

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-583

MEDICAL REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-583
Type of Application	Complete response to approvable action
Applicant	Pharmacia & Upjohn Company, a subsidiary of Pfizer, Inc.
Proprietary Drug Name	depo-subQ provera 104
Established Drug Name	Medroxyprogesterone acetate injectable suspension, USP
Dosage Form	Sterile aqueous suspension in prefilled syringe
Dosage Strength	160 mg/mL (delivered dose is 104 mg/0.65 mL per syringe)
Dosing Regimen	Subcutaneous injection once every 3 months
Indication	Prevention of pregnancy in women
PDUFA Date	December 17, 2004
Date of Memorandum	December 15, 2004
Reviewer	Scott E Monroe, MD Clinical Team Leader, DRUDP

RECOMMENDATIONS

Recommendation regarding Approvability

It is recommended that medroxyprogesterone acetate injectable suspension, USP (depo-subQ provera 104, hereafter referred to DMPA-SC) be approved for marketing for prevention of pregnancy in women. This recommendation for approval is based on the data presented in the original NDA dated June 30, 2003, the Applicant's complete response dated October 15, 2004, and final revised labeling submitted on December 13, 2004. In clinical trials, DMPA-SC has been shown to be highly effective (no pregnancies were detected among 2,042 women treated for up to one year). The safety profile is acceptable for a highly effective contraceptive that requires dosing only once every 3 months. The Applicant has satisfactorily addressed all of the labeling issues that were referred to in the Approvable Letter of August 2, 2004.

Recommendation on Phase 4 Studies and/or Risk Management Steps

No new Phase 4 studies are recommended. DMPA-SC should have a risk profile similar to the presently marketed product (administered by intramuscular [IM] injection) that was approved in the U.S. in 1992 for prevention of pregnancy. The Applicant has an ongoing study of the reversibility of bone mineral density (BMD) changes in adolescents who have been treated with DMPA-IM. The posttreatment follow up phase of this study will provide important data about BMD recovery in adolescents and should be reported to the Division

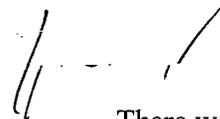
The most significant risk associated with the use of DMPA-SC (decrease in BMD) should be adequately managed by approved Physician and Patient Labeling that include a Boxed Warning.

BACKGROUND

Medroxyprogesterone acetate (MPA) is the synthetic 6-methyl analog of 17-hydroxyprogesterone. MPA has been marketed for many years as oral (Provera® Tablets) and intramuscular injection formulations (Depo-Provera® Sterile Aqueous Suspension [400 mg/mL; indication of palliative treatment of renal or endometrial cancer] and Depo-Provera® Contraceptive Injection [150 mg/mL]).

This application (NDA 21-583) is for a new formulation and dose of MPA sterile aqueous suspension for the prevention of pregnancy. The new product (DMPA-SC) differs from the currently approved product (DMPA-IM) in that (1) it is to be administered subcutaneously instead of intramuscularly and (2) the dose of MPA is lower (104 mg once every 3 months compared to 150 mg once every 3 months).

The original NDA for DMPA-SC was submitted in June 2003.



There were no statistically significant differences in the decreases in BMD over the 2-year study period in women using DMPA-SC compared to those in women using DMPA-IM. Weight gain in the women who used DMPA-SC was similar to that reported previously for women who used DMPA-IM.



A disadvantage of the SC formulation is the occurrence of local reactions that were reported as an adverse event in 5% of women in the clinical trials. Most of the events were rated as mild in intensity. None was classified as serious.

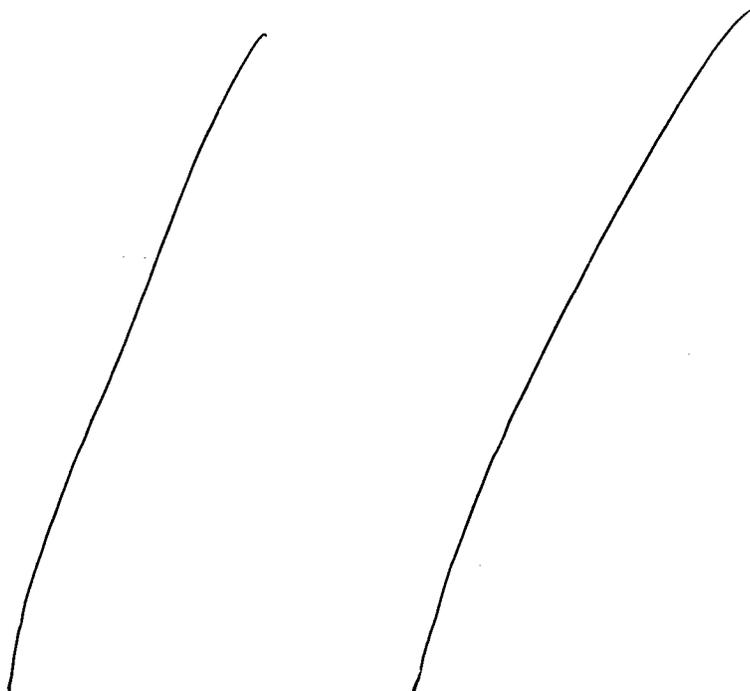
The safety and efficacy of DMPA-SC for prevention of pregnancy, based on the data provided in the Applicant's original NDA submission, are reviewed in detail in Dr. Furlong's (the primary Medical Officer) review of July 29, 2004 and the clinical Team Leader's Memorandum of August 2, 2004. In brief, data provided in the original submission, and updated in the Applicant's Complete Response, indicate that DMPA-SC is a highly effective contraceptive. In three clinical studies, no pregnancies were detected among 2,042 women using DMPA-SC for up to 1 year. The Pearl Index (PI) pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use (upper 95% confidence interval of the PI = 0.25). Clinical trial data submitted by the Applicant for DMPA-SC, and supportive postmarketing data for DMPA-IM, indicate that the safety profile for DMPA-SC is acceptable for a highly effective contraceptive that requires dosing only once every 3 months.

PRESENT SUBMISSION (COMPLETE RESPONSE TO APPROVABLE LETTER)

In the present submission, the Applicant has submitted revised drug labeling and a safety update.

Revised Labeling

The Applicant has extensively revised both the Physician and Patient Labeling for DMPA-SC in accordance with the recommendations of the Division.



Medical Officer's Comment

- *Final labeling submitted by the Applicant on December 13, 2004 is acceptable.*

Safety Update

The Applicant's Complete Response included a Safety Update for all ongoing clinical trials with DMPA-SC as well as an update of the post marketing safety experience with the IM formulation. A thorough review of the data in the Safety Update is provided in Dr. Furlong's review signed on December 9, 2004. Dr. Furlong made the following statements in her review: "*None of updated findings affect my original recommendation that DMPA-SC is effective for prevention of pregnancy and has an acceptable safety profile for a highly effective contraceptive product...The safety update revealed no new or unexpected safety issues.*"

Medical Officer's Comment

- *I concur with Dr. Furlong's assessment regarding the safety and efficacy of DMPA-SC for the prevention of pregnancy in women.*

Proprietary Drug Name

At the time of submission of the Complete Response, the Applicant wished to use the proprietary name _____ (alternative name). Neither the Division of Reproductive and Urologic Drug Products (DRUDP) nor the Division of Medication Errors and Technical Support (DMETS) supported the use of either name. _____

The proposed proprietary name “depo-subQ provera 104” is acceptable to DRUDP in that it does not suggest any clinical benefit and clearly differentiates this product from the intramuscular formulation by inclusion of (1) the term “subQ” within the name (rather than at the end of the name) and (2) the mg dose of MPA (104), which differs from that of the IM formulation.

Other Disciplines

There are no preclinical toxicology, (chemistry, manufacturing, and controls), or biopharmaceutical deficiencies. During the original review cycle, the Biopharmaceutical Reviewer had originally requested (and the Applicant had agreed) to characterize further the metabolic pathways for MPA in an in vitro study. After further review of the presently available information regarding the metabolism of MPA and the likely clinical benefit that would be derived from the additional information, the Biopharmaceutics Reviewer concluded that a Phase 4 commitment to obtain additional metabolic data for MPA was not needed.

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this page is the manifestation of the electronic signature.**

/s/

Scott Monroe
12/16/04 09:26:15 AM
MEDICAL OFFICER

Donna Griebel
12/16/04 12:15:53 PM
MEDICAL OFFICER

I have read Dr. Monroe's review and concur with
his assessments and recommendation for approval.

CLINICAL REVIEW

Application Type	21-583
Submission Number	000
Submission Code	AZ
Letter Date	15-Oct-2004
Stamp Date	18-Oct-2004
PDUFA Goal Date	15-Dec-2004
Reviewer Name	L. Furlong
Review Completion Date	8-Dec-2004
Established Name	Medroxyprogesterone acetate
Trade Name	depo-subQ provera 104
Therapeutic Class	Progestin
Applicant	Pfizer
Priority Designation	S
Formulation	Suspension
Dosing Regimen	104 mg in 0.65 ml every 12 to 14 weeks
Indication	Prevention of pregnancy in women of childbearing potential
Intended Population	Women of childbearing potential

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of depot medroxyprogesterone acetate subcutaneous injection (DMPA-SC) for prevention of pregnancy in women of childbearing potential.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Routine postmarketing surveillance should be adequate. The product label may need updating when final results of a Phase 4 study (Study 261) in adolescents are available.

1.3 Summary

On August 2, 2004, FDA issued an approvable action for NDA 21-583 because labeling had not been finalized. The present submission includes Pfizer's response to FDA's labeling recommendations, as well as a routine safety update. The submission addresses all items requested in FDA's approvable letter.

During the original NDA review, FDA requested extensive changes throughout the labeling, including, but not limited to, text about

- Bone mineral density
- Return to ovulation and fertility
- Pregnancy and lactation
- Weight changes
- Injection site reactions
- Adverse Events

The Executive Summary of my review of the original NDA is in the Appendix to provide an overview of the issues identified.

Pfizer has agreed with most of FDA's requested changes and has proposed other changes that are acceptable.

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✓ Draft Labeling

 Deliberative Process

7 INTEGRATED REVIEW OF SAFETY

7.2.9 Safety Update

Most of the safety information submitted by the Applicant in the safety update has already been submitted to the NDA, except for updated postmarketing safety assessments for DMPA-IM and limited data available from on-going studies of DMPA.

7.2.9.1 Update of Clinical Studies

Table 1 summarizes the studies included in the update.

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Table 1. Clinical Studies Involving DMPA-SC or DMPA-IM

Study Number	Objective	Treatment Group (n)	Comparator (n)	Planned Duration
Phase 4 contraception Studies (IM)				
234	To evaluate and compare BMD in adult women aged 25 to 35 years who were assigned to either DMPA-IM or to a control group not using hormonal contraception.	DMPA-IM 150 mg Every 3 months. n = 248	Control group not using hormonal contraception n = 360	240 weeks Follow up for 2 years
261	To evaluate and compare BMD in adolescent female subjects aged 12 to 18 years who were assigned to either treatment with DMPA -IM or to a control group.	DMPA-IM 150 mg Every 3 months n = 197	Untreated group not using hormonal contraception n = 216	240 weeks Follow up for 2 years (ongoing)
009	To evaluate and compare changes in BMD in adult women aged 18 to 35 years after treatment with either DMPA-IM or Lunelle, as a contraceptive	DMPA-IM 150 mg Every 3 months n = 247	Lunelle (DMPA-IM 25 mg and estradiol cypionate 5 mg) every month n = 484	2 years
Phase 3 contraception Studies (SC)				
267	To establish the safety, efficacy of and subject satisfaction with DMPA-SC as a contraceptive	DMPA-SC 104 mg every 3 months N=722	None	1 year
269	To establish the safety, efficacy of and subject satisfaction with DMPA-SC as a contraceptive	DMPA-SC 104 mg every 3 months N=1065	None	1 year
267BMD	To evaluate BMD changes in women receiving either DMPA-SC or DMPA-IM as a contraceptive	DMPA-SC 104 mg every 3 months n = 266	DMPA-IM 150 mg every 3 months n = 268	2 years, extended to 3 years (ongoing)
Phase 3 Endometriosis Studies				
268	To establish that DMPA-SC and leuprolide offer equivalent efficacy for a reduction in endometriosis -associated pain.	DMPA-SC 104 mg at 3 month intervals n = 136	Leuprolide IM 11.25 mg at 3 month intervals (2 injections) n = 138	6 months active treatment, 12 months follow-up
270	To establish that DMPA-SC and leuprolide offer equivalent efficacy for a reduction in endometriosis -associated pain.	DMPA-SC 104 mg at 3 month intervals n = 153	Leuprolide SC 3.75 mg monthly for 6 injections n = 146	6 months active treatment, 12 months follow-up

Source: Safety Update, p. 65

The analysis was integrated for treatment and indication. Table 2 shows the size of the safety database from clinical trials for both products for the contraception indication.

Table 2. Number of Subjects in Contraception Clinical Trials in the Safety Update

Study	DMPA-SC (n)	DMPA-IM (n)
267	722	0
269	1,065	0
267BMD	266	268
234	0	248
009	0	245
TOTAL	2,053	761

Source: Safety Update, p.12

Table 3 shows the extent of exposure for the contraception indication in the present safety update compared with the original NDA submission. For the DMPA-SC group, the difference between the original NDA submission, which included 1,980 subjects treated with DMPA-SC, and the current submission, which included 2,053 subjects treated with DMPA-SC, is the data from 73 subjects in Study 267BMD, an ongoing 3-year study. Most subjects treated with DMPA-SC had four injections (or one year of treatment).

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Table 3. Number of DMPA-SC and DMPA-IM Injections in Contraception Clinical Trials (ITT)

	Original Submission		Present Safety Update			
	269+267+267BMD (partial 1 year data for 267BMD)		269+267+267BMD (2 Year Data for 267BMD)		009+234+267BMD (2 Year Data for 267BMD)	
	DMPA-SC N=1,980		DMPA-SC N=2,053		DMPA-IM N=2,814	
No. of Injections	n	%	n	%	n	%
1	173	8.7	177	8.6	100	13.1
2	206	10.4	213	10.4	88	11.6
3	111	5.6	117	5.7	69	9.1
4	1490	75.3	1388	67.6	68	8.9
5			22	1.1	43	5.7
6			7	0.3	31	4.1
7			4	0.2	28	3.7
8			125	6.1	237	31.1
9					7	0.9
10					6	0.8
11					3	0.4
12					4	0.5
13					10	1.3
14					3	0.4
15					4	0.5
16					1	0.1
17					3	0.4
18					4	0.5
19					6	0.8
20					42	5.5
21					4	0.5
Total	1,980	100.0	2,053	100.0	761	100.0

Source: Safety Update, p. 13

Comparing the data in the original submission to the data in the present safety update, there were slight changes in

- demographic parameters (weight, mean age, and race) from the original submission to the safety update (p. 14).
- reasons for withdrawal from the study (p. 16)
- percentage of subjects reporting adverse events, serious adverse events, adverse events leading to discontinuation, or drug-related adverse events (p. 17)

No additional deaths were reported in the safety update.

Nine new serious adverse events (SAEs) were reported in the safety update. These are summarized in Table 4.

Table 4. Subjects with Treatment-Emergent Serious Adverse Events in Studies 009, 234, 267BMD, and 261 (ITT)

Study	DMPA-SC	DMPA-IM	Total	Number of New SAEs *	Subject Number - SAE
009	0	6	6	1	00241 – pulmonary embolism
234	0	10	10	0	
267BMD 2 Yr	8	4	12	5	2263 – thyroid carcinoma 2382 – appendicitis 2497 – suicide attempt 2254 – unintended pregnancy 2491 – road traffic accident
267BMD 3 Yr	2	1	3	3	2096 – road traffic accident 2214 – staphylococcal infection at site of spider bite 2287 – hospitalization for elective breast reduction surgery
261	0	10	10	0	
Total	10	31	41	9	

Source: Safety Update, p. 25

After review of case report forms and case narratives, I think that three of the nine new SAEs may have been exacerbated by treatment. All three had underlying risk factors for their SAEs. Brief narratives follow:

1. Subject 00241 was a 27-year-old woman who had a pulmonary embolism, confirmed by angiogram, after 21 months of therapy with DMPA-IM. She weighed 211 pounds at baseline.
2. Subject 2497 was an 18-year-old who attempted suicide less than one month after her first dose of DMPA-SC. She had lost her boyfriend to suicide earlier in the year, and her 3-week-old baby died 4 months before her suicide attempt. She had a history of depression and suicide attempts.
3. Subject 2287 was a 19-year-old who was 178 pounds and 5 feet 5 inches tall at baseline and 193 pounds by month 33 of DMPA-IM therapy. She underwent breast reduction surgery.

The single new treatment failure occurred Subject 2254. She was a 24-year-old Brazilian woman who received DMPA-IM for 21 months and became pregnant shortly before her last injection.

There were no significant changes in the profile of women who stopped treatment for adverse events. Among 202 women who stopped therapy for adverse events in the DMPA-SC group, the most common reasons were:

- Uterine bleeding irregularities (34.7%)
- Increased weight (19.3%)

- Decreased libido (10.9%)
- Acne (9.9%)
- Injection site reactions (5.4%)

Small changes were detected in the adverse events profile, possibly related to the longer duration of exposure for some subjects (p.19). Three events moved from the less than 1% incidence category to the 1 to 5% incidence category:

- Injection site atrophy (0.9% to 1.1%)
- Bronchitis (0.9% to 1.1%)
- Vaginitis (0.96% to 1.4%)

Regarding laboratory studies and vital signs, there were no significant changes noted in the safety update.

Regarding safety issues of special interest,

- Weight gain,
- Injection site reactions
- Bleeding problems
- Bone mineral density (BMD) changes

the update provided slight changes in the numbers for labeling but no change in conclusions. The only study that directly compared DMPA-IM and DMPA-SC, Study 267BMD, did not detect a significant difference between the two formulations in terms of bone loss, bleeding, or weight gain.

Comment: None of updated findings affect my original recommendation that DMPA-SC is effective for prevention of pregnancy and has an acceptable safety profile for a highly effective contraceptive product.

7.2.9.2 Update of Postmarketing Reports for DMPA-IM

The Applicant provided a summary of the postmarketing database. Among 26,488 non-clinical study cases, 23 cases reported fracture-related events, and 34 cases reported events related to decreased bone mineral density with fractures. The Applicant provided a review of each case and concluded that "a contributory role of medroxyprogesterone to decreased bone mineral density events or fracture events cannot be excluded in these cases."

7.2.9.3 Reviewer's Conclusions

The safety update revealed no new or unexpected safety issues. Because of the extra data from ongoing Study 267BMD, the safety update supports minor numerical changes in labeling.

9.4 Labeling Review

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10 APPENDIX

Executive Summary from Clinical Review of the Original NDA

1 Recommendations

1.1 Recommendation on Approvability

Depot medroxyprogesterone acetate *subcutaneous* injection (DMPA-SC) is a reduced dose and new formulation of depot medroxyprogesterone acetate *intramuscular* injection (DMPA-IM), a product approved in 1992 for prevention of pregnancy in women of childbearing potential. Like DMPA-IM, DMPA-SC is a depot progestin contraceptive given by injection every 3 months.

Although the total drug exposure is less with DMPA-SC compared with DMPA-IM, the 2 products had similar profiles in clinical trials. In particular, bone loss and weight gain was similar in women using either product. The only differences detected were

- Nonserious injection site reactions occurred in 5% of DMPA-SC users and did not occur in DMPA-IM users

I recommend approval of DMPA-SC after changes to the proposed label.

1.2 Recommendation on Phase 4 Studies or Risk Management Steps

The Applicant has an ongoing study of bone mineral density (BMD) in adolescents treated with DMPA-IM. This study will provide important data about BMD recovery in adolescents. It is in the follow-up phase, and should be reported within 2-3 years.

No risk management is recommended other than revised labeling

2 Summary of Clinical Findings

2.1. Brief Overview of Clinical Program

DMPA-SC is a progestin for subcutaneous administration. In this NDA, the Applicant studied the indication, "prevention of pregnancy in women of childbearing potential."

The Phase 3 clinical program included three year-long contraception studies. 1,980 women received DMPA-SC in the Phase 3 clinical program, and efficacy data were obtained for 1,971 of 1,980 women. Another 193 women received DMPA-IM.

The clinical program also included

- three Phase 1/2 studies that exposed 116 women to single doses of DMPA-SC
- interim safety data from 298 women exposed to DMPA-SC in 2 trials that studied DMPA-SC as treatment for endometriosis
- one Phase 3 study that provided 2 years of bone mineral density data

The endometriosis trials included a 6-month treatment phase and a 12-month follow-up phase.

2.2 Efficacy

No pregnancies were detected in studies of 1,971 women using DMPA-SC for up to 1 year (20,607 women-months). The pregnancy rates in women 35 and under, based on cycles in which they used no other contraceptive methods was:

Pearl Index: 0 pregnancies per 100 women-years (upper 95% C.I. is 0.25)

All three Phase 3 trials used the same primary endpoint: treatment failure cumulative pregnancy rate at 1 year defined as a positive pregnancy test before the next scheduled dose. Subjects were healthy, sexually active women between 18 and 49 years old.

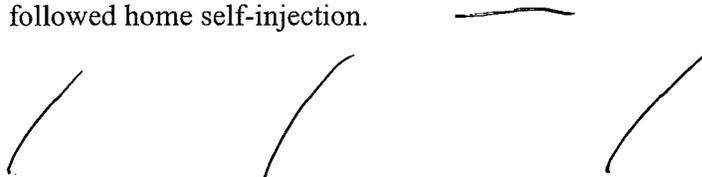
Although placebo treatment could not be used for ethical reasons, historical studies show that 85 to 90 of 100 sexually active women desiring pregnancy will become pregnant after 1 year of unprotected sexual activity. Therefore 0 pregnancies represent a strong treatment effect.

The table below summarizes experience with contraceptive products, and shows DMPA among the most highly effective methods.

Approximate Percentage of Women Who Become Pregnant During the First Year of Use of a Birth Control Method*	
METHOD	PREGNANCIES PER 100 WOMEN PER YEAR
estrogen/progestin injection levonorgestrel implants levonorgestrel IUD and copper IUD <i>medroxyprogesterone acetate injection</i> sterilization	Fewer than 1
estrogen/progestin contraceptive products: • pills • skin patch • vaginal ring	1
progestin-only pills	2
condom (male) diaphragm	15
spermicides	25 or more

* The estimates for drugs, condoms, diaphragms, and IUDs come from clinical trial data reviewed by the Food and Drug Administration. The estimates for sterilization and spermicides come from the medical literature. Source: prepared by reviewer from FDA internal data and literature review.

Only 5% of cycles followed home self-injection.



2.3 Safety

Total patient exposure met general guidelines for drug development and specific FDA recommendations for this product. 1,980 women were treated with DMPA-SC, and 1,490 women received 4 injections (one year of treatment). Overall, on-treatment data were collected for 20,607 women-months. Collection of adverse event data was adequate except for adverse events associated with dropouts. Adverse events associated with dropouts were probably underestimated because the design of the case report forms allowed investigators to check off "withdrawal of consent" without prompting for a reason. However, many of the women who withdrew consent also complained of adverse events, and this information was adequately captured on adverse event forms even if it did not show up as a reason for dropping out.

Treatment emergent serious adverse events (SAEs) occurred in 1% of subjects. The most common SAE was excessive uterine bleeding, which occurred in 4 subjects. All 4 subjects recovered. Although DMPA-SC may have contributed to excessive uterine bleeding, this is not an unusual problem in women of reproductive age.

About 10% of subjects dropped out for adverse events. The single most common reason for dropping out was uterine bleeding abnormalities, accounting for 40% of dropouts. Other common causes for dropping out included weight gain (22%), decreased libido (14%), and acne (13%). About 5% of dropouts were for injection site reactions. Injection site reactions were

only seen in subjects treated with DMPA-SC, and though infrequent, injection site reactions represent a disadvantage of the SC formulation. The typical reaction prompting dropout was chronic induration at the injection site, described by one investigator as "about the size of a nickel." Although investigators rated these reactions as not serious, women who dropped out of the studies for injection site reactions rated their likelihood of ever using DMPA-SC again as "extremely unlikely".

Common adverse events reported in more than 5% of subjects included headache (8%), intermenstrual bleeding (7%), increased weight (7%), and amenorrhea (6%). These adverse events also occur in women using DMPA-IM.

Although there were no formal studies of drug-drug interactions in this NDA, no efficacy or safety issues were detected among women who used concomitant medication. The Phase 3 database included 75 women taking CYP 3A4 inducers and 111 women taking CYP 3A4 inhibitors. In recent years it has become clear that MPA is metabolized by liver P450 enzymes. Since the clearance of MPA approximates liver blood flow, the Applicant postulated that enzyme induction should have limited effect on MPA levels. However, a published study suggests that MPA concentrations decrease by more than 50% when combined with aminoglutethimide, an inducer of hepatic microsomal enzymes, which suggests that MPA concentrations may be affected by liver enzyme induction. However, this is the only drug-drug interaction that has been reported for DMPA-IM. There have been no reports of reduced efficacy as a result of drug-drug interactions.

Trial exclusions may have improved the safety and efficacy profile somewhat compared with what may occur after marketing. For example, by requiring that women have regular cycles, postpartum women were excluded. This is a group at increased risk for thrombotic events, and DMPA is a popular contraceptive for postpartum women.

The effect of trial exclusions can be assessed by looking at the reasons for screening failures. Overall, 24% of subjects failed screening. Reasons were collected for 962 subjects. Most screening failures were related to consent and ability to comply with study procedures, and should not affect the applicability of trial results to the general population. However, there were 4 screening failures with liver or kidney disease, 22 with irregular cycles, and 58 with low bone mineral density at baseline (T-scores less than -1.0). Since it is not standard practice to prescreen healthy young women for these problems before starting hormonal contraception, exclusion of these women may have improved safety over what might occur after marketing. Nonetheless, most women of reproductive age who seek contraception are in good health, and, overall, the study population was a reasonable approximation of the expected population.

Warnings should be consistent with the DMPA-IM label, and include

- Bleeding irregularities
- Decrease in bone mineral density
- Cancer
- Thromboembolic disorders
- Ocular disorders (a subtype of thromboembolic disorder)
- Ectopic pregnancy

The safety profile of DMPA-SC is different from progestin-only pills in the following areas:

- weight gain
- BMD loss
- delayed return to fertility
- injection site reactions

These problems should be measured against the advantages of dosing every 3 months and the high effectiveness of DMPA-SC.

The current label for DMPA-IM states, "Use of Depo-Provera Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall." However, the Applicant's data indicate that bone loss is progressive over at least a 5-year period of observation. BMD recovery after treatment was also progressive, and not complete at 96 weeks for women who had more than 1 year of therapy. In Study 267BMD, women had median bone loss consistent with previous studies of DMPA-IM: after 1 year of treatment, -1.4% change in femoral BMD and -2.4% change in spinal BMD, and, after 2 years of treatment, -3.3% change in femoral BMD and -4.3% change in spinal BMD. No difference in BMD loss was detected between DMPA-IM and DMPA-SC after 2 years of treatment.

Published studies suggest that the BMD loss is at least partially reversible in adults who use DMPA-IM for contraception; however, this issue is unresolved for adolescents. The Applicant has an ongoing study of adolescents using DMPA-IM to address the issue. The study is in the follow-up stage. For balance, it should be noted that weight gain and BMD loss are also seen following pregnancy and lactation, conditions prevented by DMPA-SC. However, unlike the hormonal changes produced by pregnancy and lactation, the hormonal changes produced by DMPA can continue uninterrupted for many years.

Mean weight gain was 3.3 lb at 1 year for all subjects, and 4.4 lb at 1 year for US subjects. No difference in weight gain was detected between DMPA-IM and DMPA-SC. Weight gain can be a serious problem for some women,

Delayed return to fertility should be part of the counseling for every woman considering this method. Among 21 women who stopped treatment to become pregnant, only 1 became pregnant within 1 year of her last injection of DMPA-SC. DMPA-SC may not be a good choice for a woman who wants to become pregnant soon after discontinuing contraception.

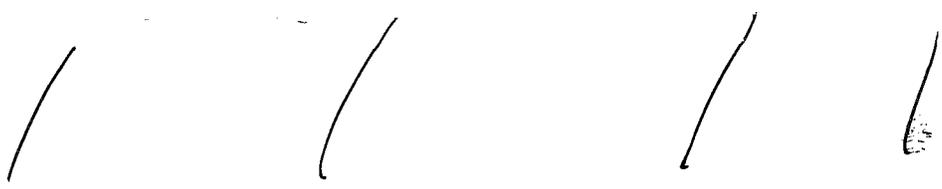
Injections site reaction occurred in 5% of subjects treated with DMPA-SC. Although not medically serious, these reactions caused 10 women to stop treatment. Only 1 of these 10 women was rated "recovered", suggesting that scarring may have occurred in the others.

Whether use of DMPA increases the risk of thromboembolic events remains unclear. The data are conflicting. Limited data from a single case-control study suggest little or no increased risk. Limited clinical trial data are consistent with a risk similar to the risk in women using

combination oral contraceptives. Until the issue is resolved, the product label should continue to include thromboembolic disease as a contraindication to DMPA use.

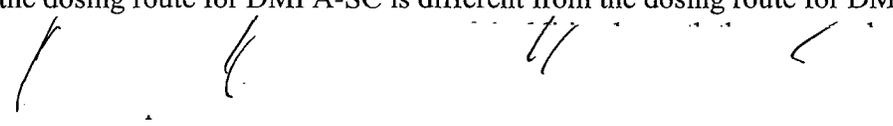
2.4 Dosing

The Applicant reasonably chose the lowest dose to suppress ovulation based on Phase 1/2 trials.



The Applicant plans to co-package DMPA-SC with a needle appropriate for SC dosing, and this should enhance safety. The shorter, finer gauge needle for the SC product will serve as a visual reminder that the dosing route for DMPA-SC is different from the dosing route for DMPA-IM.

2.5 Special Populations



Since the indication applies only to women of reproductive age, data analysis by age and gender was unnecessary. Pediatric studies were not done because the risk/benefit profile was expected to be the same for postmenarcheal girls and older women of reproductive age. The Phase 3 studies included an adequate mix of racial groups: 68% White, 21% Asian or Pacific Islander, 8% Black, and 3% Mixed Race. No race-related safety or efficacy issues were detected.

DMPA-SC may be inadvertently used in pregnant women. Epidemiologic studies suggest that inadvertent exposure to medroxyprogesterone in early pregnancy is *not* associated with an increase in adverse pregnancy outcome. Postmarketing reports received by the FDA for DMPA-IM do not suggest any pattern of fetal anomalies following inadvertent pregnancy exposures. Published lactation studies support the use of medroxyprogesterone during lactation.

Although the IM formulation has been marketed for over 40 years, there are no studies in subjects with renal or hepatic impairment. Since DMPA is chiefly metabolized in the liver, severe hepatic dysfunction is a labeled contraindication. The effect of renal disease on the pharmacokinetics of DMPA is unknown.

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this page is the manifestation of the electronic signature.**

/s/

Lesley-Anne Furlong
12/10/04 10:06:02 AM
MEDICAL OFFICER

Scott Monroe
12/10/04 12:51:02 PM
MEDICAL OFFICER

I concur with Dr. Furlong's recommendation that depot medroxyprogesterone acetate subcutaneous injection should be approved for prevention of pregnancy in women of childbearing potential.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

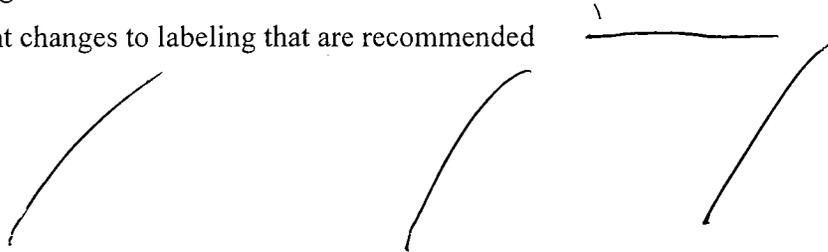
NDA NDA 21-583
Type of Application Original NDA
Applicant Pharmacia & Upjohn, a subsidiary of Pfizer Inc.
Ann Arbor, MI
Proprietary Drug Name To be determined
Established Drug Name Medroxyprogesterone acetate injectable suspension, USP
Indication Prevention of pregnancy in women of childbearing potential
Route of administration Subcutaneous injection
Dosage Form Sterile aqueous suspension in prefilled syringe
Dosage Strength 160 mg/mL (delivered dose 104 mg/0.65 mL per syringe)
Dosing Regimen Subcutaneous injection once every 3 months
Date of Submission June 30, 2003
CDER Receipt Date July 2, 2003
PDUFA Date May 2, 2004 (original)
August 2, 2004 (based on 3-month extension)
Date of Memorandum August 2, 2004
Reviewer Scott E. Monroe, MD
Clinical Team Leader, DRUDP

EXECUTIVE SUMMARY

RECOMMENDATION REGARDING APPROVABILITY

Approval of medroxyprogesterone acetate injectable suspension, USP (hereafter referred to as DMPA-SC) for marketing for prevention of pregnancy in women at risk for pregnancy is recommended subject to significant revisions of the Applicant's proposed Package (Physician) and Patient Labeling.

The most significant changes to labeling that are recommended



The clinical trial data for DMPA-SC demonstrated that the drug product is highly effective for preventing pregnancy. No pregnancies conceived during treatment with DMPA-SC were

identified in the three Phase 3 trials designed to study contraceptive effectiveness. These studies included more than 1,980 women and more than 20,634 months of treatment with DMPA-SC. The safety profile of DMPA-SC is acceptable for a highly effective contraceptive drug product and is similar to that of Depo-Provera® Contraceptive Injection (DMPA-IM), the presently marketed formulation of medroxyprogesterone acetate injectable suspension that was approved for the prevention of pregnancy in 1992. The impact of DMPA-SC on bone health and body weight should be considered by the healthcare provider and the patient before deciding to use DMPA-SC for long-term contraception.

There are no preclinical toxicology, (chemistry, manufacturing, and controls), or biopharmaceutical deficiencies.

RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

No new Phase 4 studies are recommended. DMPA-SC should have a risk profile similar to the marketed product, DMPA-IM. The Applicant has an ongoing study of the reversibility of BMD changes in adolescents who have been treated with DMPA-IM. The posttreatment follow up phase of this study will provide important data about BMD recovery in adolescents and should be reported to the Division

The most significant risks associated with the use of DMPA-SC (decrease in BMD and increase in body weight) should be adequately managed by appropriate Physician and Patient Labeling.

INTRODUCTION AND BACKGROUND

MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate (MPA) is the synthetic 6-methyl analog of 17-hydroxyprogesterone. MPA has been marketed for many years as oral (Provera® Tablets) and intramuscular injection formulations (Depo-Provera® Sterile Aqueous Suspension [400 mg/mL; indication of palliative treatment of renal or endometrial cancer] and Depo-Provera® Contraceptive Injection [150 mg/mL]). Depo-Provera® Contraceptive Injection (DMPA-IM) was approved for prevention of pregnancy in the U.S. in 1992. It is administered by a healthcare professional as a single 150-mg intramuscular dose every 3 months.

DMPA-IM is one of the most effective reversible methods for preventing pregnancy, with a failure rate of less than 1 percent. This rate is similar to that reported for SC progestin implants (e.g., Norplant® System), levonorgestrel and copper IUDs, and sterilization, and somewhat better than that reported for combination oral contraceptives (COCs) and the contraceptive skin patch. DMPA-IM is particularly useful for prevention of pregnancy in women who have had difficulty in complying with the daily dosing regimen required by COCs. The most serious adverse events associated with the use of DMPA-IM are a decrease in bone mineral density (BMD) and increase in body weight. The most commonly reported adverse events relate to irregular bleeding, a complaint associated with the use of all progestin-only contraceptive products. Following discontinuation of DMPA-IM, there is generally a long delay in the return of normal ovarian function.

This application (NDA 21-583) is for a new formulation and dose of MPA sterile aqueous suspension for the prevention of pregnancy. The new product (DMPA-SC) differs from the

currently approved product (DMPA-IM) in that (1) it is to be administered subcutaneously instead of intramuscularly and (2) the dose of MPA is lower (104 mg once every 3 months compared to 150 mg once every 3 months).

DMPA-SC is not presently approved for marketing in any country.

IMPORTANT MILESTONES IN PRODUCT DEVELOPMENT

Table 1 summarizes significant interactions between the Applicant and the FDA during product development.

Table 1 Pre-NDA Regulatory Interactions

Date	Communication	Highlights
02-Oct-2000	Pre-IND guidance meeting	FDA and Applicant discussed general plan for developing a SC, lower dose formulation of injectable DMPA for both contraception and endometriosis indications.
13-Dec-2000	Special Protocol Assessment and IND	FDA and Applicant agreed on Phase 3 trial design.
03-Jan-2001	Guidance t-con	FDA and Applicant discussed issues regarding self-injection protocol.
15-Jul-2002	Pre-NDA meeting	FDA and Applicant agreed on analyses and general format of NDA. Applicant agreed to supply return to ovulation data during the NDA review by 4-month safety update.

Source: Primary Medical Review and FDA Division Files.

The Applicant filed a major amendment to the NDA late in the review period, and therefore the review period was extended by an additional 3 months to allow time for adequate review of the new information. The amendment included the Final Report for Study 234, a 7-year study of BMD changes in women using DMPA-IM, and an updated Interim Report for Study 267BMD, one of the 3 primary efficacy and safety trials used to support the NDA.

OVERVIEW OF CLINICAL DATA SUBMITTED IN SUPPORT OF APPLICATION

The clinical program for DMPA-SC included 6 studies, including three Phase 1/2 clinical pharmacology studies and three Phase 3 efficacy and safety studies (Table 2). The clinical pharmacology studies included a dose-finding study (Study 265), a pharmacokinetic (PK) / pharmacodynamic (PD) study in Asian women (Study 271), and a PK/PD study in which the PD of DMPA-SC was compared to that of DMPA-IM (Study 272). The Phase 3 studies included 2 open-label, noncomparative, multinational, 1-year trials (Studies 267 and 269) to evaluate the efficacy and safety of DMPA-SC when administered at a dose of 104 mg every 3 months. A substudy of Study 267 (Study 267BMD) was conducted in a separate population and had as its primary safety objective comparing changes in BMD in women receiving DMPA-SC to those in women receiving DMPA-IM over a 2-year treatment period. Studies 267 and 269 also included an option for subjects to self-administer DMPA-SC in the practitioner’s office or at home after appropriate training.

Table 2 Summary of Principal Clinical Trials Included in NDA 21-583

Study ID	Objective(s) of Study	Design	DMPA Regimen	N	Treatment Duration
267	Phase 3 contraception	Open-label, non-comparator, multinational	104 mg SC every 3 months	722	1 year
269	Phase 3 contraception	Open-label, non-comparator, multinational	104 mg SC every 3 months	1065	1 year
267 BMD	Phase 3 contraception and BMD changes	Randomized, evaluator-blinded, to compare DMPA-SC and DMPA-IM	DMPA-SC 104 mg every 3 months or DMPA-IM 150 mg every 3 months	386:* 193 SC 193 IM	2 years
265	Determine PK and PD (suppression of ovulation)	Open-label, randomized, single-dose (4 levels), outpatient, parallel groups	Single SC injection of either a 50-mg, 75-mg, 100-mg, or 150-mg dose of MPA	47	Single dose
271	Determine duration of ovulation suppression in Asian women	Single center, open-label, single-dose, outpatient, parallel group	Single SC injection of 104 mg DMPA	24	Single dose
272	Compare cumulative rate of ovulation at 12 months	Single center, evaluator-blinded, single-dose, outpatient	Single injection of either DMPA-SC 104 mg or DMPA-IM 150 mg	68: 45 SC 23 IM	Single dose

* Represents subjects enrolled by 15 September 2001 for whom 1-year data were available for the Interim Report submitted with the original NDA in June 2003. A total of 535 subjects were subsequently enrolled in this study. Source: Modified from Applicant's Table 5.1 in Module 5.2, "Tabular Listing of All Clinical Studies."

Additional studies not conducted to assess the effectiveness of DMPA-SC for prevention of pregnancy that provided supportive safety data for NDA 21-583 included Studies 268 and 270 (6-month treatment of women with endometriosis with DMPA-SC), Study 234 (assessment of bone mineral density in women receiving DMPA-IM for up to 5 years for prevention of pregnancy), and Study 261 (evaluation of BMD changes in adolescents using DMPA-IM or a non-hormonal contraceptive method for prevention of pregnancy).

PHARMACOKINETIC/PHARMACODYNAMIC FINDINGS

The PK and PD of MPA were characterized in women of reproductive age following a single dose of DMPA-SC in three Phase 1/2 studies. These studies included dose-ranging Study 265 with ovulation suppression as the primary endpoint, PK/PD Study 271 conducted in Asian women, and time to return of ovulatory function in Study 272. Multiple-dose PK data were obtained in Phase 3 Study 267BMD. The to-be-marketed formulation was used in the Phase 1/2 studies (with the exception of Study 265) and all Phase 3 clinical studies.

PHARMACOKINETIC FINDINGS

Following a single administration of DMPA-SC, considerable inter-subject variability in MPA concentrations was apparent. Serum MPA concentrations peaked approximately 9 days (range, 2 – 80 days) after dosing. The mean MPA C_{max} was approximately 1.56 ng/mL (range, — ng/mL) with a mean apparent terminal t_{1/2} of 43 days. The mean trough MPA concentration at 91 days after dosing was 0.402 ng/mL (range, — ng/mL).

Studies did not detect any clinically important race or weight effects. Suppression of ovulation was maintained across all BMI and race categories. There was a lower AUC and C_{min} in obese women. There was a longer time to T_{max} in black subjects. Injection into the anterior thigh or

abdomen produced similar PK/PD profiles except for a higher Cmax with injection into the anterior thigh.

A substudy of Study 267BMD provided PK data relevant to multiple dosing. In this substudy, subjects had MPA trough levels drawn at 6 months and 12 months of treatment. No unexpected accumulation of MPA was observed. Mean (SD) MPA trough concentrations at 6 months were 0.67 (0.36) ng/mL (n=157) and at 12 months were 0.79 (0.36) ng/mL (n=144).

Medical Officer's Comments

- *The Biopharmaceutical Reviewer reported that, based on a cross study comparison, the mean values of Cmax and AUCinf for MPA following a single administration of DMPA-SC (NDA 21-583, Study No. 272) were about 46 % and 31 % lower, respectively, than those following a single administration of DMPA-IM (NDA 20-246).*
- *No studies were done in women with impaired renal or hepatic function. The proposed label for Depo-Provera IM states that " _____ / / / /*
- *Since MPA is extensively metabolized by the liver and excreted in the urine, women with impaired renal or hepatic function may have elevated MPA or MPA metabolite levels. There is no evidence that this is a safety concern.*
- *Formal assessments of drug-drug interactions involving DMPA-SC were not conducted. Aminoglutethimide administered concomitantly with DMPA-SC may decrease the serum concentrations of MPA, thereby possibly decreasing the efficacy of DMPA-SC. _____*
- *The sponsor has agreed to conduct an in-vitro metabolism study to characterize the metabolic pathways of MPA as a Phase 4 commitment.*

The primary Medical Reviewer, using interim PK data provided in the original submission for Study 267BMD, calculated the mean trough MPA concentrations at 6 and 12 months of treatment in the DMPA-SC and DMPA-IM treatment groups (Table 3).

Table 3 Trough Serum Concentrations of MPA (Study 267BMD)

Parameter	DMPA-SC Group	DMPA-IM group
At 6 months:		
N	113	108
Mean MPA concentration (pg/ml)	656 (95% CI: 535 to 777)	764 (95% CI: 655 to 873)
At 12 months:		
N	103	99
Mean MPA concentration (pg/ml)	844 (95% CI: 752 to 936)	830 (95% CI: 744 to 916)

Source: Calculated by primary Medical Reviewer (Dr. Furlong) from Applicant's data set labeled pkdata.xpt (Interim Report for Study 267BMD submitted with the original NDA).

Medical Officer's Comment

- *Trough concentrations of MPA at 6 and 12 months of treatment were similar for both formulations, although the dose of the IM product was almost 50% greater (150 mg vs. 104 mg).*

DOSE SELECTION AND PHARMACODYNAMIC FINDINGS

Study 265 provided data to support dose selection for the Phase 3 trials. It was an open-label, randomized, dose-ranging trial of 4 single doses (50, 75, 100, or 150 mg) using the marketed DMPA-IM products given subcutaneously.

According to the Applicant, the threshold serum level of MPA needed to maintain ovulation suppression is between 100-200 pg/ml. In Study 265, the 100-mg dose was the lowest dose that achieved the desired concentration over 3 months, and suppressed ovulation (defined as a progesterone concentration <4.7 ng/ml) in all but one subject. (The subject who did not maintain a MPA concentration > 200 pg/ml ovulated on day 70 after injection.)

Based primarily on these findings, the Applicant selected a dose of approximately 100 mg of SC MPA once every 3 months for the Phase 3 clinical trials. (The actual dose selected was 104 mg/0.65 mL based on manufacturing considerations.)

Medical Officer's Comments

- *Although the to-be-marketed product was not used in Study 265, the Biopharmaceutical Reviewer did not believe that this had a significant effect on the findings in or interpretation of Study 265.*
- *The Applicant's selection of 104 mg MPA to achieve suppression of ovulation during the first 90 days of treatment is reasonable. However, because of the long effective half-life of DMPA-SC, trough concentrations at Month 6, and thereafter, are likely to be greater than needed to maintain suppression of ovulation. However, since serum concentrations of MPA in subjects receiving 104-mg DMPA-SC are similar to or lower than those in subjects receiving 150-mg DMPA-IM, the Applicant's selection of 104 mg of MPA by SC injection every 3 months is acceptable.*

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• _____

PHASE 3 CLINICAL TRIALS

GENERAL DESCRIPTION OF TRIALS

The three Phase 3 studies enrolled non-pregnant, sexually active women of childbearing potential, 18 to 49 years of age for Studies 267 and 269 and 18 to 35 years of age for study 267BMD, who desired long-term contraception. Study 267BMD excluded woman with decreased BMD, defined by either a lumbar spine or femur BMD T-score of less than -1.0 or a history of having had a pathologic or compression fracture. Subjects in Studies 267 and 269 were to receive a single 104-mg dose of DMPA-SC every 3 months (at Study Weeks 0, 13, 26,

and 39) during the 1-year study. Subjects in Study 267BMD were to receive a single 104-mg dose of DMPA-SC or a 150-mg dose of DMPA-IM every 3 months (at Study Weeks 0, 13, 26, 39, 52, 65, 78 and 91) during the 2-year study.

Study 267 took place at 74 sites in the Americas. Most sites were in the U.S. (36) or Canada (23), with the remaining sites in Brazil (4), Chile (3), Mexico (4), and Peru (4). Study 267BMD took place at 48 sites in the Americas. Most sites were in the U.S. (36), with the remaining sites in Canada (9) and Brazil (3). Study 269 took place at 64 sites in Europe and Asia, including sites in Russia (21), Bulgaria (6), Estonia (5), Indonesia (2), Latvia (5), Poland (6), Romania (5), and the United Kingdom (3).

The primary endpoint for Studies 267 and 269 was the treatment failure cumulative pregnancy rate at 1 year, which was defined as a positive pregnancy test before the next scheduled dose of study drug. Study 267BMD

(BMD findings are described in the Safety Section of this Memorandum).

DEMOGRAPHICS

In the Applicant’s original submission of June 2003, clinical data from a total of 1,980 subjects who received one or more doses of DMPA-SC were provided. Demographic characteristics of the subjects enrolled in the three Phase 3 clinical trials are listed in Table 4. Across the 3 trials, the majority of the subjects were white (83%, 1643 of 1980) and 4.7% (93 of 1980) were black. The overall mean age was 30.1 years at entry and 1542 of the 1980 subjects (77.9%) were ≤ 35 years of age.

Table 4 Demographic Characteristics of ITT Population

Demographic Parameter	Study 267 n =722	Study 267BMD N = 193 *	Study 269 N = 1065
Race			
White	67%	60%	98%
Black	8%	16%	0.1%
Other	24%	24%	2%
Age			
Mean (yr.)	28.2	26.1	32.2
≤ 35 yr.	85%	100%	69%

* Represents subjects enrolled in the DMPA-SC group by 15 September 2001 for whom 1 year data were available for the Interim Report submitted with the original NDA in June 2003.

Medical Officer’s Comment

- *During the course of the review, the Applicant submitted 2 updated Interim Reports for Study 267BMD. The latter of the reports (Revision No. 2) included safety and efficacy data for all subjects treated in Study 267BMD (266 in the DMPA-SC group and 268 in the DMPA-IM group) through 2-years post first dose of study drug. Data from the original NDA submission that included 193 of the 266 of the subjects through one year of treatment in the DMPA-SC group are presented, for the most part, in the tables and narrative of this Memorandum. An exception is the Section on BMD changes in which data from all subjects are presented.*

SUBJECT DISPOSITION

The disposition of subjects through 1 year of treatment is summarized in Table 5. Across the three Phase 3 studies, 1,454 subjects (73.4%) completed 1 year of treatment.

Table 5 Disposition of Subjects through 1 Year of Treatment (ITT DMPA-SC Population)

Subject Disposition	Combined		269		267		267BMD	
	N = 1980		N = 1065		N = 722		N = 193	
	n	%	n	%	n	%	n	%
Completed 1 year of treatment	1454	73.4	856	80.4	489	67.7	109*	56.5
Did not complete 1 year of treatment	526	26.6	209	19.6	233	32.3	84	43.5
W/D due to adverse event **	186	9.4	56	5.3	98	13.6	32	16.6
W/D due to protocol violation	18	0.9	5	0.5	8	1.1	5	2.6
Consent withdrawn	220	11.1	116	10.9	78	10.8	26	13.5
Lost to follow-up	102	5.2	32	3.0	49	6.8	21	10.9

* Subjects ongoing in second year of study

** W/D = withdrawn

Source: Table 2, Page 10, Summary of Clinical Efficacy Module, Module 2.7.3

EFFICACY OF DMPA-SC

Efficacy data were obtained from the three Phase 3 trials, Studies 267, 269, and 267BMD. The trials included 1,980 women who received at least 1 injection of DMPA-SC (Table 6). Efficacy data were obtained from 1,971 of these women. Among the 1,971 subjects, there were 20,607 women-months of exposure to DMPA-SC, calculated by multiplying the number of injections by 3. Approximately 75% of subjects completed 1 year of treatment. No pregnancies conceived during treatment were reported in any of the three Phase 3 clinical trials. The overall Pearl Index (number of pregnancies per 100 woman-years of use) across all studies was 0.00 with an upper bound of 0.22 (95% confidence interval for 2 sided test, calculated by FDA statistician).

**APPEARS THIS WAY
ON ORIGINAL**

Table 6 Number of Subjects, Months of Exposure to DMPA-SC, and Upper Bound of 95% Confidence Interval for Pearl Index (ITT Population, All Studies)

Study and Parameter	Number of Subjects	Months of Exposure	Number of Confirmed Pregnancies ^A	Pearl Index Upper Bound 95% CI
Study 267				
All subjects	722	7,215	0	0.61
≤ 35 Yr. of age	610	6,045	0	0.73
≤ 35 Yr. and no other contraception	508	5,223	0	0.84
Study 267BMD¹				
All subjects	193	1,929	0	2.27
≤ 35 Yr. of age	193	1,929	0	2.27
≤ 35 Yr. and no other contraception	173	1,794	0	2.44
Study 269				
All subjects	1,065	11,490	0	0.39
≤ 35 Yr. of age	739	7,941	0	0.56
≤ 35 Yr. and no other contraception	708	7,812	0	0.57
All Studies				
All subjects (Total)	1,980²	20,634²	0	0.22
≤ 35 Yr. of age	1,542	15,915	0	0.28
≤ 35 Yr. and no other contraception	1,389	14,829	0	0.30

^A All pregnancy tests were negative during treatment except for one indeterminate pregnancy test. In addition, there was a clinical pregnancy (likely conceived prior to treatment) recognized by a miscarriage 3 weeks after the first dose of DMPA-SC. Both women were in Study 267.

¹ Includes exposure only in the DMPA-SC group and only those subjects enrolled by 15 September 2001 for whom 1-year data were available for the Interim Report submitted with the original NDA in June 2003.

² Nine (9) subjects received a single injection of DMPA-SC but provided no efficacy data. Elimination of months of exposure for subjects without any reported efficacy data reduces months of exposure to 20,607.

Source: From FDA Statistical Review (Table 3)

Medical Officer's Comments

- *All pregnancy tests were negative during treatment except for one indeterminate pregnancy test. In addition, there was a clinical pregnancy recognized by a miscarriage 3 weeks after the first dose of DMPA-SC. According to the Applicant, this latter pregnancy occurred before treatment. Although the clinical course for this subject is most consistent with a pregnancy that occurred in the week before treatment, conception on the first day or two following initiation of treatment can not be totally excluded.*
- *In these studies, there were 1,542 women ≤ 35 years of age at entry. Among these women, no other method of contraception was used during 14,829 months of exposure. The upper bound of the 95% CI for the Pearl Index for these subjects was 0.30.*
- *During the review, the Applicant provided updated data through Year 2 for Study 267BMD. No pregnancies were reported in the updated data.*
- *In Studies 267 and 269, healthcare providers trained women to self-inject and for the last 1 or 2 injections, allowed women to self-inject in the office or at home. However, only 5% of treatment cycles involved home self-injection, and only 2 women gave themselves more than 1 home self-*

injection (2 home self-injections for each woman).

- ***In summary, the applicant has provided adequate clinical data to support the effectiveness of DMPA-SC for prevention of pregnancy in women of childbearing potential.***

SAFETY OF DMPA-SC

OVERVIEW OF SAFETY DATA FOR MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate (MPA), administered as a 150 mg IM injection (DMPA-IM) once every 3 months was approved for the prevention of pregnancy by the FDA in 1992. According to the Applicant, it is currently approved for prevention of pregnancy in more than 100 countries. During the 3-year period from 1999 through 2001, worldwide exposure to DMPA-IM was estimated to be _____ woman-years (_____ woman-years in the U.S.) based on total vials sold. The overall safety profile of DMPA-IM is well characterized, based both on the clinical trials that supported its registration in the U.S. (reviewed in NDA 20-246) and postmarketing safety reports. The new formulation of MPA that is being reviewed in the present NDA is administered as a subcutaneous injection once every 3 months at a total dosage of 104 mg/injection.

In this Memorandum, a comprehensive review of the safety findings for DMPA-SC based on the safety data in NDA 21-583 will not be provided. Rather, this Memorandum will focus upon those safety issues and adverse events that are of most concern to the patient and her healthcare provider. The primary medical review of NDA 21-583 by Dr. Furlong has provided a comprehensive review of the overall safety profile of DMPA-SC based on (1) the information provided in NDA 21-583 for DMPA-SC and (2) postmarketing safety reports and published data for DMPA-IM.

EXTENT OF SAFETY DATA FOR DMPA-SC

In the present submission, the safety of DMPA-SC for prevention of pregnancy was supported primarily by data from three Phase 3 clinical trials (Studies 267, 267BMD, and 269) conducted with DMPA-SC for the prevention of pregnancy. The integrated review of safety, included in the original NDA submission of June 2003, contained safety data from 1,980 subjects who

received one or more doses of DMPA-SC. Of these subjects, 1490 received 4 injections of DMPA-SC. Total months of exposure to DMPA-SC in the 1,980 subjects (based on multiplying the number of doses administered by 3) was approximately 20,634.

Medical Officer's Comments

- *The Applicant has provided adequate data to assess the safety profile of DMPA-SC for the prevention of pregnancy.*
- *During the review of the NDA, additional safety data from ongoing Study 267BMD were submitted for an additional 73 subjects receiving DMPA-SC and the treatment period for which safety data were provide for Study 267BMD was increased from 1 to up to 2 years. In most instances, the numbers cited in this Memorandum are from the Applicant's original submission based on a total of 1,980 subjects followed for up to 1 year. For some safety assessments (e.g., changes in BMD and body weight) data from all subjects enrolled in Study 267BMD for up to 2 years are cited. Inclusion of these additional data from Study 267BMD in the other analyses would have no impact on the overall assessment of the safety profile of DMPA-SC.*

DEATHS

One death was reported in the original NDA submission (Study 267, Case ID 47037-0479). A 32-year-old woman received her first injection on June 22, 2001. She was seen for her second injection on _____ and died in a car accident 5 days later, or _____

A second death was reported in the four-month safety update. A 27-year-old subject in Study 274 died suddenly after 16 months of therapy with DMPA-SC. Based on autopsy and histologic findings, the cause of death was listed as arrhythmia due to myocarditis. (Study 274 is an elective study designed to study home self-injection in subjects who completed Study 267.)

Medical Officer's Comment

- *Neither death appears to be related to the use of DMPA-SC.*

ADVERSE EVENTS

Table 7 summarizes the number of subjects treated with DMPA-SC in Studies 267, 267BMD, and 269 for whom adverse events were reported. One or more adverse events were reported in 57.7% (1137/1971) of the subjects who received at least 1 injection of DMPA-SC. Serious adverse events and adverse events leading to discontinuation were reported for 1.4% (28/1971) and 9.5% (188/1971) of subjects, respectively.

Overall, the most frequently reported adverse events were headache (8.1%, 160/1971), intermenstrual bleeding (7.1%, 139/1971), amenorrhea NOS (6.6%, 130/1971), and weight increased (6.3%, 124/1971). These were the only adverse events reported in at least 5% of the subjects.

Medical Officer's Comment

- *The most commonly reported adverse events are consistent with the current labeling for DMPA-IM.*

Table 7 Summary of Adverse Events

	DMPA-SC Subjects	
	n	%
Total subjects	1971 **	100.0
Any adverse events	1137	57.7
Drug-related adverse events	743	37.7
Serious adverse events	28	1.4
Adverse events leading to discontinuation	188	9.5

** Number of subjects for whom safety data were available.
Source: Table 6, pg. 14 of Module 2.7.4 (Summary of Clinical Safety).

DISCONTINUATIONS SECONDARY TO ADVERSE EVENTS

Overall, 9.5% (188/1971) of all subjects treated with DMPA-SC discontinued from the study because of 1 or more adverse events. The most frequently reported adverse events leading to discontinuation in subjects treated with DMPA-SC were increased weight (1.7%, 33/1971), intermenstrual bleeding (1.1%, 22/1971), decreased libido (1.1%, 22/1971), acne (1.0%, 19/1971), vaginal hemorrhage (0.9%, 18/1971), and depression (0.7%, 13/1971).

Medical Officer's Comment

- *Increased weight gain and abnormal uterine (menstrual) bleeding are also among the most frequently reported adverse events, occurring in more than 6% of subjects in the Phase 3 clinical trials.*

SERIOUS ADVERSE EVENTS

Serious adverse events were reported in 1.4% (28/1971) of the subjects treated with DMPA-SC for whom complete data were available. Only abdominal pain NOS, calculus ureteric, menometrorrhagia, and uterine hemorrhage were reported in more than 1 subject each; these were each reported in 2 subjects who had been treated with DMPA-SC. One of the 2 events of menometrorrhagia was considered drug-related. Other serious adverse events (all single cases) considered to be related to treatment with DMPA-SC by the Investigators included depression, weight increase, difficulty in walking, and pain in limb, as well as both cases of uterine hemorrhage.

MEDICAL OFFICER'S COMMENT

- *The number and types of serious adverse events considered to be related to treatment with DMPA-SC reported cross the three Phase 3 clinical trials are not worrisome and are compatible, for the most part, with the well known and expected safety profile for DMPA-IM.*
- *Abnormal uterine bleeding was the most commonly reported serious adverse event with 4 cases (2 cases each of menometrorrhagia and uterine hemorrhage).*

ADVERSE EVENTS OF SPECIAL INTEREST OR CONCERN

THROMBOTIC AND THROMBOEMBOLIC ADVERSE EVENTS

There were 2 cases of a thrombotic/thromboembolic adverse event. A 35-year old woman who was receiving DMPA-IM in Study 267BMD had surgery for gallstones. One week after surgery she had a stroke followed 2 months later by a deep vein thrombosis. Another woman, who was being treated with DMPA-SC in an endometriosis clinical trial, developed a probable pulmonary embolus at Month 4 of treatment.

Medical Officer's Comment

- *Two cases of a thrombotic/thromboembolic adverse event in more than 20,000 months of treatment with either DMPA-SC or DMPA-IM, along with the postmarketing safety profile for DMPA-IM, do not raise any safety concerns.*
- *Combination oral contraceptives (COCs) are known to increase the risk of developing a thrombotic adverse event. Labeling for both COCs and DMPA-IM includes a contraindication to their use in women with a history of thrombophlebitis or thromboembolic disorders. Labeling for oral progestin-only contraceptives, which are believed to pose less of a thrombotic risk, does not include this contraindication.*

CHANGES IN BONE MINERAL DENSITY (BMD)

The current label for DMPA-IM states "Use of Depo-Provera Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall."

In this NDA, the Applicant provided the following data regarding BMD:

- An Interim Report for Study 267BMD, in which BMD changes in subjects using DMPA-SC were compared to those in subjects using DMPA-IM for up to 2 years of treatment.
- A Final Report for Study 234, a 7-year observational study of BMD changes in adult women using DMPA-IM for up to 5 years, with a 2-year no treatment follow-up period.
- A short Interim Report for Study 261, a 7-year observational study of BMD changes in which adolescent women were to use DMPA-IM for up to 5 years. The treatment phase of this study was stopped early by the data safety monitoring board because of the magnitude of the decrease in BMD and to start the follow-up recovery phase.

Study 267BMD

The median percent changes from baseline for BMD of the femur (total hip) and lumber spine after the first and second year of treatment with DMPA-SC are summarized in Table 8. Also shown are the numbers (and percentages) of subjects with a T-score of less than -1. In general, subjects had modest decreases in femur and spinal BMD during the first year of treatment with a further decrease in BMD during the second year of treatment. The median percent changes from baseline in BMD of the femur were -1.4% (Year 1) and -3.3% (Year 2). The median percent

change from baseline in BMD of the spine was -2.4% (Year 1) and -4.3% (Year 2). Decreases in BMD of the femur and spine in subjects treated with DMPA-IM were similar.

Table 8 Study 267BMD: Median Percent Change from Baseline for BMD and T-scores by Treatment Month

Visit	Parameter	Femur	Spine
Baseline			
	N	264	264
	Baseline BMD (g/cm ²)	1.03	1.16
	T score less than -1.0 [n (%)]	1 (0.4%)	2 (0.8%)
Month 12			
	N	166	166
	Median Percent Change from Baseline	-1.4	-2.4
	Range	-19.9 to 4.9	-9.9 to 4.2
	T score less than -1.0 [n (%)]	1 (0.6%)	14 (8.4%)
Month 24			
	N	106	106
	Median Percent Change from Baseline	-3.3	-4.3
	Range	-22.7 to 8.1	-10.8 to 3.4
	T score less than -1.0 [n (%)]	5 (4.7%)	13 (12.3%)

Source: Modified from Table 7 (pg. 65) and Table 10 (pg. 69), Interim Report for Study 267BMD (Revision No. 2).

Table 9 shows categorical percentage changes in femur (total hip) and spine BMD from baseline through 1 and 2 years of treatment.

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Table 9 Study 267BMD: Categorical Percentage Change in BMD from Baseline

Visit	Categorical Percent Change from Baseline	Femur		Spine	
		n	(%)	n	(%)
Month 12	2.6 to 5.0	4	(2.4)	4	(2.4)
	0.1 to 2.5	32	(19.3)	13	(7.8)
	-2.4 to 0	72	(43.4)	69	(41.6)
	-4.9 to -2.5	45	(27.1)	46	(27.7)
	-7.4 to -5.0	8	(4.8)	27	(16.3)
	-9.9 to -7.5	4	(2.4)	7	(4.2)
	≥ -10.0	1	(0.6)	0	(0)
Total Reported		166		166	
Month 24	7.6 to 10.0	1	(0.9)		
	5.1 to 7.5	0	(0)		
	2.6 to 5.0	2	(1.9)	2	(1.9)
	0.1 to 2.5	11	(10.4)	10	(9.4)
	-2.4 to 0	27	(25.5)	16	(15.1)
	-4.9 to -2.5	35	(33.0)	38	(35.8)
	-7.4 to -5.0	21	(19.8)	30	(28.3)
	-9.9 to -7.5	6	(5.7)	8	(7.5)
≥ -10.0	3	(2.8)	2	(1.9)	
Total Reported		106		106	

From Tables 8 and 9, pg. 67 and 68, Interim Report for Study 267BMD (Revision No. 2).

Medical Officer's Comments

- *A T-score below -1 is considered to reflect osteopenia (low BMD). Women with a T-score of -1 or below were not to be enrolled into the clinical trial. This restriction is a weakness of the study design because it precludes assessing the extent of BMD change in those women with the lowest BMD values who might use DMPA-SC and who potentially would be at the greatest risk of developing osteoporosis.*
- *The decrease in BMD, based on changes in T-score, appear to be greater in the spine than in the hip (Table 8). For the femur, the percentage of women with a T-score of less than -1 increased from 0.4% at baseline to 0.6% and 4.7% at 12 and 24 months, respectively. For the spine, the percentage of women with a T-score of less than -1 increased from 0.8% at baseline to 8.4% and 12.3% at 12 and 24 months, respectively.*
- *Of particular interest is the incidence of femur (total hip) and spine BMD loss of 5% or more (Table 9). At Years 1 and 2, 7.8% (13/166) and 28.3% (30/106) of subjects, respectively, had a 5% or greater loss in total BMD of the hip. At Years 1 and 2, 20.5% (34/166) and 37.7% (40/106) of subjects, respectively, had a 5% or greater loss in total BMD of the spine.*
- *The long-term risk of these changes, in terms of developing osteoporosis and a possible fracture, is not known. If most of the decrease in BMD is reversible and the underlying architecture of the bone is not permanently disrupted (e.g., no permanent disruption of*

trabecular architecture), the risk will be minimal. Limited information about the reversibility of these changes is provided by the data from Study 234 (see below).

Study 234

When the FDA approved Depo-Provera[®] IM for contraception in 1992, the company made a postmarketing commitment to assess the effects of long-term treatment with DMPA-IM on BMD. The primary objective of Study 234 was to evaluate BMD changes in women receiving DMPA-IM for up to 240 weeks and compare them to changes in BMD in a cohort not using hormonal contraception, matched at each study site on the basis of race and current smoking status. Subjects in the DMPA-IM group were to be followed for an additional 96 weeks (recovery period) after completing or stopping treatment. Mean BMD changes from baseline for the spine, total femur, and femoral neck in the DMPA-IM and control groups and the adjusted differences in BMD percent changes ([DMPA-IM BMD % change from baseline] minus [control BMD % change from baseline]) are listed in Table 10.

Table 10 Percentage Change in BMD from Baseline (Study 234-Adult Women)

Duration of Treatment	DMPA-IM		Control		% Difference [DMPA-IM – Control] Adjusted mean change (95% CI) **
	n *	Mean % change	n	Mean % change	
Spine BMD					
Week 24	178	-1.41	291	0.19	-1.87 (-2.37 - -1.36)
Week 48	135	-2.86	253	0.22	-3.11 (-3.72 - -2.51)
Week 96	94	-4.11	197	0.29	-4.43 (-5.10 - -3.75)
Week 144	71	-4.89	159	0.31	-5.21 (-6.06 - -4.35)
Week 192	59	-4.93	137	0.35	-5.17 (-6.18 - -4.17)
Week 240	33	-5.38	105	0.43	-5.65 (-7.06 - -4.23)
Total Femur (Hip) BMD					
Week 24	108	-0.72	144	0.57	-1.34 (-1.93 - -0.76)
Week 48	88	-1.56	125	0.95	-2.58 (-3.22 - -1.94)
Week 96	57	-3.06	94	0.69	-3.59 (-4.64 - -2.55)
Week 144	42	-3.89	77	-0.06	-3.66 (-4.80 - -2.53)
Week 192	31	-4.52	70	-0.02	-4.34 (-5.75 - -2.93)
Week 240	21	-5.16	65	0.19	-5.47 (-7.10 - -3.84)
Femoral Neck BMD					
Week 24	179	-1.24	289	0.22	-1.60 (-2.42 - -0.78)
Week 48	137	-2.85	254	0.28	-3.23 (-4.10 - -2.35)
Week 96	95	-3.99	195	-0.22	-3.50 (-4.66 - -2.34)
Week 144	72	-4.80	159	-0.23	-4.45 (-5.63 - -3.27)
Week 192	58	-5.90	138	-0.53	-4.79 (-6.12 - -3.45)
Week 240	34	-6.12	106	-0.27	-5.75 (-7.86 - -3.64)

* Number of subjects.

** Covariates included in the analysis were race, smoking status, BMI, dietary calcium, the screening BMD, and exercise level.

Source: Modified from Table on pg. 44 of Final Report for Study 234.

Medical Officer's Comments

- *The decrease in BMD in the DMPA-IM treated subjects appears progressive throughout the 5 years of treatment in that the percentage decreases in BMD do not reach a plateau. Over the 5-year treatment period, a mean BMD decrease of 5-6% in the DMPA-IM subjects, compared to no significant change in BMD in the control group, was observed.*
- *The decline in BMD was more pronounced in the first two years of use, with smaller declines in subsequent years. Mean percent changes from baseline in lumbar spine BMD in the DMPA-IM group (adjusted for changes in the control group) were -3.11%, -4.43%, -5.21%, -5.17%, and -5.65% after 48, 96, 144, 192, and 240 weeks of treatment, respectively. Decreases in BMD of the total hip and femoral neck were similar or slightly less.*

After stopping treatment with DMPA-IM, there was partial recovery of BMD toward baseline values. Longer durations of treatment were associated with less complete recovery assessed at 96-weeks posttreatment. Table 11 shows the extent of posttreatment recovery of BMD for women who completed treatment with DMPA-SC for periods of time ranging from 12-48 weeks (1-4 injections) up to 240 weeks (20 injections).

Table 11 Recovery of BMD (Mean Percent Change from Baseline) at Posttreatment Week 96

Number of Injections *	Percent Change from Baseline		
	Spine (N) **	Total Femur (N)	Femoral Neck (N)
1-4	1.26% (10)	0.15% (6)	0.02% (10)
5-8	-0.46% (9)	0.89% (7)	-2.10% (9)
9-12	0.33% (3)	0.20% (2)	-3.13% (3)
13-16	-3.70% (3)	0.00% (2)	-3.90% (3)
17-20	-2.94% (16)	-1.58% (8)	-5.34% (17)
20	-3.13% (12)	-1.34% (7)	-5.38% (13)

* An injection is administered once every 12-13 weeks.

** N = number of subjects for each observation.

Source: Derived from Final Report for Study 234 (additional analyses requested by primary Medical Reviewer).

Medical Officer's Comments

- *The extent of posttreatment recovery, based on percentage change from baseline, was related to duration of treatment. For treatment periods of 3 years or less (12 injections or less), there appeared to be no residual decrease in BMD values (i.e., there was near complete recovery of BMD) for the spine and total femur at 96-weeks (2-years) posttreatment.*
- *Posttreatment recovery of BMD at the femoral neck, however, was incomplete for all treatment periods greater than 1 year (i.e., 5 or more injections of DMPA-IM).*

Study 261

BMD Changes in Adolescents and Young Adult Women. Preliminary results from an ongoing, open-label clinical study in *adolescent* females (12-18 years of age) indicate that the use of DMPA-IM for prevention of pregnancy is associated with a significant decline in BMD, relative to the control group, at the spine, total femur (hip), and femoral neck. In contrast, the

control group of adolescents showed an increase in BMD from baseline during the observation period.

Table 12 Mean Percent Change in BMD from Baseline in Adolescents Treated with DMPA-IM for up to 5 Years or in an Age Matched Control Group

Duration of Treatment	DMPA-IM		Control		%Difference [DMPA-IM – Control] Adjusted Mean Change (95% CI)
	n *	Mean % Change	n	Mean % Change	
Spine BMD					
Week 60	104	-2.42	171	3.47	-5.33 (-6.18 to -4.49)
Week 144	46	-2.78	111	5.41	-7.01 (-8.98 to -5.04)
Week 240	9	-4.17	70	5.12	-9.72 (-15.22 to -4.21)
Total Femur BMD					
Week 60	103	-2.82	171	1.32	-4.19 (-5.03 to -3.34)
Week 144	45	-6.16	111	1.74	-7.29 (-9.16 to -5.43)
Week 240	9	-6.92	69	1.12	-8.05 (-13.12 to -2.97)
Femoral Neck BMD					
Week 60	103	-3.05	171	1.87	-4.31 (-5.41 to -3.21)
Week 144	45	-6.01	111	2.54	-7.15 (-9.62 to -4.69)
Week 240	9	-6.06	69	1.45	-6.83 (-12.80 to -0.85)

* Number of subjects.

Source: Modified from Table 1, Appendix A, submission of May 19, 2004, Interim Analysis of Study 261.

Medical Officer's Comments

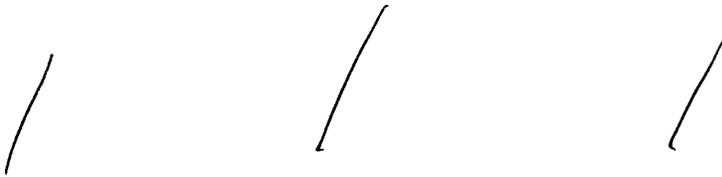
- *Adolescents have not attained peak bone mass. Therefore, one would expect to see an increase in BMD in the control adolescents as was observed in this trial. The magnitude of the decrease in BMD in the DMPA-IM adolescent group (when adjusted for the observed increase in BMD in the control group) appears to be greater than that observed in adults (see Table 10).*
- *Preliminary data from a small number of adolescents have shown some recovery of BMD during a 2-year follow-up period.*

Consultations. FDA's Division of Metabolic and Endocrine Drug Products (DEM DP) and an academic endocrinologist with expertise in bone disease were consulted regarding BMD changes associated with treatment with DMPA. Consultants were provided with data from Studies 267BMD, 234, and 261. Both consultants agreed that the Applicant's proposed labeling

Medical Officer's Comments Regarding Clinical Significance of BMD Changes

- *The decrease in BMD is dependent on duration of treatment and is progressive over a 5-year treatment period, the longest period studied to date by the Applicant. The decrease is most pronounced during the first 2 years of treatment and appears to progress at a slower rate thereafter.*

- *Study 234 provided support for partial recovery of BMD following discontinuation of treatment. The extent of posttreatment recovery, based on percentage change from baseline, was related to duration of treatment. For treatment periods of 3 years or less (12 injections or less), there appeared to be no residual decrease in BMD values (i.e., there was near complete recovery of BMD) for the spine and total femur at 96 weeks (2 years) posttreatment. Posttreatment recovery of BMD at the femoral neck, however, was incomplete for all treatment periods greater than 1 year (i.e., 5 or more injections of DMPA-IM).*
- *The clinical significance of the loss of BMD in DMPA users is unknown. There have been no reports of an increase in fractures among users of DMPA-IM. For perspective, pregnancy and lactation, conditions prevented by DMPA, also decrease BMD. The decrease in BMD associated with lactation is 3-7%, which is similar to the bone loss experienced by users of DMPA-IM for up to 5 years. Lactation is not a risk factor for osteoporosis in observational studies, suggesting that BMD loss from lactation is reversible.*
- *The impact of the use of DMPA-SC for prevention of pregnancy on BMD must be adequately addressed in labeling. The most recent label for DMPA-SC proposed by the Applicant* ~



CHANGES IN BODY WEIGHT

Mean body weights and mean body weight changes by visit for subjects in Study 267BMD are summarized in Table 13. Most subjects gained weight with increasing duration of treatment. In the DMPA-SC group at Month 12, 76.9% (133/173) of subjects had gained weight and 23.1% (40/173) of subjects had lost or had no change in weight. At Month 24, 75.9% (88/116) of subjects had gained weight and 24.1% (28/116) of subjects had lost or had no change in weight. Overall, the mean weight gain in subjects in the DMPA-SC group was 2.6 kg by Month 12 and 3.4 kg by Month 24. Body weight changes from baseline by weight category and visit for these subjects are summarized in Table 14. Relative to enrollment, 11.0% (23/209) of subjects in the DMPA-SC group had weight gains greater than or equal to 4.7 kg by Month 6, which increased to 28.3% (49/173) and 37.1% (43/116) of subjects by Month 12 and Month 24, respectively.

Table 13 Mean Weight (Kg) and Change in Weight (Kg) from Baseline (Study 267BMD)

	Baseline	Month 6		Month 12		Month 18		Month 24	
		Weight	Change	Weight	Change	Weight	Change	Weight	Change
N	265	209		173		129		116	
Mean	69.2	70.4	1.2	71.8	2.6	71.6	3.3	71.9	3.4
±SD	±17.7	±18.1	±3.2	±18.2	±4.7	±18.9	±6.8	±19.0	±7.8

Source: Table 22, pg. 98, Interim Report for Study 267BMD (Revision No. 2).

Table 14 Body Weight Change (Kg) from Baseline by Weight Category (Study 267BMD)

Weight Change from Baseline (kg)	Month 6	Month 12	Month 18	Month 24
	Percentage of Subjects in Category			
>9.1	0.5	5.8	13.2	11.2
7.0 to 9.1	1.9	7.5	7.8	8.6
4.7 to 6.9	8.6	15.0	13.2	17.2
2.4 to 4.6	23.9	20.8	21.7	24.1
0.1 to 2.3	29.7	27.7	21.7	14.7
-2.2 to 0	23.9	16.8	14.7	13.8
-4.5 to -2.3	7.2	4.0	5.4	5.2
-6.8 to -4.6	2.9	0.6	0.0	2.6
-9.1 to -6.9	1.0	0.0	0.0	0.9
<-9.1	0.5	1.7	2.3	1.7

Source: Table 24, pg. 99, Interim Report for Study 267BMD (Revision No. 2).

Medical Officer's Comments

- *Weight gain is a common complaint in DMPA users and a reason for discontinuation of therapy. In many women, the gain in weight is clinically significant.*

CHANGES IN MENSTRUAL BLEEDING PATTERNS (ABNORMAL UTERINE BLEEDING)

Uterine bleeding was the most frequently reported serious adverse event, occurring in 4 subjects in the three Phase 3 clinical trials. Intermenstrual bleeding and/or vaginal hemorrhage was listed as the cause of premature termination for 22 (1.1%) and 18 (0.9%) of subjects, respectively.

During the initial period of treatment (first 90 days of treatment), 66% of subjects reported having had prolonged and/or frequent bleeding and 12% of subjects reported having had either amenorrhea or less and/or infrequent bleeding. During the fourth treatment period (Treatment Days 274-364) 28% of subjects reported having had prolonged and/or frequent bleeding and 56% of subjects reported having had either amenorrhea or less and/or infrequent bleeding (See Table 15).

Table 15 Bleeding Patterns in Subjects Using DMPA-SC for up to One Year

Treatment Period *	No of Subjects	Percentage of Subjects with Respective Bleeding Pattern				
		Amenorrhea	Less or Infrequent Bleeding	Normal Bleeding	Irregular Bleeding	Prolonged and/or Frequent Bleeding
1	1780	1.7%	9.8%	6.3%	16.5%	65.6%
2	1644	20.4%	16.3%	6.1%	11.3%	45.9%
3	1475	32.9%	16.3%	6.5%	11.4%	32.5%
4	1299	39.4%	16.3%	9.5%	6.9%	27.6%

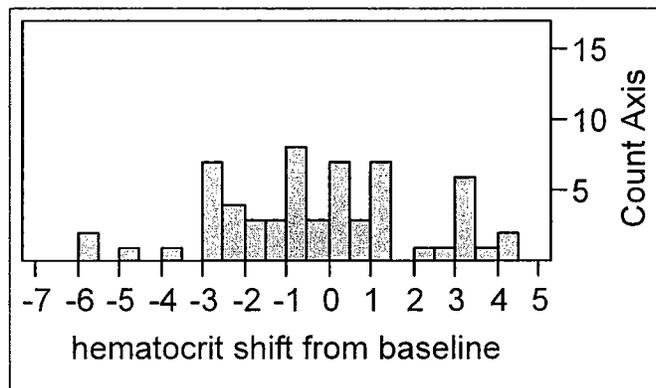
* A treatment period is approximately 91 days.

Source: Modified from Table T14.1, pg. 122-124, Summary of Clinical Safety, Tables for Module 2.7.4.

Medical Officer's Comments

- *The primary Medical Reviewer (Dr. Furlong) performed additional analyses to determine if women who terminated prematurely from the study for heavy bleeding had clinically significant decreases in hematocrit values. The Medical Reviewer identified 65 subjects who terminated from the study because of abnormal uterine bleeding. Among these 65 women, most did not have clinically significant drops in hematocrit from baseline (see Figure 1). The mean hematocrit shift was a drop of 0.4%. The largest negative shift was a drop of 6% for 2 women. One of these women dropped her hematocrit from 43% to 37% during treatment with DMPA-SC. The second woman dropped her hematocrit from 35% to 29%, followed by an increase to 38% four months later.*

Figure 1 Hematocrit Shifts from Baseline for Women Who Terminated Prematurely for Excessive Uterine Bleeding



Source: Primary Medical Review for NDA 21-583.

- *Abnormal uterine bleeding in women using DMPA-SC does not result in a clinically significant decrease in hematocrit values, except in an occasional user.*

RETURN TO OVULATION AND FERTILITY

A substudy of Study 267 assessed return to ovulation in 15 U.S. subjects after their third injection of DMPA-SC. Return to ovulation was defined as a progesterone level >4.7 ng/mL, and was assessed weekly. Twelve (12) of 15 subjects ovulated within one year, 2 failed to ovulate within one year, and 1 withdrew from the study. The median and mean number of days

to return to ovulation was 291 and 287 days, respectively, after the last injection. The earliest return to ovulation was 176 days (6 months).

To assess return to fertility, women who terminated from Studies 267 and 269 wishing to become pregnant were followed for up to 485 days following their last dose of DMPA-SC. Among 21 women who wished to become pregnant, only 2 were successful within 485 days of their last dose of DMPA-SC. One became pregnant 310 days after her last injection, and one became pregnant at 443 days after her last injection.

Medical Officer's Comment

- *Delayed return of ovulation and fertility may be a problem for some women and should be part of contraceptive counseling. Only 1 of 21 (5%) women who wanted a pregnancy was pregnant within 1 year after her last injection of DMPA-SC.*

INJECTION SITE REACTIONS

Of the subjects who received treatment with DMPA-SC, 5.1% (101/1971) experienced 130 injection site reactions that were reported as adverse events. Most of the events were rated as mild in intensity. None was classified as serious. The incidences of injection site reactions (by composite term, with 1 or more occurrences per subject) were: injection site nodule/lump (1.6%, 32/1971), injection site atrophy/dimpling (1.4%, 27/1971), injection site pain/tenderness (1.4%, 27/1971), and injection site reaction general (1.3%, 26/1971). Ten (0.5%) women stopped treatment because of injection site reactions.

No injection site reactions were reported in 193 subjects who were administered DMPA-IM.

Medical Officer's Comment

- *A small number DMPA-SC users may develop persistent induration at the injection site. For at least 10 women in the clinical trials, injection site reactions caused them to discontinue treatment with DMPA-SC. For at least 7 of these 10 women, the injection site reactions persisted at follow-up.*

NON CLINICAL REVIEW ISSUES

CHEMISTRY (CMC)

The Chemistry Reviewer (J. Salemme, Ph.D.) stated the following in her review:

"Deficiencies conveyed to the sponsor during the review cycle have been adequately addressed. The Office of Compliance has recommended the manufacturing sites for approval. The manufacturing and controls with regard to sterility assurance have been reviewed by the Microbiologist reviewer and found acceptable. The chemistry, manufacturing, and controls for the drug substance and drug product have been adequately characterized. From a CMC perspective, this NDA is recommended for approval although the trade name for this NDA has not yet been decided. No Phase 4 commitments were recommended."

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Myong-Jin Kim, Pharm.D) stated the following in her review:

“The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-583 submitted on June 30th, 2003. The overall Human Pharmacokinetic Section is acceptable.”

The Biopharmaceutics Reviewer also stated in her review that “the sponsor was advised to characterize the metabolic pathways of MPA and address the drug interaction potential to appropriately address this information in the label (teleconference on June 23, 2004). As a Phase IV commitment, the sponsor has agreed (July 15, 2004) to undertake an in-vitro metabolism study Based on the findings from the in-vitro study, an in-vivo confirmatory study may be considered.”

Significant clinical pharmacology and biopharmaceutics findings are summarized earlier in this Memorandum.

TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

One new toxicity study was submitted in support of this NDA. This study demonstrated that the proposed SC formulation in female rabbits was well tolerated locally unless it was inadvertently administered into the dermis.

The primary Toxicology Reviewer (Dr. Krishan Raheja) stated the following in his review:

“Since the dosage of the new subcutaneous formulation is lower than the currently approved intramuscular formulation, and systemic exposure is essentially similar with the administration of both formulations, Pharmacology recommends approval of NDA 21-583 for Depo-Provera SC 104 mg to be administered every 3 months.”

STATISTICS

The Statistical Reviewer (Shahla Farr, M.S.) stated the following in her review:

“From a statistical standpoint, the sponsor has provided studies that are adequate for demonstrating the effectiveness of Medroxyprogesterone Acetate SC in the prevention of pregnancy. No pregnancies occurred, and the upper bounds of the two-sided 95% CI for the Pearl Index ranged from 0.39 to 2.44.”

Medical Officer's Comment

- *This Medical Reviewer concurs with the recommendations of the chemistry, clinical pharmacology and biopharmaceutics, toxicology and preclinical pharmacology, and biometrics primary reviewers.*

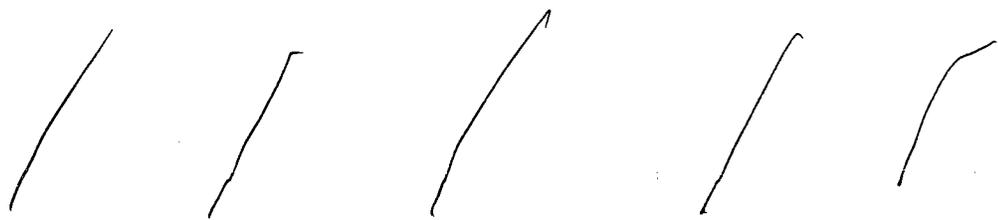
DIVISION OF SCIENTIFIC INVESTIGATION (DSI)

DSI conducted an inspection of 3 clinical sites (those of Dr. Purdon [Tucson, AZ], Dr. Jain [Los Angeles, CA], and Dr. Pogue [Boise, ID]). A Form 483 was issued to Dr. Jain noting “inadequate/inaccurate records, that the study was not conducted per the signed investigator agreement, and that there were inadequate records for drug disposition.” Per DSI, Dr. Jain responded in writing, providing adequate responses to the observations noted in the Form 483.

CONCLUSION

RECOMMENDATION REGARDING APPROVABILITY

Approval of medroxyprogesterone acetate injectable suspension, USP for marketing for prevention of pregnancy in women at risk for pregnancy is recommended subject to significant revisions of the Applicant's proposed Package (Physician) and Patient Labeling.



The clinical trial data for DMPA-SC demonstrated that the drug product is highly effective for preventing pregnancy. No pregnancies conceived during treatment with DMPA-SC were identified in the three Phase 3 trials designed to study contraceptive effectiveness. These studies included more than 1,980 women and more than 20,634 months of treatment with DMPA-SC. The safety profile of DMPA-SC is acceptable for a highly effective contraceptive drug product and is similar to that of DMPA-IM, the presently marketed formulation of medroxyprogesterone acetate injectable suspension that was approved for the prevention of pregnancy in 1992. The impact of DMPA-SC on bone health and body weight should be considered by the healthcare provider and the patient before deciding to use DMPA-SC for long-term contraception.

There are no preclinical toxicology, (chemistry, manufacturing, and controls), or biopharmaceutical deficiencies.

RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

No new Phase 4 studies are recommended. DMPA-SC should have a risk profile similar to the marketed product, DMPA-IM. The Applicant has an ongoing study of the reversibility of BMD changes in adolescents who have been treated with DMPA-IM. The posttreatment follow up phase of this study will provide important data about BMD recovery in adolescents and should be reported to the Division

The most significant risks associated with the use of DMPA-SC (decrease in BMD and increase in body weight) should be adequately managed by appropriate Physician and Patient Labeling.



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Cc: HFD-580/D. Griebel/S. Monroe/L. Furlong

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/s/

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8/2/04 02:39:07 PM
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Donna Griebel
8/2/04 04:02:18 PM
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I have read Dr. Monroe's review and concur with
his recommendation that this application is approvable, subject
to substantial labeling revisions, including detailed information to
support a warning about product risks of decreased
bone mineral density.

NDA 21-583 Clinical Review

Drug Name: Depot medroxyprogesterone acetate injectable suspension

Proposed Trade Name: _____

Pharmacologic Category: Progestin

Route of Administration: Subcutaneous injection

Dosage: 104 mg in 0.65 ml

Indication: Prevention of pregnancy in women of childbearing potential

Applicant: Pharmacia & Upjohn Company, purchased by Pfizer Inc. during the review cycle

Related NDAs: 12-541 and 20-246

Related INDs:

- 45,275
- 61,388
- 61,389

Reviewer: Lesley-Anne Furlong, M.D

Date Received: 30-Jun-03

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Abbreviations

Abbreviation	Full Name
AE	Adverse event
AERS	Adverse event reporting system
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum concentration
CRF	Case report form
CYP	Cytochrome P450
DEXA	Dual energy X-ray absorptiometry
DMPA	Depot medroxyprogesterone acetate
DMPA-IM	Depot medroxyprogesterone acetate- intramuscular
DMPA-SC	Depot medroxyprogesterone acetate-subcutaneous
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EOTC	End-of-treatment questionnaire
FDA	Food and Drug Administration
HDL	High density lipoprotein
IM	Intramuscular
IND	Investigational new drug
ITT	Intent to treat
LDL	Low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medroxyprogesterone acetate
NDA	New drug application
NEC	Not elsewhere classified
NOS	Not otherwise specified
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SHBG	Sex hormone binding globulin
T_{1/2}	Half-life
VLDL	Very low density lipoprotein
VTE	Venous thromboembolic event

Executive Summary

1 Recommendations

1.1 Recommendation on Approvability

Depot medroxyprogesterone acetate *subcutaneous* injection (DMPA-SC) is a reduced dose and new formulation of depot medroxyprogesterone acetate *intramuscular* injection (DMPA-IM), a product approved in 1992 for prevention of pregnancy in women of childbearing potential. Like DMPA-IM, DMPA-SC is a depot progestin contraceptive given by injection every 3 months.

Although the total drug exposure is less with DMPA-SC compared with DMPA-IM, the 2 products had similar profiles in clinical trials. In particular, bone loss and weight gain was similar in women using either product. The only differences detected were

- Nonserious injection site reactions occurred in 5% of DMPA-SC users and did not occur in DMPA-IM users

I recommend approval of DMPA-SC after changes to the proposed label. In particular, the section of the label related to bone mineral density needs updating.

1.2 Recommendation on Phase 4 Studies or Risk Management Steps

The Applicant has an ongoing study of bone mineral density (BMD) in adolescents treated with DMPA-IM. This study will provide important data about BMD recovery in adolescents. It is in the follow-up phase, and should be reported within

No risk management is recommended other than revised labeling, particularly to address the risks of loss of bone mineral density. DMPA-SC should have a risk profile similar to the marketed product, DMPA-IM.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

DMPA-SC is a progestin for subcutaneous administration. In this NDA, the Applicant studied the indication, "prevention of pregnancy in women of childbearing potential." By reducing the dose and developing a formulation for subcutaneous injection, the Applicant

The Phase 3 clinical program included three year-long contraception studies. 1,980 women received DMPA-SC in the Phase 3 clinical program, and efficacy data were obtained for 1,971 of 1,980 women. Another 193 women received DMPA-IM.

The clinical program also included

- three Phase 1/2 studies that exposed 116 women to single doses of DMPA-SC
- interim safety data from 298 women exposed to DMPA-SC in 2 trials that studied DMPA-SC as treatment for endometriosis
- one Phase 3 study that provided 2 years of bone mineral density data

The endometriosis trials included a 6-month treatment phase and a 12-month follow-up phase.

2.2 Efficacy

No pregnancies were detected in studies of 1,971 women using DMPA-SC for up to 1 year (20,607 women-months). The pregnancy rates in women 35 and under, based on cycles in which they used no other contraceptive methods was:

Pearl Index: 0 pregnancies per 100 women-years (upper 95% C.I. is 0.25)

All three Phase 3 trials used the same primary endpoint: treatment failure cumulative pregnancy rate at 1 year defined as a positive pregnancy test before the next scheduled dose. Subjects were healthy, sexually active women between 18 and 49 years old.

Although placebo treatment could not be used for ethical reasons, historical studies show that 85 to 90 of 100 sexually active women desiring pregnancy will become pregnant after 1 year of unprotected sexual activity. Therefore 0 pregnancies represents a strong treatment effect.

The table below summarizes experience with contraceptive products, and shows DMPA among the most highly effective methods.

Approximate Percentage of Women Who Become Pregnant During the First Year of Use of a Birth Control Method	
METHOD	PREGNANCIES PER 100 WOMEN PER YEAR
estrogen/progestin injection levonorgestrel implants levonorgestrel IUD and copper IUD <i>medroxyprogesterone acetate injection</i> sterilization	Fewer than 1
estrogen/progestin contraceptive products: • pills • skin patch • vaginal ring	1
progestin-only pills	2
condom (male) diaphragm	15
spermicides	25 or more

*The estimates for drugs, condoms, diaphragms, and IUDs come from clinical trial data reviewed by the Food and Drug Administration. The estimates for sterilization and spermicides come from the medical literature. Source: prepared by reviewer from FDA internal data and literature review.

Only 5% of cycles followed home self-injection.

2.3 Safety

Total patient exposure met general guidelines for drug development and specific FDA recommendations for this product. 1,980 women were treated with DMPA-SC, and 1,490 women received 4 injections (one year of treatment). Overall, on-treatment data were collected for 20,607 women-months. Collection of adverse event data was adequate except for adverse events associated with dropouts. Adverse events associated with dropouts were probably underestimated because the design of the case report forms allowed investigators to check off "withdrawal of consent" without prompting for a reason. However, many of the women who withdrew consent also complained of adverse events, and this information was adequately captured on adverse event forms even if it did not show up as a reason for dropping out.

Treatment emergent serious adverse events (SAEs) occurred in 1% of subjects. The most common SAE was excessive uterine bleeding, which occurred in 4 subjects. All 4 subjects recovered. Although DMPA-SC may have contributed to excessive uterine bleeding, this is not an unusual problem in women of reproductive age.

About 10% of subjects dropped out for adverse events. The single most common reason for dropping out was uterine bleeding abnormalities, accounting for 40% of dropouts. Other common causes for dropping out included weight gain (22%), decreased libido (14%), and acne (13%). About 5% of dropouts were for injection site reactions. Injection site reactions were

only seen in subjects treated with DMPA-SC, and though infrequent, injection site reactions represent a disadvantage of the SC formulation. The typical reaction prompting dropout was chronic induration at the injection site, described by one investigator as "about the size of a nickel." Although investigators rated these reactions as not serious, women who dropped out of the studies for injection site reactions rated their likelihood of ever using DMPA-SC again as "extremely unlikely".

Common adverse events reported in more than 5% of subjects included headache (8%), intermenstrual bleeding (7%), increased weight (7%), and amenorrhea (6%). These adverse events also occur in women using DMPA-IM.

Although there were no formal studies of drug-drug interactions in this NDA, no efficacy or safety issues were detected among women who used concomitant medication. The Phase 3 database included 75 women taking CYP 3A4 inducers and 111 women taking CYP 3A4 inhibitors. In recent years it has become clear that MPA is metabolized by liver P450 enzymes. Since the clearance of MPA approximates liver blood flow, the Applicant postulated that enzyme induction should have limited effect on MPA levels. However, a published study suggests that MPA concentrations decrease by more than 50% when combined with aminoglutethimide, an inducer of hepatic microsomal enzymes, which suggests that MPA concentrations may be affected by liver enzyme induction. However, this is the only drug-drug interaction that has been reported for DMPA-IM. There have been no reports of reduced efficacy as a result of drug-drug interactions.

Trial exclusions may have improved the safety and efficacy profile somewhat compared with what may occur after marketing. For example, by requiring that women have regular cycles, postpartum women were excluded. This is a group at increased risk for thrombotic events, and DMPA is a popular contraceptive for postpartum women.

The effect of trial exclusions can be assessed by looking at the reasons for screening failures. Overall, 24% of subjects failed screening. Reasons were collected for 962 subjects. Most screening failures were related to consent and ability to comply with study procedures, and should not affect the applicability of trial results to the general population. However, there were 4 screening failures with liver or kidney disease, 22 with irregular cycles, and 58 with low bone mineral density at baseline (T-scores less than -1.0). Since it is not standard practice to prescreen healthy young women for these problems before starting hormonal contraception, exclusion of these women may have improved safety over what might occur after marketing. Nonetheless, most women of reproductive age who seek contraception are in good health, and, overall, the study population was a reasonable approximation of the expected population.

Warnings should be consistent with the DMPA-IM label, and include

- Bleeding irregularities
- Decrease in bone mineral density
- Cancer
- Thromboembolic disorders
- Ocular disorders (a subtype of thromboembolic disorder)

- Ectopic pregnancy

The safety profile of DMPA-SC is different from progestin-only pills in the following areas:

- weight gain
- BMD loss
- delayed return to fertility
- injection site reactions

These problems should be measured against the advantages of dosing every 3 months and the high effectiveness of DMPA-SC.

The current label for DMPA-IM states, "Use of Depo-Provera Contraceptive Injection may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall." However, the Applicant's data indicate that bone loss is progressive over at least a 5-year period of observation. BMD recovery after treatment was also progressive, and not complete at 96 weeks for women who had more than 1 year of therapy. In Study 267BMD, women had median bone loss consistent with previous studies of DMPA-IM: after 1 year of treatment, -1.4% change in femoral BMD and -2.4% change in spinal BMD, and, after 2 years of treatment, -3.3% change in femoral BMD and -4.3% change in spinal BMD. No difference in BMD loss was detected between DMPA-IM and DMPA-SC after 2 years of treatment.

Published studies suggest that the BMD loss is at least partially reversible in adults who use DMPA-IM for contraception; however, this issue is unresolved for adolescents. The Applicant has an ongoing study of adolescents using DMPA-IM to address the issue. The study is in the follow-up stage. For balance, it should be noted that weight gain and BMD loss are also seen following pregnancy and lactation, conditions prevented by DMPA-SC. However, unlike the hormonal changes produced by pregnancy and lactation, the hormonal changes produced by DMPA can continue uninterrupted for many years.

Mean weight gain was 3.3 lb at 1 year for all subjects, and 4.4 lb at 1 year for US subjects. No difference in weight gain was detected between DMPA-IM and DMPA-SC. Weight gain can be a serious problem for some women,

Delayed return to fertility should be part of the counseling for every woman considering this method. Among 21 women who stopped treatment to become pregnant, only 1 became pregnant within 1 year of her last injection of DMPA-SC. DMPA-SC may not be a good choice for a woman who wants to become pregnant soon after discontinuing contraception.

Injections site reaction occurred in 5% of subjects treated with DMPA-SC. Although not medically serious, these reactions caused 10 women to stop treatment. Only 1 of these 10 women was rated "recovered", suggesting that scarring may have occurred in the others.

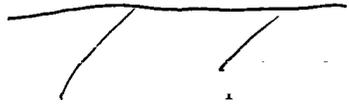
Whether use of DMPA increases the risk of thromboembolic events remains unclear. The data are conflicting. Limited data from a single case-control study suggest little or no increased risk. Limited clinical trial data are consistent with a risk similar to the risk in women using combination oral contraceptives. Until the issue is resolved, the product label should continue to include thromboembolic disease as a contraindication to DMPA use.

2.4 Dosing

The Applicant reasonably chose the lowest dose to suppress ovulation based on Phase 1/2 trials.



The Applicant plans to co-package DMPA-SC with a needle appropriate for SC dosing, and this should enhance safety. The shorter, finer gauge needle for the SC product will serve as a visual reminder that the dosing route for DMPA-SC is different from the dosing route for DMPA-IM.



2.5 Special Populations

Since the indication applies only to women of reproductive age, data analysis by age and gender was unnecessary. Pediatric studies were not done because the risk/benefit profile was expected to be the same for postmenarcheal girls and older women of reproductive age. The Phase 3 studies included an adequate mix of racial groups: 68% White, 21% Asian or Pacific Islander, 8% Black, and 3% Mixed Race. No race-related safety or efficacy issues were detected.

DMPA-SC may be inadvertently used in pregnant women. Epidemiologic studies suggest that inadvertent exposure to medroxyprogesterone in early pregnancy is *not* associated with an increase in adverse pregnancy outcome. Postmarketing reports received by the FDA for DMPA-IM do not suggest any pattern of fetal anomalies following inadvertent pregnancy exposures. Published lactation studies support the use of medroxyprogesterone during lactation.

Although the IM formulation has been marketed for over 40 years, there are no studies in subjects with renal or hepatic impairment. Since DMPA is chiefly metabolized in the liver, severe hepatic dysfunction is a labeled contraindication. The effect of renal disease on the pharmacokinetics of DMPA is unknown.

Clinical Review

3 Introduction and Background

3.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Medroxyprogesterone acetate injectable suspension is a progestin for the prevention of pregnancy in women of childbearing potential. The proposed dose is 104 mg in 0.65 ml, given subcutaneously every 3 months. The Applicant proposed 2 trade names:

At the time that this review was completed, a final trade name had not been determined.

3.2 State of the Art for Indication(s)

Depo-Provera (DMPA-IM) was first approved for palliative therapy of renal and endometrial cancer in 1960 in a dose of 400-1000 mg each week. Over 30 years later, on October 29, 1992, DMPA-IM was approved for contraception as an intramuscular injection in a dose of 150 mg in 1 ml every 3 months. DMPA-IM is a highly effective, reversible method of contraception. Although users need to visit a healthcare provider every 3 months, they do not need to remember a daily pill or use a device with each act of intercourse. The main safety issues of DMPA-IM include a loss of bone mineral density and an increase in weight in long-term users. In the present NDA, the Applicant developed *a lower dose, subcutaneously injected* formulation with the

Hormonal choices for contraception include progestin-only products (pills, implants, and IUDs), and combination estrogen/progestin products (such as pills, a skin patch, and a vaginal ring). Progestin-only methods are usually associated with more irregular bleeding than the combination estrogen/progestin products. However, progestin-only methods are favored by healthcare providers for women who have contraindications to estrogen use. DMPA-IM is unique among progestin-only methods because the dose of progestin is high enough to consistently suppress ovulation. Other progestin-only methods do not consistently suppress ovulation. In addition, return to fertility is slower for DMPA-IM than for any other reversible method because ovulation is suppressed for more than 3 months following each injection.

3.3 Important Milestones in Product Development

Table 1 briefly summarizes interactions between the Applicant and the FDA during product development.

Table 1. Pre-NDA Regulatory Interactions

Date	Communication	Highlights
02-Oct-2000	Pre-IND guidance meeting	FDA and Applicant discussed general plan for developing a SC, lower dose formulation of injectable DMPA both for contraception and for endometriosis indications.
13-Dec-2000	Special Protocol Assessment and IND	FDA and Applicant agreed on Phase 3 trial design.
03-Jan-2001	Guidance t-con	FDA and Applicant discussed issues regarding self-injection protocol.
15-Jul-2002	Pre-NDA meeting	FDA and Applicant agreed on analyses and general format of NDA. Applicant agreed to supply return to ovulation data during the NDA review by 4-month safety update.

Source: FDA Division Files

In addition, the Applicant filed a major amendment to the NDA late in the review period, and therefore the review period was extended an additional 3 months to allow time for adequate review. The amendment included the study report of a 7-year study of bone mineral density in women using DMPA-IM, and a final report for Study 267BMD, one of the 3 contraception trials used to support the NDA.

3.4 Other Relevant Information

DMPA-SC is not marketed elsewhere. The Applicant states that there have been no requests from foreign regulatory agencies related to bone safety.

3.5 Important Issues with Pharmacologically Related Agents

Public health issues with DMPA-IM include bone mineral density loss and weight gain. For balance, it should be noted that these are also issues of pregnancy and lactation, conditions prevented by DMPA-IM.

The loss in bone density is greater with longer duration of use and younger age at initiation of use. There is evidence in older reproductive-aged women that the bone density loss is at least partially reversible; however, there are only limited data on reversibility in adolescents. The Applicant is doing a Phase 4 study on bone loss in adolescents that will provide more data on reversibility. Although there is no evidence that these effects on bone density increase fracture rate, detecting an increase in fracture rate in women of reproductive age would be difficult because the reproductive years are the time of peak bone density.

The weight issues with DMPA-IM are well-summarized in the current label, and include an average weight gain of 5.4 lb at 1 year, 8.1 lb at 2 years, 13.8 lb at 4 years, and 16.5 lb at 6 years.

Other issues for DMPA-IM include:

- Observational studies have shown either no increase or a small increase in breast cancer risk for women using DMPA-IM.
- Like all progestin-only methods, irregular vaginal bleeding is a problem for some women.
- Return to fertility is slower than for other hormonal methods because DMPA-IM is a depot formulation.
- There is recent evidence that DMPA is metabolized by the CYP 3A4 enzymes, and therefore drug-drug interactions are a potential problem. The current label does not address CYP 3A4 metabolism.
- Whether or not DMPA-IM increases the risk of venous thromboembolism is a matter of debate. The current label lists a history of thromboembolic events as a contraindication. However, the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO) endorse the use of progestin-only methods in women with a history of thrombosis.

4 Clinically Relevant Findings from Other Reviews

4.1 Chemistry

DMPA-SC is preloaded in a syringe and co-packaged with a 26-gauge x 3/8-inch needle. In contrast, DMPA-IM is co-packaged with a 22-gauge, 1.5 inch needle.

Comment: The Applicant's decision to co-package DMPA-SC with a needle appropriate for SC dosing was a good one. The shorter, finer gauge needle for the SC product will serve as a visual reminder that the dosing route for DMPA-SC is different from the dosing route for DMPA-IM.

4.2 Microbiology

The microbiology reviewer recommended approval on the basis of product quality microbiology.

4.3 Biopharmaceutics

The biopharmaceutical reviewer determined that, for single-dose injections, C_{max} was 46% lower and $AUC_{(0-inf)}$ was 31% lower, for DMPA-SC compared with DMPA-IM. (The data for the DMPA-IM came from NDA 20-246.)

5 Human Pharmacokinetics and Pharmacodynamics

5.1 Pharmacokinetics

In single dose studies the $t_{1/2}$ for MPA after a single injection of DMPA-SC was about 40 days. C_{max} was reached 1-2 weeks after injection. Body mass index (BMI) had small effects on MPA kinetics. Obese women had a lower AUC and C_{min} than nonobese women. From previous studies, MPA binding to plasma proteins averages 86%. Binding is mainly to albumin, not sex hormone binding globulin (SHBG).

A substudy of Study 267BMD provided PK data relevant to multiple dosing. In this substudy, subjects had MPA trough levels drawn at 6 months and 12 months. Table 2 shows the results. There was no statistically significant difference in MPA trough levels between treatment groups at 6 months or 12 months.

Citing internal data, the Applicant stated that an MPA concentration of 200 pg/ml is necessary to inhibit-ovulation. In Study 267BMD, 24 subjects had MPA concentrations less than 200 pg/ml on treatment (20 in the DMPA-IM group and 4 in the DMPA-SC group). None of these subjects became pregnant, although 3 of the 24 women had serum progesterone concentrations suggestive of ovulation.

Table 2. Trough Serum Concentrations of MPA from Study 267BMD by Treatment

	DMPA-SC	DMPA-IM
At 6 months:		
N	113	108
Mean MPA concentration (pg/ml)	656 (95% CI 535 to 777)	764 (95% CI 655 to 873)
At 12 months:		
N	103	99
Mean MPA concentration (pg/ml)	844 (95% CI 752 to 936)	830 (95% CI 744 to 916)

Source: Created by reviewer using JMP software from Applicant dataset labeled pkdata.xpt in unblinded interim report for Study 267BMD

Comment: Trough concentration of MPA are similar for both formulations, even though the dose of the IM product is almost 50% greater. In fact, no statistically significant difference in trough concentration was detected between the formulations at either 6 or 12 months.

Even though the mean MPA concentrations were 3-4x the concentrations needed to maintain ovulation suppression, there was great variability.

Study 267BMD also provided data on steady state concentrations of MPA in a few DMPA-SC-treated subjects during the first and second year, shown in Table 3.

Table 3. Serum Concentrations of MPA from Study 267BMD in Subjects Treated with DMPA-SC for Two Years

	6 month	12 month	2 nd year within 1 dosing interval						24 month
			2 week	4 week	6 week	8 week	10 week	12 week	
N	8	8	7	8	8	8	7	8	2
Mean MPA concentration in pg/ml	594	969	943	1,485	1,316	1,099	937	943	773

Source: Modified from Applicant's table in 4-Month Safety Update - Revision 1: Amendment G for Phase III contraception Study of DMPA-SC in Women of Childbearing Potential in the Americas, p. 21.

Comment: Based on a small number of samples, blood levels reached steady state by 12 months.

Studies did not detect any clinically important race or weight effects. Suppression of ovulation was maintained across all BMI and race categories. There was a lower AUC and C_{min} in obese women. There was a longer time to t_{max} in black subjects. Injection into the anterior thigh or abdomen produced similar PK/PD profiles except for a higher C_{max} with injection into the anterior thigh.

The Applicant relied on previous studies of MPA for protein binding, metabolism, and drug-drug interactions. MPA is metabolized by liver P450 enzymes, with more than 10 metabolites identified. Most of the metabolites are excreted in the urine. The clearance of MPA approximates the liver blood flow and therefore the Applicant postulated that enzyme induction should have limited effect on MPA levels.

Comment: Although the Applicant presents a rationale for enzyme induction being of limited effect on MPA levels, in one study, MPA levels decreased by more than 50% when combined with aminogluthetimide, an inducer of hepatic microsomal enzymes.¹

No studies were done in women with impaired renal or hepatic function. The label for Depo-Provera IM states that "The effect of hepatic and/or renal disease on the pharmacokinetics of Depo-Provera Contraceptive Injection is unknown." Also, liver dysfunction is a labeled contraindication.

Comment: Since DMPA is extensively metabolized by the liver and excreted in the urine, women with impaired renal or hepatic function may have elevated MPA or MPA metabolite levels. There is no evidence that this is a safety concern.

¹ Van Deijk, et al. Influence of aminogluthetimide on plasma levels of medroxyprogesterone acetate: its correlation with serum cortisol. Cancer Treatment Reports. 1985; 69:85-90

5.2 Pharmacodynamics

Three Phase 1/2 studies explored the inhibition of ovulation:

- Study 265
- Study 271
- Study 272

Study 265 provided data to support dose selection for the Phase 3 trials. It was an open-label, randomized, dose-ranging trial of 4 single doses (50, 75, 100 or 150 mg), using the marketed DMPA-IM products given subcutaneously.

According to internal company data, the threshold serum level needed to maintain ovulation suppression is between 100-200 pg/ml. In Study 265, the 100 mg dose was the lowest dose that achieved the desired concentration over 3 months, and suppressed ovulation (defined as progesterone concentration <4.7 ng/ml) in all but one subject. (The subject who did not maintain a MPA concentration > 200 pg/ml ovulated on day 70 after injection. Based on her pharmacokinetic profile, she may have had an intravascular injection.) Both t_{max} and C_{max} varied little with dose. T_{max} was between 16 and 25 days. The mean $t_{1/2}$ ranged from 27 to 37 days. The Applicant chose 104 mg in 0.65 ml as the Phase 3 dose, rather than 100 mg, for manufacturing reasons.

Comments: The Applicant states there has been one observation of possible intravascular injection based on PK/PD in their PK database of about 300 women (single injection).

The to-be-marketed product was not used in Study 265.

Study 271 studied the PK and PD in 24 Asian women following a single dose of DMPA-SC 104 mg/0.65 ml. Serum hormone levels and MPA levels were assessed weekly for 3 months. The reason for the study was a 1987 WHO study that suggested enhanced metabolism or clearance of MPA in Thai women, and a faster return of ovarian function in Thai women compared with women from other countries. Only 2 Thai women were included in the study and their mean serum concentrations of MPA were similar to the other subjects' serum concentrations. MPA levels > 200 pg/ml were seen in 23 of 24 women for >91 days. One Malaysian woman had an MPA trough level of \sim μ g/ml, but maintained ovulation suppression. Progesterone levels were suppressed in 23 of 24 women for at least 112 days after dosing. One Filipino women had an elevated progesterone level (\sim g/ml) 57 days after injection, but her estradiol, LH, and FSH concentrations were not consistent with ovulation. In addition, her serum progesterone levels on days 50 and 64 were \sim ng/ml. There was no difference between abdominal and thigh injection except that mean C_{max} was higher (1.7ng/ml compared to 0.9 ng/ml) in women receiving the injection in the anterior thigh.

Comment: A single dose of DMPA-SC 104 mg in 0.65 ml suppressed ovulation in this sample of 24 Asian women.

Study 272 compared return to ovulation, duration of ovulation suppression, and return of ovulation following a single injection of DMPA-SC (104 mg in 0.65 ml) or DMPA-IM (150 mg in 1 ml). Ovulation was defined as a serum progesterone level > 4.7 ng/ml. Table 4 shows selected results from Study 272.

Table 4. Study 272 Results by Treatment Group

	DMPA-SC	DMPA-IM
N	39	19
Suppressed ovulation for 14 weeks	Yes	Yes except for 1 subject
Earliest return of ovulation	106 days	70 days
Median return of ovulation	30 weeks	26 weeks
Cumulative rate of return to ovulation at 1 year	97%	95%
MPA above 200 pg/ml through 14 weeks	Yes	Not measured
Terminal $t_{1/2}$	43 days	-
Mean C_{max}	1.56 ng/ml	-

Source: Created by reviewer from Applicant's Study Report for Study 272

Comment: Delayed return to ovulation can be a problem for some women. Although DMPA-SC provides a lower dose of MPA than DMPA-IM, this study did not show a faster return to ovulation for women receiving DMPA-SC. Return to ovulation after multiple doses of DMPA-SC is discussed in "Return to Ovulation and Fertility", below.

6 Description of Clinical Data and Sources

6.1 Overall Data

The Applicant's clinical data comes from 8 clinical trials, listed in the next section.

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6.2 Table Listing the Clinical Trials

Table 5. Summary of Clinical Trials Included in NDA

Study ID	Objective(s) of Study	Design	DMPA Regimen	N	Treatment Duration	Status
267	Phase 3 contraception	Open-label, multinational, multicenter	104 mg SC every 3 months	722	1 year	Complete
269	Phase 3 contraception	Open-label, non-comparator, multinational, multicenter	104 mg SC every 3 months	1065	1 year	Complete
267BMD	Phase 3 contraception and BMD changes	Randomized, evaluator-blinded to compare DMPA-SC and DMPA-IM	DMPA-SC 104 mg SQ every 3 months or DMPA-IM 150 mg IM every 3 months	386: 193 SC 193 IM	2 years	Ongoing*
265	Determine PK and PD (suppression of ovulation)	Open-label, randomized, single-dose (4 levels), outpatient, parallel groups	Single SC injection of either a 50-mg, 75-mg, 100-mg, or 150-mg dose of MPA	47	Single dose	Complete
271	Determine duration of ovulation suppression in Asian women	Single center, open-label, single-dose, outpatient, parallel group	Single SC injection of 104 mg DMPA	24	Single dose	Complete
272	Compare cumulative rate of ovulation at 12 months	Single center, evaluator-blinded, single-dose, outpatient	Single injection of either DMPA-SC 104 mg or DMPA-IM 150 mg	68: 45 SC 23 IM	Single dose	Complete
268/270	Phase 3 endometriosis trials	Randomized, evaluator-blinded, multicenter, comparator-controlled	DMPA-SC 104 mg every 3 months	298	6 months	Ongoing**, included for coagulation and lipid data, safety summary only

*The Applicant filed a 2-year study report for this study late in the review, along with a study report for a 7-year study of BMD, prompting an extension of the review period by 3 more months to allow time for review.

**Study was ongoing at time of NDA submission.

Source: Modified from Applicant's Table 5.1 in Module 5.2, "Tabular Listing of All Clinical Studies"

6.3 Postmarketing Experience

DMPA-SC is not marketed elsewhere, and therefore postmarketing data for this formulation was not available. However, postmarketing data for DMPA-IM is available and was used for this review because DMPA-SC and DMPA-IM are expected to have similar postmarketing profiles.

6.4 Literature Review

The Applicant reviewed the literature published between 21-Dec-1995 and 30-Oct-2002 and concluded there were no new safety concerns about the use of DMPA-IM. There was no discussion of the method of literature review, or of the reason for setting the date limits.

My own search of PubMed using the search term "medroxyprogesterone acetate" on January 12, 2004, revealed 4,294 articles. I scanned the titles of the 203 articles from the year 2003 to the present for articles that might raise safety issues. Otherwise, I used targeted searches for specific issues, for example, "medroxyprogesterone acetate" AND "thrombosis". I found no Cochrane review of medroxyprogesterone acetate (search done in July 2003). My own search revealed no unexpected areas of concern.

7 Clinical Review Methods

7.1 How the Review was Conducted

The three Phase 3 trials used to support efficacy and safety were reviewed in detail. The remaining trials received a less detailed review for supportive pharmacokinetic and safety information. Datasets were explored using the software JMP 4.

7.2 Overview of Materials Consulted in Review

Materials consulted included:

- Electronically submitted NDA 21-583 (including multiple submissions from the Applicant in response to FDA information requests during the review cycle)
- 4-month safety update
- Division files for related INDs 61,388, 61,389, and 45,275
- Postmarketing reports for Depo-Provera in FDA's AERS DataMart
- Search of Cochrane Reviews
- PubMed literature searches
- ReproTox database
- Electronically submitted NDA 21-584

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

An FDA inspector evaluated 3 US clinical sites. Because no suspicions about the data were evident during the review, inspection sites were selected based on number of enrollees at each site, convenience of location, and whether the site had been recently inspected. All 3 sites had satisfactory inspections.

One site in Study 267BMD was inspected as part of FDA's Bioresearch Monitoring Program to ensure that the rights, safety, and welfare of the subjects were protected. The site had a satisfactory inspection.

The Applicant conducted audits at selected clinical investigator sites for all Phase 3 clinical trials for contraception.

7.4 Ethical Standards

The trials were conducted in accordance with accepted ethical standards. Institutional Review Boards or Independent Ethics Committees reviewed the trial protocols before starting each trial. The Applicant then monitored each trial to ensure that it met the ethical principles in the Declaration of Helsinki.

7.5 Evaluation of Financial Disclosure

The Applicant provided financial disclosure information for Studies 267, 267 BMD, and 269, the Phase 3 trials relied upon to show efficacy. Two investigators in Study — disclosed significant financial interests (Table 6) and 4 subinvestigators did not disclose financial information. No investigator enrolled more than 4% of total participants (Table 7).

Table 6. Two Investigators Who Disclosed Significant Financial Interests

Study	Investigator	Amount Disclosed	Applicant's Assessments for Data Integrity
—	—	\$10,000 to 20,000 annually in consultant and speaker fees	<ul style="list-style-type: none"> ▪ Enrolled only — patients ▪ Monitoring visits every 10-12 weeks ▪ Average number of edits
—	—	Consultant fees, amount not disclosed.	<ul style="list-style-type: none"> ▪ Enrolled — patients in — ▪ Monitoring visit performed every 10-12 ▪ Average number of edits

Source: Created by reviewer from data presented in NDA Module 1, section 1.2.a.6, titled Financial Information.

Table 7. Maximum Number of Subjects Enrolled by a Single Investigator, by Study

Study	No. of Investigators	Maximum number of subjects enrolled by a single investigator
267 BMD	49	61
267	75	79
269	67	49

Source: Created by reviewer from information presented in the Applicant's individual Study Reports.

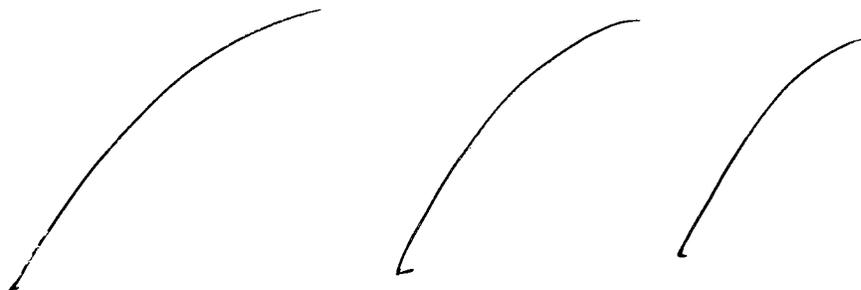
Comments: The financial interests disclosed by two investigators were unlikely to bias the trials because of the small number of subjects enrolled by each investigator. For the same reason, lack of financial disclosure for 4 subinvestigators was unlikely to jeopardize the integrity of the trials. No investigator enrolled more than 4% of the subjects in all 3 Phase 3 trials.

8 Integrated Review of Efficacy

8.1 Brief Statement of Conclusions

DMPA-SC is highly effective for preventing pregnancy. No pregnancies were detected in the 3 Phase 3 trials designed to study contraceptive efficacy. A single pregnancy was detected in 2 Phase 3 trials designed to study efficacy in the treatment of endometriosis.

The Applicant's proposed label states, ' _____



Pearl Index: 0 pregnancies per 100 women-years (upper 95% C.I. is 0.25)

8.2 General Approach to Review of the Efficacy of the Drug

Efficacy data came from 3 Phase 3 trials, Studies 267, 269, and 267BMD. These studies were reviewed in detail. They included 1,971 women who received at least 1 injection of DMPA-SC and provided efficacy data. (The safety database contained the same 1,971 women plus 9 women who received at least 1 injection but did not provide efficacy data.)

There were 20,607 women-months of DMPA-SC exposure, calculated by multiplying the number of injections by 3. 1,109 women aged 35 years or younger completed 1 year of treatment. Among DMPA-SC users, 75% received 4 injections (1 year of treatment). Table 8 shows women-months of exposure for months with sexual activity and months without use of other methods of contraception.

Table 8. All Woman-Cycles of Exposure (ITT Efficacy Population)

Protocol/Treatment	Woman-Cycles of Exposure (All Ages)			
	Total months	Months with barrier use every time subtracted*	Months with barrier use sometime or every time subtracted*	Months with barrier use or months without intercourse subtracted*
267 DMPA-SC	7209	6960	6605	5616
269 DMPA-SC	11,472	11,093	10,699	10,407
267BMD DMPA-SC	1,926	1,834	1,738	1,505
Total DMPA-SC	20,607	19,887	19,042	17,528
267BMD DMPA-IM	1,899	1,783	1,674	1,411

* Subjects noted monthly whether they had had sexual intercourse and if they had used a barrier contraceptive (e.g., condom, diaphragm), and if so, how often (every time or sometimes).

Source: Modified from Applicant's Table 4 in Module 2, Section 2.7.3, Summary of Clinical Efficacy

Comment: Studies 267, 269, and 267BMD provided more than enough drug exposure to meet general regulatory requirements for a new formulation of an approved hormonal contraceptive.

In Studies 267 and 269, healthcare providers trained women to self-inject, and for the last 1 or 2 injections, allowed women to self-inject in home or office. Table 9 shows the exposure by type of injection.

Table 9. DMPA-SC Exposure by Type of Injection for Studies 267 and 269

Study	Type of Injection	Number of Injections	Total Women-Months of Exposure
Studies 267 and 269	Office Expert Injection	4,134	12,402
	Office Self-Injection	1,814	5,442
	Home Self-Injection	279	837

Source: Modified from Applicant's Table T11, Module 5, Section 5.3.5.3.1, Summary of Clinical Efficacy

Comment: Only 5% of cycles followed home self-injection, and only 2 women gave themselves more than 1 home self-injection (2 home self-injections for both women).

I did not review the endometriosis studies (see Table 2) in detail, but used them as supportive studies.

8.3 Detailed Review of Trials 267, 269, and 267BMD for Contraception Indication

8.3.1 Protocol

Objectives

The primary objective of all 3 trials was to assess contraceptive efficacy of DMPA-SC given every 3 months for one year. Secondary objectives included safety assessments, subject satisfaction, and

Overall Design

The studies were Phase 3, open-label, multicenter, and multinational. Only Study 267BMD had an active comparator group. Studies 267 and 267BMD involved sites in the Americas, whereas Study 269 involved sites in Europe and Asia.

Study 267 took place in 74 sites in the Americas. Most sites were in U.S. (36) or Canada (23), with the remaining sites in Brazil (4), Chile (3), Mexico (4) and Peru (4).

Study 267BMD took place in 48 sites in the Americas. Most sites were in the U.S. (36), with the remaining sites in Canada (9) and Brazil (3).

Study 269 took place in 64 sites in Europe and Asia, including sites in Russia (21), Bulgaria (6), Estonia (5), Indonesia (2), Latvia (5), Poland (6), Romania (5), and the United Kingdom (3).

Population and Procedures

Investigators recruited healthy women who were sexually active and between the ages of 18 and 49. More inclusion and exclusion criteria follow.

Inclusion Criteria

- Desiring long-term contraception
- Having been off oral contraceptives for the 2 months before enrollment, when applicable, and having used a barrier method of contraception or having been sexually inactive during this prescreening period
- Having a negative urine pregnancy test
- Willing to rely upon DMPA-SC for contraception for at least 1 year
- Menstruating regularly during the 3 months (cycle length of 25 to 35 days) prior to enrollment

Exclusion Criteria

- Having been treated with oral contraceptives, contraceptive implants, or hormone-medicated intrauterine devices in the past 2 months or having had DMPA-IM administered in the 10 months prior to enrollment
- Having abnormal cervical cytology smear required within 12 months prior to enrollment, including any of the following results: atypical glandular cells of undetermined significance, low-grade squamous intraepithelial lesions, or high-grade squamous intraepithelial lesions. However, subjects with a finding of atypical squamous cells of undetermined significance were permitted in this study.
- Having a history of breast cancer or having results from a mammogram that were suspicious of malignant disease or that required a 6-month follow-up
- Having a well-documented history of a thrombotic event such as stroke or venous thromboembolism (deep vein thrombosis or pulmonary embolus; this did not include superficial thrombophlebitis)
- Having undiagnosed abnormal genital bleeding
- Having a known or suspected pregnancy
- Having a history of alcoholism or other drug abuse within the 5 years prior to enrollment
- Having confirmed uncontrolled hypertension (ie, systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg)
- Having hypersensitivity to study medications or contraindication to progestin
- Concurrently using other investigational medication(s)
- Having previously participated in this study
- Having active hepatic or renal disease, or having a history of either, where hepatic disease was defined as having AST/SGOT or ALT/SGPT or total bilirubin elevated by 2.5 times the upper limit of normal. Renal disease was defined as having a creatinine value of greater than 1.8 mg/dL.
- Having insulin-dependent diabetes mellitus or noninsulin-dependent diabetes mellitus that was poorly controlled
- Having had a tubal ligation, a known diagnosis of infertility, or having partner(s) who were sterile
- Taking aminoglutethimide (anticancer agent)
- Having a condition (eg, serious medical disease) that might make strict compliance with the study instructions impossible

In Study 269, other exclusion criteria included

- Having a significant risk of osteoporosis (as determined by the investigator)
- Receiving concomitant treatment with a strong CYP450 3A4-inducing effect such as phenobarbital, phenytoin, carbamazepine and rifampin (in Denmark only, as an amendment to the original protocol)

In Study 267BMD, another exclusion criterion was:

- Having an increased risk of osteoporosis, defined by either lumbar spine or femur T-score of less than -1.0 or having a history of pathologic or compression fracture

Comments: The study population excluded some women who might use DMPA-SC. In particular, the protocol excluded lactating or postpartum women who were not yet cycling regularly. Also, women with renal disease, hepatic disease, or low bone mineral density (in Study 267BMD only) were excluded, and may not be excluded in actual practice, since it is not standard of care to prescreen asymptomatic women for these conditions before starting hormonal contraception. It is possible that these exclusions produced a more favorable safety profile in the clinical trials than would be expected in practice. However, it is unlikely that these exclusions affected efficacy.

The reason for excluding women using CYP450 3A4 inducers at Danish sites inducers was not stated in the amendment; however, in 2000, an article appeared suggesting that CYP3A4 is involved in the metabolism of MPA in human liver microsomes.²

Study Drug

In all studies, DMPA-SC 104 mg was given subcutaneously in the anterior thigh or abdomen every 91 ± 7 days for 1 year. In Study 267BMD, the DMPA-IM treatment group received 150 intramuscularly in the upper arm or buttock.

Procedures

The flow sheet for Study 267 follows.

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² Kobayashi K, et. al. Role of human cytochrome P450 3A4 in metabolism of medroxyprogesterone acetate. Clin Cancer Res.2000; 3297-303.

Assessments	Visit Time (Weeks)						
	0	1	2*	3	4	5	6†
	-4-0‡	§	6	12-14	25-27	38-40	51-53
Informed consent	X						
Inclusion/exclusion	X						
Medical history	X						
Physical exam	X						X
Demographics	X						
Sitting blood pressure	X	X		X	X	X	X
Body weight	X	X		X	X	X	X
Mammogram (>35 years)	X¶						X
Pelvic exam	X						X
Cervical cytology	X¶						X
Urinalysis	X						X
Urine pregnancy test	X	X	X	X	X	X	X
Bleeding pattern diary		X		X	X	X	X
Blood samples: chemistry/hematology	X				X		X
Study drug injection		X		X	X**	X**	X‡‡
Interview phone call					X††	X††	
Concomitant medications	X	X	recorded at each visit / interview phone call				
Adverse events			recorded at each visit / interview phone call				
PSQ		X			X		X
EOTQ							X

Abbreviations: EOTQ = End-of-Treatment Questionnaire, PSQ = Patient Satisfaction Questionnaire

* Subjects were contacted by telephone at home.

† These assessments were done between weeks 51 and 53 or upon study discontinuation, study termination, or early withdrawal visit.

‡ Baseline visit could have taken place up to 4 weeks prior to visit 1.

§ Injection visit.

¶ If not done in the last 12 months.

** Home self-injection was available for appropriately trained subjects.

†† Subjects who elected home self-injection were phoned at approximately days 93 to 98.

‡‡ Possible for subjects in Brazil.

(Only subjects in Brazil received a fifth dose of DMPA-SC by Amendment F.)

The procedures in Study 267BMD were similar to those of Study 267 except for:

- Additional visits at 64-66 weeks (Visit 7), 77-79 weeks (Visit 8), 90-92 weeks (Visit 9), and 103-105 weeks (Visit 10)
- Additional injection of study drug at Visits 7,8, and 9
- Blood samples for MPA Cmin at visits 4, 6, and 10 (103-105 weeks)
- Blood samples for hormone profile at visits 1, 4, 6, and 10. Hormone profiles included SHBG, serum estradiol, and progesterone.
- BMD at visits 0, 6, and 10
- No EOTQ

The procedures in Study 269 were similar to those of Study 267 except for:

- Endometrial biopsy for about 10 subjects at each of visits 3, 4, and 5 and endometrial biopsy for remaining subjects at visit 6
- Hormone profile at visits 1, 4, and 6. Hormone profiles included SHBG, serum estradiol, and progesterone.

In all 3 contraception studies, women were offered the choice of home self-injection for the 3rd or 4th injections if they were willing to receive training and perform an observed self-injection in the office first. Women who chose to self-inject went home with their next dose and reminder stickers. In addition, investigators telephoned these women between days 93 and 98 after the preceding injection.



Evaluations/Endpoints

The primary endpoints for all studies was the treatment failure cumulative pregnancy rate at 1 year, which was defined as a positive pregnancy test before the next scheduled dose. In addition, Study 267BMD was designed to show superiority (less of a decrease in BMD) in DMPA-SC-treated subjects compared with DMPA-IM-treated subjects after 2 years of treatment. At the time of NDA submission, only 1-year data were available for Study 267BMD; however, 2-year BMD data were submitted during the review.

Statistical Plan

The incidence of treatment failure was assessed by calculating pregnancy rates using the Pearl Index and the life table method, and providing a 95% confidence interval around the rates. The Pearl Index is the number of pregnancies per 100 woman-years.

8.3.2 Results

Subject Disposition

The following diagram shows subject flow through the 3 trials.

Figure 1. Flow Diagram through Studies 267, 267BMD, and 269

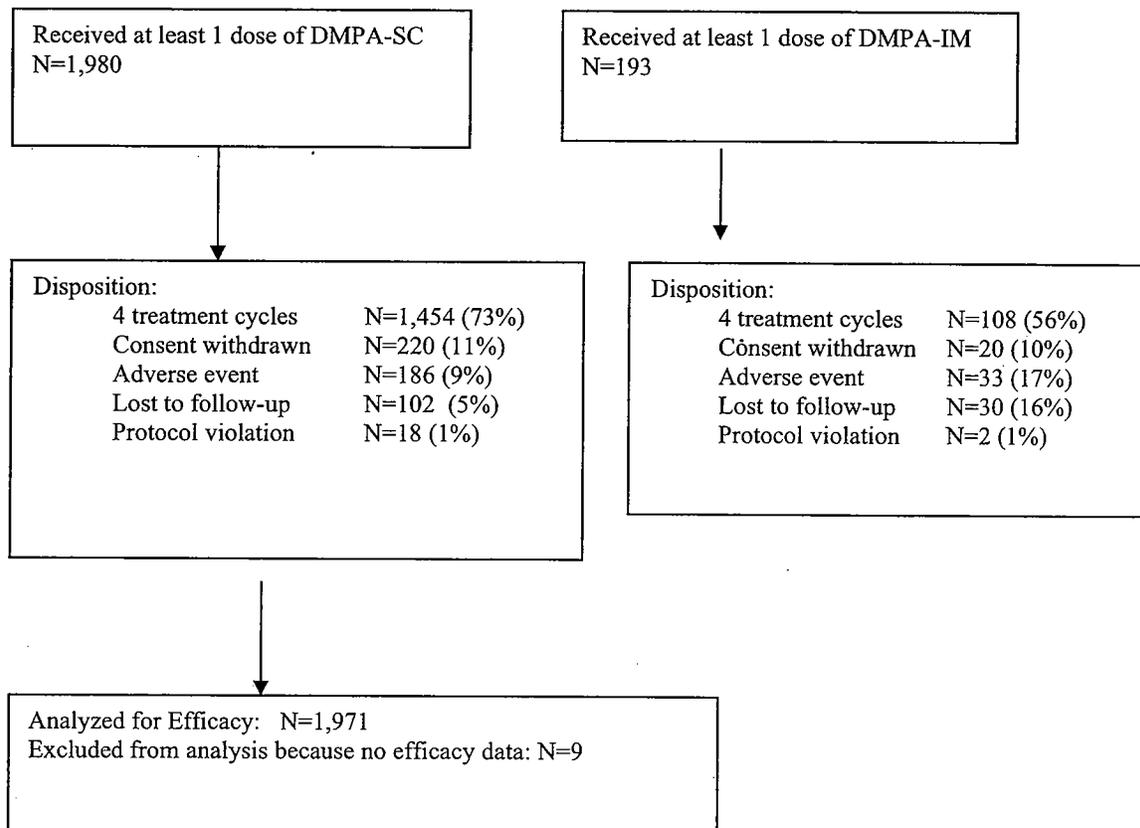


Table 10 shows disposition by study. Studies 267 and 267BMD had higher discontinuation rates than Study 269. Discontinuation rates by study ranged from 20-44%. Differences in adverse event percentages accounted for most of the difference among studies in discontinuation rates.

Comment: The case report form allowed investigators to check off "Consent withdrawn" as a reason for study termination, without prompting investigators for a reason for withdrawal of consent. As a result, more women dropped out of the study for "consent withdrawn" than for adverse events. It is likely that at least some of these women had adverse events which caused them to withdraw from the study.

Table 10. Subject Disposition by Study and Treatment Group

Disposition	Treatment Group	All Studies	Study 267	Study 269	Study 267BMD
		% of treated	% of treated	% of treated	% of treated
Completed	SC	73%	68%	80%	56%
	IM	56%			56%
Discontinued	SC	27%	32%	20%	44%
	IM	44%			44%
Discontinued for:					
AE	SC	9%	14%	5%	17%
	IM	17%			17%
Protocol Violation	SC	1%	1%	<1%	3%
	IM	1%			1%
Consent withdrawn	SC	11%	11%	11%	13%
	IM	10%			10%
Lost to follow-up	SC	5%	7%	3%	11%
	IM	16%			16%

Source: Modified from Applicant's Table 2, Module 2.7.3, Summary of Clinical Efficacy.

Comments: A possible reason for the differences in discontinuation rates may be in differences in the study populations. The lowest discontinuation rate was in Study 269, the only study done in Europe and Asia. Studies 267 and 267BMD were done in the Americas.

Twenty-four percent of subjects failed screening. Only U.S. sites recorded reasons for screen failures. Of 962 screened U.S. subjects, 58 were excluded because of low bone density (T score in femur or spine < -1.0 or history of pathologic and/or compression fracture), 4 were excluded because of either a history of or active liver or renal disease at baseline, and 1 was excluded because of a past history of thrombotic disease.

Demographic data was summarized in a dataset containing all 1,980 subjects in the safety database. U.S. sites enrolled 21% of study participants. Table 11 shows the numbers of U.S. and non-U.S. study participants in the three studies for the DMPA-SC treatment group.

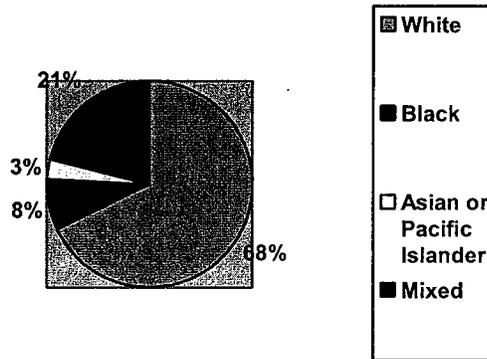
Table 11. Number of Subjects in each Study, by Foreign and Domestic Sites

Study Number	N (DMPA -SC)	U. S.	Non-U.S.
267	722	259	463
267 BMD	193	153	40
269	1,065	0	1065
Totals	1,980	412	1568

Source: Created by reviewer using JMP software and Applicant's dem.xpt file in ias dataset

Figure 2 shows the distribution by racial groups. In Studies 267 and 267BMD (done in the Americas), 11% of women were Black.

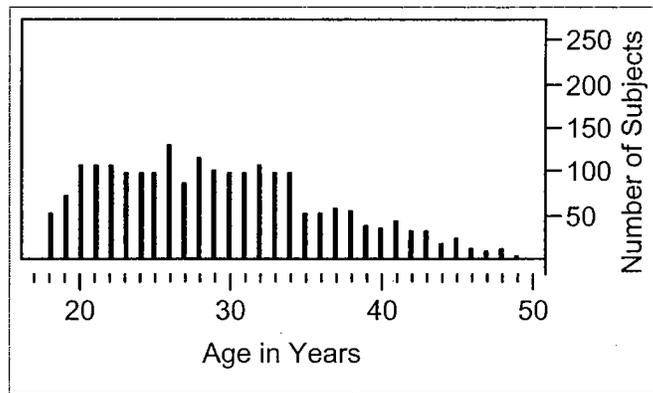
Figure 2. Distribution of Subjects by Racial Group



Source: Created by reviewer from data in Applicant's dem.xpt file in ias dataset

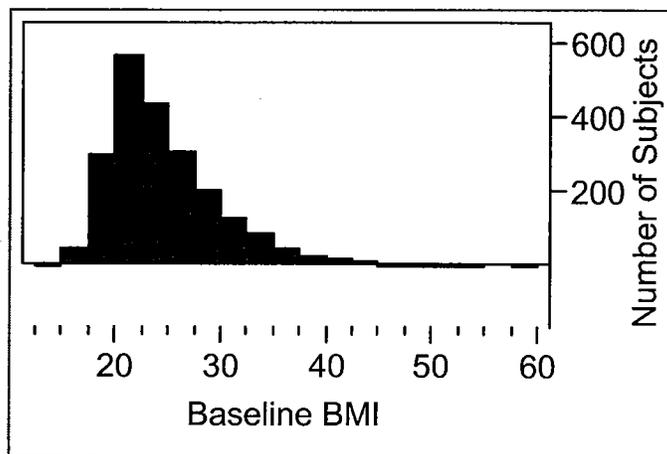
The mean age of the ITT group for all studies combined was 30 years old (S.D. = 7 years). The mean age for Study 269 (32 years old) was greater than the mean age for Studies 267 and Studies 267 BMD combined (28 years old). Women 35 years and younger comprised 78% of the ITT group. Figure 3 shows the age distribution for all women in the 3 studies.

Figure 3. Distribution of Baseline Age for ITT Group, Studies 267, 269, and 267 BMD



Source: Created by reviewer from data in Applicant's dem.xpt in folder named ias

The mean BMI for all studies combined was 24.6 kg/m². For US subjects, the mean baseline BMI was 27.0 and for non-US subjects the mean baseline BMI was 23.7 kg/m². Figure 4 shows the distribution of baseline BMI for the combined studies.

Figure 4. Distribution of Baseline BMI for ITT Group, Studies 267, 269, and 267 BMD

Source: Created by reviewer from data in Applicant's dem.xpt in folder named ias

Eighty-four women took medications known to be CYP3A4 inducers during treatment. Although most of these medications were short courses of therapy, 27 women took CYP 3A4 inducers for more than 30 days. One hundred eleven women took CYP 3A4 inhibitors, and 24 of the 111 took CYP 3A4 inhibitors for more than 30 days.

Efficacy Endpoint Analysis

All pregnancy tests were negative on treatment except for one indeterminate pregnancy test. In addition, there was a clinical pregnancy recognized by miscarriage 3 weeks after the first dose of Depo-Provera. Both women were in Study 267. Their case histories follow.

Patient ID 48961-0558: A 20-year-old woman in Brazil miscarried 3 weeks after her first injection. She had had a negative pregnancy test at screening on June 20, 2001. A pregnancy test was again negative on _____, when she received her first and only injection. She had a miscarriage 3 weeks later, on _____. There was microscopic confirmation of villi, although no fetal tissue was seen. She had a normal exam and negative pregnancy test on July 24, 2001. Pregnancy tests on August 13 and August 30 were both negative. Her BMI at baseline was 24 kg/m² and she did not take concomitant medications.

Comments: According to the Applicant, this pregnancy occurred before treatment. Although the clinical course is most consistent with a pregnancy that occurred in the week before treatment, conception in the day or two following treatment can be neither ruled out nor proven.

Patient ID 50126-0425: A woman in Canada had an indeterminate pregnancy test 6 weeks after her first and only injection, which was given on June 16, 2001. She was then lost to follow-up. Her BMI at baseline was 33.5 kg/m². She was taking no CYP3A4 inducers or inhibitors,

although she was taking Amoxicillin on June 15-25, Anaprox in July, and Penicillin on August 30-Sept 9, 2001.

Comments: The patient may have had a pregnancy that she terminated. However, without further information, a pregnancy is speculative.

8.3.3 Conclusions

There were no confirmed pregnancies on treatment. Therefore the pregnancy rate using either the Pearl Index or life table method was 0. According to an analysis by the FDA statistical reviewer, the upper bound of the 95% confidence interval of the Pearl Index for women who were less than 36 years old at baseline, using only months when no barrier contraception was used, was 0.25.

Table 12 shows the Applicant's analysis of the Pearl Index with the upper bound of the 95% confidence interval for other subgroups. This table was a response to an FDA request to provide the Pearl Index and upper 95% C.I. for women 35 years old and younger at baseline, using treatment cycles in which no other contraceptive methods were used. The Applicant's responded with a slightly different age cut than that requested (< than 35 years old at baseline, instead of \leq 35 years old at baseline), and did the analysis only for cycles in which intercourse was recorded. Using either the FDA's or the Applicant's analysis provides the same conclusion: DMPA-SC is effective for the prevention of pregnancy.

Table 12. Upper Bound of 95% Confidence Interval for Pearl Index for Total ITT Group and Selected Subsets

Group	Pearl Index	All Months	Upper Limit of 95% Confidence Interval for Pearl Index**	Months with intercourse and no barrier use***	Upper Limit of 95% Confidence Interval for Pearl Index** using months with intercourse and no barrier use
Total ITT group	0	20,607	0.17	17,528	0.21
Women under 35 years old at start of study	0	15,888	0.27	13,290	0.27
BMI (kg/m ²):					
• ≤ 25	0	13,365	0.27	11,486	0.32
• > 25 to ≤ 30	0	4,683	0.77	3,974	0.90
• > 30	0	2,532	1.42	2,049	1.75

* Pearl Index is the number of pregnancies per 100 women-years.

** Based on probability of a rare event, where 0 events are observed in a sample of size n cycles.

*** Subjects were to note monthly whether they had had sexual intercourse and if they had used a barrier contraceptive (for example, condom or diaphragm), and if so, how often (every time or sometimes).

Source: Modified from Applicant's response to FDA request, response dated October 29, 2003, filed as NDA 21-583/ N000/BZ in folder labeled "pearl events"

8.4 Supportive Studies for Efficacy

Endometriosis Studies 268 and 270 provided pregnancy data. Women in these studies received the same dose of DMPA-SC as women in the contraception studies. The treatment phase of these studies lasted 6 months. Pregnancy testing was done monthly. A total of 289 women received DMPA-SC, with most women (248) receiving 2 injections.

A single pregnancy was detected on treatment (Study 268). The case history follows:

Patient ID 34921-00093: A 23 year-old woman had her first injection on 28-Oct-2001. She had negative pregnancy tests on 09-Nov-2001 and 07-Dec 2001, and then a positive test on 07-Jan-2001. By ultrasound her estimated date of conception was 18-Dec-2001. She electively terminated the pregnancy. Her BMI at baseline was 21.9 kg/m². She did not take CYP3A4 inducers, but did take Aspirin, ibuprofen, lysine, Oscal, Tylenol and Vagisil during the study.

Comment: A single pregnancy in the endometriosis studies supports efficacy.

It is interesting that the 1 confirmed pregnancy in the endometriosis studies and the 2 speculative pregnancies from the contraception studies were all detected in the first treatment cycle. The first treatment cycle may be the cycle most vulnerable to occurrence of pregnancy because MPA levels may be at their lowest in the first cycle. (See Pharmacokinetics, above.)

Additional supportive data for efficacy came from a 2-year interim report for Study 267BMD, submitted by the Applicant late in the review cycle. (The integrated review of efficacy included 1-year data, but Study 267BMD was a 2-year study and was completed during review of the original NDA data.) 116 subjects in the DMPA-SC arm and 108 subjects in the DMPA-IM arm completed 2 years. There were no pregnancies in the 2-year study in the DMPA-SC arm, and 1 pregnancy in the DMPA-IM arm.

8.5 Efficacy Conclusions

DMPA-SC is highly effective contraception with a Pearl Index of 0. Three Phase 3 contraception studies included an acceptable number of women in different weight, race, and age groups, as well as users of CYP 3A4 inducers.

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