impact of DMPA appears to persist for years in women who use it for more than two years.

- Discuss "fragility" vs. "traumatic" fractures and the appropriateness of considering non-fragility (non-osteoporotic) fractures in premenopausal DMPA users

  Response: *A fragility fracture is defined as a fracture that results from a fall from a standing height or less. The locations of typical fragility fractures include those of the spine, hip, femur, ankle, pelvis, ribs, humerus, and forearm. Fractures of the skull, nose, face, hands, feet, patella, clavicle and sternum are generally not considered "fragility" or osteoporotic fractures.*

  Once women with a history of DMPA use become postmenopausal, epidemiology studies in this population may help discern the impact of DMPA use in adolescents and young adulthood on fragility fracture risk later in life. Fractures in adolescents are typically related to trauma. Carefully designed epidemiology studies in premenopausal DMPA users might help clarify if there is an increased risk of fractures other than osteoporotic fractures with DMPA use such as stress fractures or traumatic fractures.

  Dr. Jaffe further noted that another Lappe et al. paper[25] suggested that DMPA may increase the risk for stress fractures, which would also not be considered fragility fractures. In addition, while the GPRD study showed an increase in appendicular

[25] Lappe J, Davies K, Recker R, et al. Quantitative ultrasound: use in screening for susceptibility to stress fractures in female army recruits. J Bone Miner Res 2005;20:571–8.

fractures among DMPA users (IRR =1.38, 95% CI 1.30-1.46), some of the sites included in this category would be typical sites of osteoporotic fractures.

- Address the utility of BMD as a surrogate for bone strength and osteoporosis

  Response: *DXA remains the gold standard clinical tool for assessing BMD. Furthermore, BMD in adolescence and premenopausal women has been demonstrated to correlate with fracture risk.*

  Dr. Jaffe cited the publication by Wasserman et al.[26] in stating that BMD in premenopausal women, including adolescents, "is standard of care to assess skeletal health and changes in areal bone mineral content and density over time, as well as to gain insight into fracture risk. Further, BMD assessed by DXA has been used to assess bone loss and/or fracture risk in children and adolescents with various co-morbidities that increase risk (e.g., anorexia, glucocorticoid use). She cited other studies that indicate a relationship between BMD and fractures in young women.

  Dr. Jaffe noted that early adolescence is a period of concern for increased fracture risk due to a temporary increase in bone fragility because linear bone growth may outpace bone mineralization. She expressed concern that DMPA, which may add to demineralization, may compound this risk in young women.

  Dr. Jaffe discussed the fact that BMD is only one determinant of fracture risk, and that other properties of bone that are relevant are not assessed by BMD. While there are other evaluation methods that may be better able to assess these properties, they are "not practical for use in clinical practice or large studies."

- Comment on the Applicant's claim that DMPA users in Study 261 were more "skeletally mature" than non-users, [redacted] (b) (4)

  Response: *While bone mass accrual is accelerated during the adolescent growth spurt, bone mass accrual continues into the 3rd decade.* [redacted] (b) (4)

  Dr. Jaffe agreed that the user and non-user groups in Study 261 differed in characteristics that could affect BMD, but disagreed with the Applicant's assertion [redacted] (b) (4) In addition, "Data are currently not available to address whether bone loss during adolescence or failure to reach peak bone density in adolescents treated with DMPA impacts osteoporotic fracture risk during adulthood or after menopause."

[26] Wasserman H, O'Donnell JM, Gordon CM. Use of dual energy X-ray absorptiometry in pediatric patients. Bone. 2016 Dec 15. pii: S8756-3282(16)30370-2. doi: 10.1016/j.bone.2016.12.008. [Epub ahead of print]).

8.6 Deaths and Serious Adverse Events

Deaths and serious adverse events were not specifically evaluated in the information submitted by the Applicant.

8.7 Other Adverse Events

The information submitted by the Applicant did not evaluate adverse events other than fractures.

8.8 Postmarketing Safety Findings

A consult was done during the review of S-036 by the Division of Pharmacovigilance 2 (DPV2) to evaluate cases in the Adverse Events Reporting System (AERS) relating to osteoporosis, osteopenia, decreased BMD or bone loss in adolescent females, that were reported in association either with DMPA-IM or depo-subQ provera 104. At that time, only three evaluable cases were identified, so no further AERS search was undertaken in this review cycle.

8.9 Safety Update

The Applicant did not submit a safety update for these efficacy supplements; they are not based on any ongoing clinical trials.

8.10 Overall Assessment of Safety Findings

The Applicant's arguments are repeated below, with comments regarding FDA findings on these points during this, and previous, review cycles.

- (b) (4)

  Dr. Jaffe has explained (b) (4)

- (b) (4)

  Dr. Jaffe stated that there is no evidence substantiating the Applicant's proposition (b) (4) She also noted that most fractures in postmenopausal women occur in women whose BMD is in the range categorized as osteopenia, not osteoporosis, suggesting that such fractures occur even in the absence of marked BMD loss.

- (b) (4)

- (b) (4)

(b) (4)

With regard to these two points, Dr. Jaffe cited recent publications to argue that BMD is, in fact, an accepted measure to assess skeletal health, changes in BMD, and risk of fracture in premenopausal women, including adolescents. She acknowledged that bone characteristics beyond BMD alone have an impact on fracture risk, and that there are other measures that may be more appropriate to evaluate such bone properties, but stated that they are not likely to be utilized in clinical practice or large clinical trials.

Dr. Jaffe further discussed the fact that some of the fracture sites considered in the GPRD study, which showed an elevated IRR for DMPA users, would be typical sites of osteoporotic fracture. In addition, she and Dr. Liu discussed the findings of a number of epidemiologic studies that indicate an increased risk of fracture (including stress fractures) in DMPA users.

- *Study 234 in adults showed* (b) (4) *and findings of Study 261 in adolescents* (b) (4)

No new analyses of these studies were provided. Labeling approved for DMPA-IM when Study 234 (and interim data from Study 261) was first reviewed in 2004 indicated that use of DMPA is associated with "significant loss" of BMD and that "the decrease in BMD appears to be at least partially reversible after Depo-Provera CI is discontinued." Tabular data showed that BMD did not return to baseline levels by two years post-discontinuation in women who had used DMPA for five years. A Boxed Warning was added to state that DMPA should only be used beyond two years if other methods of contraception are inadequate for the patient.

In 2010, when the final study report of Study 261 was reviewed, FDA analyzed the recovery data by duration of use, dichotomized as ≤ 2 years vs. > 2 years. Based on this analysis, labeling was added to indicate that BMD loss in adolescent users of DMPA was persistent even after discontinuation, and that total hip and femoral neck BMD did not return to baseline even by 60 months post-treatment for those who had used DMPA for > 2 years. The Boxed Warning was slightly strengthened to recommend that DMPA should not be used beyond two years unless other methods of contraception are inadequate for the patient.

- *Results of Study 261 shows* (b) (4)

The Division's interpretation of Study 261 has been described in detail previously. FDA's analysis of the recovery data (stratified by duration of DMPA use) differed from that in the study report, and published by Harel et al.[1] However, as Dr. Sewell points out in her review, even the unstratified data reported in Harel et al. show that DMPA users' mean % change from baseline was still negative (i.e., decreased) 180 weeks after stopping DMPA for total hip BMD, and 240 weeks (the longest period of follow-up) for femoral neck BMD.

Regarding the GPRD study, labeling was revised in 2011 based on FDA's review, which concluded that the new data extended the earlier findings that use of DMPA-IM is associated with decreased BMD, to show that the actual risk of fracture is also increased. The revised labeling noted the significantly elevated IRR for any fracture for DMPA users vs. non-users [1.41 (95% CI 1.35, 1.47)], while commenting on the inability of the study to determine whether this increased risk was due to DMPA use or to other factors that might differ between the cohorts evaluated. FDA rejected inclusion in (b) (4)

Further, the epidemiologic literature is fairly consistent in showing a small increased risk in fracture associated with DMPA use. Dr. Liu noted that four studies[2, 3, 6, 22] showed a statistically significantly increased risk of fracture in women with > 2 years of DMPA use. Other studies found increased risk of fracture at certain sites for DMPA users (i.e., two studies[3, 4] showed increased risk of osteoporotic fractures, the GPRD study showed an increased risk of appendicular and miscellaneous fractures but not axial fractures, and one study[5] found an increased risk of stress fractures).

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this SE-8 supplement.

10. Pediatrics

Review by the Pediatric Review Committee (PeRC) was not needed for this efficacy supplement, as no changes in indication or population were proposed.

11. Other Relevant Regulatory Issues

No DSI inspection was requested, as the submissions contained only literature reports and reanalyses of previously submitted study data.

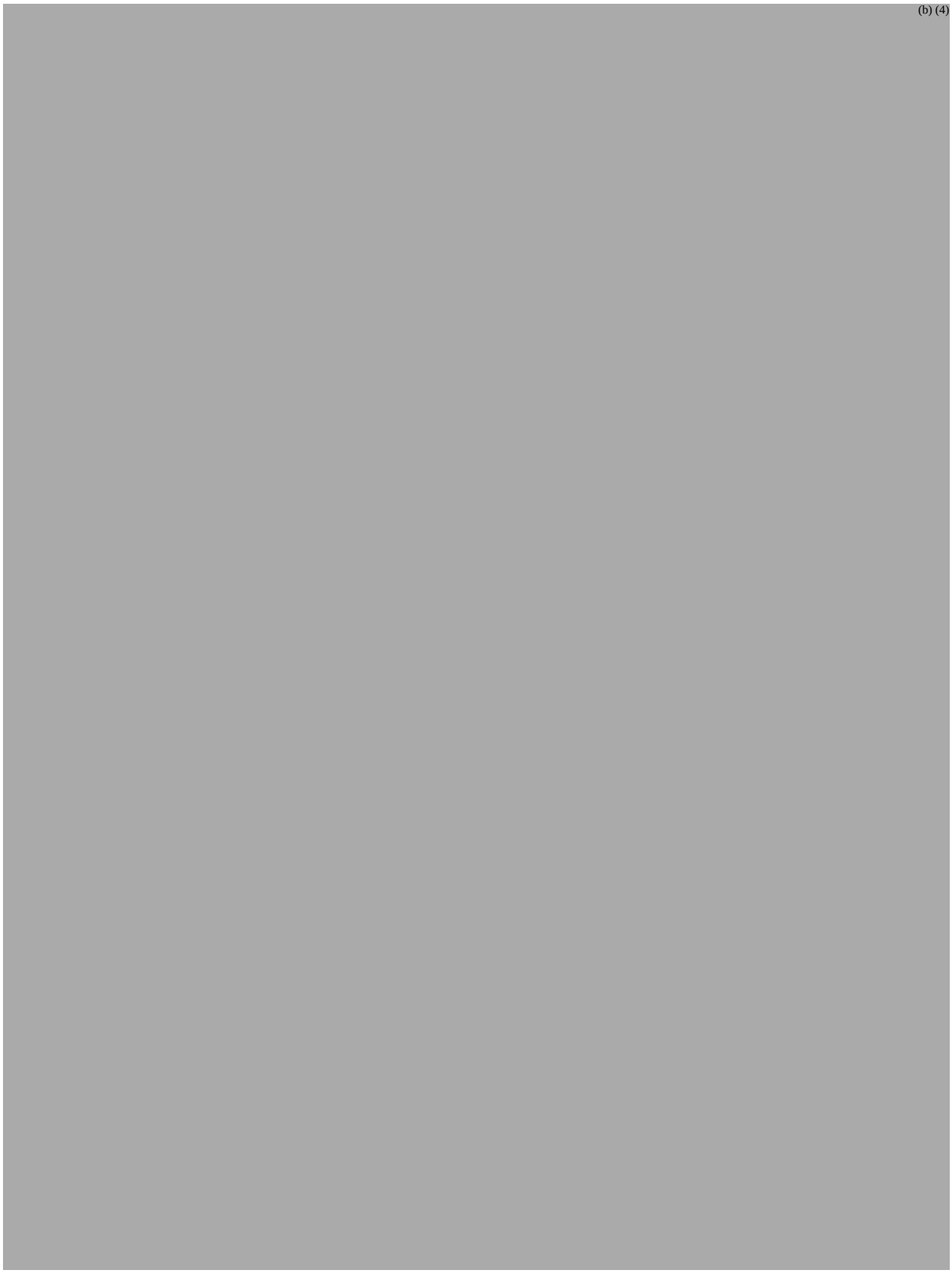
12. Labeling

The DMPA-IM label was submitted in the Physician Labeling Rule (PLR) format. At the time of submission, the depo-subQ provera 104 labeling had a pending labeling supplement for PLR conversion.

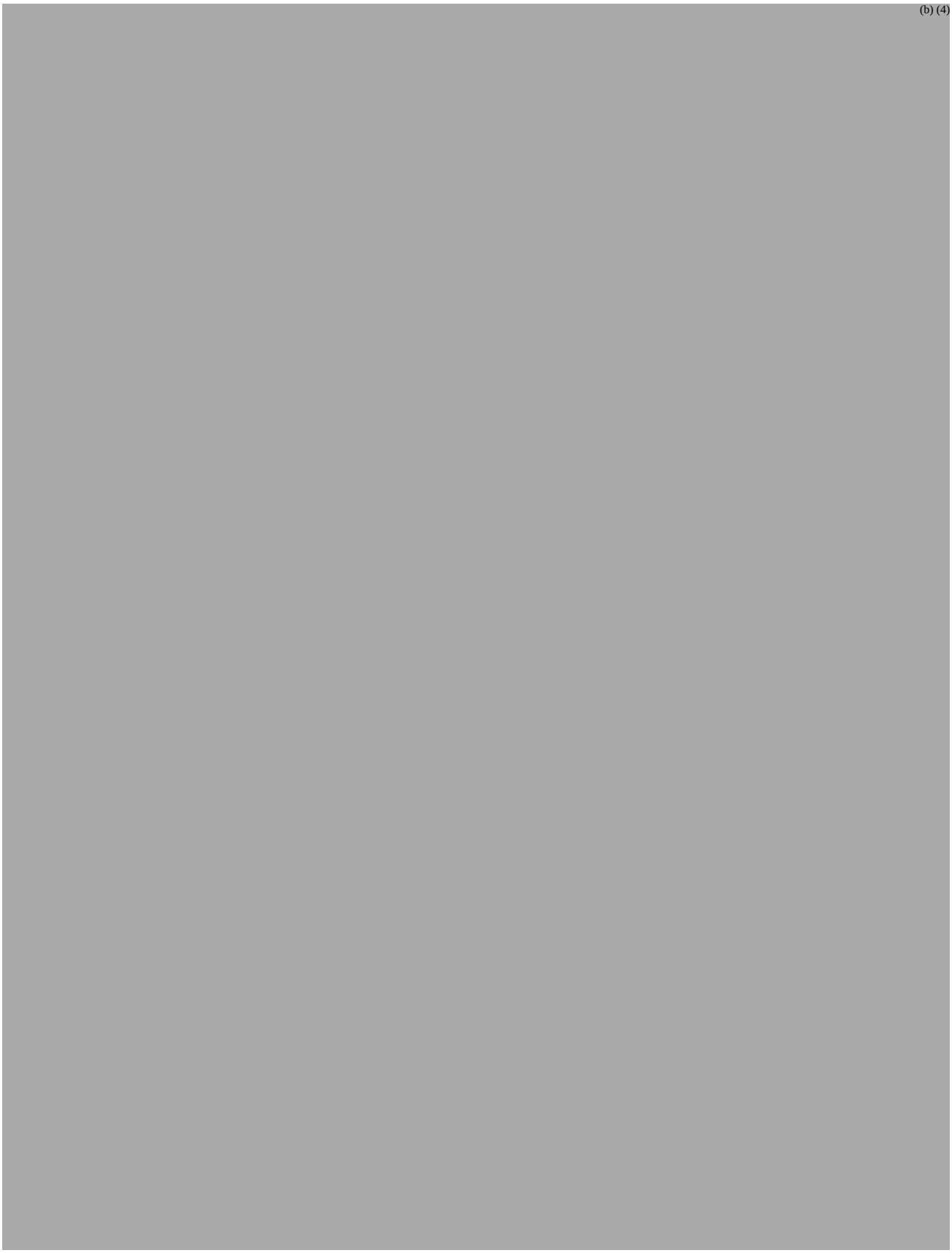
The Applicant sought to make the following revisions to labeling relating to the impact of the drug on BMD (proposed additions are underlined; deletions are struck through; proposed labeling shown here is that for NDA 20-246, which is in PLR):

(b) (4)

(b) (4)



(b) (4)



(b) (4)

Commensurate changes were also proposed for the patient labeling.

During the review cycle, the Applicant was requested to submit revised labeling to address the Pregnancy and Lactation Labeling Rule (PLLR) in Section 8. However, due to the planned Complete Response action on these supplements, revision to incorporate PLLR language will be deferred to a future labeling supplement.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that these efficacy supplements receive Complete Response actions, because the Applicant has not provided new information that warrants revision of the current labeling, which was agreed-upon after thorough review of Studies 234, 261, the GRPD study and epidemiologic studies.

13.2 Risk Benefit Assessment

The risk/benefit profile of DMPA for prevention of pregnancy (and for management of endometriosis-associated pain for NDA 21-583) as described in the currently approved labeling has been determined to be acceptable following thorough review of NDAs 20-246 and 21-583, and continues to be acceptable following extensive postmarketing experience and review of the current submissions.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

No postmarketing studies are recommended.

13.5 Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
10/05/2017

CHRISTINE P NGUYEN
10/05/2017
I concur with Dr. Soule's conclusions and recommendation of a Complete Response.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplements
Application Number(s)	20246, S 060 & S062 21583, S 033 & S 034
Priority or Standard	Standard
Submit Date(s)	October 6, 2016 (without user fee)
Received Date(s)	December 9, 2016
PDUFA Goal Date	October 9, 2017
Division / Office	DBRUP/ODE III/CDER
Reviewer Name(s)	Catherine A. Sewell, MD, MPH
Review Draft Date	August 23, 2017
Review Completion Date	October 2, 2017
Established Name	Medroxyprogesterone Acetate
(Proposed) Trade Name	Depo-Provera Contraceptive Injection (and Depo-SubQ Provera 104)
Therapeutic Class	Progestin: 17-α hydroxyprogesterone analogue
Applicant	Pharmacia and Upjohn (subsidiary of Pfizer, Inc.)
Formulation(s)	Intramuscular injection (and subcutaneous injection)

Dosing Regimen	150 mg every 3 months administered by deep IM injection (and 104 mg every three months administered by SQ injection)
Indication(s)	Prevention of pregnancy NDA 21583: also management of endometriosis-associated pain
Intended Population(s)	Women of reproductive age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a Complete Response for these efficacy supplements (ES) with no changes to the label.

1.2 Risk Benefit Assessment

Depo-Provera 150 mg contraceptive injection (hereafter referred to as DMPA) has been approved since 1992 for the indication of prevention of pregnancy. The current label contains information about bone mineral density (BMD) and osteoporotic fracture risk in adolescent and adult Depo-Provera users during and after DMPA therapy. In this efficacy supplement, the Applicant provided no new data, but provided 1) additional analyses for Study A6791032, conducted using the General Practitioner's Research Database (hereafter referred to GPRD), a retrospective cohort study of 312,295 women, on the incidence of fracture at any site in DMPA users compared to users of other contraceptives, as well as 2) literature discussing the study design of Study A6791022 (hereafter referred to as Study 261) and 3) literature discussing the mechanisms of bone loss and resumption of bone mass. Based on these data, the Applicant proposes to update the label, (b) (4), and change the (b) (4), Warnings and Precautions, (b) (4) and Clinical Studies sections.

A summary of findings is as follows:

- In the original review of the GPRD
  - The crude incidence of any fracture with any use of DMPA was 9.0 per 1,000 person-years, while that of nonusers was 6.4 per 1,000 person-years.
  - The crude IRR for any fracture with any use of DMPA was 1.41 (95% CI: 1.35-1.47).
  - The IRR for any DMPA use compared with no DMPA use, standardized for age, was 1.44 (1.38-1.50).
- In the supplementary analyses in the current submission, evaluating a subcohort of 166,367 women who had 6-24 months of data prior to the index date for initiating DMPA use
  - The fracture risk remains higher in DMPA users compared to nonusers, and the risk appears to increase slightly by duration of use.

    - There may still be residual confounding due to missing data or lack of control for other established risk factors for fracture.

- The literature submitted in support of the proposed labeling changes does not adequately address the issue of unidentified confounders in the GRPD population or in the adolescent population previously evaluated in Study 261. The additional published post hoc analyses of Study 261 confirm that the study groups are different and should not be directly compared; the current label already notes that "the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density." Data continue to demonstrate that after DMPA use > 2 years, subjects did not recover to their baseline BMD level at the femoral neck and total hip even up to 60 months.
- A review of epidemiologic studies showed consistent findings across different study designs and populations, with an increased risk for fractures associated with DMPA use. The relative risk (RR) from these studies ranges from 1.5 to 2.5. Some studies bear some evidence of a dose-response relationship. A statistically significant higher risk of fracture was observed in females with > 2 years of DMPA use compared to use of other contraceptives. (See Section 9.1 of this review.)

Review of these data was performed by the Division of Reproductive and Urologic Products (DBRUP) Reproductive and Bone Teams, and the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI). The additional analyses and publications do not provide support for a change in labeling. The labeling should not be changed (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

DMPA is a medroxyprogesterone acetate injectable suspension approved on October 29, 1992 for the prevention of pregnancy in women of childbearing potential. The approved dose is 150 mg in 1 ml, given intramuscularly every 3 months.

DMPA was first approved for palliative therapy of renal and endometrial cancer in 1960 at a dose of 400-1000 mg each week; it was subsequently approved in a lower dose as a contraceptive 30 years later. The SQ version was approved for female contraception on December 17, 2004 under NDA 21-583, and subsequently approved for the endometriosis indication in 2005. DMPA is a highly effective and reversible method of contraception that works primarily by inhibiting the secretion of pituitary gonadotropins with subsequent anovulation, amenorrhea, and decreased serum estradiol. It has been widely used among U.S. adolescents because it is not tied to specific sexual activity or partner compliance and does not require daily dosing. The main safety issues of DMPA include loss of BMD and weight gain in long-term users.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple progestin-only products available for contraception, including pills, implants and intrauterine systems (IUSs), as well as combination estrogen/progestin products (such as pills, a skin patch, and a vaginal ring).

Table 1 Currently Available Treatments for the Proposed Indication

Progesterone-Containing Contraceptives
Progesterone-only methods
Oral tablet
Levonorgestrel IUSs (Mirena, Skyla, Liletta, Kyleena)
Dermal implant (Nexplanon)
Progesterone-estrogen combinations
Oral tablet
Transdermal contraceptive delivery system [Ortho Evra (discontinued), Xulane]
Vaginal ring

Progestin-only methods of contraception are favored by healthcare providers for women who have contraindications to estrogen use; however, these products can be associated with more frequent irregular bleeding than the combination estrogen/progestin products. DMPA is unique among progestin-only methods because the dose of progestin is high enough to consistently suppress ovulation. This can result in a slower return to fertility after DMPA than for any other reversible method.

2.3 Availability of Proposed Active Ingredient in the United States

Medroxyprogesterone acetate (MPA), the active ingredient of DMPA, is available in multiple dosage forms for several indications in the U.S.:

1. Depo Provera contraceptive injection: 150 mg IM every 3 months for prevention of pregnancy
2. Depo-subQ-Provera 104: 104 mg/0.65 mL every three months for prevention of pregnancy and management of endometriosis-associated pain
3. Depo Provera sterile aqueous suspension: 100 and 400 mg/ml IM each week for adjunctive therapy and palliative treatment of inoperable recurrent and metastatic endometrial or renal carcinoma
4. Provera tablets: 2.5, 5 and 10 mg p.o. for secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology such as fibroids or uterine cancer; and to reduce the incidence of endometrial hyperplasia in non-hysterectomized postmenopausal women receiving 0.625 mg of conjugated estrogen

2.4 Important Safety Issues With Consideration to Related Drugs

Depo-Provera injectable contraceptive is marketed in two formulations: at 150 mg/ml to be given intramuscularly, and at 104 mg/0.6 ml to be given subcutaneously. An extensive safety database is available for DMPA, which has been marketed in the U.S. since 1992 for contraception. The major safety issue observed for this product is loss of BMD, which increases with duration of use and appears not to be fully reversible with cessation of treatment. Additional concerns include weight gain of about 5 pounds in the first year of use and increased weight gain with continued administration. Irregular vaginal bleeding is noted in “most” users of the intramuscular formulation, according to the DMPA CI label. Return to fertility is delayed with both injectable formulations, beyond the time seen with other reversible contraceptive methods. The median time to conception is 10 months following the last DMPA CI injection, with a range of 4 to 31 months.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In late 2004, a Boxed Warning, as well as text in the Indications and Usage and Warnings and Precautions sections, was added concerning loss of BMD.

In December 2009, following the completion of Study 261, the Applicant submitted an efficacy supplement that addressed the risk and reversal of decreased BMD in adolescent users vs. nonusers of DMPA-CI. The supplement was approved in October 2010, with labeling changes differing from the Applicant’s proposed label.

Subsequently, In September 2010, the Applicant submitted the integrated summary report of the GPRD fracture study as an efficacy supplement (S-035) and the label was amended in July 2011 to include information from this study. Subsequent to that submission, the FDA requested that the Applicant conduct additional analyses including a more detailed examination of the possible association between the extent of DMPA exposure and fracture incidence, where exposure would be defined in several different ways (e.g., with a look-back period of 6-24 months prior to DMPA use) and an examination of fracture rates before and after DMPA treatment in the sub-cohort of women with 6-24 months of pre-index history before any contraceptive use. The Applicant conducted these analyses in 2012. In December 2016, the Applicant submitted this efficacy supplement, including the additional analyses of the GPRD and literature to support requested labeling changes.
In April 2013, Drs. Andrew Kaunitz and David Grimes submitted a Citizen's Petition (CP) to FDA requesting the removal of the labeled boxed warning for the risk of fracture. The Petitioners claimed that the warning is based on BMD, an invalid surrogate endpoint known not to predict fracture risk. However, as stated in the Agency's denial of the petition, "given the lack of full BMD recovery five years after discontinuation of DMPA in adolescents, it remains to be seen whether young women who receive DMPA will achieve peak bone mass similar to that of women who do 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."

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no Division of Scientific Investigation (DSI) inspections sought for the study in this NDA efficacy supplement as this was a re-analysis of data from previously submitted studies along with literature, not a clinical trial. In addition, this product is not a new molecular entity, no new efficacy data were presented.

3.2 Compliance with Good Clinical Practices

This was a re-analysis of datasets as well as of an epidemiological study, conducted on an anonymized dataset; therefore, compliance with GCP is not applicable. The GPRD study was previously approved by the Independent Scientific Advisory Committee (ISAC) of the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA).

3.3 Financial Disclosures

Financial disclosures are not required for this reanalysis. The Applicant did not submit any financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This efficacy supplement contains solely a reanalysis of clinical data. Therefore, other review disciplines including CMC, Clinical Microbiology, Clinical Pharmacology and Pharmacology/Toxicology did not have any new data to review.

OSE was consulted regarding the Applicant's submission and was asked to:

- Review the GPRD database study—new analyses with a look-back 6-24 months prior to DMPA use.
- Conduct a literature search and review articles on DMPA and bone mineral density or DMPA and fracture risk published since previous reviews by DBRUP and DEPI for this product, particularly assessing the impact of duration of use and of type of user on the risk of fracture.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The NDA supplements include several parts.

Table 2 Studies Evaluating the Effect of DMPA on Bone Density

Studies and Literature Applicant is relying on to support labeling changes in Box Warning, Section 5.1 and Section 14.3	
Protocol A6791022 (Study 261) "Evaluation of Bone Mineral Density and Total Body Calcium in Adolescent DP150CI Users and Non Hormonal Contraceptive Users"	Submitted to FDA September 7, 2008 Reviewed in entirety by FDA October 12, 2010 (ES-36)
Study 234 "Assessment of Bone Mineral Density in Women Receiving DEPOPROVERA® Contraceptive Injection"	Final study report submitted to FDA under IND 45275 February 27, 2004 and to NDA 21583 April 7, 2004 Reviewed in entirety by FDA July 29, 2004
Johnson CC, Burkman RT, Gold MA, et al. Contraception 2008; 77:239-48.* This study reports on the methodology of Study 261.	**Submitted to FDA January 18, 2017**
Literature Discussion on bone loss	
Hui SL, Slemenda CW, Johnston CC. J Clin Invest 1988; 81(6):1804	Submitted to FDA and reviewed in its entirety July 28, 2011
Harel Z, Johnson CC, Gold MA. Contraception 2010; 81:289-91.*	**Submitted by Applicant to FDA January 18, 2017; Harel *et al*, Karlsson *et al* and Orr-Walker *et al* reviewed by the Division previously in response to the Citizen's Petition June 24, 2015**
Riggs BL, Khosla S, Melton LJ. J Bone Miner Res 1998;13:763–773.*	
Bauer W, Aub JC, Albright F.J Experimental Med1929;49:145-161.*	
Karlsson C, Obrant KJ, Karlsson M. Osteopor Int 2001;12:828-834.*	
Orr-Walker BJ, Evans MC, Ames RW, Clearwater JM, Cundy T, Reid IR. Clin Endocrinol 1988;49:615-618.*	

*New for review this submission

Table 3 Studies Evaluating the Effect of DMPA Use and Fracture Risk

Studies and Literature Applicant is relying on to support labeling changes in Box Warning, Section 5.1 and Section 14.3	
Protocol A6791032 (GPRD) "The Association of Bone Fractures and Use of Depo-Medroxyprogesterone Acetate (DMPA) in Women in the General Practice Research Database (GPRD)"*	**Originally reviewed by FDA 10/12/2010; Additional analyses and responses to FDA questions, August 10, 2012, submitted January 18, 2017**
Lanza LL, McQuay LJ, Rothman KJ, et al. Obstet Gynecol 2013; 121: 593-600*	**Submitted by Applicant to FDA January 18, 2017 Reviewed by the Division previously in response to the Citizen's Petition June 24, 2015**
Literature Discussion on fracture risk	
Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. J Clin Endocrinol Metab. 2010;95(11):4909-4916.	Reviewed in entirety by FDA March 4, 2011
Vestergaard P, Rejnmark L, Mosekilde L. Contraception. Dec 2008;78(6):459-464.	
Hui SL, Slemenda CW, Johnston CC. J Clin Invest1988; 81(6):1804	
Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS. J Bone Miner Res 2003;18:1947*	**Submitted January 18, 2017**
Kanis JA. Lancet 2002;359:1929-1935.*	
Kanis JA, McCloskey EV, Johansson H, Strom O, Bergstrom F, Oden A. Osteopor Int 2008;19:1395-1408.*	

*New for review this submission

5.2 Review Strategy

Given that Studies 261 and 234 as well as previous analyses of the GPRD study and some publications were fully evaluated by FDA previously, this review focused on the additional analyses of the GPRD study as well as on the publications by Johnson (which references Study 261) and Lanza (which references the GPRD), which were new submissions in this efficacy supplement. Review of the new literature submitted as part of the discussion on DMPA and bone density or fracture risk, as well as analysis of articles FDA culled from an updated literature search provided supportive information.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Study Title

"The Association of Bone Fractures and Use of Depo-Medroxyprogesterone Acetate (DMPA) in Women in the General Practice Research Database (GPRD)"

5.3.2. Study Design and Objectives

Please refer to Dr. Vaishali Popat's review dated June 30, 2011 for a full assessment of this study. To review briefly, this was a retrospective cohort study of DMPA users vs. nonusers (including users of nonhormonal contraceptives or hormonal contraceptives that were not DMPA). The objective was to estimate the effect of DMPA on the risk of fracture, calculated as an incidence rate ratio, exploring which aspects of exposure might affect risk of fracture (ever-use vs. never-use, cumulative DMPA exposure, duration of effect after exposure). The data covered the period between January 1, 1987 and December 31, 2005.

Additional Analyses

After the complete review of the GPRD study in 2011, the Division requested that the Applicant conduct additional analyses of the study population; specifically, that each analysis be performed in four separate cohorts of patients, with differing amounts of time with data available prior to the Index Date of contraceptive use. This was an attempt to identify whether DMPA users and "nonusers" actually had prior exposure to DMPA prior to the Index Date.

The 4 proposed cohorts were:

- All patients (full cohort), i.e., patients with available pre-treatment data and those with no available pre-treatment data
- Subcohort #1 with >6 months of pre-treatment data available
- Subcohort #2 with >12 months of pre-treatment data available
- Subcohort #3 with >24 months of pre-treatment data available

The Sponsor offered a counter-proposal suggesting comparisons in (1) the full cohort and (2) a single subcohort with pre-treatment data of at least 6-24 months with the rationale that this approach has more power to detect differences between exposure levels than smaller subcohorts. The Division agreed to this plan.

5.3.3. Study Population

The eligibility criteria were described previously in the review by Vaishali Popat MD, MPH, dated June 30, 2011 and the table is reproduced below. The study population consisted of 312,395 females 15-50 years old. Among them, 25% were DMPA users and the remainder was nonusers. A subcohort of women who had at least 6 months of

pre-index data in the same GPRD practice was also created (n=166,367,53.3%) in order to evaluate baseline variables that might be confounders of any relation between DMPA use and fracture.

Table 4 GPRD Study Population

Criteria (Yes = Required)	Full Cohort	Subcohort
Female	Yes	Yes
Birth date known	Yes	Yes
Acceptable patient by GPRD standard data checks	Yes	Yes
Contraceptive record dated		
-before age 50	Yes	Yes
-between 1 Jan 1987 and 31 Dec 2004	Yes	Yes
-after practice up to standard date	Yes	Yes
-after patient's registration date	Yes	Yes
-before practice's last data collection	Yes	Yes
-before patient death or transfer out date	Yes	Yes
Prescription contraceptive type		
-Depo-Provera or	Yes	Yes
-Nonhormonal contraceptive or	Yes	Yes
-Other hormonal (not Depo-Provera)	Yes	Yes
No hysterectomy/oophorectomy before index contraceptive	Yes	Yes
Six months of baseline data before index contraceptive	No*	Yes

* No = not required; women did not have to have 6 months of documented GPRD history before index contraceptive.

Source: reproduced from Table 1, Clinical Review, Vaishali Popat MD, MPHH dated June 30, 2011 available at http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80233f41

5.3.4. Time at Risk of Fracture

The time at risk of fracture was the observed person-years. It was used to calculate denominators for incidence rates of fractures. The eligible observed time per person was calculated from:

- The start date (index date) for observation--the latest of the following dates:
  - The woman's date of registration in her general practice
  - The practice's up-to-standard date (when the data recorded by the practice met standard GPRD criteria for quality and completeness.)
  - 1 January 1987

- The woman's first record with a contraceptive code before age 50.

- The termination date was the first of the following dates:
  - The practice's last date of contributing data to GPRD
  - 31 December 2005 (end of the study period)
  - The woman's first fracture date after entering the study
  - The date when the woman terminated from the practice due to moving away or death

5.3.5. Study Subject and Analysis Population

DMPA exposure

DMPA exposure was ascertained from prescription records for the product codes for injection of Depo-Provera 150 mg/mL or medroxyprogesterone acetate contraceptive injection 150 mg/mL. For each DMPA prescription, active exposure was constructed by creating a start date (the prescribing date) and an end date (89 days later), accounting for overlaps in prescribing. Each DMPA user's cumulative DMPA exposure was estimated by summing the days of exposure for her episodes of current, active DMPA contraception. For each DMPA user, (b) (4) also assigned counts for number of DMPA injections for each DMPA episode and calculated the cumulative number of injections over time, adjusting for possible overlaps. Subjects were divided into three categories of DMPA "exposure" based on the time since last use:

- Current: active DMPA exposure time, while the patient was actually exposed to DMPA
- Recent: the period that ended 730 days after the date of the last injection (inclusive)
- Past: the period more than 730 days after the date of the last injection and before any subsequent DMPA episode or the end of follow-up

Non-DMPA contraceptives

For women who never used DMPA during the study period, all of their observed time was classified as comparison (non-DMPA) time. Women who began the study on a contraceptive other than DMPA and then switched to DMPA contributed some non-DMPA time up to the point when their DMPA exposure began. They then accumulated DMPA exposure time as long as they did not have an event that terminated follow-up, such as a fracture.

Reviewer comment: There were many anomalies in DMPA prescription recording in the database; (b) (4) made many assumptions in order to characterize DMPA exposure. Dr. Popat discusses these anomalies and assumptions in her review. These were the best constructs and estimates possible.

5.3.6. Primary Outcome Measure

The primary outcome was fracture at any bone site [using the Read and Oxford Medical Information System (OXMIS) dictionary terms for hip, long bones of the arm, vertebrae, pelvis, fingers, legs, toes, skull, fractures with site unspecified or any site.] Arm, hip, and vertebra were considered to be bone sites that are vulnerable to fracture in patients with osteoporosis.

Reviewer's comment:

Dr. Popat's review gave thoughtful consideration to the types of fractures the Applicant/(b) (4) included in the assessment. The Applicant and (b) (4) determined that:

- **The effect of DMPA on osteoporotic fractures should be part of the evaluation, given DMPA's effect in terms of suppression of ovulation and decrease in estrogen levels.**
- **In terms of determining the utility of distinguishing fractures primarily due to external trauma vs. osteoporosis, (b) (4) concluded all fractures should be included as an outcome. This conclusion was based on the following:**
  - **In the GPRD, codes for trauma were unavailable before 1995**
  - **Though "low energy" or non-trauma-related fractures are conceptually considered characteristic of osteoporosis, the exclusion of high trauma fractures in women over 50 years of age may result in underestimation of the contribution of osteoporosis to fractures. Clinically, fractures of the vertebrae, hip and distal forearm are considered the quintessential osteoporotic fractures. However, large prospective studies have shown that almost all types of fractures are increased in patients with low bone density.**

Primary Safety Analyses

The predefined main measures were incidence rate ratios (IRR) and incidence rate differences (IRD). Fractures per 1,000 woman-years during relevant DMPA exposure were compared with the incidence rates during exposure to the other prescription contraceptives or non-users of contraception.

The first fracture reported by each patient after her index date was recorded. If fractures at more than one bone site occurred on the same day, only one fracture event was counted for the incidence rates. For each participant, the time between first

fracture and last use of cohort-specific contraceptive was recorded. The Applicant did not obtain any radiographic confirmation for any fractures.

Additional analyses in the current submission

As noted above, the FDA requested the following additional analyses:

- A more detailed examination of a possible association between the extent of DMPA exposure and fracture incidence in the DMPA group, where exposure would be defined in several different ways.
- Fracture rates before and after DMPA treatment in the subcohort of women with at least 6 months of pre-Index history

FDA also posed the following questions to the Applicant:

1. For how many women (and what percentage of the total sample) was the "practice up-to-standard" date later than the date of first record with a contraceptive code before age 50? Provide this broken down by ever users vs. never users of Depo-Provera.
2. What percentage of practices that participate in the GPRD stop contributing data to the GPRD database in a given year?
3. What percentage of all contraceptive injections are prescribed by family planning units in the UK? If available, discuss whether this proportion is believed to be the same for the women included in the GPRD database.

The Applicant used the following categories of duration of DMPA exposure in the analysis: none (unexposed to DMPA), ≤1 year, >1 year but ≤2 years and >2 years.

6 Review of Efficacy

This supplement contains only safety data. There are no efficacy data for analysis.

7 Review of Safety

Safety Summary

A summary of FDA's findings is as follows:

- In the original review of the GPRD
  - The cohort comprised 312,385 women with 1,722,355 person-years of follow-up. There were 11,822 bone fractures.
  - The crude incidence of any fracture with any use of DMPA was 9.0 per 1,000 person-years, compared to that of nonusers, which was 6.4 per 1,000 person-years.

  - The crude IRR for any fracture with any use of DMPA was 1.41 (95% CI: 1.35-1.47).
  - The IRR for any DMPA use compared with no DMPA use, standardized for age, was 1.44 (1.38-1.50).
  - Due to the retrospective nature of the study, causal association could not be established and the study could not determine whether use of DMPA has an effect on fracture rate later in life.

- In the supplementary analyses in the current submission, evaluating a subcohort of 166,367 women who had 6-24 months of pre-index history
  - The fracture risk remains higher in DMPA users compared to nonusers (the crude incidence of any fracture was 9.1 per 1,000 person-years, compared to that of nonusers, which was 7.3 per 1,000 person-years), and the risk appears to increase slightly by duration of use.
  - There may still be residual confounding due to missing data or lack of control for other established risk factors for fracture.
- The literature submitted in support of the labeling changes does not adequately address the issue of unidentified confounders in the GRPD population.
- The additional published *post hoc* analyses of the adolescent population in Study 261 confirm that the study groups are different at baseline, and the data continue to demonstrate that after DMPA use > 2 years, subjects did not recover to their baseline BMD level at the femoral neck and total hip even up to 60 months.
- A review of epidemiologic studies shows consistent findings across different study designs and populations, with an increased risk for fractures associated with DMPA use. The relative risk (RR) from these studies ranges from 1.5 to 2.5. Some studies bear some evidence of a dose-response relationship. A statistically significant higher risk of fracture was observed in females with > 2 years of DMPA use compared to use of other contraceptives.
- The Applicant's discussion including additional literature on DMPA and bone mass and fracture risk is fraught with unsubstantiated assumptions and does not provide a strong scientific argument for (b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of safety in this submission is primarily based on the additional *post hoc* analyses of the GPRD as well as on discussion of literature submitted (see Section 5.1).

7.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant submitted *post hoc* analyses of the GPRD study as well as literature; pooling of data is not applicable for this submission.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The full cohort had a total of 1,722,356 person-years, of which 78% came from women observed for at least 5 years. The average follow-up from the index date was 5.9 years for users and 5.4 years for nonusers of DMPA. As Dr. Popat noted in her review dated June 30, 2011, while the exposure is adequate to evaluate the effect of DMPA on the risk of fractures, the study did not follow postmenopausal women sufficiently to determine whether there is an increased risk of osteoporotic fracture later in life.

7.2.2 Explorations for Dose Response

Dose exploration is not applicable for this submission as only one dose, 150 mg every 3 months, was evaluated in this study.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission.

7.2.4 Routine Clinical Testing

Not applicable for this submission.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable for this submission.

7.3 Major Safety Results

7.3.1 Deaths

Not applicable for this submission.

7.3.2 Nonfatal Serious Adverse Events

Not applicable for this submission.

7.3.3 Dropouts and/or Discontinuations

Not applicable for this submission.

7.3.4 Significant Adverse Events

Not applicable for this submission.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 DMPA and Fracture Risk: Original Results

The results from previous analyses of fracture rates in the GPRD are found in Dr. Popat's review dated June 30, 2011. As previously noted, the primary endpoint was the incidence rate ratio (IRR) of any fracture at any site. Overall, 11,822 incident fractures were found for an incidence rate of 6.9 per 1,000 person years. The crude incidence of any fracture with any use of DMPA was 9.0 per 1,000 person-years, while that of non-users was 6.4 per 1,000 person-years. See Table 5. The crude IRR for any fracture with any use of DMPA was 1.41 (95% CI: 1.35-1.47).

Table 5 Crude Incidence of fracture by 1,000-Person-Years any site by ever use of DMPA

Events	Non user	DMPA	Total
Person-years	1,395,040	327,315	1,722,356
Total number of events, any site	8,887	2,935	11,822
Total rate per 1,000 P-Y, any site	**6.4**	**9.0**	**6.9**

Source: reproduced from Table 4, Clinical Review, Vaishali Popat MD, MPHH dated June 30, 2011 available at http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80233f41

The rates were also standardized by age, using weights from the age distribution of the entire cohort. The IRR for any DMPA use compared with no DMPA use, standardized

for age, was 1.44 (1.38-1.50). After standardizing for age and each potential confounder, the incident rate ratios (IRR) for any DMPA use remained close to the IRR of 1.44 with similarly narrow confidence intervals (CIs), thereby providing little evidence of confounding from the baseline variables. The IRR similarly showed increases with current use as compared with recent or past use. See Table 6.

Table 6 Age-Standardized Incidence of Fracture per 1,000 Person-Years by Time from Last DMPA Injection

Exposure Category	Crude Fracture Rate Per 1000 Person-Years	**Crude IRR**	Crude IRR CI	Age-adjusted fracture rate/100 Person-Years	**Age adjusted IRR**	Age-standardized IRR CI
None	6.4	**1.00**		6.3	**1.00**	
Total past	8.4	**1.32**	1.24 -1.41	8.5	**1.34**	1.25 - 1.44
Total recent	9.0	**1.41**	1.31 - 1.50	9.2	**1.45**	1.34 - 1.56
Total current	9.6	**1.51**	1.41 - 1.61	9.6	**1.51**	1.41 - 1.62

CI = confidence interval; IRR = incidence rate ratio
Source: reproduced from Table 5, Clinical Review, Vaishali Popat MD, MPH dated June 30, 2011 available at http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80233f41

Notably, very few fractures of the axial skeleton were observed; there were only eight subjects with hip fracture and 35 with vertebral fracture out of >79,000 women who used DMPA. This could be due to the fact that the population included young women who would be unlikely to have osteoporotic fractures. Further, in the GPRD, fractures were not confirmed radiographically, so all vertebral fractures, which are often silent, may not have been identified.

In the previous submission, the Applicant had provided a *post hoc* analysis comparing pre- and post-treatment fracture rates in the subcohort of subjects who had six months of baseline data before the index date (N=166,367). This analysis had originally been planned to evaluate confounding. However, the Applicant used it to compare DMPA users to nonusers. They found that the IRR for any fracture "before treatment" (IRR 1.28, 95 % CI 1.07, 1.53) was similar to the IRR "after treatment" (IRR 1.37, 95% CI 1.29, 1.45), yielding a relative risk of fracture in DMPA users post-treatment compared with pre-treatment of 1.08 (0.92-1.26). The Applicant concluded that, in women using DMPA, (b) (4). Dr. Popat noted that such *post hoc* analyses should be limited to developing hypotheses for confirmation in studies designed specifically to test them in the future. The analysis performed was not prespecified. Further, she found that the analysis of fracture incidence in the short six months preceding the onset of contraceptive use was not nearly as robust as results obtained over a longer duration of follow-up, noting that the number of fractures in a six-month period might be more subject to chance than that over the longer 18-year period

of time. Dr. Popat determined that a 6-month look-back period was also not long enough to accurately ascertain past use of DMPA. Because women tend to go back to the same contraceptive method they tried previously, it was reasonable to assume that the group defined as non-users in the six months prior to the index date could include women who had used DMPA in the more distal past, which could have an effect on BMD during the study period. Dr. Popat was also concerned that in the UK, hormonal contraceptives can be prescribed in family planning clinics—outside of those practices included in the GPRD, which may also lead to exposure misclassification.

7.3.5.2 Additional Analyses

In the latest additional analyses, the Applicant attempted to address the concerns about misclassification. The Applicant provided information on a single subcohort with pre-treatment data of 6-24 months, detailing the IRR in four categories of duration of DMPA exposure. The Applicant concluded that, compared with nonuse of DMPA, among categories of cumulative exposure (i.e., over intermittent periods of use) of women who used DMPA, (b) (4) The Applicant also calculated the IRR in the same four categories for the full cohort, which did show a trend toward an increased IRR of fracture with increasing duration of DMPA exposure. See Table 7 and Table 8.

Table 7 Incidence of Fracture During Follow-Up in Subcohort of 166,367 Women With 6-24 Months of Pre-index History, by Four Categories of Cumulative DMPA Exposure

Extent of DMPA Use in Years	Number of Fractures	Person-years	Fractures per 1,000 Person-years	IRR (95% CI)
None	4,939	744,242	6.6	1.00
≤ 1	1,055	117,953	8.9	1.35 (1.26-1.44)
> 1 and ≤ 2	249	29,376	8.5	1.28 (1.12-1.45)
> 2	270	26,385	10.2	1.54 (1.36-1.74)

CI = confidence interval; DMPA = depot medroxyprogesterone acetate; IRR = incidence rate ratio.
Source: NDA 20246 S62, GPRD Additional Analyses 2012, Table 1, page 11/23
For comparison, the Applicant also provided these data for the full cohort.

Table 8 Incidence of Fracture in Full Cohort of 312,295 Women, by Four Categories of Cumulative DMPA Exposure

Extent of DMPA Use	Number of Fractures	Person-years	Fractures per 1,000 Person-years	IRR (95% CI)
None	8,887	1,395,040	6.4	1.00
≤ 1 year	1,872	213,879	8.8	1.37 (1.31-1.44)
> 1 year and ≤ 2 years	507	57,404	8.8	1.39 (1.27-1.52)
> 2 years	556	56,033	9.9	1.56 (1.43-1.70)

CI = confidence interval; DMPA = depot medroxyprogesterone acetate; IRR = incidence rate ratio.
Source: NDA 20246 S 62, GPRD Additional Analyses 2012, Appendix A, Table A-1 page 21/23

Reviewer comment: In the full cohort, the IRRs for DMPA use indicate an increased risk of fracture with increasing duration of exposure. In the subcohort with 6-24 months of pre-index data, there also appears to be a trend toward increased risk of fracture with increasing duration of exposure, most noticeable with >2 years of DMPA exposure.

Additionally, the Applicant displayed fractures, person-time, and rates by the cumulative number of injections from zero to 25, restricted to women with 6-24 months of pre-index history. They performed a weighted least-squares regression line fit through all nonzero categories. The slope of the fitted line is 0.045 fractures per 1,000 person-years per added injection (95% CI -0.068 to 0.159 fractures per thousand person-years per added injection). The Applicant asserts that this indicates (b) (4)

Among the subcohort of women with at least 6 months of records prior to the index date, the IRR for fracture in DMPA users vs. nonusers before contraceptive use started was 1.31 (95% CI 1.19-1.45), while after contraceptive use began it was 1.23 (95% CI 1.16-1.30). The Applicant argues that (b) (4) he Applicant again calculated a relative risk of fracture in DMPA users post-treatment compared with pre-treatment and found the pre- to post-treatment IRR to be 1.01 (0.92-1.11), based on fracture incidences of 9.0 vs. 9.1 per 1,000 women-years in the DMPA users with at least 6 months of baseline history available in the GPRD. In contrast, for the equivalent non-user cohort, the pre- to post-treatment IRR was 1.07 (1.01-1.14).

The Applicant also re-examined the change in fracture incidence with current, recent or past use and found that the observed fracture incidence was 9.6 fractures/1000 woman-years during "current" use, 9.0 fractures/1000 woman-years during "recent" use and 8.4 fractures/1000 woman-years during "past" use of DMPA. (b) (4)

(b) (4)

Practice up-to-standard
The Applicant addressed FDA's practice up to standard question. According to the Medicines and Healthcare products Regulatory Agency (MHRA)/GPRD research standard guidelines, the practice-up-to-standard date is the date at which the data in the practice are considered to have continuous high quality fit for use in research. The Applicant stated that the only contraceptive records they considered to be valid for use in this analysis were those that occurred after the practice-up-to-standard date, patient's first registration date with the practice, and study start date. They assigned the index date of contraception for each patient as the date of the first contraceptive record in the therapy data set that occurred on or after these dates. Among the subcohort of women with at least 6 months of pre-index data (n = 166,367), 20,071 (12%) had a contraceptive record that occurred before the practice-up-to-standard date. By definition, the women in the subcohort had no recorded use of contraceptive therapy records during baseline. All of these women were aged < 50 years at the index date and therefore were aged < 50 years on the date of their invalid contraceptive records. Among the 312,395 women in the full cohort (i.e., with no restriction as to the minimum amount of baseline), 57,378 (18%) had a contraceptive therapy record with a date before the corresponding practice-up-to-standard date and therefore had a contraceptive record before the first "valid" record of contraception.

During the years 1987 through 1999, practices were only added to GPRD (i.e., no practices stopped contributing). From 2000 through 2005, on average, only 1.6% of practices stopped contributing data at some point during a given year.

Reviewer comment: This information suggests that most practices included in the GRPD over time were up-to-standard, indicating the data in the practice should be of a quality useful for research over the decades. However, no information was provided as to the type of contraception used for the 18% of the sample who had a contraceptive therapy record prior to the "practice-up-to-standard date;" thus, there remains a potential for misclassification of exposure.

Use of Family Planning Services
To address the issue of misclassification of contraceptive use, the Applicant relied on the report Contraception and Sexual Health 2006/07 which found that over half of women aged 16-49 (57 per cent) had used one or more family planning services during the five years before interview and that patients aged 16-19 years old were equally likely to use their general practitioners/practice nurses as they were to use Family Planning Clinics (28% vs. 29%). A survey of community contraceptive clinics for the NHS bulletin, found that the number of women who attended community contraception clinics remained fairly constant (~1.1 million per year) for the fiscal years 1994-1995 through 2006-2007. Overall, only 3% of women aged less than 50 years (and only 4%

of women under 50 using contraception) chose hormonal injection as a method of contraception, with women aged 20 to 24 years being the most likely (11%).

Reviewer comment: The numbers indicate that some degree of misclassification is possible, given that women use family planning clinics and general practitioners (almost 30% of women aged 16-19) to obtain contraception. The Applicant argues that the percentage of women using injectable hormonal contraceptives is a small portion of the overall number of contraceptive users, but this does not negate the fact that a significant portion of women getting DMPA could have done so outside of the GPRD.

7.3.5.3 Literature Upon Which Applicant Relies to Support Labeling Changes Regarding Fracture Risk

The Applicant is relying on one article to support labeling changes regarding fracture risk.

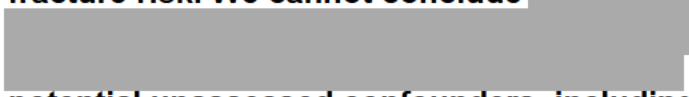
1. Lanza LL, McQuay LJ, Rothman KJ, et al. Obstet Gynecol 2013; 121: 593-600
   The first three authors of this publication are employees of RTI Health Solutions, which was under contract to Pfizer for analysis of the GPRD data, while all the other authors except one (Andrew Kaunitz) were either employees of Pfizer or (b) (6).

   The article summarizes the GPRD study; it has been described in detail in Section 5 above. This article asserts that in the subcohort of 166,367 women who had at least six months of baseline history available in the GPRD, there was little confounding by age within the age range of the study population and, that when controlling for age, none of the other potential confounders (past fracture at any site, alcohol abuse or dependence, drug abuse, inflammatory bowel disease, epilepsy, asthma, oral corticosteroid therapy, baseline fall, estrogen replacement therapy, current smoking, pregnancy at < 20 years old) contributed any material confounding to the overall IRR for DMPA and fractures. When they expanded the study population to the full cohort of 312,395 women, both before and after use of contraception started, DMPA users had a greater fracture incidence than nonusers. This risk did not increase after starting DMPA and was present before DMPA was initiated. Compared with nonuse, DMPA users had more codes for appendicular and miscellaneous (fingers, toes, face, skull, multiple trauma, and unspecified) fractures; however, there was no excess risk for axial fracture codes (hip, pelvis, and symptomatic or clinical vertebral fractures; IRR 0.95, 95% CI 0.74–1.23). They postulate that the lack of difference in axial fractures coupled with the higher IRR of appendicular and miscellaneous fracture in DMPA users is likely unrelated to a decrease on BMD but could be due to differential risks for traumatic injury. According to the authors, the association between DMPA use and higher fracture risk may represent inherent differences in fracture risk

between women who elected to use DMPA and women who used other prescription contraceptives.

Applicant's Overall Conclusion: The Applicant's overall conclusion based on the additional *post hoc* analyses and this Lanza article (b) (4)

Reviewer comment: The additional *post hoc* analyses presented do not contain any new information and do not allow for drawing any new conclusions, particularly about the effect of pre-exposure fracture risk on post-exposure fracture risk. We cannot conclude (b) (4)



We can make no assumptions about potential unassessed confounders, including the possibility that some women may have also had a past history of DMPA use during the pre-exposure period, which could have a carry-over effect on BMD measured in follow-up. Current DMPA users may be more likely than current non-users to have been past DMPA users. This clinical reviewer as well as the DEPI reviewers find that the data still show a statistically significant higher risk for fracture during follow-up in DMPA users compared to nonusers. The data also show increasing risk with increasing duration of use and with an increase in the cumulative number of DMPA injections, although there is no clear evidence of a dose-response relationship. The DEPI reviewer notes that there may still be residual confounding due to missing data or lack of control for other established risk factors for fracture including socioeconomic status or physical activity. This does not negate the conclusion of increased fracture risk with DMPA.

The DEPI reviewers recommend use of a different study design, a restriction approach, be applied (i.e., a inception cohort design) to better minimize the impact of prior history of fracture on the future fracture risk. In such an approach, all fracture events prior to the treatment initiation would be excluded.

The DEPI reviewer also disagrees with the Applicant's conclusion (b) (4) [redacted] **DEPI believes that the self-controlled cohort method used in this GPRD study is not appropriate for sustained exposure and for outcomes resulting from cumulative exposure and may not be appropriate for quantification of the magnitude of a risk. Alternative designs such as a retrospective incident user cohort design plus sufficient confounding control should be considered in these cases.**

While the 2016 supplementary analyses provided data from a longer look-back allowing for identification of more pre-exposure fracture events, missing information on prior DMPA use remains an issue. This small chance of exposure misclassification (differential or non-differential) could either over- or under-estimate the IRRs. The increased risk of fracture with DMPA may be attributable to residual confounding but nevertheless exists.

This reviewer and the DEPI reviewer agree that the number of osteoporotic fractures is too small to allow any meaningful inference on the risk of osteoporotic fracture.

7.3.5.4 Literature Submitted in Discussion of Fracture Risk

The Applicant provides several articles to support their argument regarding fracture risk. Two articles (Meier C et al and Vestergaard et al) were submitted previously and reviewed by the FDA and determined not to be supportive of the Applicant's argument. The following additional articles were presented in the current submission and are reviewed here.

2. Hui SL, Slemenda CW, Johnston CC. J Clin Invest 1988; 81(6):1804

   This is a prospective study of 521 Caucasian women who had repeated bone density measurements over 15 years in order to follow the natural history of bone loss. Subjects were gynecology patients and workers at Indiana University Medical Center as well as their friends and residents of the local community, in addition to ambulatory residents of a retirement home. Subjects who had medical problems or medications that affected bone metabolism were excluded. Subjects had one to four visits annually for BMD measurements and inquiries about the history of recent fracture. Only fractures requiring physician visits and diagnosis were included. Spinal fractures or those resulting from motor vehicle accidents were excluded. The average subject had 24.6 bone mass measurements over 6.5 years. Follow-up periods were divided by age (<45, five-year intervals from 45-79, and >79). Each

interval was classified by the mean bone mass. Fractures per person-year for each age and bone mass interval were obtained. The authors then estimated the fracture rate for each category as a function of age and bone mass in a log-linear model. The first set of analyses included 138 fractures in 3,388 person-years, with the most frequent sites being the hip (n=34). The rate of all non-spinal fractures increased with increasing age and decreasing radius bone mass; these two variables had an independent effect on the outcome. An analysis of a subset showed that age was a stronger predictor of hip fractures, while radius bone mass was a stronger predictor of fracture in the distal arm. They concluded that bone mass is a useful predictor of fractures but other age-related factors need to be identified.

Reviewer comment: The Hui paper provides a discussion of the natural history of bone loss and the rate of fracture with bone mass and age. The Applicant uses it in their argument about bone loss in menopause.

3. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS. J Bone Miner Res 2003;18:1947

This is from the Study of Osteoporotic Fractures, a prospective study of risk factors for hip and other osteoporotic fractures in 9,704 community-dwelling women aged 65 years and older, who were recruited between 1986 to 1988 from four areas of the United States: Baltimore, Maryland; Minneapolis, Minnesota; the Monongahela Valley, Pennsylvania; and Portland, Oregon. Black women were excluded at the start of the study because of their low incidence of hip fracture. BMD scans were performed at baseline and again two years later in the 9,483 surviving members of the cohort. Subjects were then followed with phone or mail contact every four months to ascertain the incidence of fractures during that time period. In addition, participants were asked to notify the clinical center as soon as possible after any fracture. All fractures were radiographically confirmed and coded according to degree of trauma. Subjects were followed for an average of 10.4 years, with fracture follow-up over 98% complete. Fractures due to severe trauma were excluded, as were types of fracture that occurred less than 20 times during the follow-up period (sternum, skull, scapula, coccyx). The authors used Cox proportional hazards models to estimate the age-adjusted risk of fracture per SD decrease in BMD. They also repeated the analyses described stratified on follow-up time ($\leq$5 versus >5 years from BMD scan). The average age of participants was 71.7 years at the baseline examination. After an average of 10.4 years of follow-up since baseline (Visit 1), 4,172 non-spine fractures occurred in 2,901 women, including 721 hip fractures, 744 wrist fractures, and 439 humerus fractures. For all analyses, the comparison group included 6,137 women who experienced no incident clinical fractures. Similarly, with an average of 8.5 years of follow-up since the second visit, 3,278 fractures occurred in 2,372 women, including 622 hip, 561 wrist, and 362 humerus fractures. Between Visits 1 and 3 (mean follow-up of 3.7 years), 389 women suffered incident spine fractures. Peripheral BMD was significantly associated with all types of fractures studied except facial fractures. Hip BMD is

somewhat more strongly related to most of the fracture types studied than spine or peripheral BMD measures. The proportion of fractures attributable to osteoporosis (based on a standard definition of osteoporosis) is modest, ranging from <10% to 44% based on the most commonly used definition of osteoporosis (BMD T-score <2.5). Overall, the relationship between BMD and fracture risk is similar over the short-term (≤5 years) and long-term (>5 years). The authors stress the importance of finding effective prevention strategies for fractures in older women besides treatment for osteoporosis, such as prevention of falls and other fracture risk factors.

Reviewer comment: The study is large, has a prospective design and long follow-up, and provides useful information about the risk of fracture with declining BMD. A major limitation is that the study included only white women and may not be generalizable to the U.S. population. The authors note they later enrolled black women to gain information on that population in the future. The study does not address the risk of fracture as it relates to past history of DMPA use. The Applicant has included this study only as part of their discussion on the types of fractures that are influenced by BMD. The Applicant maintains that some skeletal sites (spine, hip, pelvis) are more likely to sustain osteoporotic or fragility fractures than other sites (fingers, toes, face, skull, which are sites for traumatic fractures not influenced by BMD).

Dr. Jaffe from the Bone Team in DBRUP, in her review dated June 30, 2017, concurs that fragility fractures, which are defined as those resulting from a fall from a standing height or less, typically occur at the spine, hip, femur, ankle, pelvis, ribs, humerus, and forearm. Fractures of the skull, nose, face, hands, feet, patella, clavicle and sternum are generally not considered "fragility" or osteoporotic fractures. However Dr. Jaffe disagrees with the Applicant's suggestion that *most* osteoporotic fragility fractures occur with a fall because the definition of a fragility fracture also includes morphometric vertebral fractures that may be completely asymptomatic and atraumatic, or present as height loss. Further, spontaneous collapse of the femoral neck is not typical of osteoporotic fracture. Additionally, stress fractures are not considered fragility fractures, but usually result from repeated damage from repetitive use injuries, which ultimately exceeds the intrinsic ability of the bone to repair it. They can occur in individuals with normal bone or with decreased bone strength and individual risk factors such as occur in the athlete's triad (oligo-amenorrhea, low energy intake and low BMD) also factor here. There are minimal data addressing whether DMPA increases the risk of stress fractures in groups of women other than female non-Hispanic white military recruits. Also, insufficient time has passed since the approval of DMPA to assess the impact of DMPA use by younger women on perimenopausal BMD levels and on postmenopausal future fracture risk.

4. Kanis JA. Lancet 2002;359:1929-1935

This article provides a summary on the diagnosis of osteoporosis and assessment of fracture risk. The diagnosis of osteoporosis is based on the assessment of BMD and is defined as a BMD 2.5 SD or more below the average value for premenopausal women (T score <-2.5 SD). Severe osteoporosis denotes the added presence of one or more fragility fractures. Diagnosis is made with dual x-ray absorptiometry (DXA) and the recommended site is the proximal femur. The predictive value of BMD can be enhanced by use of biochemical indices of bone resorption and clinical risk factors such as age, previous fragility fracture, premature menopause, family history of hip fracture, and the use of oral corticosteroids.

5. Kanis JA, McCloskey EV, Johansson H, Strom O, Bergstrom F, Oden A. Osteopor Int 2008;19:1395-1408

The aim of this study was use the FRAX tool to develop a case-finding strategy for men and women from the UK at high risk of osteoporotic fracture by delineating the fracture probabilities at which BMD testing or intervention should be recommended. Treatment was cost-effective at all ages (50-80 years old). Assessment thresholds for testing with BMD (6–9% at the age of 50 years) also rose with age (18–36% at the age of 80 years). The use of these thresholds in a case-finding strategy would identify 6–20% of women as eligible for BMD testing and 23–46% as eligible for treatment, depending on age.

Reviewer comment: The Applicant includes these articles by Kanis, who developed the FRAX tool in concert with the WHO, mainly to argue that the algorithm does not include pregnancy/lactation history or history of DMPA use as risk factors for future osteoporotic fractures. This is a specious argument. The FRAX algorithm includes known independent risk factors for fracture. At this time, we know there is incomplete BMD recovery five years after discontinuation of DMPA in adolescents. However, we do not know whether young women who receive DMPA achieve peak bone mass similar to that of women who do not use DMPA, and not enough time has elapsed since the approval of DMPA to assess the impact of its use on BMD levels and fracture risk later in life. Further studies are needed to determine this. When these data do become available, if DMPA is shown to be a risk factor, algorithms could be modified to include it. Whether or not DMPA use is currently included in the FRAX tool does not preclude an assessment of the impact of the drug on BMD based on presently-available information and implementing warnings in order to protect public health in the intervening time frame.

The Applicant also argues that, (b) (4) **The**

Applicant argues (b) (4) [redacted]

Dr. Jaffe asserts that DXA is "the standard tool for assessing bone mass and fracture risk and for monitoring changes in bone density over time in children, adolescents and adults. Normative data are available for BMD for children, adolescents and adults through the NHANES III database." The association between BMD and fracture in postmenopausal women is clear. However, while BMD provides an assessment of fracture risk, BMD does not predict who will actually fracture, because the majority of postmenopausal patients who fracture have a BMD in the range of osteopenia rather than osteoporosis. Obviously additional factors contribute to fracture risk.

In premenopausal women, including adolescents, data on the relationship between BMD and fracture risk are less robust. The relationship between BMD and fracture has also been demonstrated in young women in cross-sectional studies.[1,2,3,4] In the premenopausal population, among patients with underlying conditions such as anorexia nervosa, cystic fibrosis, inflammatory bowel disease, cerebral palsy, and glucocorticoid and DMPA use, BMD by DXA remains the standard of care to assess skeletal health and fracture risk; DXA has been reliably used to assess bone loss and/or fracture risk in these patients.[5] Factors that may add to demineralization such as DMPA could further compound fracture risk. While other tools can assess bone health, these carry risks of exposure to higher doses of radiation, are expensive and invasive, and not practical for use in clinical practice or in large studies. Per Dr. Jaffe, these data support the use of BMD by DXA to predict fracture risk in adolescents and premenopausal women and support the association between a reduction in BMD and the increased risk of fracture in this population.

1 Hung LK ,Wu HT, Leung PC, et al. Low BMD is a risk factor for low-energy Colles' fractures in women before and after menopause. Clin Orthop Relat Res 2005;435:219–25.
2 Lappe J, Davies K, Recker R, et al. Quantitative ultrasound: use in screening for susceptibility to stress fractures in female army recruits. J Bone Miner Res 2005;20:571–8.
3 17. Myburgh KH, Hutchins J, Fataar AB, et al. Low bone density is an etiologic factor for stress fractures in athletes. Ann Intern Med 1990;113:754–9.
4 Lauder TD, Dixit S, Pezzin LE, et al. The relation between stress fractures and bone mineral density: evidence from active-duty Army women. Arch Phys Med Rehabil 2000;81:73–9.
5 Wasserman H, O'Donnell JM, Gordon CM. Use of dual energy X-ray absorptiometry in pediatric patients. Bone. 2016 Dec 15. pii: S8756-3282(16)30370-2. doi: 10.1016/j.bone.2016.12.008. [Epub ahead of print]).

7.3.5.5 Literature Upon Which Applicant Relies to Support Labeling Changes Regarding Bone Density

The Applicant is relying on data from one article to support labeling changes related to the effect of DMPA on bone density.

1. Johnson CC, Burkman RT, Gold MA, et al. Contraception 2008; 77:239-48.

   This publication is based on Study 261, which, as noted above, was already reviewed by FDA. This was a nonrandomized, open-label, fixed-dose, prospective, unmatched observational cohort study in which female adolescents aged 12–18 years, who presented at the study clinics having self-selected their contraceptive method, were invited to participate. The study included 389 adolescents, 169 DMPA users and 220 nonusers (26 elected non-hormonal forms of contraception, almost exclusively condoms; 194 were sexually abstinent). DMPA users received injections every 12 weeks, for a treatment period of up to 240 weeks (20 injections), with an additional post-treatment follow-up period of 120 weeks. Participants using non-hormonal contraception or who were sexually abstinent were followed for up to 360 weeks. Baseline data collected included anthropometric measures, age at menarche, gynecologic age and sexual maturity rating, family medical history (e.g., osteoporosis), previous pregnancies, smoking status, alcohol use and level of physical activity. Serum and urine chemistry, BMD, whole body BMC (by DXA) and serum biochemical markers of bone remodeling were collected at Screening and at Weeks 24, 60, 84, 120, 144, 180, 204 and 240. Measurement of BMD and whole body BMC was also conducted at Week 300 and at Week 360 or the final visit. Any participant with significant bone loss compared with her baseline level had a serum sample analyzed for intact parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D at the next visit and at the following visit, approximately 6 months later, to screen for other disorders that might account for the loss.

   Beginning in 2003, study participants were asked to report calcium and vitamin intake from their diet and supplements. Chronologic and gynecologic ages were more advanced, and the proportion of black participants was greater, in the DMPA user cohort. There was a nonsignificant trend at baseline toward higher BMD at the lumbar spine and the femoral neck among DMPA users, compared with all nonusers. Concentrations of all bone markers differed significantly across the three cohorts paralleling the between-group differences in mean gynecologic age, reflecting a relative skeletal immaturity among the non-users. Black subjects had significantly higher baseline BMD. The authors suggested that because Black adolescents may gain bone earlier during adolescence, their rate of BMD accrual may plateau earlier. Each of these factors would contribute to a greater skeletal maturity at the onset of the study and would make it more likely that the DMPA users would demonstrate smaller increases in BMD during follow-up, apart from any effect of DMPA administration. These differences at

baseline would contribute to greater skeletal maturity in the DMPA user cohort and would predict more modest subsequent gains in BMD in that group during the period of observation. The authors stated that the DSMB recommended analyzing the study cohorts independently, without direct comparison.

7.3.5.6 Literature Submitted in Support of a Discussion on Bone Density

2. Harel Z, Johnson CC, Gold MA. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010; 81:289-91.

   This publication is also based on Study 261, which, as noted above, was already reviewed by FDA. The authors use this paper to argue that the definition of the time needed for "full recovery" of BMD, if it occurs, cannot be determined simply by inspection of the data without appropriate statistical analysis of the post-treatment BMD changes across the whole population (N=98).The DSMB chair engaged an external statistician to perform these analyses which were not included in the final Clinical Study Report for Study 261. The authors employed a mixed model analysis of variance to examine BMD changes at the lumbar spine, total hip and femoral neck across time after the final DMPA injection (EOT) to determine time to full recovery of BMD to pre-treatment values, as signified by $p>0.05$ for the comparison of follow-up BMD values to baseline values. Adjustments were made for the number of injections, and race (black, white), gynecologic age and BMI were included as covariates. The model was run for all participants and then separately by race (black, white). BMD and whole body bone mineral content (BMC) percent changes from baseline were also assessed according to participants' reported calcium intake. A total of 191 participants received at least one injection of DMPA and 98 of them provided post-treatment BMD data. Again, the authors note that mean baseline BMD Z-scores suggest that adolescents who received DMPA had higher bone density at baseline than the age-specific reference population and were particularly high in the younger participants (aged ≤14 years).

   Looking at BMD during DMPA use, participants with $\geq$5% BMD losses had received a significantly greater number of DMPA injections (median=13) over time than did participants without such losses (median=5) ($p<0.001$). Similarly, participants with BMD declines of 8% or more received more injections (median= 13) than those with declines of less than 8% (median=6) ($p<0.001$). At the time of the final DMPA injection, participants had received a median of nine DMPA injections, and mean BMD declines from baseline were 2.7% at the lumbar spine, 4.1% at the total hip and 3.9% at the femoral neck ($p<0.001$ at all 3 sites).

   The crux of the paper centers on the following: the mixed model analysis of variance showed that mean lumbar spine BMD recovered to pre-treatment levels 60 weeks after the last DMPA injection ($p=0.554$), and then continued to increase

to 240 weeks. By 240 weeks after DMPA discontinuation, 84% of participants had a lumbar spine BMD value that exceeded their baseline value and the mean lumbar spine BMD value was 4.7% greater than at baseline. Full recovery of mean BMD to baseline value at the total hip required 240 weeks (p=0.634) and femoral neck BMD required at least 180 weeks (p=0.058; p=0.232 at 240 weeks). Post-DMPA BMD increases were smaller in those participants who exhibited a ≥5% BMD loss during DMPA treatment than in participants who had less BMD decline during DMPA use.

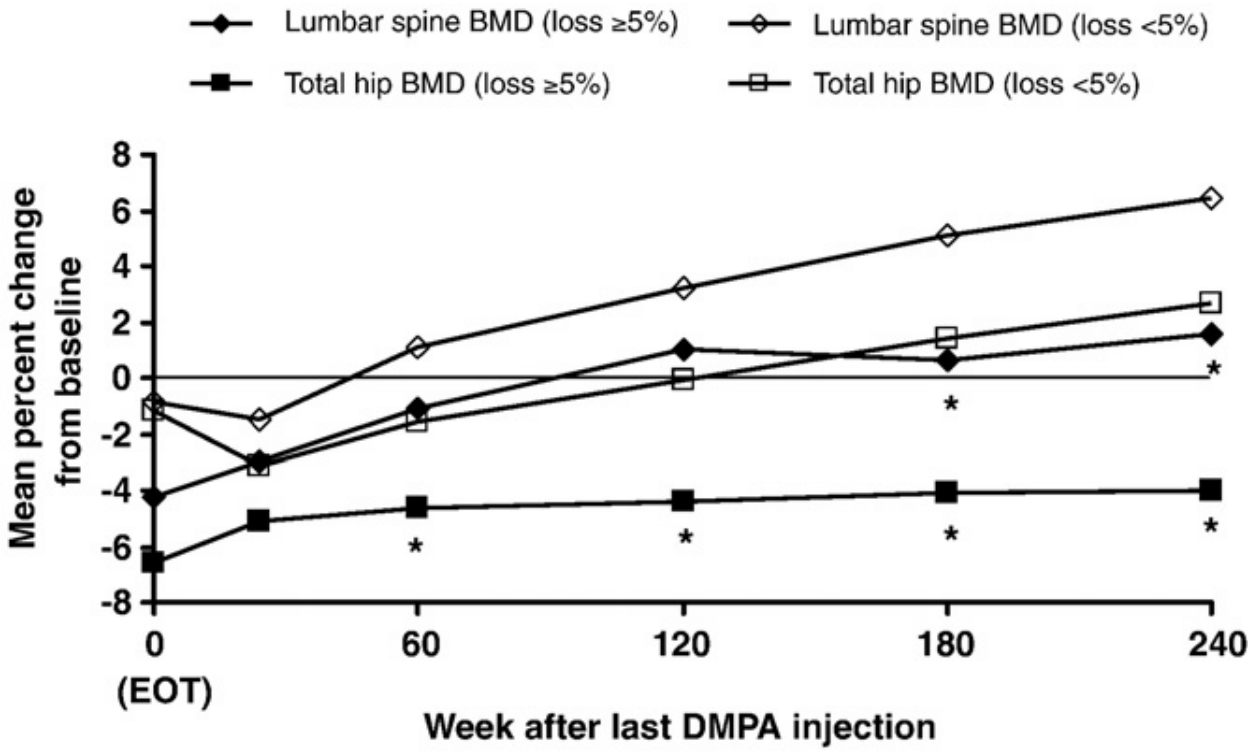
Table 9 Percentage changes from baseline in BMD and BMC after discontinuation of DMPA

Week after DMPA discontinuation	N	Median No. of injections	Mean % change (S.E.M.) from baseline to end of treatment[a]	Mean % change (S.E.M.) from baseline to post-DMPA visit	Participants with BMD or BMC ≥baseline at end of treatment (%)	Participants with BMD or BMC ≥baseline level at post-DMPA visit (%)
Lumbar spine BMD						
0 (final DMPA injection)	98	9	−2.7 (0.4)	N/A	29.6	N/A
24	74	9	−2.1 (0.5)	−2.0 (0.6)	33.8	31.1
60	70	8	−2.2 (0.5)	0.5 (0.7)	30.0	52.9
120	52	10	−2.6 (0.6)	2.4 (0.7)	28.8	67.3
180	39	7	−2.3 (0.8)	3.5 (0.8)	30.8	76.9
240	25	9	−2.5 (0.8)	4.7 (1.0)	32.0	84.0
Total hip BMD						
0 (final DMPA injection)	98	9	−4.1 (0.4)	N/A	25.5	N/A
24	74	9	−3.8 (0.6)	−3.7 (0.6)	33.8	25.7
60	71	8	−3.2 (0.5)	−2.5 (0.6)	28.2	31.0
120	52	10	−4.2 (0.6)	−1.6 (0.7)	21.2	36.5
180	39	7	−3.4 (0.8)	−0.6 (0.8)	25.6	38.5
240	25	9	−3.2 (0.7)	0.3 (1.0)	20.0	56.0
Femoral neck BMD						
0 (final DMPA injection)	98	9	−3.9 (0.5)	N/A	25.5	N/A
24	74	9	−3.6 (0.6)	−3.8 (0.7)	29.7	25.7
60	71	8	−3.0 (0.6)	−3.3 (0.7)	32.4	22.5
120	52	10	−3.7 (0.7)	−1.7 (0.8)	26.9	36.5
180	39	7	−3.6 (0.9)	−0.7 (1.0)	28.2	41.0
240	25	9	−3.4 (0.9)	−0.8 (1.3)	24.0	40.0
Whole body BMC						
0 (final DMPA injection)	97	9	0.6 (0.5)	N/A	54.1	N/A
24	73	9	1.1 (0.6)	1.7 (0.7)	30.1	60.3
60	67	8	1.6 (0.6)	3.7 (0.6)	61.2	80.9
120	50	10	1.6 (0.8)	5.3 (1.0)	60.0	74.0
180	39	7	1.1 (0.8)	6.1 (1.1)	53.8	84.2
240	25	9	1.4 (1.0)	8.7 (1.3)	48.0	95.7

[a] Data presented for the population assessed at each follow-up visit after last DMPA injection.

Source: Table 3, Harel et al

Figure 1



*p<.05 versus participants who had BMD loss of <5% while receiving DMPA.
EOT= end of treatment.

Source: figure, Harel et al

When adjusted for EOT BMD levels in the mixed model analysis of variance, there was no statistically significant effect of dietary calcium intake, race or gynecologic age. The mixed model analysis of variance also showed that baseline BMI was a significant factor ($p<0.001$) in determining the rate of BMD recovery after discontinuation of DMPA, with a greater BMD increase in participants with a higher baseline BMI.

Reviewer comment: In the Harel paper, the Applicant does not present any new data from Study 261, but provides a *post hoc* analysis via a mixed model ANOVA to argue that recovery to baseline BMD occurs earlier than previously noted in the clinical study report and in the DMPA label. Even using the mixed model analysis, in Table 10 the column "mean % change from baseline to post-DMPA visit" does not show full recovery at the total hip until 240 weeks (as distinct from 180 weeks as the Applicant claims) and does not show total recovery at the femoral neck even by 240 weeks. The graph in Figure 1 is illustrative in demonstrating that among those subjects who lost ≥5% of their BMD, recovery is much slower and at the total hip, by 240 weeks, BMD is still not at baseline. The slow trajectory and lack of full recovery at the hip in DMPA users is concerning and it still remains unknown if use of DMPA in younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life. Given that the data continue to show there is greater loss of BMD with greater duration of use of DMPA, the warning that DMPA should not be used unless other birth control methods are inadequate, and that consideration of the patient's age and skeletal maturity should be taken into account still stands.

The Applicant relies on the Johnson article to argue that because the two cohorts (DMPA users versus non-hormonal contraceptive users) were different at baseline, they should not be directly compared. The Division agrees that the DMPA users and non-users cohorts differ in characteristics that could affect the BMD response to DMPA treatment and to recovery after withdrawal, and therefore should not be compared. However, Dr. Jaffe does not agree with the Applicant's suggestion that (b) (4) " The Applicant does not provide evidence to support this claim and the references to Johnson and Harel do not address this issue. Their estimates of the trajectory of gains in bone mass according to age that were generated from their cross-sectional baseline data are hypothesis-generating and further prospective studies would be needed to answer this question. Dr. Jaffe further notes that while bone mass accrual is accelerated in adolescence, bone mass accrues into the third decade. Many factors affect the timing and attainment of peak bone mass (skeletal site and bone compartments, gender, maturational timing, genetics, hormones, body composition, and lifestyle factors). Slowing in the rate of natural bone mass accrual cannot adequately explain the lack of full recovery of bone mass after cessation of DMPA. The lack of full recovery at the hip in DMPA users remains concerning, and is magnified by fact that the skeleton fully recovers bone mass after losses during pregnancy and lactation in adolescent and adult women.

This assessment is consistent with previous FDA reviews of Study 261. The previous review of Study 234 by Dr. Furlong on July 29, 2004 also supports this conclusion. Study 234 showed that BMD loss was progressive for the five years

of treatment, and that there was partial and progressive recovery during the 2 years of follow-up. At 5 years, the difference between the control group and the DMPA treatment group in percentage change from baseline in BMD ranged from -5.47% (femur total) to -6.55% (femoral trochanter).

The following additional articles are provided in support of the Applicant's argument regarding bone loss.

3. Bauer W, Aub JC, Albright F.J Experimental Med1929;49:145-161.

   The authors note that there are many factors which add to or subtract from the body's calcium supply, including pregnancy and lactation, and hypothesizes that the trabeculae are a reserve supply of calcium for excretion in these circumstances. They hypothesize that the bone is divided into two parts, a larger portion which makes up the structural component, and a smaller less stable portion which acts as a reserve deposit for use when the body needs calcium. They argue the anatomy supports such a theory. This paper presents a series of experiments in rabbits, adult cats, kittens and rats to determine whether the bone trabeculae act as a reserve supply of calcium. Among the findings from the experiments are findings of: 1) a diminishment of the trabeculae but not cortex when: a) parathormone is administered over a long time, b) animals are fed a low calcium diet; 2) calcium is deposited in the trabeculae when animals are on a high calcium diet; 3) when bones are growing, the cortex grows, while the trabeculae are reduced. The authors state the experiments prove the trabeculae of bones serve as a source of calcium and are a readily available reserve supply of calcium. This protects the bone shafts from depletion, until the point when the trabeculae do not have enough to meet the demand for calcium, such as during repeated pregnancies or Grave's disease.

   Reviewer comment: The studies provide an elegant demonstration of bone metabolism in animals. However, they do not directly demonstrate that humans have a reserve of calcium in trabecular bone that can be sourced while on DMPA, nor whether in humans on DMPA, calcium depletion actually occurs from reserves in trabecular bone or that these reserves can be readily replaced. The studies do not demonstrate whether calcium could come from the cortex of bone if trabecular reserves were theoretically to be depleted on DMPA. The studies do not demonstrate any hormonal changes that regulate bone metabolism in humans on DMPA, as occurs in pregnancy and lactation. A discussion on the concept of reserve bone follows below.

4. Hui SL, Slemenda CW, Johnston CC. J Clin Invest1988; 81(6):1804

   This article has already been reviewed and discussed above.

5. Riggs BL, Khosla S, Melton LJ. J Bone Miner Res 1998;13:763–773

This paper discusses a new model for the pathophysiology of involutional osteoporosis, identifying estrogen deficiency as the cause of all phases of bone loss in post-menopausal women and as a contributing cause of the continuous phase of bone loss in aging men.

6. Karlsson C, Obrant KJ, Karlsson M. Osteopor Int 2001;12:828-834

This study evaluated BMD in 73 healthy premenopausal women who were a few days postpartum. These subjects were compared with 55 healthy women derived from their normative database who were not pregnant and had not been pregnant or lactating within the past year. A total of 65 women were followed at 4.5 and 11.5 months after delivery to determine the influence of lactation on bone density. They were divided into breastfeeding for 1-6 months, breastfeeding for > 6 months and non-breastfeeding (nursed for < 1 month). They were also compared with 39 women who had had multiple (4-7) pregnancies and had breastfed, but not within the past year and compared with 58 age-matched healthy premenopausal women with a maximum of two pregnancies. The aim was to evaluate the effect of multiple pregnancies on bone density. When adjusted for total fat mass and total lean mass, women who had just delivered had 7.6% lower lumbar spine bone density and 3.9% lower total body bone density than controls. There was also greater BMD loss in breastfeeding mothers compared with non-breastfeeding mothers during the first 5 months of lactation, but no additional bone loss with lactation longer than 6 months. BMD did not decrease significantly in non-breast feeding mothers. The authors found incomplete BMD recovery five months after weaning. BMD was no lower in women with ≥4 pregnancies compared with women with ≤2 pregnancies. The authors concluded that neither multiple pregnancies nor an extended lactation period is a risk factor for future osteoporosis.

Reviewer comment: The Hui paper provides a discussion of the natural history of bone loss and the rate of fracture with bone mass and age. The Applicant uses it in their argument about bone loss in menopause. The Applicant cites the Riggs article to support their argument (b) (4) **The articles do not address bone loss related to DMPA use.**

Dr. Jaffe argues against the Applicant's assertion about bone mineral reserve:

"the Applicant's assertion that (b) (4)

(b) (4)

In contrast…at the time of menopause, women experience an accelerated rate of bone loss on the order of 1- 2% per year for the first few years of menopause, with a slowing in the rate of loss to less than 1% per year thereafter… A rate of loss of 5% per year over 4-6 years leading to a 20-30% loss in bone mass would be considered accelerated beyond the expected physiological rate, and underlying secondary pathologic causes of bone loss other should be sought. As noted in the NHANES III reference data base, there is a range of BMD in the normal healthy population. Some women will have a BMD close to 2 SD below the mean even at the time of their peak bone mass, related to a combination of genetic and lifestyle factors. Low BMD at baseline may put them at greater risk for fracture with little bone loss. Furthermore, most fractures occur in women with BMD in the range of osteopenia and not osteoporosis, (b) (4)

The Karlsson cross-sectional study provides information on BMD resulting from pregnancy and lactation and on recovery after weaning. The Applicant cites this article to support (b) (4) **In her review, Dr. Jaffe notes that while DMPA prevents ovulation, she disagrees with the sponsor's claims** (b) (4)**. Dr. Jaffe outlines the unique hormonal and physiological changes that affect calcium and vitamin D handling with pregnancy and lactation, which are not induced by DMPA treatment. In pregnancy, estrogen levels are markedly increased. In addition, she notes that there are several physiologic compensatory mechanisms engaged to meet the calcium needs of the growing fetus. Specifically addressing the Applicant's focus on lactation, Dr. Jaffe states:**

> **"increased calcium demands are met primarily by mobilization of calcium from the skeleton via the action of parathyroid hormone-related protein (PTHrp) in addition to the prolactin-mediated decline in estrogen levels. PTHrp may also play a role in the observed increase in renal tubular reabsorption of calcium, a compensatory mechanism that is not induced by use of DMPA. Markers of both bone resorption and bone formation are elevated during lactation, consistent with a high turnover state. Animal studies in lactation have demonstrated that BMD is reduced by 1-3% per month, in contrast to 1-3% per year in early postmenopausal women. Upon weaning, gains of 0.5-2% per month have been seen, which exceeds that reported after DMPA withdrawal."**

Dr. Jaffe notes that most epidemiologic studies of pre- and postmenopausal women have found no adverse effect of a history of pregnancy and lactation on peak bone mass, bone density, or hip fracture risk. With respect to adolescent women and attainment of peak bone mass, in an NHANES III analysis of 819 women aged 20–25, those who had been pregnant as adolescents had the same BMD as women who had never been pregnant or had been pregnant as adults. Interestingly, adolescents who breastfed actually achieved higher BMD than women who had not breastfed or who were never pregnant. Thus, it appears that, although adolescents lose bone during lactation, they recover fully without any long-term adverse skeletal effects. Transient and reversible lowering of BMD associated with pregnancy and lactation in young women is generally not a concern.

Unlike the hormonal changes that occur during pregnancy and lactation, the hormonal changes produced by DMPA may persist for many years if DMPA is used for an unrestricted duration. The lack of full recovery of hip BMD even after five years off treatment seen in women who used DMPA for more than two years duration as noted in the studies included in the current labeling remains concerning.

7. Orr-Walker BJ, Evans MC, Ames RW, Clearwater Jm, Cundy T, Reid IR. Clin Endocrinol 1988;49:615-618.

This is a cross-sectional study from Auckland New Zealand of bone density in 346 postmenopausal women, 34 of whom were former users of DMPA. Subjects were involved in studies of osteoporosis prevention in the authors' department. Past hormonal contraceptive use was ascertained via questionnaire and DXA scans were performed. The median age at which DMPA use began was 41 years and the median duration of use was 3 years. The authors found no significant differences in bone density at any site between the DMPA users and controls; however there was a trend toward lower bone density in former DMPA users who had been exposed for > 2 years. The authors noted no correlations between bone density and age at discontinuation or time between DMPA discontinuation and menopause. The authors concluded that their study provided reassurance that there may not be residual osteopenia such that women enter the postmenopausal years with low bone density and have substantially higher rates of fracture if they use DMPA. In the discussion, they argue that any residual effects of DMPA on bone density are small and that the effect of DMPA on bone density is completely reversible within two years of restoration of eugonadism. Though some of their subjects took DMPA within two years of menopause, they reason that bone loss in that time frame is low and that most of the bone loss associated with DMPA takes place at the time of initiation.

Reviewer comment: The authors do acknowledge that the number of women in the DMPA past-use group is small. Further, ascertainment of DMPA use was by recall, without confirmation from an external source, such as medical records or claims/prescription records. They do acknowledge that more research on the long-term effects of DMPA on bone is warranted, including on larger numbers of women with longer durations of use. However, they believe these data will never be available, because the number of former long-term users will be small, and bone densitometers are evolving. It is possible that such information may not become available. The authors conclude that a small group of women who have a significant fracture risk premenopausally should avoid DMPA, including those with pre-existing bone disease, anorexia nervosa and steroid use, athletes and military personnel (who load their skeletons more than average). DMPA is not currently contraindicated in these conditions/subjects, nor should it be, though clinicians likely do assess subjects' risk when prescribing new medications, including DMPA.

The Applicant uses this article to argue various points. The Applicant argues that the small number of past DMPA users does not preclude drawing conclusions because though the changes in BMD between the past DMPA users and nonusers are not statistically significant, they present a mixed picture, with different degrees of loss at different measurement sites, suggesting random variation rather than consistently lower BMD at all sites in the DMPA cohort. They argue (b) (4) **The Applicant suggests** (b) (4) **Our previous review of Study 261 actually found that in women who used DMPA for > two years, only lumbar spine BMD recovered to baseline levels after the treatment was discontinued. However, at the femoral neck and total hip sites, BMD did NOT return to baseline for up to 5 years posttreatment in subjects treated for > 2 years.**

The Applicant also argues that bone loss due to menopause is also not a fixed amount but a proportional amount, so while the past DMPA users might enter menopause with lower BMD, their absolute loss in bone density during early menopause might have been slightly attenuated since some bone loss had already occurred (as a result of DMPA exposure). The Applicant also argues that past DMPA use is not considered an important predictor of postmenopausal fracture risk and therefore is not included in the FRAX algorithm. These arguments have been addressed in previous reviewer's comments. The Applicant makes too many assumptions based on a small number of patients in this article and does not provide data to support them.

7.4 Supportive Safety Results

Not applicable for this submission.

7.5 Other Safety Explorations

Not applicable for this submission.

7.6 Additional Safety Evaluations

Not applicable for this submission.

7.7 Additional Submissions / Safety Issues

Not applicable for this submission.

8 Postmarket Experience

No additional postmarket data were reviewed for this submission.

9 Appendices

9.1 Literature Review/References

DBRUP also conducted a literature search which yielded the following publications; they are reviewed here.

1. Lopez LM, Chen M, Mullins Long S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Syst Rev. 2015 Jul 21;(7):CD009849. doi: 10.1002/14651858.CD009849.pub3. Review.

   This was a systematic review of the evidence from observational studies of hormonal contraceptives used for contraception and the risk of fracture in women. Fourteen studies (7 case-control and 7 cohort studies) which examined oral contraceptives (OCs), DMPA, and the hormonal intrauterine device (IUD) were included; six of which included moderate to high quality evidence. Two case-control studies examined progestin-only contraceptives. One reported increased fracture risk for DMPA ever-use (OR 1.44, 95% CI 1.01 to 2.06), more than four years of use (OR 2.16, 95% CI 1.32 to 3.53), and women over 50 years old. The other reported increased risk for any past use, including one or two prescriptions (OR 1.17, 95% CI 1.07 to 1.29) and for current use of 3 to 9 prescriptions (OR 1.36, 95% CI 1.15 to 1.60) or 10 or more (OR 1.54, 95% CI 1.33 to 1.78). The authors conclude that DMPA users may have an increased fracture risk.

Reviewer comment: The key articles included on DMPA in this Cochrane review, Vestergaard and Lanza, have been reviewed by FDA already. The review also mentions the case-control study by Meier, also reviewed by FDA previously, and a cohort study by Kaunitz in 2006, in which new users of DMPA between the ages of 25-35 were compared with similarly aged users of non-hormonal contraceptive methods. The primary endpoint was change in BMD. Fracture was recorded as an adverse event, and shown for the treatment phase and the post-treatment follow-up. Fracture risk was not adjusted for potential confounding factors; the study groups did not differ significantly for fracture risk. These two studies were not included in the sensitivity analysis upon which the review bases its conclusions on DMPA as they did not meet the required level of evidence.

2. Modesto W, Bahamondes MV, Bahamondes L. Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate. J Womens Health (Larchmt). 2015 Aug;24(8):636-40. doi: 10.1089/jwh.2014.5077.

This was a cross-sectional study comparing 47 long-term (10 years or more) DMPA users and 41 copper IUD users, evaluating BMD at the lumbar spine and femoral neck as measured by DXA. The participants were 27 to 57 years of age, had initiated use of the method prior to 40 years of age and had Follicle-stimulating Hormone values <40 mIU/mL. The authors found that 68.1% and 36.6% of the DMPA and copper IUD users, respectively, had low bone mass and 29.8% and 2.4% of DMPA and copper IUD users, respectively, had osteoporosis. They also found an association between decreasing BMD and increasing number of years of DMPA use. The authors concluded that long-term DMPA use was associated with low bone mass and osteoporosis in women who had used the method for 10 years or more and that DMPA users with longer duration of use showed a greater bone mass loss.

Reviewer comment: This study took place in Brazil, included a small number of subjects and did not take into account variables that could impact BMD, such as family history of osteoporosis, fractures, calcium intake, coffee consumption or sun exposure. The results may not be generalizable to the US population but do confirm data that show a reduction in BMD with long-term DMPA use and decreasing BMD with increasing duration of use. The DEPI review of this study in concert with others concludes that the existing literature suggest an increased risk for bone fractures with DMPA use overall, and some studies suggest that the fracture risk may increase with increasing duration of DMPA use. The major strength is that the studies show relative consistent findings across different study designs and populations.

3. Viola AS, Castro S, Bahamondes MV, Fernandes A, Viola CF, Bahamondes L. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011 Nov;84(5):e31-7. doi: 10.1016/ j.contraception.2011.06.012.

   This was a cross-sectional study comparing forearm BMD in 232 DMPA users with 232 copper IUD users matched for age, BMI and years of use. The women were divided into groups according to the length of DMPA use: 1–3, 4–6, 7–9, 10–12 and 13–15 years of use. Copper IUD users were more likely to be white, have greater parity and physical activity than DMPA users. There was no significant difference in BMD measurements at the distal or ultra-distal radius between the current users of DMPA and IUD users; however, women who had used DMPA for 13–15 years showed significantly lower BMD at the distal and ultradistal radius when compared to IUD users. For both DMPA and IUD users, the authors noted a direct correlation between higher BMD and BMI (kg/m^2) and an inverse correlation between BMD and age.

4. Viola AS, Castro S, Marchi NM, Bahamondes MV, Viola CF, Bahamondes L. Long-term assessment of forearm bone mineral density in postmenopausal

former users of depot medroxyprogesterone acetate. Contraception. 2011 Aug;84(2):122-7. doi: 10.1016/j.contraception.2010.11.007.

This study evaluated BMD in the non-dominant forearm using DXA over a period of up to 5 years in 79 postmenopausal women, 24 of whom were former DMPA users and 55 of whom were former copper IUD users. There were no statistically significant differences in forearm BMD measurements between postmenopausal women who had been long-term users of DMPA and those who had been long-term users of an IUD. Evaluation of BMD after the menopause showed slightly higher values in former DMPA users compared with non-users. The authors suggest that the hypoestrogenism induced by DMPA use appears to exert little effect on BMD after the menopause, even when BMD was evaluated as long as 5 years after menopause.

Reviewer comment: This study included a small number of subjects who had follow-up out to five years post-menopause; the DMPA cohort is especially small. This may account for the lack of statistically significant differences. With this small sample size, it is not possible to conclude that DMPA use results in no deleterious effects after menopause (b) (4) **The DMPA users had an average of ten years of exposure, whereas the IUD users had 17.8 years of exposure (p<0.001). This confounding factor could also influence findings related to relative BMD in the two groups.**

5. Pongsatha S, Ekmahachai M, Chaovisitsaree S, Suntornlimsiri N, Morakote N. Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: a cross sectional study. J Med Assoc Thai. 2009 Oct;92(10):1263-7.

   This was a cross-sectional study of 100 Thai women, 50 of whom used DMPA for at least 2 years and 50 of whom were non-hormonal users. BMD was measured at the lumbar spine, femur and distal radius, and ulna once at enrollment. There were no differences between groups in mean age, BMI or parity. The mean duration of DMPA use was 73.6 months (±56 months). There was significantly lower BMD at the lumbar spine in the DMPA group but there was no significant difference in BMD between groups at the femur, distal radius, and ulna. The authors conclude that long-term use of DMPA has a negative impact on lumbar spine BMD, which has a high content of trabecular bone.

Reviewer comment: DEPI also reviewed these four articles and one additional article identified in their search. DEPI concluded: "that the existing literature suggest an increased risk for bone fractures with DMPA overall, and some studies suggest that the fracture risk may increase with increasing DMPA use."

The major strength of the analysis is that the studies show relatively consistent findings across different designs and populations. However, the studies have

limitations, including small sample size, potential misclassification of exposure and outcome, inadequate control for potential residual confounding factors such as history of fall, history of epilepsy, sociodemographic status (age, education), and behavioral factors (sports/physical activity). New studies published since DEPI's last review of the literature continue to suggest that prolonged use of DMPA is associated with an increased risk of fracture.

9.2 Labeling Recommendations

The Applicant proposed changes to the label, specifically to (b) (4), and change the (b) (4), Warnings and Precautions, (b) (4) and Clinical Studies sections. An example is of the Boxed Warning below. Proposed additions to current USPI text are shown in **bold-underline** and proposed deletions are shown as ~~strike-through~~.

The proposed changes to other sections of the label mirrored those above.

We disagree with the Applicant's assertions that the studies (b) (4); our findings indicate an association between DMPA use, loss of bone mineral density, and increased risk of fracture. We disagree with (b) (4)

Therefore, we do not recommend any changes to the label.

9.3 Advisory Committee Meeting

An advisory committee meeting was not required for this supplement.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHERINE A SEWELL
10/02/2017

LISA M SOULE
10/02/2017
I concur with Dr. Sewell's conclusions and recommendation.

Memorandum of Consultation

NDA 20246 Supplements 060 and 062

NDA 21583 Supplements 033 and 034

SPONSOR: Pfizer

PRODUCT: Depo-medroxyprogesterone Acetate (DMPA)

Indication: Prevention of pregnancy

DATE OF SUBMISSIONS: Oct 6, 2016 (Clinical Overview)

REQUESTED BY: Catherine Sewell, MD

RESPONSE DATE: July 2, 2017

BONE TEAM CONSULTANT: Linda S. Jaffe, M.D.

BONE TEAM LEADER: Theresa Kehoe, M.D.

BACKGROUND

Depo-Provera CI (NDA 20246) is a long-acting progestin-only contraceptive containing 150 mg of medroxyprogesterone acetate (MPA), administered intramuscularly (IM) every three months. Depo-SubQ provera 104 (NDA 21583), is a similar quarterly injection, but is given in a lower dose (104 mg) and administered subcutaneously in the anterior thigh or abdomen. In 2004, FDA added a boxed warning to the labels regarding the risk of bone density loss and the possibility of osteoporotic fracture. The current boxed warning reads as follows:

> ***WARNING: LOSS OF BONE MINERAL DENSITY***
>
> • *Women who use Depo-Provera Contraceptive Injection 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 longterm birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate."*

In July of 2011, FDA approved an efficacy supplement with changes to the label including more recent data on fracture risk. The Applicant, Pfizer, has now submitted efficacy supplements with literature and **additional analyses of previously submitted data**, with the aim of changing the boxed warning, (b) (4), and to make changes to the (b) (4), Warnings and Precautions, (b) (4) and Clinical Studies sections consistent with that.

The Applicant proposes the following changes to the boxed warning (removed text ~~strikethrough~~, added text <u>underlined</u>):

DEPI has been asked to review the analysis of the General Practice Research Database (GPRD) UK study, providing fracture data in adult users of DMPA as well as the updated literature review provided by the sponsor. The bone team has been asked to review the concepts and rationale presented in the sponsor's Clinical Overview and address the following 4 questions:

1. **Comment on Applicant's theory of premenopausal women having a bone 'reserve' from which calcium can be mobilized without impacting normal bone strength (e.g., during pregnancy and lactation). The Applicant also claims that DMPA pharmacologically mimics pregnancy and (i) prevents ovulation, which is its intended effect, but also (ii) triggers the same mobilization of calcium as do**

pregnancy/lactation, [redacted] (b) (4) . Please comment on the validity of this claim.

2. **Provide accepted list of each type of fracture (fragility vs. traumatic). Comment on whether it is appropriate to evaluate fractures other than fragility/osteoporotic fractures in epidemiologic studies of premenopausal users of DMPA in attempting to assess whether the drug's adverse impact on BMD may translate into adverse clinical effects (i.e., increased rate of fracture).**

3. **Comment on Applicant's position that BMD is a handy tool to assess bone strength but does not provide fundamental definition of osteoporosis. They say actual bone density cannot be measured in life. Do we have any better tools? Is this the best surrogate we have?**

4. **The adolescent study was already reviewed by the FDA in 2010-2011 and was used in our argument to strengthen the boxed warning about bone density. BUT the Applicant has a new argument about that study— [redacted] (b) (4) in their proposed labeling (they reference Johnson CC et al. Longitudinal study of depot medroxyprogesterone acetate (Depo-Provera) effects on bone health in adolescents: study design, population characteristics and baseline bone mineral density. Contraception 2008;77:239-48.)This is where (the) new question lies. They argue that the population of 12-18 year olds who got DMPA in that study were skeletally more mature at baseline—higher BMD, especially the younger girls, when compared with the girls who were not using any hormonal contraception. Because they were skeletally more mature, they would not be expected to accrue bone mass at the same rate, but at a lower rate. Therefore, the fact that they have a significant amount of bone loss on DMPA and then regain bone mass more slowly and accrue less for their age (more slowly than and less than the non-hormonally treated girls accrue bone mass) is due to the baseline differences [redacted] (b) (4) (The) question is: is this true, that skeletally more mature teens accrue bone mass more slowly through adolescence (say, over 5 years) than less mature ones? Does this make sense, given that we gain bone mass up until like 30—long past when people are "skeletally mature"?**

RESPONSES

Question 1. Comment on Applicant's theory of premenopausal women having a bone 'reserve' from which calcium can be mobilized without impacting normal bone strength (e.g., during pregnancy and lactation). The Applicant also claims that DMPA pharmacologically

mimics pregnancy and (i) prevents ovulation, which is its intended effect, but also (ii) triggers the same mobilization of calcium as do pregnancy/lactation, (b) (4) Please comment on the validity of this claim.

Response: A 20-30% bone mineral reserve in women is not supported by current evidence. Important compensatory hormonal and physiological changes with respect to calcium and vitamin D handling occur with pregnancy and lactation that are not induced by DMPA treatment.

Discussion:

The premise that women have a 20-30% reserve in bone mineral that is lost prior to experiencing an increased risk of fracture has not been substantiated in the medical literature or in studies of bone physiology and mineral homeostasis. In contrast to the sponsor's suggestion, at the time of menopause, women experience an accelerated rate of bone loss of on the order of 1- 2% per year for the first few years of menopause, with a slowing in the rate of loss to less than 1% per year thereafter (Macdonald HM et al. 2004, Shieh A et al 2016). A rate of loss of 5% per year over 4-6 years leading to a 20-30% loss in bone mass would be considered accelerated beyond the expected physiological rate, and underlying secondary pathologic causes of bone loss other should be sought.

As noted in the NHANES III reference data base, there is a range of BMD in the normal healthy population. Some women will have a BMD close to 2 SD below the mean even at the time of their peak bone mass, related to a combination of genetic and lifestyle factors. Low BMD at baseline may put them at greater risk for fracture with little bone loss. Furthermore, most fractures occur in women with BMD in the range of osteopenia and not osteoporosis, which is inconsistent with a concept of a universal 20-30% BMD reserve (Siris ES, et al. Osteoporos Int. 2006). While DMPA prevents ovulation, its intended effect, we disagree with the sponsor's claims that DMPA mimics pregnancy and lactation (b) (4)

Pregnancy

DMPA reduced estrogen levels, thereby increasing the risk for bone loss and fracture. In contrast, in pregnancy, estrogen levels are markedly increased. In addition, there are a number of physiologic compensatory mechanisms that exist to meet the calcium needs of the growing fetus, including a doubling of the intestinal absorption of calcium as well as placental hydroxylation of vitamin D to 1, 25-dihydroxyvitamin-D thereby doubling levels of this hormone. PTHrp levels also increase during pregnancy and may play a role in activation of vitamin D as well as the inhibition of maternal osteoclastic bone resorption (Kovacs CS and Kronenberg HM, 2013).

BMD studies in pregnancy are limited as expected, and confounded by the fact that the postpartum BMD measurement is often performed 2-6 weeks postpartum when women are lactating. Nonetheless, some have shown decreases in spine BMD of up to 5%. Numerous studies of osteoporotic or osteopenic women have failed to find a significant association of parity with bone density or fracture risk (Kovacs CS et al, 1997, Sowers M et al, 1996).

Lactation

Postpartum, 1,25-dihydroxyvitamin D levels and intestinal calcium absorption decrease to pregravid levels within days. During lactation, increased calcium demands are met primarily by mobilization of calcium from the skeleton via the action of PTHrp in addition to the prolactin-mediated decline in estrogen levels. PTHrp may also play a role in the observed increase in renal tubular reabsorption of calcium, a compensatory mechanism that is not induced by use of DMPA. Markers of both bone resorption and bone formation are elevated during lactation, consistent with a high turnover state. Animal studies have demonstrated that BMD is reduced by 1-3% per month, in contrast to 1-3% per year in early postmenopausal women. Upon weaning, gains of 0.5-2% per month have been seen, which exceeds that reported after DMPA withdrawal.

The vast majority of epidemiologic studies of pre- and postmenopausal women have found no adverse effect of a history of pregnancy and lactation on peak bone mass, bone density, or hip fracture risk (risk (Kovacs CS et al, 1997, Sowers M et al, 1996). With respect to adolescent women and attainment of peak bone mass, an NHANES III analysis of 819 women aged 20–25, those who had been pregnant as adolescents had the same BMD as women who had never been pregnant or had been pregnant as adults. Interestingly, adolescents who breastfed actually achieved higher BMD than women who had not breastfed or who were never pregnant (Chantry CJ 2004). Thus, it appears that, that although adolescents lose bone during lactation they recover fully without any long-term adverse skeletal effects.

Rarely, both pregnancy and lactation have been associated with osteoporosis and fracture. Underlying low bone mass and low calcium and vitamin D intake may be a contributing factor in these women. BMD tends to recover upon weaning. Transient osteoporosis of the hip is a focal abnormality characterized by a focal reduction in bone mass and focal edema that does not appear to be related to changes in calcitropic hormones.

Unlike the hormonal changes that occur during pregnancy and lactation, the hormonal changes produced by DMPA may persist for many years if DMPA is used for an unrestricted duration. Transient and reversible lowering of BMD associated with pregnancy and lactation in young women is generally not a concern. On the other hand, the lack of full recovery of hip BMD even after five years off treatment seen in women who used DMPA for more than two years duration

as noted in the studies included in the most recent labeling remains concerning. As stated in the Citizen Petition response (Docket No. FDA 2013-P-0380/CPI; submission date 4/26/13, signed 6/25/15): "Given the lack of full BMD recovery five years after discontinuation of DMPA in adolescents, it remains to be seen whether young women who receive DMPA will achieve peak bone mass similar to that of women who do 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. At this point, insufficient time has elapsed in the USA since the 1992 approval of DMPA to answer 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."

Question 2. Provide accepted list of each type of fracture (fragility vs. traumatic). Comment on whether it is appropriate to evaluate fractures other than fragility/osteoporotic fractures in epidemiologic studies of premenopausal users of DMPA in attempting to assess whether the drug's adverse impact on BMD may translate into adverse clinical effects (i.e., increased rate of fracture).

Response: A fragility fracture is defined as a fracture that results from a fall from a standing height or less. The locations of typical fragility fractures include those of the spine, hip, femur, ankle, pelvis, ribs, humerus, and forearm. Fractures of the skull, nose, face, hands, feet, patella, clavicle and sternum are generally not considered "fragility" or osteoporotic fractures.

Once women with a history of DMPA use become postmenopausal, epidemiology studies in this population may help discern the impact of DMPA use in adolescents and young adulthood on fragility fracture risk later in life. Fractures in adolescents are typically related to trauma. Carefully designed epidemiology studies in premenopausal DMPA users might help clarify if there is an increased risk of fractures other than osteoporotic fractures with DMPA use such as stress fractures or traumatic fractures.

Discussion:

In contrast to the sponsor's suggestion, most osteoporotic fragility fractures occur with a fall. A fragility fracture is defined as a fracture that results from a fall from a standing height or less. This definition also includes morphometric vertebral fractures that may be completely asymptomatic and atraumatic, or present as height loss as the sponsor suggests. However, spontaneous collapse of the femoral neck is not typical of osteoporotic fracture. Osteoporotic hip fractures also typically occur as a result of a fall from standing height or less. The locations of typical fragility fractures include those of the spine, hip, femur, ankle, pelvis, ribs, humerus, and forearm. Fractures of the skull, nose, face, hands , feet, patella, clavicle and sternum are generally not considered "fragility" or osteoporotic fractures.

In addition, stress fractures are not considered fragility fractures. Stress fractures result from repetitive use injuries in which the accumulation of microdamage exceeds the intrinsic ability of the bone to repair that damage, resulting in a clinical fracture. They have been known to occur in individuals with both normal bone as well as bone with decreased bone strength. Identifying individual factors in addition to repetitive force that increase the risk for this type of fracture is complex since clinical factors often track together such as in the athletes' triad (oligo-amenorrhea, low energy intake and low BMD.) The extent to which hypoestrogenemia alone plays a role is uncertain. (see Review by Moreira CA and Bilezikian JP 2017.) Data regarding whether DMPA is associated with an increased risk for stress fractures are sparse. Female military recruits have been observed to have an increase in the risk for stress fracture in general, but an even greater risk (48-71% increased risk) has been seen among non-hispanic white military recruits who use DMPA (Lappe JM, et al 2001, Lappe, JM et al 2008). There are no additional data addressing whether DMPA increases the risk of stress fractures in other groups of women.

On March 4, 2011, DEPI reviewed data and post-hoc analyses from The General Practice Research Database (GPRD) study as well as an updated literature review of DMPA use and fracture that were submitted by the sponsor. The GPRD study is a large retrospective cohort study performed in the UK to examine the association between DMPA use and fracture. A post –hoc analysis was submitted to examine types of fractures. Both this study as well as the literature submitted had limitations, but there was a suggestion of an increased risk of appendicular fractures. In a post hoc analysis pf the GPRD submitted by the sponsor, an increase in appendicular fractures was noted (IRR =1.38, 95% CI 1.30-1.46). However, "appendicular sites" included the arm, leg, hand, foot, hip, shoulder, wrist, ankle, clavicle, rib and sternum, and some of these sites are typical sites of osteoporotic fracture. In addition, the nature of this post hoc analysis and the other studies are hypothesis generating but do not allow for conclusions (see full review in DARRTS.) Additional data from the GPRD study has recently been submitted by the sponsor and is currently under review by DEPI.

Question 3. Comment on Applicant's position that BMD is a handy tool to assess bone strength but does not provide fundamental definition of osteoporosis. They say actual bone density cannot be measured in life. Do we have any better tools? Is this the best surrogate we have?

Response: DXA remains the gold standard clinical tool for assessing BMD. Furthermore, BMD in adolescence and premenopausal women has been demonstrated to correlate with fracture risk.

Discussion:

Dual x-ray absorptiometry (DXA) measures bone mineral content (BMC) and area and computes areal bone mineral density (BMD) in gm/cm2. BMD by DXA is the standard tool for assessing bone mass and fracture risk and for monitoring changes in bone density over time in children, adolescents and adults. Normative data are available for BMD for children and adolescents ages 5 to 20 (Zemel et al, 2011) as well as adults ages 20-84 through the NHANES III database.

The relationship between BMD and fracture in postmenopausal women is robust. There is an exponential relationship between BMD and fracture risk, with approximately a doubling of fracture risk for each 1 SD decline from the mean (Marshall D et al, 1996). That relationship is exponentially strengthened with advancing age. It is noteworthy that while BMD provides an assessment of fracture risk, BMD does not predict who will actually fracture; the majority of patients who fracture have a BMD in the range of osteopenia (T-score between -1.0 and -2.5) rather than osteoporosis (T-score $\leq$ -2.5) (Siris ES et al, 2006). Factors in addition to BMD contribute to fracture risk as discussed below.

In premenopausal women, including adolescents, data informing the relationship between BMD and fracture risk are less robust. Therefore, the WHO criteria and diagnostic categories according to T-score (ie-osteopenia and osteoporosis) are generally not applied to this population in the absence of known secondary causes of osteoporosis. The International Society for Clinical Densitometry (ISCD) recommends using age-matched comparisons (Z-scores) to assess whether or not a patient's BMD is within the expected range for age, defined as within 2 SD of the age-matched mean. In this population, BMD by DXA is standard of care to assess skeletal health and changes in areal bone mineral content and density over time, as well as to gain insight into fracture risk (Wasserman H et al, 2016). In children and adolescents, DXA has been a reliable tool to assess bone loss and/or fracture risk in patients with underlying conditions such as anorexia nervosa, cystic fibrosis, inflammatory bowel disease, cerebral palsy, glucocorticoid use as well as DMPA treatment.

A relationship between BMD and fracture has also been demonstrated in young women. Cross-sectional studies have demonstrated that premenopausal women who experience Colles' fractures and female military recruits and athletes who experience stress fractures have lower BMD than those who do not fracture fracture (Hung LK ,et al 2005; Lappe J, et al 2005; Lauder TD et al, 2000; Myburgh KH, et al 1990). Furthermore, fractures in premenopausal women predict fractures later in life. Women who fracture while premenopausal have a 35%-74% greater likelihood of experiencing a fracture when postmenopausal as compared to those who do not fracture (Hosmer WD et al 2002; Wu F, et al 2002.) In children, a 1 SD decrease in BMD has been associated with a 40% increase in fracture risk. Additionally, forearm fractures in children reflect deficits in bone mineralization throughout the skeleton, not just at the forearm (Kalkwarf HJ, et al 2011).

Early adolescence is a particular period of concern for increased fracture risk. At that time, linear bone growth may outpace bone mineralization, leading to less skeletal mineralization overall, and risk for a transient increase in bone fragility and fracture (Rauch F, 2012). Therefore, it is concerning that factors that may add to demineralization such as DMPA could further compound this risk.

BMD is only one determinant of fracture risk. Other intrinsic properties of bone such as microarchitecture, material properties, quality and geometry are not assessed by BMD. With aging, cell senescence and the release of local inflammatory cytokines may play an additional role in skeletal fragility that is not detected by DXA. In addition, sarcopenia may further compound fracture risk in the elderly. pQCT allows for more information with respect to characteristics of the individual bone compartments including total bone volume; trabecular bone volume, thickness, spacing; and cortical thickness and porosity. Double tetracycline labeled bone biopsy is the gold standard for assessing microarchitecture, cellular composition, bone turnover and other material properties of bone. However, these latter 2 tests expose patients to higher doses of radiation, are expensive and invasive, and not practical for use in clinical practice or large studies.

Overall, these data support the use of BMD by DXA to predict fracture in adolescents and premenopausal women and support the association between a reduction in BMD and the increased risk of fracture in this population.

Question 4. The adolescent study was already reviewed by the FDA in 2010-2011 and was used in our argument to strengthen the boxed warning about bone density. BUT the Applicant has a new argument about that study— (b) (4) **in their proposed labeling (they reference Johnson CC et al. Longitudinal study of depot medroxyprogesterone acetate (Depo-Provera) effects on bone health in adolescents: study design, population characteristics and baseline bone mineral density. (Contraception 2008;77:239-48.) This is where (the) new question lies. They argue that the population of 12-18 year olds who got DMPA in that study were skeletally more mature at baseline—higher BMD, especially the younger girls, when compared with the girls who were not using any hormonal contraception. Because they were skeletally more mature, they would not be expected to accrue bone mass at the same rate, but at a lower rate. Therefore, the fact that they have a significant amount of bone loss on DMPA and then regain bone mass more slowly and accrue less for their age (more slowly than and less than the non-hormonally treated girls accrue bone mass) is due to the baseline differences** (b) (4) **(The) question is: is this true, that skeletally more mature teens accrue bone mass more slowly through adolescence (say, over 5 years) than less mature ones? Does this make sense, given that we gain bone mass up until 30—long past when people are "skeletally mature"?**

Response: While bone mass accrual is accelerated during the adolescent growth spurt, bone mass accrual continues into the 3rd decade. (b) (4)

Discussion:

Bone mineral accrual parallels percentile charts for height velocity. During growth, vertebral cancellous density is stable prior to puberty, and increases significantly between the ages of 12 and 17 years in boys and 10-15 years in girls. Over half of the skeleton is laid down during adolescent years, with the greatest accruals occurring about 6 months after the adolescent growth spurt. Gains continue for years thereafter with some studies demonstrating gains in the 3rd decade of life. In the axial skeleton, bone acquisition peaks at the time of sexual and skeletal maturity, while appendicular properties do not peak but rather continue to change throughout life with ongoing periosteal and endosteal expansion. BMD is similar for blacks and whites through Tanner stage 3, but diverges at Tanner stages 4-5, with higher BMD in blacks. (Gordon CM et al, 2017).

The timing and attainment of peak bone mass is dependent upon the skeletal site and bone compartments, gender, maturational timing, genetics, hormones (including estrogens, androgens, growth hormone/IGF-1), body composition, and lifestyle factors (including activity, nutrition, calcium and vitamin D intake, and smoking/smoke exposure.) Cross-sectional BMD data demonstrate that BMD peaks at about age 29 and decreases thereafter, with accelerated bone loss at the time of menopause in women. pqCT studies have demonstrated that trabecular bone loss occurs in the peripheral skeleton as early as the early 20s, while cortical loss starts after age 40.

As the sponsors have pointed out in their early supplements, the study of adolescents by Johnson et al. demonstrated that the DMPA and control groups were dissimilar at baseline and therefore, a meaningful comparison of BMD changes over time between users and non-users was not appropriate. We agree that the two groups differ in characteristics that could affect the BMD response to DMPA treatment and to recovery after withdrawal, and therefore should not be compared. The sponsor suggests (b) (4) However, the studies by Johnson and Harel do not address this issue nor do they provide evidence to support this claim. Estimates of the trajectory of gains in bone mass according to age that were generated from their cross-sectional baseline data are hypothesis generating; prospective studies are required to answer this question. It is noteworthy that the skeleton fully recovers bone mass after losses during pregnancy and lactation in women of both similar as well as older ages, raising concerns about lack of full recovery at the hip in DMPA users.

Data are currently not available to address whether bone loss during adolescence or failure to reach peak bone density in adolescents treated with DMPA impacts osteoporotic fracture risk during adulthood or after menopause. As addressed in the Citizen Petition, at this point, DMPA has not been marketed long enough to have sufficient data on the risk of postmenopausal (osteoporotic) fractures in former DMPA users. Depo-Provera was approved in 1992, so it has only been marketed in the US for 25 years (it became available in the UK in 1987). Therefore, in general, women who took DMPA in adolescence and early adulthood have not yet become postmenopausal or are just entering menopause. Future studies will be needed to determine whether DMPA use in adolescents or the premeneopausal years impacts osteoporotic fracture risk later in life.

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/s/

LINDA S JAFFE
08/30/2017

THERESA E KEHOE
08/30/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

NON-CLINICAL REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Date:	November 19, 2020
NDA # SDN #	20-246 Depo-Provera IM SDN 690 Efficacy supplements 60 and 62 Class 2 resubmissions
NDA # SDN #	21-583 Depo-Provera SC SDN 222 Efficacy supplements 33 and 34 Class 2 resubmissions
Sponsor:	Pharmacia and Upjohn
Drug:	Depo Medroxyprogesterone Acetate (DMPA)
Indication:	Prevention of pregnancy
Reviewer:	Leslie McKinney, PhD

This memo addresses efficacy supplements submitted to NDAs 20-246 and 21-583.

These supplements were originally submitted on 10-06-2016 but were CR'd on 10-6-17 based on clinical concerns. They were resubmitted on 6-5-20 for additional clinical review.

The purpose of the efficacy supplements is to report the results of post-marketing clinical trials that assess the effect of Depo-Provera on fracture risk in premenopausal women, and to update the labels with the results of these trials. There were no nonclinical data submitted and there were no modifications to the nonclinical sections of the labeling. No nonclinical input is necessary. We defer to the clinical team for final approval.

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/s/

LESLIE C MCKINNEY
11/25/2020 03:16:47 PM

KIMBERLY P HATFIELD
11/25/2020 03:20:58 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	020246 S60 & S62 021583 S33 & S04
Drug Name:	Depo-Provera and Depo-SubQ Provera 104 (medroxyprogesterone acetate)
Indication(s):	Prevention of Pregnancy
Applicant:	Pharmacia and Upjohn Co (subsidiary of Pfizer, Inc.)
Date(s):	Submission Date: October 6, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Catherine Sewell, M.D., Clinical Reviewer
Project Manager:	Charlene Williamson

Keywords: Clinical studies, NDA review

Memorandum

This submission provides the supportive clinical reports and literature articles referenced in the Clinical Overview accompanying the submission of October 6, 2016 regarding current understanding of the effect of product use on bone and fracture risk of Depo-Provera and Depo-SubQ Provera 104 (medroxyprogesterone acetate). This submission is referenced to NDA 20246 for Depo-Provera (medroxyprogesterone acetate) Contraceptive Injection Supplement S-060 and S-062 and NDA 21583 for Depo-SubQ Provera 104 (medroxyprogesterone acetate) Supplement S-033 and S-034.

No additional clinical data were submitted in this application and statistical review is not necessary.

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/s/

WEIYA ZHANG
10/06/2017

MAHBOOB SOBHAN
10/06/2017

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	020246
Drug Name:	DEPO-PROVERA® (medroxyprogesterone acetate, USP) Contraceptive Injection 150 mg/mL
Indication(s):	Prevention of Pregnancy
Applicant:	Pfizer Essential Health Research & Development
Date(s):	Submission Date: January 18, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Catherine Sewell, M.D., Clinical Reviewer
Project Manager:	Charlene Williamson

Keywords: Clinical studies, NDA review

Memorandum

This submission provides the supportive clinical reports and literature articles referenced in the Clinical Overview accompanying the submission on 6 October 2016 regarding current understanding of the effect of product use on bone and fracture risk of Depo-Provera® (medroxyprogesterone acetate, USP). This submission is referenced to NDA 20-246 for Depo-Provera® (medroxyprogesterone acetate, USP) Contraceptive Injection and the Prior Approval Supplement S-060 and S-062 submitted on 6 October 2016.

No clinical data were submitted in this application and statistical review is not necessary.

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/s/

WEIYA ZHANG
09/21/2017

MAHBOOB SOBHAN
09/21/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review

Date:	June 29, 2017
Reviewers:	Wei Liu, Ph.D., MSc, Division of Epidemiology II (DEPI II) Jessica Kim, Ph.D. Division of Biometric VII (DB VII)
Team Leaders:	Jie (Jenni) Li, Ph.D. Division of Epidemiology II (DEPI II) Clara Kim, Ph.D. Division of Biometric VII (DB VII)
Division Director:	CAPT Dave Moeny, R.Ph., M.P.H, USPHS Division of Epidemiology II (DEPI II)
Subject:	Review of new analyses submitted by sponsor regarding the A6791032 GPRD study of depot medroxyprogesterone acetate and risk of fracture
Drug Name(s):	Depot medroxyprogesterone acetate (DMPA)
Application Type/Number:	NDA 20-246 (Depo-Provera CI) (ANDA 78-711, ANDA 76-553), NDA 21583 (Depo-subQ Provera 104)
Applicant:	Pfizer and generic manufacturers
OSE RCM #:	2017-430

CONTENTS

EXECUTIVE SUMMARY

Depot medroxyprogesterone acetate (DMPA) injections including Depo Provera® and Depo subQ Provera 104® are long-acting progestin-only contraceptives indicated for prevention of pregnancy. Use of DMPA reduces serum estrogen level and is associated with bone mineral density (BMD) loss (in Boxed Warning), possibly leading to osteoporosis and fracture. The sponsor conducted a retrospective cohort study in the General Practice Research Database (GPRD) to satisfy a post-marketing commitment (PMC) on the safety issue. Division of Epidemiology (DEPI) previously reviewed the early study reports and conducted a review of the published literature and concluded that the overall results and trends suggest an association between DMPA use and risk of fractures. In 2011, the GPRD study results were added into the product label. In December of 2016, the sponsor submitted supplementary analyses of the GPRD data to FDA and requested updates to several sections of the DMPA labeling package (b) (4). The Division of Bone, Reproductive and Urologic Products (DBRUP) requested a DEPI review of the supplementary analyses, an update the literature review, and recommendations on potential regulatory action.

In the Sponsor's 2016 supplementary analyses of a subcohort of women who had 6-24 months of preindex history, the fracture risk was still higher in DMPA users compared to nonusers, and the risk appeared to increase slightly by duration of use (e.g., ≤ 1, >1 and ≤ 2, or > 2 years of use). When exposure was defined as a continuous variable (e.g., cumulative number of DMPA injections from zero up to 25), the results showed a consistent higher fracture risk in DMPA users compared to nonusers, but no evidence of a dose-response relationship.

In the literature, six epidemiologic studies (including the GPRD study) consistently showed an increased risk for fractures (any skeletal site) associated with DMPA use. The relative risk (RR) from these studies ranges from 1.5 to 2.5. In four studies, there was some evidence of a dose-response relationship with a higher risk associated with increasing DMPA use. A statistically significant higher risk of fracture was observed in females with > 2 years of DMPA use compared to use of other contraceptives. As noted in previous DEPI reviews, major limitations of these studies include potential misclassification of exposure and outcome, inadequate control for potential confounders such as history of fall, sociodemographic status, as well as behavioral factors associated with risk of fractures. The major strengths of the studies include the relatively consistent findings across different study designs and populations, and a positive dose (duration) relationship observed in some studies.

In conclusion, the recent epidemiology studies, as well as the 2016 supplementary analyses of the GPRD data, did not provide any new safety information beyond what was known on the association between DMPA use and fracture risk at the time of labeling changes in 2011. Although the epidemiology studies published to date unavoidably have various limitations such as residual confounding, potential misclassification of exposure and outcome, small number of outcome events (osteoporotic fractures) and inappropriate use of the self-controlled cohort method, the relative consistency of the findings suggest that there is likely an association between DMPA use and fracture risk. Our view remains unchanged; the GPRD study and the published literature suggest a small increased risk for fracture with DMPA use. DEPI disagrees with the sponsor's proposed labeling update (b) (4) as we deem the current labeling language appropriate based on the currently available observational data. We do not recommend any additional regulatory action at this point.

1 INTRODUCTION

1.1 BACKGROUND

Depot medroxyprogesterone acetate (DMPA) injections including Depo Provera® and Depo subQ Provera 104® are long-acting progestin-only contraceptives indicated for prevention of pregnancy. Depo Provera is administered intramuscularly and Depo subQ Provera subcutaneously once every 3 months. Depo Provera releases DMPA to body which suppresses serum estrogen level and is associated with bone mineral density (BMD) loss possibly leading to osteoporosis and fracture.[1,2] In November 2004, the FDA added a boxed warning to the DMPA labeling package to highlight the fact that prolonged use of DMPA may result in significant loss of BMD. The warning states that women should not use DMPA for more than two years unless other birth control methods are considered inadequate.[a]

Despite the evidence that use of DMPA reduces BMD, data on the risk for fracture with DMPA use is limited. To estimate the extent to which DMPA might increase fracture risk, the sponsor conducted a post-marketing commitment (PMC) study on the fracture risk in DMPA users compared to users of non-DMPA contraceptives (i.e., 'nonusers') using the General Practice Research Database (GPRD) in the United Kingdom (UK). The sponsor submitted the original Final Study Report to FDA in 2007 which showed that DMPA users experienced more fractures than nonusers.[b] However, supplemental analyses conducted in 2008 reported that DMPA users had higher fracture risk than nonusers even before start of contraception.[c] Based on the supplementary analyses, the sponsor proposed a labeling change stating that (b) (4) (b) (4). In 2011, the Division of Epidemiology (DEPI) reviewed the submitted GPRD study reports (e.g., original Final Study Report (2007); Supplementary Analytic Report (2008); Integrated Summary Report (2008[d])), as well as published literature on DMPA and fracture risk, and concluded that the study results and trends observed in the GPRD study and the literature suggest an association between DMPA use and fractures, particularly for long-term use (Fatmatta Kyuateh. March 4th 2011, OSE RCM #2010-2580). DEPI disagreed with the sponsor's proposed labeling change (b) (4). In July 2011, FDA added the GPRD study results to DMPA labeling (Section 14.4 - Clinical Studies).[e] See the current labeling in the section below.

In April 2013, Drs. Andrew Kaunitz and David Grimes submitted a Citizen's Petition (CP) to FDA requesting the removal of the labeled box warning for the risk of fracture. The Petitioners claimed that the warning is based on BMD, an invalid surrogate endpoint known not to predict fracture risk. To respond to the CP, DEPI conducted a literature search and reviewed 5 published epidemiology studies (3 studies and the early draft of GPRD study were reviewed by DEPI in 2011) on the association between DMPA and fracture (2 case-control, 2 cohort, and 1 cross-sectional),[3-7] including the GPRD study.[3] The DEPI reviewer noted that although these studies have various limitations in

[a] http://chastityproject.com/wp/wp-content/uploads/2013/05/depo-bone-loss.pdf
[b] (b) (4) Final Report: The effect of depo medroxyprogesterone acetate on risk of bone fracture. November 20, 2007.
[c] Supplementary Analytic Report: The association of bone fractures and use of depo medroxyprogesterone acetate (DMPA) in women in the General Practice Research Database (GPRD). September 25, 2009
[d] Integrated Summary Report: The association of bone fractures and use of depo medroxyprogesterone acetate (DMPA) in women in the General Practice Research Database (GPRD). June 19, 2008
[e] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020246s035ltr.pdf

design or conduct, they were relatively consistent in showing a moderately elevated risk for bone fracture with DMPA use, and the risk seemed to increase with age and duration/dose of DMPA use. Based on the literature review, DEPI recommended no change of product labeling (Monique Falconer. October 23, 2013. OSE RCM #2013-1051).

In December 2016, the sponsor submitted an efficacy supplement application with recent literature and additional analyses of the GPRD data.[f] In this submission, the sponsor also addressed DEPI's prior comments on the GPRD analyses (see below "Additional analyses and responses to FDA questions" submitted in December 2016). The sponsor (b) (4) with proposed changes to the (b) (4) *Warnings and Precautions*, (b) (4) and *Clinical Studies* sections consistent with the statement (see sponsor proposed languages in the next section). DBRUP requested that DEPI review the supplemental 2016 GPRD data analyses, review five recently published studies identified by DBRUP, and provide recommendations on potential regulatory responses to the proposed labeling update.

Per DEPI's request, the sponsor conducted additional analyses and addressed the following questions in their 2016 report:

- *More detailed examination of the possible association between the extent of DMPA exposure and fracture incidence, where exposure will be defined in several different ways (e.g., with a look-back period of 6-24 months prior to DMPA use)*
- *Additional analysis of fracture rates before and after DMPA treatment in the subcohort of women with 6-24 months of preindex history before any contraceptive use*
- *Provide data on how many women (and what percentage of the total sample) having the "practice up-to-standard" date occurred later than the date of first record with a contraceptive code before age 50?Provide this number broken down by ever users versus never users of DMPA*
- *Provide data on the percentage of practices stops contributing data to GPRD in a given year*
- *Comment on what percentage of all contraceptive injections are prescribed by family planning units in the UK; if available, discuss whether this proportion is believed to be the same for the women included in the GPRD database study?*

DEPI consulted the Division of Biometrics VII (DB7) to review the self-controlled cohort method.[8] DB7's comments are available in Section 4.

1.2 PRODUCT LABELING

Current labeling packages for Depo Provera® and Depo-subQ Provera 104® contain a boxed warning on the loss of BMD:

[f] Effect of depot medroxyprogesterone acetate on the risk of bone fracture: additional analyses and Reponses to FDA questions. August 10, 2012.

"*Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. 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. 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 (see WARNINGS, section 1).*"

The **Clinical Studies** section (Section 14.4) of Depo Provera labeling also includes information about the GPRD study:

"*A retrospective cohort study to assess the association between DMPA injection and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the UK. The incidence rates of fracture were compared between DMPA users and contraceptive users who had no recorded use of DMPA. The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). It is not known if this is due to DMPA use or to other related lifestyle factors that have a bearing on fracture rate.*

In the study, when cumulative exposure to DMPA was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.

There were very few osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in DMPA users compared to non-users. Importantly, this study could not determine whether use of DMPA has an effect on fracture rate later in life."

The Sponsor is proposing the following language for the boxed warning: (b) (4)

In addition, in this NDA submission, the sponsor proposed (b) (4)

2 REVIEW MATERIALS

- "Effect of depot medroxyprogesterone acetate on the risk of bone fracture: additional analyses and responses to FDA questions. August 10, 2012" submitted by the sponsor in December 2016

The sponsor's Integrated Summary Report (2008) and a paper published by Lanza LL *et al.* 2013[3] provided background information about the GPRD study in terms of its design and preliminary results:

- "Integrated Summary Report: The association of bone fractures and use of depo medroxyprogesterone acetate (DMPA) in women in the General Practice Research Database (GPRD). June 19, 2008."
- Lanza LL, McQuay LJ, Rothman KJ, et al. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. Obstet Gynecol 2013; 121: 593-600.[3]

DBRUP requested DEPI review the following articles:

- Lopez LM, Chen M, Mullins Long S, et al. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Sys Rev 2015; 21(7).[9]
- Modesto W, Bahamondes MV, Bahamondes L. Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate. J Women's Health (Larchmt). 2015 Aug;24(8):636-40.[10]
- Viola AS, Castro S, Bahamondes MV, et al. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011 Nov;84(5):e31-7.[11]
- Viola AS, Castro S, Marchi NM, et al. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. Contraception. 2011 Aug;84(2):122-7.[12]
- Pongsatha S, Ekmahachai M, Chaovisitsaree S, et al. Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: a cross sectional study. J Med Assoc Thai. 2009 Oct;92(10):1263-7.[13]

Finally, DEPI updated a literature search using PubMed and EMBASE for cohort, case-control, and cross-sectional studies on DMPA and fractures published after January of 2013 (e.g., last DEPI literature review on this topic). The key words or free text words used for this search included depo provera, medroxyprogesterone acetate, bone density, osteoporosis, and fracture. We limited this search to human studies and English literature. DEPI identified and reviewed two recent publications:

- Kyvernitakis I, et al. The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK. Osteoporos Int 2017; 28: 291-297.[14]
- Nieves JW, et al. Eating disorders, menstrual dysfunction, weight change and DMPA use predict bone density change in college-aged women. Bone, 2016. 84: p. 113-9.[15]

3 REVIEW RESULTS

3.1 RETROSPECTIVE COHORT STUDY IN GPRD

3.1.1 Overview of GRPD study results reviewed by FDA before 2016

This was a retrospective cohort study conducted in the GPRD primary care research database. The study assessed the fracture incidence (overall and by fracture type) associated with DMPA use (e.g., dose, duration, and recency of use). The primary safety outcome of interest is the occurrence of fractures (all sites), and osteoporotic fracture as one of the secondary outcomes. It compared fracture risk among DMPA users to that among non-users in the primary analysis. The 2008 supplementary analysis compared the fracture incidence before and after initiation of DMPA use. Details of the study design are presented in **Appendix #1**.

A high level summary of study results contained in the Integrated Summary Report (2008) and Lanza LL *et al.* paper (2013[3]) is provided below. **Appendix #2** summarizes the findings in detail.

- The study population consists of 312,395 females 15-50 years old. Among them, 25% were DMPA users and the remaining were users of non-DMPA contraceptives ('nonusers'). A subcohort of women who had at least 6 months of preindex data was also created (n=166,367, 53.3%).
- Compared to 'nonusers', DMPA users were younger, more likely to be a current smoker, a drug or alcohol abuser, to have a higher prevalence of following conditions during the baseline period (epilepsy, fall, fracture, inflammatory bowel disease, or asthma), and more likely to have previously used oral corticosteroids or estrogen therapies.
- In the full cohort, 11,822 incident fractures occurred during 1,722,356 person-years (PYs) of follow-up. Crude fracture incidence at any skeletal site during follow-up was 6.4 per 1,000 PYs for nonusers and 9.0 per 1,000 PYs for DMPA users. In the subcohort, 6,513 fractures occurred during 917,955 PYs of follow-up. The crude fracture incidence rate was 6.6 per 1,000 PYs for non-users and 9.1 per 1,000 PYs for DMPA users.
- Except for age, there was little evidence of confounding by other baseline factors. Adjustment for age and additional baseline variables, one at a time, did not make a meaningful difference in the effect estimate compared to the age-standardized risk estimate.
- In the full cohort, there was a statistically significant increased risk of fractures ('any fracture') for DMPA use compared with nonuse. The crude incidence rate ratio (IRR) for any fracture was 1.41 (95% CI 1.35-1.47) and the age-standardized IRR was 1.44 (95% CI 1.38-1.50).
- In the sub-cohort, the crude IRR was 1.37 (95% CI 1.29-1.45) and the age-standardized IRR was 1.40 (95% CI 1.32-1.49[3]). The multivariate-adjusted IRR after controlling for age and other baseline factors (e.g., baseline covariates included in the Appendix Table A3) was 1.21 (95% CI 1.14-1.28). In the sub-cohorts:
    - Compared to nonusers, fracture risk was higher in all three exposure categories (current, recent, and past exposures). The age-standardized IRR was 1.51 (95% CI 1.41-1.62), 1.41 (95% CI 1.31-1.50), and 1.32 (95% CI 1.24-1.41) in current, recent and past exposure groups, respectively, in the full cohort.
    - Among past or recent users of DMPA, the fracture rates were similar for both low (1-7 injections) and high (≥ 8 injections) cumulative exposure compared to nonusers. For current users, however, the rate was higher for low cumulative exposure (age-standardized IRR 2.16, 95% CI 1.75-2.67) compared with high cumulative exposure (age-standardized IRR 1.06, 95% CI 0.95-1.18).

- There was no suggestion of an association between DMPA use and osteoporotic type fractures (e.g., pelvis, hip, symptomatic or clinical vertebral fractures). However, an elevated risk was reported for fractures not typically associated with osteoporosis (e.g., ankle, arm, foot, hand, leg, and rib/sternum).
- Fracture risk was significantly higher in DMPA users compared to nonusers within the six months before their first recorded contraceptive prescriptions. The crude IRR was 1.28 (95% CI 1.07-1.53) before contraceptive initiation; the IRR was 1.41 (95% CI 1.35-1.47) after the index contraceptive had been prescribed. There was no statistically significant difference in crude incidence of fractures before and after the contraceptive use within each of the cohorts (e.g., DMPA users and non-users).

3.1.2 Supplementary analyses of the GPRD data submitted by the sponsor to the FDA in 2016

(1) Additional analysis assessing the fracture risk by extent of DMPA use

The sponsor evaluated the fracture risk during follow-up (i.e., after the "index date") in the subcohort of 166,367 women with 6-24 months of baseline history, stratified by cumulative duration of DMPA use (e.g., ≤ 1, >1 and ≤ 2, or > 2 years of use). As shown in **Table 1**, the fracture risk was significantly higher in DMPA users compared to nonusers, and the risk showed a small increase by duration of use.

Table 1 Incidence of fracture during follow-up in a subcohort of 166,367 women with 6-24 months of preindex history, by four categories of cumulative DMPA exposure

Extent of DMPA use	No. of fractures	Person-years	Rate per 1,000 PYs	IRR (95% CI)
None	4,939	744,242	6.6	1.0 (reference)
≤ 1 year	1,055	117,953	8.9	1.35 (1.26-1.44)
>1 and ≤2 years	249	29,376	8.5	1.28 (1.12-1.45)
>2 years	270	26,385	10.2	1.54 (1.36-1.74)

¶ Source: Additional analyses and responses to FDA questions (2017) – Table 1

Per DEPI's request, the sponsor also conducted analyses that examined the fracture risk during follow-up by number of injections as a continuous variable (e.g., cumulative number of injections from zero up to 25). The analyses showed that facture rate was consistently higher in DMPA users compared to the reference group (nonusers), but there was little evidence of a higher fracture rate associated with higher cumulative exposure.

(2) Practice up-to-standard date

In the GPRD database, data quality checks are conducted regularly at each GP practice. The practice-level quality assurance is manifested by the practice's up-to-standard date.[16] The validity and completeness of the data are questionable if a prescription is written before the up-to-standard date. All prescriptions written before the 'up-to-standard' date were dropped from the 2016 analyses.

According to the 2016 supplementary analyses, about 12% of women in the subcohort had a contraceptive record written before the 'up-to-standard' date. The corresponding rate in the full cohort was 18%. However, it is unclear how the low-quality data were distributed among ever *versus* never users of DMPA.

(3) Annual percentage of practices ceasing data contributions

Patient follow-up time has to be terminated when a practice stops contributing data to GPRD. According to the supplementary analyses, no practice ceased data contribution during 1987 through 1999. From 2000 to 2005, only 1.6% of practices stopped contributing data at a given calendar year.

(4) *Percentage of all contraceptive injections that were prescribed by family planning units*

In UK healthcare system, a woman can receive contraceptive prescriptions at family planning clinics (FPC). For contraceptive prescriptions written by nurses at the FPCs, the prescription data is not recorded in the GPRD database, which can lead to exposure misclassification. The sponsor cited two reports (The Information Centre 2007[g] & Smnibus Survey Report 2007[h]) which showed that the percent of women attending FPCs ranges from 1% to 11%; the proportion of females attending community contraception clinics decreases with age, with the highest frequency seen in females 20-24 years (11%).

(5) 2-year pre-exposure fracture rates in the subcohort of 166,367 women with 6-24 months of preindex history

As noted in previous DEPI reviews, the look-back period (e.g., unspecified in full cohort, 6 months in the subcohort) was not long enough to capture prior DMPA use. Prior DMPA use may reduce bone density and increase the risk for bone fracture, an adverse effect that could last for up to 730 days (2 years) prior to the index date. If the DMPA cohort included disproportionately more undetected preindex DMPA users, it could show in post-exposure follow-up a higher risk of BMD reduction or fracture than the nonuser cohort (Fatmatta Kuyateh. OSE RCM # 2010-2580).

To address DEPI's comments, the sponsor *re-analyzed the fracture rates within two years before the start of contraception use.* The fracture rates before the index contraceptive prescription date were assessed in the same subcohort population (n=166,367) as the 2008 analysis, but calculating the risk within 2 years before the index date. In the previous analysis, only 6-month preindex risk was calculated.[3]

Also in the latest 2016 supplementary analyses, if a woman entered the study cohort based on a non-DMPA contraceptive use before her index DMPA prescription, the person-years between initiation of the non-DMPA treatment and the date of her index DMPA prescription was excluded from the analysis to avoid misclassification of exposure.

[g] The Information Centre. NHS contraceptive services: England 2006-07. October 9, 2007.
[h] Lader D. Contraception and sexual health 2006/07. Omnibus Survey Report No. 33. London: Office for National Statistics; 2007

As shown in Table 2 below, the 2-year pre-treatment fracture incidence in DMPA users and nonusers, as well as the pre-treatment crude IRR were similar to the 6-months pre-exposure estimates observed in the 2008 study reports (**Appendix Table A5**). The average preindex time in cohorts of DMPA users and nonusers was almost identical (approximately 18 months, Table 2). The crude IRR was 1.31 (95% CI 1.19-1.45) comparing DMPA use to nonuse before starting contraception; the crude IRR was 1.23 (95% CI 1.16-1.30) after start of contraception. The post-exposure incidence remained the same as the 2008 analysis. Within the DMPA cohort, the pre- and post-exposure incidence was almost identical.

Table 2 Incidence of fracture before and after use of DMPA in the subcohort of 166,367 women with 6-24 months of preindex history

	Before starting DMPA or other index contraceptive			After starting DMPA or other index contraceptive			IRR after/before (95% CI)
	Fractures	PYs	Rate per 1,000 PYs	Fractures	PYs	Rate per 1,000 PYs	
DMPA users (n=41,876)	582	64,737	9.0	1,574	173,713	9.1	1.01 (0.92-1.11)
Nonusers (n=124,491)	1,320	192,748	6.8	4,939	672,052	7.3	1.07 (1.01-1.14)
Crude IRR (DMPA vs. nonusers)	1.31 (1.19-1.45)			1.23 (1.16-1.30)			

¶ Source data: Additional analyses and responses to FDA questions 2017 – Table 3

3.2 OTHER PUBLISHED STUDIES SINCE 2013

3.2.1 Case-control study using IMS Health data in UK (Kyvernitakis I, et al. 2017)

In this study, Kyvernitakis *et al.* matched 4,189 women 20-44 years old with a first-time fracture (including vertebral and non-vertebral fractures) diagnosed between 2010 and 2015 with 4,189 fracture-free women based on their age. Patients were classified as current users if the last prescription for a study drug (DMPA *or* non-DMPA contraceptives) was recorded less than 180 days or as past users if it was recorded 180 or more days before "index date" (e.g., the date of first fracture diagnosis from January 2010 to December 2015). The multivariable-adjusted odds ratio (OR) for incident fractures was 0.97 (95% CI 0.51-1.86), 2.41 (1.42-4.08), and 1.46 (0.96-2.23) for current use of 1-2, 3-9, and ≥ 10 prescriptions, respectively. The ORs appeared to increase by number of prescriptions of past use, but not number of prescriptions of current use (smaller case numbers in current use analyses) (Table 3 below).

Table 3 Exposure to DMPA and other hormonal contraceptives and relative risk of fractures

No. of injections	No. of cases	Percent, %	No. of controls	Percent, %	Adjusted OR[†]
Non-use	3,729	89.0	3,866	92.3	Reference
Current use					
1-2	20	0.5	19	0.5	0.97 (0.51-1.86)
3-9	54	1.3	20	0.5	2.41 (1.42-4.08)

≥10	61	1.5	37	0.9	1.46 (0.96-2.23)
Past use					
1-2	119	2.8	107	2.6	0.96 (0.73-1.26)
3-9	128	3.1	94	2.2	1.14 (0.86-1.51)
≥10	78	1.9	46	1.1	1.55 (1.07-2.27)

† Adjusted for BMI, smoking, asthma, epilepsy, use of progestin (single preparation), medroxyprogesterone acetate low dose, beta-blockers, proton pump inhibitors, systematic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anticonvulsants, paracetamol, opioids, non-steroidal anti-rheumatics, and contraceptive not under investigation

3.2.2 Systematic review on steroidal contraceptives and bone fractures (Lopez LM, et al 2015)

Lopez *et al.* conducted a systematic review of observational studies of hormonal contraceptive use and the risk of bone fracture. The authors searched PubMed, POPLINE, Cochrane Central Register of Controlled Trials, LILACS, EMBASE, CINAHL, and Web of Science through June 2015. The authors included four studies (Kaunitz 2006[17]; Vestergaard 2006[18]; Meier 2010[4]; Lanza 2013[3]). Except Kaunitz et al. (2006[17]), the other three studies reported a statistically significant increased risk of fractures in DMPA users compared to users of non-DMPA contraceptives ("nonusers"). All 4 studies included in this systematic review have been reviewed by DEPI before (Table 4).

Table 4 Observational studies included in Lopez *et al.* (2015[9]) systematic review

Study	Data source	Design	Participants	Results
Kaunitz 2006	Multiple clinical sites in the US	Prospective cohort, 7-year study (240 weeks treatment + 96 weeks follow-up)	Women 25-35 years	BMD declines during DMPA use; significant increase in BMD after discontinuation through 96 weeks posttreatment. No differences in fracture rates between DPMA group and non-hormonal control group
Vestergaard 2006	National Hospital Discharge Register (NHDR), Denmark, 1996-2000	Case-control (3 randomly selected controls, matched on year of birth)	Females in NHDR data	<2.5 years of use: OR=0.8 (0.4-1.6) 2.6-4 years: OR=1.5 (0.7-3.5) ≥4 years: **OR=2.2 (1.3-3.5)**
Meier 2010	UK GPRD, 1995-2008	Case-control	Females 24-44 years	1-2 prescriptions: OR=1.2 (0.9-1.5) 3-9 prescriptions: **OR=1.3 (1.1-1.6)** ≥10 prescriptions: **OR=1.5 (1.3-1.8)**
Lanza 2013	GPRD, UK, 1987-2005	Retrospective cohort	Females 15-50 years	Current DMPA users vs. nousers **Crude RR=1.5 (1.4-1.6)** Current users/high dose vs. nonusers: Crude RR=1.1 (1.0-1.2) Current users/low does vs. nonusers: Crude RR=1.9 (1.8-2.1) Subcohort with 6 months baseline data: **Age-standardized RR: 1.4 (1.3-1.5)**

3.2.3 Studies of bone mineral density loss in DMPA users

DBRUP requested DEPI to review 4 articles that evaluated the relationship between DMPA use and BMD. DEPI identified one additional study through the literature search. Of these 5 studies (3 cross-sectional, 2 prospective), one study compared forearm BMD in postmenopausal women (age range: 46-61 years) who were former users of DMPA (n=24) or copper intrauterine device (IUD) (n=55).[12] The mean duration of contraceptive use was 10.1±1.1 years for women in the DMPA group and was 17.8±0.8 years for women in the copper IUD group. The study found no statistically significant differences in forearm BMD measurements between postmenopausal women who had been long-term users of DMPA and those who had been long-term users of an IUD. Two studies evaluated BMD in long-term DMPA users compared to long-term users of IUD.[10,11] Both studies found that long-term DMPA use (>10 years) was associated with low bone mass. Pongsatha et al. (2009) conducted a cross-sectional study among Thai woman of reproductive age who used DMPA for at least 2 years and non-hormonal contraceptive users (duration of use unspecified in the paper).[13] The study found there was significantly lower BMD at the lumbar spine in the DMPA group but there was no effect on BMD at other sites (femur, distal radius, and ulna). Nieves et al. conducted a prospective cohort study among healthy physically active college women in the US Military Academy.[15] Use of oral contraceptive and DMPA were reported annually by written questionnaire. BMD was measured annually by dual X-ray absorptiometry. The study found DMPA use was associated with spine, hip, and calcaneus bone loss.

4 DISCUSSION

4.1 DEPI ASSESSMENT OF EVIDENCE FROM THE 2016 SUPPLEMENTARY ANALYSES OF GPRD DATA AND OTHER PUBLISHED OBSERVATIONAL STUDIES

4.1.1 2016 supplementary analyses of GPRD data

Most of the sponsor's 2016 supplementary analyses are straightforward and some analyses were to address FDA's comments from a previous DEPI review which asked for a longer look-back period than 6 months. In the 2016 supplementary analyses, the sponsor evaluated the fracture risk in the subcohort of 166,367 women with 6-24 months of preindex history. Similar to the primary analysis results submitted to FDA in 2008, the new analyses still showed a statistically significant higher risk during the study follow-up for fracture in DMPA users compared to nonusers, and the risk appeared to increase slightly by duration of use (e.g., ≤ 1, >1 and ≤ 2, or > 2 years of use). When exposure was defined as a continuous variable (e.g., cumulative number of DMPA injections from zero up to 25), the results showed a consistent higher fracture risk in DMPA users compared to nonusers, although there was no evidence of a dose-response relationship.

The primary and secondary analyses in the GPRD study only removed the effect of differing age-distribution between DMPA and nonuser cohorts. We acknowledge that there may be residual confounding (e.g., due to missing data on past fracture, use of corticosteroids, etc.) attributable to this observed elevated, small risk. The sponsor presented results from a multivariate regression analysis in 2008. After adjusting for all baseline covariates listed in the **Appendix Table A3**, there was still a small but statistically significant increased fracture risk comparing ever to never use of DMPA (adjusted IRR=1.21, 95% CI: 1.14-1.28). In our opinion, this analysis, although considered a stronger analysis because it has included a number of important confounders, can still be subject to residual

confounding because it does not control for other established risk factors of fractures such as socioeconomic status or physical activity that may also predict the use of different contraceptives.[19] Finally, in order to minimize the impact of prior history of fracture on the future fracture risk, a restriction approach ought to be applied (i.e., inception cohort design) where all fracture events prior to the treatment initiation (i.e., occurring during the "wash-out period") need to excluded (refer to DB7 comments in Section 4.2 below).[20]

The sponsor believes that the post-exposure risk difference between the two cohorts is attributable to the pre-exposure difference between DMPA user and non-user cohorts to which we disagree. The GPRD study was not originally designed to compare pre-exposure incidence rates between the two cohorts; nor was it a self-controlled design (e.g., case-crossover studies in which each individual is compared with him/herself). Similar to other self-controlled designs in pharmaco-epidemiology, the self-controlled cohort method used in this GPRD study is not appropriate for sustained exposure and for outcome resulting from cumulative exposure (e.g., fracture risk due to DMPA use).[21] In addition, the self-controlled cohort method may not be appropriate if the goal of the study is to quantify the magnitude of a risk (also refer to DB7 comments in Section 4.2).[8]

The 2016 supplementary analyses were primarily conducted to address DEPI's previous comment regarding the potential disproportionate distribution of prior DMPA use in two study groups (e.g., DMPA users may be more likely to have used DMPA in the past compared with nonusers). Additionally, the 6-month look-back period was not long enough to capture the effect of prior DMPA exposure which in theory could last for 2 years. This may lead to overestimate of the post-exposure fracture risk in both groups and overall this could lead to either over- or under-estimate of IRRs between DMPA use and fractures. In the 2016 supplementary analyses, eligible subjects in the subcohort had 6-24 months of preindex data. Although the longer preindex data resulted in more pre-exposure fracture events, because not every subject in the 2016 supplementary analyses had a minimum 24-month of preindex data (the average preindex time was 18 months in both groups), missing information on prior DMPA use remains as an issue.

Furthermore, there was a small chance of exposure misclassification (differential or non-differential) because some women could have received contraceptives from FPCs. The sponsor cited two survey reports (not conducted in women enrolled in the GPRD data) which showed that up to 11% of reproductive age women in UK may have received contraceptive prescriptions from FPCs and women of younger age groups are more likely to have attended the FPCs. Although there was no information on the details of the survey design and we cannot draw any conclusion on how survey participants are similar to/different from the GPRD population, we agree with previous DEPI reviewer that potential exposure misclassification cannot be ruled out in the GPRD study. The misclassification could either over- or underestimate the IRRs, depending on the nature/underlying mechanism of the exposure misclassification (differential or non-differential).

We disagree with the sponsor's proposed language in the boxed warning (b) (4) [redacted] Because the number of osteoporotic fractures was too small to allow any meaningful inference and hence preclude any definite conclusion on the risk of osteoporotic fracture.

Overall, the supplementary analyses submitted by the sponsor in 2016 did not contain any new information which is inconsistent with what is already known about the fracture risk based on the previous study reports. Therefore, our view on the safety issue remains unchanged which is that the GPRD study suggests a small increased risk for fracture with DMPA use; however the observed increase in risk with DMPA may be attributable to residual confounding,

4.1.2 DMPA use and fracture risk from other published observational studies

Recently published literature on this topic consistently showed a small, increased risk for fractures (any skeletal site) associated with DMPA use. The RR from these studies ranges from 1.5 to 2.5. In four studies; and there were suggestions of a dose-response relationship between DMPA use and risk of fractures (Vestergaard 2008[5]; Meier 2010[4]; Lanza 2013[3] & Supplementary analyses of 2016; Kyvernitakis 2017[14]). In these studies, a statistically significant higher risk of fracture risk was observed in females with > 2 years of DMPA use compared to use of other contraceptives.

Four studies analyzed the association between risk of fracture by site and DMPA use. Two reported an increased risk of osteoporotic-associated fractures among DMPA users compared to nonusers (Watson 2006[7]; Meier 2010[4]). However, in the GPRD study, DMPA use was associated with a higher risk of appendicular and miscellaneous (fingers, toes, skull, and unspecified) fractures, not with axial fractures (hip, pelvis, and symptomatic or clinical vertebral fractures). Lappe et al. (2013) included female military recruits and found an increased risk of stress fracture (e.g., occurred in lower extremity or pelvis) in DMPA users compared to nonusers.

Thus, we conclude that the existing literature suggest an increased risk for bone fractures with DMPA overall, and some studies suggest that the fracture risk may increases with increasing DMPA use. There has been no definitive answer on fracture risk according to anatomic site primarily due to the small sample size. The major limitations of these studies include potential misclassification of exposure and outcome, inadequate control for potential residual confounding factors such as history of fall, history of epilepsy, sociodemographic status (age, education), and behavioral factors (sports/physical activity). The major strengths of the studies include the relative consistent findings across different study design and population. Finally, as the previous DEPI reviewer noted, there was a suggestion of a positive duration-response relationship between DMPA use and risk of facture in published observational studies (Monique Falconer. October 23, 2013. OSE RCM #2013-1051). New studies published after 2013 continued to suggest that prolonged use of DMPA was associated with an increased risk of fracture.

4.2 DB7'S COMMENTS ON THE VALIDITY OF SELF-CONTROLLED COHORT METHOD

1) Patrick Ryan[8] stated the following regarding the self-controlled cohort design.

> "*If the objective for a risk identification system is one of discrimination, the self-controlled cohort method shows promise as a potential tool for risk identification. However, if a system is intended to generate effect estimates to quantify the magnitude of potential risks, the self-controlled cohort method may not be suitable, and requires substantial calibration to be properly interpreted under nominal properties.*"

DB7 Reviewer comment: Since the goal of the study is to quantify the fracture risk comparing DMPA to non-DMPA use, it might not be suitable to make claims on the basis of a risk estimate generated from a self-controlled cohort design. Alternative designs such as a retrospective incident user cohort design plus sufficient confounding control should be considered in these cases.

2) Patients with an event were not excluded from the analysis. Women with fractures before exposure to DMPA might be more prone to fractures than women without fractures. Additionally, the decrease in the after-exposure IRR compared to before was because the rate of fractures increased in the nonuser cohort, and not a decrease in the DMPA cohort. Therefore, it is difficult to attribute the decrease of risk to the safety of DMPA.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, the recent epidemiology studies, as well as the 2016 supplementary analyses of the GPRD data, did not provide any new safety information beyond what was known on the association between DMPA use and fracture risk at the time of labeling changes in 2011. Although the epidemiology studies published to date unavoidably have various limitations such as residual confounding, potential misclassification of exposure and outcome, small number of outcome events (e.g., osteoporotic fractures) and inappropriate use of the self-controlled cohort method, the relative consistency of the findings suggest that there is likely an association between DMPA use and fracture risk. Our view remains unchanged; the GPRD study and the published literature suggest a small increased risk for fracture with DMPA use. DEPI disagrees with the sponsor's proposed labeling update (b) (4) as we deem the current labeling language appropriate based on the currently available observational data. We do not recommend any additional regulatory action at this point.

6 APPENDIX #1 SUMMARY OF GPRD STUDY DESIGN

Objective/Aim/Scope	To examine the incidence of bone fractures in women who used DMPA with incidence in women who used other types of prescription contraceptives (e.g., other hormonal contraceptives and non-hormonal contraceptives)
Design	
Type	Retrospective cohort design
Data source	GPRD (an electronic medical record system in UK)
Time period	January 1, 1987 – December 31, 2005
Inclusion criteria	• Female, birth date known, classified as acceptable patient by GPRD standard criteria, have at least one contraceptive prescription before age 50, and the qualified prescription has to be dated between 1/1/1987 and 12/31/2005 • To keep the study data set to a technically manageable size, a decision was made after the pilot study to take a random sample from all women with at least one qualified oral contraceptive (OC) prescription. The final data set would have twice as many OC users as DMPA users A sub-cohort of patients defined as those who had ≥ 6 months of medical records available immediately prior to their 'index date' (e.g., used to assess the impact of potential confounding factors on the risk of outcome)
Exclusion criteria	Women who had hysterectomy or oophorectomy in baseline period
Index date	The date of a woman's first qualifying contraceptive prescribed on or after the following events: study start date (January 1, 1987), her registration date, the up-to-standard date for the practice in which she is registered, and < 50 years at the "index date"
Censoring date	The censoring date is the *first* the following dates: the practice's last date of contributing data to GPRD, 12/31/2005, the woman's first fracture date after entering the study, the date when the woman terminates from the practice due to moving or death
Exposure of interest	• DMPA injections (Depo Provera®) • Non-hormonal contraceptives (e.g., IUD, cervical cap, or diaphragm), • Hormonal contraceptives that are not DMPA (e.g., OCs, IUDs that release estrogen or progesterone)
Exposure risk window	Applied the following ***assumptions*** in the study: • DMPA may confer an increased risk of fracture one month after the first injection (i.e., induction time for DMPA to affect bone is assumed to be one month) • Fracture risk is higher for at least two years of cumulative DMPA use • Fracture risk may decline after the end of DMPA exposure (e.g., 2 years after last exposed dose[i])
Definitions of Exposure	***Assumptions***:

[i] Based on a report on follow-up during and after long-term DMPA treatment which found that BMD declined during DMPA treatment, followed by substantial recovery of BMD during two years after termination of treatment (Kaunitz et al. Contraception 2006; 74(2): 90-9).

	• Injection is given on the day that DMPA prescription was recorded • DMPA is considered to remain effective in the body for 90 days after each injection (including the date of injection) • When a new DMPA prescription is dated before the end of the 90-day effective period of the last prescription, the overlapping days between these two prescriptions will be ignored, i.e., exposure would be considered as continuous in this example • The effect of DMPA use on fracture risk would still be apparent in two years after the last DMPA injection ***Exposure categories/definitions***: • Current use (e.g., 0-90 days after a DMPA injection) • Recent use (e.g., > 90 days and ≤ 2 years since last DMPA injection) • Past use (e.g., > 2 years since last DMPA injection) • Age at first exposure (e.g., age in years at initial DMPA prescription; < 18 *vs.* ≥ 18 years) • Cumulative DMPA injections (1-7 injections = 'low exposure', ≥8 injections = 'high exposure') • Estimated total duration of DMPA use (with or without gaps between prescriptions) • Duration of elapsed time since last DMPA exposure date (defined as 90th day after the last DMPA prescription) ***Non-DMPA contraceptives:*** • Non-DMPA time was defined as follow-up time during or after other non-DMPA contraception (because the fracture risk is similar for exposure to other hormonal contraception and non-hormonal contraception, data from the two groups are combined) ***"Switchers"***: • Women who began the study on a contraceptive other than DMPA and then switched to DMPA would contribute to non-DMPA time up to the point when their DMPA exposure began
Definitions of outcomes	Fractures are classified based anatomical sites into: ankle, arm clavicle, finger/toe, hand, foot, hip, leg, pelvis, ribs/sternum, shoulder, skull/face, vertebra, wrist, and unspecified. ***Primary outcome***: • The first bone fracture (any site) that occurred after entry into the cohort (defined by READ and OXMIS terms) ***In secondary analyses, fractures were regrouped as***:[j] • All fractures • All fractures except finger/toe, skull/face and unspecified • Axial skeleton fractures (vertebra + pelvis) • Appendicular skeleton fractures (arm + leg + wrist + ankle + hand + foot + rib/stenuum + clavicle + shoulder + hip)
Covariates[†]	Defined based on their associations with prevalence of exposure (ever use of DMPA) and risk of outcome (incident fracture, any site): Past fracture (any site), alcohol abuse/dependence, drug abuse, inflammatory bowel disease, epilepsy, asthma, oral corticosteroid therapy, fall, estrogen HRT, current smoking, and pregnancy < 20 years

† In subcohort of women with at least 6 months of baseline history

[j] Integrated summary report: the association of bone fractures and use of depo-medroxyprogesterone acetate (DMPA) in women in the General Practice Research Database (GRPD). Prepared by Pfizer June 19, 2008.

7 APPENDIX #2 SUMMARY OF GPRD STUDY RESULTS

Overall fracture incidence (Appendix Table A2)

The crude incidence (all fracture types) was 6.4 per 1,000 PYs for nonusers and 9.0 for DMPA users, with a crude incidence rate ratio (IRR) of 1.41 (95% CI 1.35-1.47). After standardizing for age, the IRR was 1.44 (95% CI 1.38-1.50).

In the subcohort with at least 6 months look-back period, the crude incidence rate was 6.6 for nonusers and 9.1 for DMPA users. The crude IRR was 1.37 (95% CI 1.29-1.45) and the age-adjusted IRR was 1.40 (95% CI 1.32-1.49).

Appendix Table A2 Incidence of fractures during follow-up in full cohort (n=312,395) and subcohort (n=166,367)

	DMPA users			Nonusers (Reference)			Crude IRR (95% CI)	Age-standardized IRR (95% CI)‡
	Fractures	PYs	Rate per 1,000 PYs	Fractures	PYs	Rate per 1,000 PYs		
Full cohort	2,935	327,315	9.0	8,887	1,395,041	6.4	1.41 (1.35-1.47)	**1.44 (1.38-1.50)**
Subcohort†	1,574	173,713	9.1	4,939	744,242	6.6	1.37 (1.29-1.45)	**1.40 (1.32-1.49)**

† Subjects in the subcohort had to have at least six months of baseline data before index contraceptive
‡ Using age distribution from the entire cohort as weights
* PY = person-years, CI = confidence interval, IRR = incidence rate ratio
¶ Source data: Original Final Report 2007 (Table 8); Integrated Summary Report 2008 (Summary Table 1)

Assessment of potential confounders in subcohort of women with 6 months of baseline period (Appendix Table A3)

Potential confounding factors were selected based on a priori knowledge and statistical rule which examines the percent change in crude *vs.* adjusted IRR estimates (e.g., > ±10%). In the GPRD data, patient characteristics that were associated with both fracture risk and ever use of DMPA included alcohol abuse/dependence, drug abuse, current smoking, pregnancy < 20 years, epilepsy, fall, past fracture, inflammatory bowel disease, asthma, oral corticosteroids therapy, estrogen oral contraceptives. Body mass index (BMI) can be estimated for 47% of the subcohort, and smoking history can be estimated for 59%.

As shown in Appendix Table A3, the crude IRR comparing DMPA use to nonuse was 1.37 (95% CI 1.29-1.45). The age-standardized IRR (based on age at 'index date') was 1.40 (1.32-1.49). The IRRs after standardizing age plus individual baseline factor, one factor at a time, were close to the value of 1.40 that resulted from standardizing by age alone. None of the baseline factors increased or decreased the IRR by 10% or more. Hence, none of these factors were labeled as confounders.

Appendix Table A3 Incidence rate ratios for DMPA use, standardized for age and other selected factors in subcohort of women with 6 months of baseline history available immediately prior to "index date"

Potential confounding factors	Incidence rate ratio (IRR)	95% confidence interval (CI)
Crude incidence rate ratio (IRR)	1.37	1.29-1.45
Standardized for age only (5-year categories)	**1.40**	**1.32-1.49**
Standardized for age and each baseline covariate		
Oral corticosteroids	1.40	1.32-1.49
Pregnancy < age 20	1.40	1.32-1.49
Smoking, current	1.39	1.31-1.47
Alcohol abuse	1.41	1.32-1.49
Asthma	1.39	1.31-1.48
Drug abuse	1.40	1.32-1.48
Epilepsy	1.40	1.32-1.48
Estrogen HRT	1.40	1.32-1.49
Fall	1.40	1.32-1.49
Past fracture, any site	1.41	1.32-1.50
Inflammatory bowel disease	1.40	1.32-1.48

Effect of DMPA exposure by recency of use and cumulative number of injections (Appendix Table A4)

The crude incidence of fracture among nonusers was 6.4 per 1,000 PYs. The crude incidence was 9.6, 9.0 and 8.4 per 1,000 PYs in current, recent and past users of DMPA, respectively. The age-standardized rates were similar to the crude estimates.

Fracture incidence was significantly higher in DMPA users compared to nonusers regardless of recency of exposure. Fracture rates were similar for low (1 to 7 DMPA injections) *versus* high (≥ 8 injections, equivalent to 2 years of treatment) cumulative exposure in past or recent users. The only exception was in the current exposure time, where the rate in low cumulative exposure was notably higher than the rate in high cumulative exposure.

Appendix Table A4 Incidence of any fracture per 1,000 person-years (PYs) by recency of DMPA injections and cumulative number of injections

Exposure	Fractures	PYs	Rate per 1,000 PYs	Crude IRR	Age-standardized rate per 1,000 PYs	Age-adjusted IRR
None[†]	8,887	1,395,040	6.4	1.0 (Ref.)	6.3	1.0 (Ref.)
Past use	1,011	119,928	8.4	**1.32 (1.24-1.41)**	8.5	**1.34 (1.25-1.44)**
Low[‡]	892	106,400	8.4	1.32 (1.23-1.41)	8.5	1.34 (1.25-1.45)
High[‡]	119	13,528	8.8	1.38 (1.15-1.65)	7.4	1.16 (0.96-1.41)

Recent use	931	103,984	9.0	**1.41 (1.31-1.50)**	9.2	**1.45 (1.34-1.56)**
Low	751	84,755	8.9	1.39 (1.29-1.50)	8.8	1.39 (1.27-1.52)
High	180	19,228	9.4	1.47 (1.27-1.70)	9.4	1.49 (1.27-1.74)
Current use	993	103,404	9.6	**1.51 (1.41-1.61)**	9.6	**1.51 (1.41-1.62)**
Low	645	53,123	12.1	1.91 (1.76-2.06)	13.7	2.16 (1.75-2.67)
High	348	50,281	6.9	1.09 (0.98-1.21)	6.7	1.06 (0.95-1.18)

† The follow-up time for nonusers is composed of person-years of women who did not use DMPA and of person-years of DMPA users before their fist DMPA prescription (e.g., "switchers").
‡ Cumulative exposure was low if the woman had accumulated a history of 1-7 DMPA injections, and high if she had received 8 or more
¶ Source data: Original Final Report 2007 (Tables 10 and 11)

Crude incidence of fractures by fracture type in full study population (Appendix Table A5)

Use of DMPA was not associated with osteoporotic type fractures (vertebra, hip, and pelvis fractures). A statistically significant increased risk was observed for appendicular skeleton, and wrist fractures. However, an increased risk was reported for fractures not typically associated with osteoporosis (ankle, arm, foot, hand, leg, rib/sternum).

Appendix Table A5 Fracture incidence by fracture type

	DMPA users		Nonusers (Reference)		IRR
	Fractures	Rate per 1,000 PYs	Fractures	Rate per 1,000 PYs	
Fracture groups					
All fractures	2935	8.97	8887	6.37	**1.41 (1.35-1.47)**
All fractures except finger/toe, skull/face, anatomic location unspecified‡	1700	5.19	5345	3.83	**1.36 (1.28-1.43)**
Axial skeleton	65	0.20	289	0.21	0.96 (0.73-1.25)
Appendicular skeleton	1632	4.99	5050	3.62	**1.38 (1.30-1.46)**
Osteoporosis-associated fractures					
Vertebra	35	0.11	141	0.10	1.06 (0.73-1.53)
Hip	8	0.02	38	0.03	0.90 (0.42-1.92)
Wrist	331	1.01	899	0.64	**1.57 (1.38-1.78)**
Pelvis	30	0.09	148	0.11	0.86 (0.58-1.28)
Other fractures by site†					
Ankle	248	0.76	729	0.52	1.45 (1.26-1.67)
Arm	374	1.14	1205	0.86	1.32 (1.18-1.49)
Foot	193	0.59	653	0.47	1.26 (1.07-1.48)

Hand	152	0.46	432	0.31	1.50 (1.25-1.80)
Leg	140	0.43	516	0.37	1.16 (0.96-1.39)
Rib/sternum	124	0.38	355	0.25	1.49 (1.21-1.83)

† 95% confidence intervals (CI) were not reported
‡ Finger/toe, skull/face fractures were excluded from analyses in randomized clinical trials
¶ Source data: Integrated Summary Report 2008; Supplementary Analytic Report 2008

Crude incidence of fractures before and after the first DMPA injection (Appendix Table A6)

There was no statistically significant difference between estimated IRR before *versus* after DMPA treatment. Before DMPA was started, the crude IRR comparing the fracture incidence in women who later became DMPA users (e.g., DMPA users) to women who never used DMPA (e.g., nonusers) was 1.28 (95% CI 1.07-1.52). After starting contraceptive, the crude IRR only changed slightly (IRR=1.23, 95% CI 1.16-1.30).

Appendix Table A6 Incidence of fracture before and after use of DMPA in **subcohort** of 166,367 women with 6 months of preindex history

	Before starting DMPA or other index contraceptive		After starting DMPA or other index contraceptive		IRR after/before (95% CI)
	Fractures	Rate per 1,000 PYs	Fractures	Rate per 1,000 PYs	
DMPA users (n=41,876)	176	8.4	1,574	9.1	1.08 (0.92-1.26)
Nonusers (n=124,491)	409	6.6	4,939	7.3	1.12 (1.01-1.24)
Crude IRR for DMPA vs. nonusers	1.28 (1.07-1.53)		1.23 (1.16-1.30)		

¶ Source data: Lanza L, et al. Obstet Gynecol 2013; 121: 593-600. – Table 3

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JIE J LI
09/27/2017

LOCKWOOD G TAYLOR on behalf of DAVID G MOENY
09/27/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020246Orig1s060s062

Administrative/Correspondence Document(s)

EXCLUSIVITY SUMMARY

NDA # 020246 SUPPL # 060 & 062 HFD #

Trade Name Depo-Provera Contraceptive Injection

Generic Name medroxyprogesterone acetate

Applicant Name Pfizer, Inc

Approval Date, If Known December 4, 2020

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021583

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to

3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☒ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Protocol A6791022 – Evaluation of Bone Mineral Density and Total Body Calcium in Adolescent Users and Non-Hormonal Contraceptive Users

Protocol A6791032 – The Association of Bone Fractures and Use of Depo-Medroxyprogesterone Acetate (DMPA) in Women in the General Practice Research Databases (GPRD)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☒

Explain:
These studies met the criteria for an IND exemption

Investigation #2

IND # YES ☐ NO ☒

Explain:
These studies met the criteria for an IND exemption

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☒
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Z. Charlene Williamson
Title: Regulatory Project Manager
Date: December 4, 2020

Name of Division Director signing form: Christine Nguyen, M.D.
Title: Division Director

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/s/

ZETA-MAE C WILLIAMSON
12/04/2020 06:55:55 PM

CHRISTINE P NGUYEN
12/06/2020 11:27:53 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor) Charlene Williamson, RPM, for the Division of Urology, Obstetrics, and Gynecology
REQUEST DATE: July 14, 2020	IND NO.	NDA/BLA NO. NDA 21583/S-33 & S-34, and NDA 20246/ S-60 & S-62	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Package Insert
NAME OF DRUG: Depo SubQ Provera, and Depo Provera		PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG Non-oral contraceptive DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
NAME OF FIRM: Pfizer, Inc.			PDUFA Date: December 5, 2020

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission:
NDA 21583: \\CDSESUB1\evsprod\NDA021583\021583.enx
NDA 20246: \\CDSESUB1\evsprod\NDA020246\020246.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: Pending schdule
Labeling Meetings: Pending schedule
Wrap-Up Meeting: Pending schedule

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SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

NENITA I CRISOSTOMO
07/14/2020 03:58:37 PM

NDA 021583/S-033 & 034
NDA 020246/S-060 & 062

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Pfizer Inc
Attention: Michelle Patel, R.Ph.
Manager
Pfizer Global Regulatory Affairs
235 East 42nd Street,
New York, NY 10017

Dear Ms. Patel:[1]

We acknowledge receipt of your June 5, 2020, resubmission to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEPO-SUBQ PROVERA 104 (medroxyprogesterone acetate) Injectable Suspension and DEPO-PROVERA® (medroxyprogesterone acetate, USP) Contraceptive Injection.

We consider this a complete, class 2 response to our October 6, 2017 action letter. Therefore, the user fee goal date is December 5, 2020.

If you have any questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Project Manager
Division of Regulatory Operations for Urology, Obstetrics, and Gynecology
Office of Regulatory Operations
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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/s/

ZETA-MAE C WILLIAMSON
06/11/2020 01:53:43 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020246/S-060 & S-062
NDA 021583/S-033 & S-034

GENERAL ADVICE

Pharmacia & Upjohn Company a subsidiary of Pfizer Inc.
Attention: Nestor Duci, MBA
Senior Manager
Director, Pfizer Essential Health Global Regulatory Affairs Brands
445 Eastern Point Road
Groton, CT 06340

Dear Mr. Duci:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEPO-PROVERA® (medroxyprogesterone acetate, USP) Contraceptive Injection AND DEPO-SUBQ PROVERA 104 (medroxyprogesterone acetate) Injectable Suspension.

These supplemental applications proposed (b) (4)

We also refer to your September 14,2018, submission, containing a request for an extension in which to resubmit the supplemental application, in response to our complete response letter dated October 6, 2017.

We grant your request for an extension of 90 days to resubmit this supplemental application. We remind you that per 21 CFR 314.110(c), an applicant's failure to resubmit the supplemental application within the extended time period or to request an additional extension may be considered a request by the applicant to withdraw the supplemental application.

If you have any questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ZETA-MAE C WILLIAMSON
09/28/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/ Office)*: **DB7**			FROM: DEPI-II	
DATE June 2, 2017	IND NO.	NDA NO. 20246/S-060 & 062 21583/S-033 & 034	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT December 9, 2016

NAME OF DRUG Depo Provera Injection & Depo SubQ provera 104	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Contraception	DESIRED COMPLETION DATE July 2, 2017

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Depo-Provera CI (NDA 20-246) is a long-acting progestin-only contraceptive containing 150 mg of medroxyprogesterone acetate (MPA), administered intramuscularly (IM) every three months. depo-SubQ provera 104 (NDA 21-583), is a similar quarterly injection, but is given in a lower dose (104 mg) and administered subcutaneously in the anterior thigh or abdomen. In 2004, FDA added a boxed warning to the labels regarding the risk of bone density loss and the possibility of osteoporotic fracture:

"Women who use Depo-Provera Contraceptive Injection 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."

In July of 2011, FDA approved an efficacy supplement with changes to the label including more recent data on fracture risk. The Applicant, Pfizer, has now submitted efficacy supplements with literature and additional analyses of previously submitted data, with the aim of changing the boxed warning, [redacted] (b) (4), and to make changes to [redacted] (b) (4), Warnings and Precautions, [redacted] (b) (4) and Clinical Studies sections consistent with that.

1. Please review the A6791032 GPRD database study—the Applicant provided new analyses with a look-back 6-24 months prior to DMPA use.

2. Please review the following articles from our PubMed search and any others you find in a search for DMPA and bone mineral density or DMPA and fracture risk since previous reviews by DBRUP and DEPI for this product.

    a. Lopez LM, Chen M, Mullins Long S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Syst Rev. 2015 Jul 21;(7):CD009849. doi: 10.1002/14651858.CD009849.pub3. Review.

    b. Modesto W, Bahamondes MV, Bahamondes L.Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate. J Womens Health (Larchmt). 2015 Aug;24(8):636-40. doi: 10.1089/jwh.2014.5077.

    c. Viola AS, Castro S, Bahamondes MV, Fernandes A, Viola CF, Bahamondes L. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011 Nov;84(5):e31-7. doi: 10.1016/ j.contraception.2011.06.012.

    d. Viola AS, Castro S, Marchi NM, Bahamondes MV, Viola CF, Bahamondes L. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. Contraception. 2011 Aug;84(2):122-7. doi: 10.1016/j.contraception.2010.11.007.

    e. Pongsatha S, Ekmahachai M, Chaovisitsaree S, Suntornlimsiri N, Morakote N. Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: a cross sectional study. J Med Assoc Thai. 2009 Oct;92(10):1263-7.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
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06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
03/02/2017

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/s/

MAMMAH S BORBOR-LEBBIE
06/01/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 20246/S60 **Applicant: Pfizer** **Stamp Date: 10/06/2017**

Drug Name: Depo Provera CI **NDA/BLA Type: PAS**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	x			eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			Clinical Overview 10/6/16, separated out bone mineral density (BMD) and fracture data and provided articles 1/18/17. This submission pertains to BMD
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Integrated study report addressing safety concern of BMD
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	Approved product
10.	Has the applicant submitted a benefit-risk analysis for the product?			x	Approved product
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x		x	The Applicant filed a 505(b)(1) but should file a 505 (b)(2) because articles from other sources are used to support the change
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Describe the scientific bridge (e.g., BA/BE studies)			x	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:			x	
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			x	
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	Approved product
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			Pertaining to BMD
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Approved product for postmenarchal females
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	No datasets
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses			x	No datasets, only

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	available and complete?				previously reviewed study reports
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				No raw data needed
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			x	
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	Amended study reports for A6791022 in adolescents ,and M5400-0234 in women, review of literature

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

CATHERINE A SEWELL
03/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM: Division of Bone, Reproductive and Urologic Products Attn: Charlene Williamson	
Mail: OSE				
DATE March 2, 2017	IND NO.	NDA NO. 20246/S-060 & 062 21583/S-033 & 034	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT December 9, 2016
NAME OF DRUG Depo Provera Injection & Depo SubQ provera 104	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Contraception	DESIRED COMPLETION DATE July 2, 2017

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Depo-Provera CI (NDA 20-246) is a long-acting progestin-only contraceptive containing 150 mg of medroxyprogesterone acetate (MPA), administered intramuscularly (IM) every three months. depo-SubQ provera 104 (NDA 21-583), is a similar quarterly injection, but is given in a lower dose (104 mg) and administered subcutaneously in the anterior thigh or abdomen. In 2004, FDA added a boxed warning to the labels regarding the risk of bone density loss and the possibility of osteoporotic fracture:

"Women who use Depo-Provera Contraceptive Injection 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."

In July of 2011, FDA approved an efficacy supplement with changes to the label including more recent data on fracture risk. The Applicant, Pfizer, has now submitted efficacy supplements with literature and additional analyses of previously submitted data, with the aim of changing the boxed warning, [redacted] (b) (4), and to make changes to [redacted] (b) (4), Warnings and Precautions, [redacted] (b) (4) and Clinical Studies sections consistent with that.

1. Please review the A6791032 GPRD database study—the Applicant provided new analyses with a look-back 6-24 months prior to DMPA use.

2. Please review the following articles from our PubMed search and any others you find in a search for DMPA and bone mineral density or DMPA and fracture risk since previous reviews by DBRUP and DEPI for this product.

    a. Lopez LM, Chen M, Mullins Long S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Syst Rev. 2015 Jul 21;(7):CD009849. doi: 10.1002/14651858.CD009849.pub3. Review.

    b. Modesto W, Bahamondes MV, Bahamondes L.Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate. J Womens Health (Larchmt). 2015 Aug;24(8):636-40. doi: 10.1089/jwh.2014.5077.

    c. Viola AS, Castro S, Bahamondes MV, Fernandes A, Viola CF, Bahamondes L. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011 Nov;84(5):e31-7. doi: 10.1016/ j.contraception.2011.06.012.

    d. Viola AS, Castro S, Marchi NM, Bahamondes MV, Viola CF, Bahamondes L. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. Contraception. 2011 Aug;84(2):122-7. doi: 10.1016/j.contraception.2010.11.007.

    e. Pongsatha S, Ekmahachai M, Chaovisitsaree S, Suntornlimsiri N, Morakote N. Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: a cross sectional study. J Med Assoc Thai. 2009 Oct;92(10):1263-7.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
03/02/2017

From:	Sewell, Catherine
To:	Kehoe, Theresa; Voss, Stephen; Soule, Lisa; Williamson, Charlene
Subject:	NDA 20246/S60 & 62 and NDA 21583/S33 & 34
Date:	Friday, February 17, 2017 8:34:36 PM
Attachments:	20246ClinREVIEW_2011.pdf CDTL draft DMPA IM GPRD 7 25 11.pdf DBRUP DMPA Citizen petition response.pdf

Hi, Theresa and Steve,
Below please find our questions for your consult to the DMPA efficacy supplements on BMD and fracture risk.

As you are aware, Depo-Provera CI (NDA 20-246) is a long-acting progestin-only contraceptive containing 150 mg of medroxyprogesterone acetate (MPA), administered intramuscularly (IM) every three months. depo-SubQ provera 104 (NDA 21-583), is a similar quarterly injection, but is given in a lower dose (104 mg) and administered subcutaneously in the anterior thigh or abdomen. In 2004, FDA added a boxed warning to the labels regarding the risk of bone density loss and the possibility of osteoporotic fracture:

" • Women who use Depo-Provera Contraceptive Injection 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 longterm birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate."

In July of 2011, FDA approved an efficacy supplement with changes to the label including more recent data on fracture risk. The Applicant, Pfizer, has now submitted efficacy supplements with literature and additional analyses of previously submitted data, with the aim of changing the boxed warning, (b) (4), and to make changes to (b) (4), Warnings and Precautions, (b) (4) and Clinical Studies sections consistent with that.

They provide their rationale in the Clinical Overview submitted on October 6, 2016, and if you need it, study data and literature on January 18, 2017 and labeling January 31, 2017. I am also attaching our Citizen's Petition response, and the clinical and CDTL memos from the previous supplements.

1. Comment on Applicant's theory of premenopausal women having a bone 'reserve' from which calcium can be mobilized without impacting normal bone strength (e.g., during pregnancy and lactation). The Applicant also claims that DMPA pharmacologically mimics pregnancy and (i) prevents ovulation, which is its intended effect, but also (ii) triggers the same mobilization of calcium as do pregnancy/lactation, (b) (4) Please comment on the validity of this claim.

2. Provide accepted list of each type of fracture (fragility vs. traumatic). Comment on whether it is appropriate to evaluate fractures other than fragility/osteoporotic fractures in epidemiologic studies of premenopausal users of DMPA in attempting to assess whether the drug's adverse impact on BMD may translate into adverse clinical effects (i.e., increased rate of fracture).

3. Comment on Applicant's position that BMD is a handy tool to assess bone strength but does not provide fundamental definition of osteoporosis. They say actual bone density cannot be

measured in life. Do we have any better tools? Is this the best surrogate we have?

Thanks,
Catherine

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ZETA-MAE C WILLIAMSON
03/02/2017

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 20246/S-060 & S-062 **Applicant:** Pfizer **Stamp Date:** 01/18/2017

Drug Name: DEPO-PROVERA® **NDA Type:** Supplement

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).			X	

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			X	
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kate Dwyer, Ph.D. 2/01/17

Reviewing Statistician Date

Mahboob Sobhan, Ph.D. 2/01/17

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

KATE L DWYER
02/01/2017

MAHBOOB SOBHAN
02/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020246/S-060 & S-062

PRIOR APPROVAL SUPPLEMENT
USER FEES RECEIVED

Pharmacia & Upjohn Company a subsidiary of Pfizer Inc.
Attention: Karen Baker, M.S.
Director, Pfizer Essential Health Global Regulatory Affairs Brands
235 East 42nd Street
New York, NY 10017-7555

Dear Ms. Baker:

Please refer to supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for DEPO-PROVERA Contraceptive Injection 150 mg/mL.

You were notified in our letter dated November 7, 2016, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received or waived all required fees and your application has been accepted as of December 9, 2016.

This supplemental application proposes the following two changes to the Prescribing Information related to Bone Mineral Density in adolescents and Fracture Risks.

Unless we notify you within 60 days of the above date that the supplemental application is not sufficiently complete to permit a substantive review, this supplemental application will be filed on February 8, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The supplement application number cited above should be included at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Bone, Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ZETA-MAE C WILLIAMSON
12/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20246/S-060

UNACCEPTABLE FOR FILING

Pharmacia & Upjohn Company a subsidiary of Pfizer Inc.
Attention: Greg Carrier
Senior Director, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017-7555

Dear Mr. Carrier:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEPO-PROVERA Contraceptive Injection 150 mg/ml.

This supplemental application proposes revisions to the 1) Boxed Warning, (b) (4) and 3) Warnings and Precautions Sections of the Prescribing Information.

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the appropriate user fee coversheet (Form 3397 or 3792) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number P.O. Box 979107 should be included on any check you submit.

Please cite the supplemental NDA number listed above at the top of the first page of all submissions to this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Bone, Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call the Prescription Drug User Fee staff at 301-796-7900.

If you have any questions regarding this application, contact me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ZETA-MAE C WILLIAMSON
11/07/2016