CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-584

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 21-584 SUPPL # HFD # 580

Trade Name depo-subQ provera 104

Generic Name medroxyprogesterone acetate injectable suspension

Applicant Name Pfizer, Inc

Approval Date, If Known March 25, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505 (b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 20-246 Depo-Provera (medroxyprogesterone injectable suspension), 150 mg/ml

NDA# 20-583 depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension), 104 mg/0.65 ml

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary

for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

1. Study # 268
2. Study # 270

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

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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

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

Study # 268
Study # 270

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

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

Investigation #1		!
		!
IND # 61,389	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 61389	YES ☒	! NO ☐
		! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Nenita Crisostomo, R.N.
Title: Regulatory Health Project Manager
Date: March 24, 2005

Name of Office/Division Director signing form: Donna Griebel, M.D.

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Donna Griebel
3/25/05 11:17:12 AM

DEPOT MEDROXYPROGESTERONE ACETATE SUBCUTANEOUS INJECTION (DMPA-SC) NDA #21-584 CLAIM FOR EXCLUSIVITY UNDER 21 CFR §314.108(B)(4)

The following information is provided in accordance with 21 CFR §314.50(j) and 21 CFR §314.108:

1. Pharmacia & Upjohn Company* is claiming three (3) years of exclusivity for DMPA-SC (medroxyprogesterone acetate injectable suspension).

2. 21 CFR §314.108(b)(4) supports the exclusivity claimed by Pharmacia & Upjohn.

3. Pharmacia & Upjohn sponsored and conducted clinical investigations (Protocols 839-FEH-0012-268 and 839-FEH-0012-270) from March 2001 through August 2003. Study 268 was conducted under IND 61,389. Pharmacia & Upjohn Company believes these studies are "essential" for the approval of NDA 21-584 as defined in 21 CFR §314.108(a). Pharmacia & Upjohn Company certifies that to the best of our knowledge, the clinical investigations described in NDA 21-584 meet the definition of "new clinical investigations" defined in 21 CFR §314.108(a).

4. Pharmacia & Upjohn believes there are not sufficient studies published or publicly available to support the approval of this NDA for DMPA-SC. Pharmacia & Upjohn certifies that a scientific literature search ahs been conducted. The results o f the search did not provide any published studies or publicly available reports of clinical investigations that are relevant to the conditions for which Pharmacia& Upjohn is seeking approval.

Pharmacia & Upjohn Company

By: _____

Title: Associate Director

Date: 12/3/03

*Pharmacia & Upjohn Company is a wholly owned subsidiary of Pfizer, Inc.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-584 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: January 28, 2005 Action Date: March 25, 2005

HFD 580 Trade and generic names/dosage form: depo-subQ provera 104™ (medroxyprogestreone acetate injectable suspension)

Applicant: Pfizer, Inc Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: the management of endometriosis-associated pain

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection C: Deferred Studies

Age/weight range being deferred:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

›n D: Completed Studies

Age/weight range of completed studies:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Project Manager

cc: **NDA 21-584**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ɔn D: Completed Studies

Age/weight range of completed studies:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Nenita Crisostomo, R.N.
Regulatory Project Manager

cc: NDA 21-584
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Nenita Crisostomo
3/25/05 10:19:22 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-584 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** ___

Stamp Date: December 18, 2003 **Action Date:** October 18, 2004

HFD 580 **Trade and generic names/dosage form:** _ — (depot medroxyprogesterone acetate) subcutaneous injection

Applicant: Pfizer, Inc. **Therapeutic Class:** 5s

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Endometriosis

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

Cc: NDA 21-584
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-5940-7337.

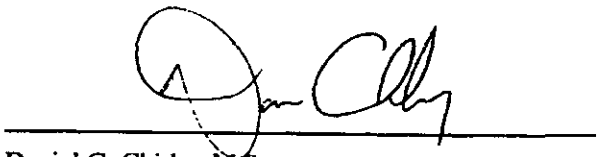
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Kober
2/19/04 10:10:13 AM

DEBARMENT CERTIFICATION FOR
Depot Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC)
NDA 21-584

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.



12/3/03

Daniel G. Chirby, M.Sc.
Associate Director
Pfizer Global Research and Development
Regulatory Affairs

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-584	Efficacy Supplement Type SE-	Supplement Number	
Drug: depo-subQ provera 104™		Applicant: Pfizer, Inc.	
RPM: Nenita Crisostomo, R.N. and Archana Reddy		HFD-580	Phone # 301-827-7260

Application Type: **(X)** 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	3S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	March 28, 2005
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4673
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No

• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "No," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	( ) Yes ( ) No

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	yes, see Exclusivity Summary 3/25/05
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	February 26, 2004

Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Approvable, October 17, 2004
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	none generated after 3/23/05 of PI & 3/25/05 PPI submissions by applicant
• Most recent applicant-proposed labeling	PI—March 23, 2005 PPI—March 25, 2005
• Original applicant-proposed labeling	December 30, 2003 January 27, 2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• DDMAC	August 12, 2004
• DMETS	March 19, 2004 June 22, 2004 July 2, 2004 December 21, 2004 February 25, 2005
• DSRCS	June 14, 2004 February 16, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	January 27, 2005
• Reviews	See CMC review, March 3, 2005
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	December 30, 2003 February 17, 2004 February 20, 2004 April 9, 2004 July 1, 2004 July 14, 2004 August 20, 2004 September 8, 2004 October 5, 2004 October 5, 2004 October 12, 2004

	December 15, 2004 February 10, 2005 March 3, 2005
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	October 2, 2000
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Type C: September 22, 2004 Type C: January 26, 2005
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Summary Reviews (e.g., *Office Director, Division Director, Medical Team Leader) (indicate date for each review)*	TL—March 25, 2005
❖ Clinical review(s) *(indicate date for each review)*	October 18, 2004 March 24, 2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review 3/18/05 & 3/24/05
Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	February 19, 2004 March 25, 2005
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	October 18, 2004 March 15, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	October 18, 2004 March 24, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	September 15, 2004
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	October 15, 2004 March 3, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	CMC review, 3/3/05, pg
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	April 2, 2004
Facilities inspection (provide EER report)	Date completed: 9/17/04 (X) Acceptable

	( ) Withhold recommendation
Methods validation—requested upon approval	( ) Completed (X) Requested ( ) Not yet requested
[redacted]	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 1, 2004 March 10, 2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 21-584	Efficacy Supplement Type SE-	Supplement Number: N/A	
Drug: medroxyprogesterone acetate		Applicant: Pfizer, Inc.	
RPM: Archana Reddy, M.P.H.		HFD-580	Phone # 7-7514

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	5s
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 18,2004
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4673
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify)
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (Project Manager, 2.26.04)

❖ Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC/08.12.04, DMETS/07.02/04/03.19.04, DSRCS/06.14.04))
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	
Minutes of Meetings	
• EOP2 meeting (indicate date)	X (October 2, 2004)
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
❖ Clinical review(s) *(indicate date for each review)*	X (10.12.04)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (See Medical Officer's Review)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X (10.12.04)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (10.12.04)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	X (10.15.04)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (10.15.04)
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (4.02.04)
❖ Facilities inspection (provide EER report)	Date completed: 2/18/04 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (3.01.04)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	X

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-584

Pfizer, Inc.
Attention: Jennifer Bingaman
Manager, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Bingaman:

Please refer to your December 17, 2003, new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for depo-subQprovera 104 (medroxyprogesterone acetate injectable suspension). We also refer to our Approvable letter to you dated October 18, 2004.

We acknowledge receipt on January 28, 2005, of your January 27, 2005, resubmission to your new drug application for Medroxyprogesterone Acetate Injection (104 mg/0.65 mL).

We consider this a complete, class 1 response to our October 18, 2004, action letter. Therefore, the user fee goal date is March 28, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, please call me at (301) 827-7260.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Nenita Crisostomo
3/3/05 02:07:20 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 14, 2005

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Nenita Crisostomo, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review #2 of Patient Labeling for depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension, USP), NDA 21-584

Summary
The sponsor submitted a complete response including safety update information and revised labeling, on January 27, 2005, in response to their October 18, 2004, Approvable Letter for depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension, USP), NDA 21-584.

Please also refer to the June 14, 2004, DSRCS consult for the Patient Package Insert (PPI).

Comments and Recommendations
We have the following suggested revisions to our June 14, 2004, PPI consult:

1. Incorporate the Heading, **"What is the most important information I should know about depo-subQ provera 104?"** and the language from the proposed PPI Boxed Warning. Patients do not comprehend the importance of a Boxed or Bolded Warning with appropriate contextual information.

"What is the most important information I should know about depo-subQ provera 104?

Use of depo-subQ provera 104 may cause you to lose calcium stored in your bones. The longer you use depo-subQ provera 104 the more calcium you are likely to lose. The calcium may not return completely once you stop using depo-subQ provera 104.

Loss of calcium may cause weak, porous bones (osteoporosis) that could increase the risk that your bones might break, especially after menopause. It is not known whether your risk of developing osteoporosis may be greater if you are a teenager when you start to use depo-subQ provera 104.

You should use depo-subQ provera 104 long-term (for example, more than 2 years) only if other treatments are not right for you."

2. Under the heading, **"What are the side effects of depo-subQ provera 104?"**, add the sentence "

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

/s/

Jeanine Best
2/14/05 09:13:51 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/16/05 10:13:02 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-584

Pfizer, Inc.
Attention: Jennifer Bingaman
Manager, Worldwide Regulatory Strategy
235 East 42nd Street
150/7/9
New York, NY 10017

Dear Ms. Bingaman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for medroxyprogesterone acetate.

We also refer to your October 29, 2004 correspondence, containing a request for clarification of our October 18, 2004, approvable letter for medroxyprogesterone acetate. We have reviewed the referenced material and have the following comments and recommendations.

Question 3: (Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.): Amendment 3 submitted April 1, 2004 and Amendment 10 submitted August 31, 2004 addressed the early discontinuation by patients during studies 268/270. Will a confirmation that this is complete suffice?

DRUDP Response: Yes, the two amendments previously submitted will suffice for Studies 268 and 270, because those studies were complete at the time of review.

Question 4: (Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.): We carried the approach as agreed during the pre-NDA review for NDA 21-583 (July 15, 2002) whereby an exemption was allowed not to submit case report forms (CRFs) and narratives for discontinuations due to adverse events that did not result in death or were not serious. Is this approach satisfactory?

DRUDP Response: We would like case report forms (CRFs) and narrative summaries for each patient who died during an endometriosis clinical study or who did not complete an endometriosis study because of an adverse event, regardless of the severity of the adverse event, if the results from the study were not previously reported to the Division (i.e., all clinical endometriosis studies other than Studies 268 and 270). For those studies in which medroxyprogesterone acetate 104 mg SC is being studied for the indication of contraception, we will continue to require CRFs and narratives only for discontinuations due to adverse events that

resulted in death or were serious. However, we reserve the right to request CRFs for other subjects based upon our review of the submission.

Question 6: Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. The subcutaneous dosage form is not yet approved in any other market. Please confirm that this question is specific to this dosage form.

DRUDP Response: We agree that, as the subcutaneous formulation is not marketed anywhere in the world, data on worldwide safety are not required.

Question 7: (Provide English translations of current approved foreign labeling not previously submitted.): Is this question specific to this dosage form? If referring to intramuscular (IM) route of administration, would labeling from major countries suffice (in addition to the Canadian label already sent for the IM)?

DRUDP Response: Yes, English translations of the IM formulation labeling from major countries would suffice.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Donna Griebel
2/10/05 03:03:23 PM

TELECONFERENCE MINUTES

Date: January 26, 2005 **Time:** 3:00 – 3:05 P.M. **Location:** Conf. Rm. 17B43

NDA: 21-584

Drug: Medroxyprogesterone acetate

Sponsor: Pfizer, Inc.

Indication: Endometriosis

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

External Participant Lead: Jennifer Bingaman

Type of Meeting: Type C (Guidance)

Participants:

FDA Participants:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jean Salemme, Ph.D., Review Chemist, DNDC II @ DRUDP (HFD-580)
Nita Crisostomo, R.N., Regulatory Project Manager, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)

Pfizer, Inc.:
Jennifer Bingaman, Manager, Worldwide Regulatory Strategy
Lisha Cole, Worldwide Regulatory Strategy
Scott Tennyson, Pfizer Global Manufacturing
Sushma Gupta, Pfizer Global Manufacturing

Background:
The sponsor submitted a bundled CBE-30 chemistry manufacturing and controls supplement on December 21, 2004 to provide for the following changes.

Facility floor diagrams have been updated to reflect changes in several rooms within the — The changes include:

Meeting Objective:
Pfizer would like to include these changes in the resubmission of the "approvable" NDA 21-584 without affecting the review clock and requested FDA to confirm it.

Discussion:
Two options were discussed with the sponsor:

1) Option 1
   The sponsor can submit the CMC changes along with their resubmission, but the review clock would be six months for the resubmission.
2) Option 2
   The sponsor can submit only the requested information as outlined in the Division's approvable letter. The review clock would be two months for the resubmission. The CMC changes can be submitted post-approval as a CBE-30 supplement.

Decision Reached:
The sponsor will submit the only the labeling and other requested information to their resubmission for their pending NDA 21-584. The sponsor will submit CMC changes post-approval as a CBE-30 chemistry supplement.

Signature: Meeting Chair
See appended electronic signature page
Moo-Jhong Rhee, Ph.D.

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

/s/

Archana Reddy
2/1/05 12:49:07 PM
CSO

Moo-Jhong Rhee
2/1/05 12:54:36 PM
CHEMIST

MaizeFrom: Toyer, Denise P
Sent: Tuesday, December 14, 2004 5:20 PM
To: Williamson, Charlene; Holquist, Carol A; Shames, Daniel A
Cc: Hoppes, Charles V; Mahmud, Alina; Hubbard, Lisa; Beam, Sammie
Subject: NDA 21-583 and NDA 21-584

Dr. Shames,

This e-mail is in response to a request from Charlene Williamson, in your Division regarding the proposed proprietary name Depo-subQ Provera 104. As noted in our proprietary name review (04-0012) and the meeting with the Division on November 5, 2004, DMETS found the use of any modifier — at the end of the Depo-Provera name unacceptable. Postmarketing evidence has shown that these modifiers may be omitted, during prescribing, resulting in medication errors (e.g., Depo Provera could be administered in lieu of —. A discussion ensued at the aforementioned meeting and the proposal to use a modifier in the middle of the name, Depo subQ Provera, was proposed. Although DMETS did not review this proposed name for any orthographic or phonetic similarities due to time constraints, we felt this proposal was more acceptable than the alternatives previously proposed. A subsequent e-mail which provided two different 'visual' presentations of the proposed name, was received by DMETS on November 17, 2004 and our preference was forwarded by to DRUDP. Several additional label comments were also provided at that time.

This e-mail serves as DMETS response to DRUDP's request for a proprietary name review for Depo-subQ Provera 104.

Please feel free to contact us if you need further assistance.

Thanks
Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors
and Technical Support
Office of Drug Safety
HFD-420, Room 6-34 Parklawn
301-827-7609
301-443-9664 (Fax)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 6 2004

Valdir Tadini, M.D.
Hospital e Maternidade Leonor
Av. Celso Garcia 2477
São Paulo- SP- Brazil

Dear Dr. Tadini:

Between August 16 and 20, 2004, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation: Protocol # 839-FEH-0012-270 entitled: "Depot medroxyprogesterone acetate vs. leuprolide acetate subcutaneous injection for reduction of endometriosis-associated pain in European and Asian women. A Phase III, randomized, parallel group, multinational, multicenter study including assessments of bone mineral density and coagulation and lipid profiles sub-studies", performed for Pfizer.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Martinez presented and discussed with you and your staff Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan (21 CFR 312.60).

   a) You did not report in the case report form all concomitant medications for subject #043 and #045 as required by the protocol.

   b) The protocol specified reporting of SAE within 24 hours with a follow-up report within 5 calendar days. You did not report to the sponsor a serious adverse event for subject #043 until approximately 4 months after the event occurred.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

FEI: 3004474433
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__x__2)VAI- no response required
_____3)VAI- response received and reviewed
_____4)OAI

Deficiencies noted:
__x__failure to notify Sponsor of SAE in timely matter
__x__failure to report all concomitant medication

cc:
HFA-224
HFD-580/Doc.Rm./NDA 21-584
HFD-580/MO/Willett
HFD-580/PM/Reddy
HFD-46/c/r/s/ GCP File # 11311
HFD-46/Carreras/Blay
HFD-46/Khin
HFR-SW150/DIB/Thornburg
HFR-SW1540/ BIMO Monitor/Field Investigator/Martinez

r/d:JAC) 11/30/04
reviewed:NK) 11/30/04
f/t:JAU: 12/1/04

O:\JAC\GCP1\21-584Tadini.letter

Reviewer Note to Rev. Div. M.O.

This investigator enrolled 23 subjects in the study. The field investigator examined 14 out of the 23 subjects enrolled. All subjects signed informed consent prior to receiving test medications. Data audit did not reveal any clinical significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable.

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

/s/

Ni Aye Khin
12/15/04 03:38:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Dale Sundwall, M.D.
Physicians Research Options, LC
10011 S. Centennial Parkway, Suite 350
Sandy, Utah 84070

Dear Dr. Sundwall:

Between April 7 and 15, 2004, Mr. Thaddeus Steinke and Ms. Ginger Sykes, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigation:

> Protocol #839-FEH-0012-268 entitled: "Phase III Study of Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC) in Women with Endometriosis in the United States and Canada", of the investigational drug, medroxyprogesterone, performed for Pfizer.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Mr. Steinke presented and discussed with you, Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated May 6, 2004, and wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

   a. The following subjects did not meet protocol-specified inclusion criteria but were randomized to the study:

      i. Subject 035 did not have a documented diagnosis of endometriosis

      ii. Subject 0225 had a pelvic pain score of less than 2

      iii. Subject 025 had a dyspareunia pain score of less than 2.

   b. The following study-related procedures were not conducted in compliance with the protocol:

      i. Subjects 035 and 036 were randomized to treatment during the first menstrual cycle after screening, not the second cycle

      ii. Subject 035 was randomized to treatment on day 6 of her menstrual cycle, not within the first five days of the cycle

iii. Subject 0260 was randomized to treatment 12 days after her previous menstrual cycle, not within the first five days of her next menstrual cycle

iv. Subjects 025 and 036 did not have DEXA scans performed at months 6 and 12

v. Visit 2 for subject 035 was 47 days after visit 1, not 27-33 days after visit 1.

vi. The protocol specifies that that the test article is to be administered subcutaneously into the abdomen or thigh. Subject 0273 was injected with the test article intramuscularly into the left deltoid muscle rather than subcutaneously into the thigh or abdomen. This subject later received the second administration of the test article intramuscularly in the right thigh.

vii. Serum samples from subjects 020 and 025 were shipped at ambient temperature, not frozen

2. You did not maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].

   a. For subject 0111, pelvic pain is noted as severe in the source document but "N/A" in the Case Report Form (CRF).

   b. Each of subjects 036 and 011 had two sets of diaries for the same time periods which contained conflicting information.

      i. Subject 036 had two diaries for the period of August 4-31, 2002. For August 24, 2002, one version of the diary on page 201 has a value of "NA" for dyspareunia while another version of the diary on page 280 has a value of "3" for dyspareunia.

      ii. Subject 0111 had two diaries for the period of October 24-27, 2001. For October 27, 2001, one version of the diary on page 121 has a value of "3" for dyspareunia while another version of the diary on page 147 has a value of "NA".

   c. Documentation of the use of concomitant medications is inadequate.

      i. Subject 0225 noted the use of opioids/analgesics in her diary, but this information is not recorded in source documents and the CRF.

      ii. The CRF notes stop dates for the use of concomitant medications (Lortab and Allegra) for subject 025 but this information is not recorded in the source documents.

      iii. Subject 036 noted the use of Tylenol in her diary but this information is not recorded in the source documents and the CRF.

iv. Subject 0260 noted the use of Tylenol with codeine in her diary but this information is not recorded in the source documents and the CRF.

d. Source documentation of the physical examinations of subject 0225 at baseline and month 6 with respect to categories such as "chest", "heart", "lungs", abdomen", and "extremities" is not recorded.

e. Drug dispensation records for subjects 020, 025, 035, and 036 were not completed in a contemporaneous manner and are inadequate to document the route and site of administration of the test article.

f. Subject 025 experienced sinus infection and bacterial vaginosis, and subject 036 experienced acne and pelvic pain. Source documents for these subjects do not indicate whether the adverse events are related to treatment with the test article.

g. Subject 0260 experienced severe nausea and seasonal allergies. Source documents do not indicate whether the nausea and allergies stopped or continued. The CRF states that the nausea stopped on June 1, 2002, and that allergies were ongoing.

We trust that the actions described in your letter will provide adequate measures to bring your site into compliance with FDA regulations. We will keep this and all related correspondence on file for future reference.

We wish to remind you that as the clinical investigator, it is your general responsibility to conduct clinical studies according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of subjects under your care.

We appreciate the cooperation shown Investigator Steinke and Sykes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

Ni A. Khin, M.D.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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

/s/

Ni Aye Khin
10/12/04 09:03:58 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT - 4 2004

Carlos Isaia Filho, M.D.
Centro de Medicina Reproductiva
Rua Padre Chagas 66/704
90570-080, Porto Alegre-RS, Brazil

Dear Dr. Filho

Between August 9 and 13, 2004, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation:

> Protocol # 839-FEH-0012-270 entitled: "Depot medroxyprogesterone acetate vs. leuprolide acetate subcutaneous injection for reduction of endometriosis-associated pain in European and Asian women. A Phase III, randomized, parallel group, multinational, multicenter study including assessments of bone mineral density and coagulation and lipid profiles sub-studies", conducted for Pfizer.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, and the documents submitted with that report, we conclude that, except for minor record keeping discrepancies, you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Ni A. Khin, M.D.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004474424
Field Classification: NAI

Headquarters Classification:
_x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm./NDA 21-584
HFD-580/MO/Willett
HFD-580/PM/Reddy
HFD-46/c/r/s/ GCP File # 011297
HFD-46/Blay
HFD-46/Khin
HFR-SW150/DIB/Thornburg
HFR-SW1540/ BIMO Monitor/Field Investigator/Martinez
HFR-SW140/DCB/Rodriguez
HFC-134/Kadar
GCF-1 Seth Ray

r/d:rab/

C:\data\royblay\nai letters\filho.doc
O:\blay\filho.doc

Reviewer's Note to Review Division's Medical Officer

24 subjects were enrolled at this site with 21 completing the study, three withdrawals, and no reports of serious adverse events. 17 of 24 subject files were reviewed, including, but not limited to, case report forms, source documents, consent forms, drug accountability, adverse event reporting, concomitant medications, and study correspondence. The data generated by this clinical site in support of the respective application appears acceptable.

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

/s/

Ni Aye Khin
10/5/04 09:18:40 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: October 5, 2004

To: Daniel Chirby, M.Sc. Associate Director, Worldwide Regulatory Strategy	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 734-622-2856	**Fax number:** 301-827-4267
Phone number: 734-622-3750	**Phone number:** 301-827-7514

Subject: Fax of information requests for your pending NDA 21-584 (DMPA)

Total no. of pages including cover: 2

Comments:

Mr. Chirby,

Please respond to the attached information requests by October 8, 2004. If there are any questions, you can call me at 301-827-7514.

Archana Reddy

Document to be mailed: ☐ YES ☑ NO

NDA: 21-584
Drug: Depot Medroxyprogesterone Acetate
Sponsor: Pfizer, Inc.

To facilitate our review of your NDA 21-584, we request that you provide the following information.

1. Provide any information that you may have concerning the Biberoglu and Behrman (B & B) scores in the study comparing placebo control to Lupron described in the 1990 Lupron NDA that was referenced in your letter to FDA dated February 23, 2001. More specifically, we would like you to provide, if available, a listing by treatment and by subject of the monthly B & B scores. If possible, we also request that you analyze these data by responder analysis using the same criteria that you employed for your analyses of Studies 268 and 270.

2. Provide a last observation carried forward (LOCF) analysis for the data represented in Tables T5.7-5.8 (Study 268) and Tables T5.7-5.8 (Study 270). In this analysis, calculate the mean (SD) change from baseline using both the observed data and the LOCF for missing values. Provide the results of the reanalyses in the same format. Only data through the end of treatment (Month 6) need to be provided.

3. We have noted a discrepancy in the sample size for the measurement of induration, compared to the sample size for pelvic tenderness (Table 10 [Final Report for Study 268] and Table 11 [final Report for Study 270]). The numbers of subjects for the category of induration in both the ITT-OC and the ITT-LOCF analyses are lower than those for the category of pelvic tenderness. We believe that this is an error since both of these parameters (induration and pelvic tenderness) would have been assessed during the same pelvic examination. Also, the numbers for induration differ in Study 268 between Tables T5.12.1, and Tables T5.2 and T5.8, and in Study 270 between Tables T5.12.1, and Tables T5.2 and T5.8.

4. During the Agency's on-going review of NDA 21-584, the Division of Scientific Integrity conducted an inspection of Dr. Sundwall's site, which enrolled 18 subjects in Study 268. A detailed review of records from 6 of the 18 subjects was conducted. This review raised questions about the quality of the data. Due to these questions, we ask that you provide us with several reanalyses of the efficacy data excluding subjects from this site. The requested reanalyses, based on the Final Report for Study 268 are:

   - Tables 10-18
   - Tables T5.7-5.8

   Provide any other significant efficacy analyses that we may have overlooked that would be impacted by excluding subjects from this site.

We request that you provide your response by COB on October 8, 2004. Provide a desk copy of your response by e-mail to both Ms. Reddy (reddya@cder.fda.gov) and Dr. Soule (soulel@cder.fda.gov).

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

/s/

Archana Reddy
10/5/04 10:57:34 AM
CSO

TELECONFERENCE MINUTES

Date: September 22, 2004 **Time:** 9:15 – 10:00 A.M. **Location:** Conf. Rm. 17B43

NDA: 21-584/21-583

Drug: Medroxyprogesterone acetate

Sponsor: Pfizer, Inc.

Indication: Endometriosis/Contraception

Meeting Chair: Ameeta Parekh, Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

External Participant Lead: Daniel Chirby, M.Sc.

Type of Meeting: Type C (Guidance)

Participants:

FDA Participants:
Scott Monroe, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Lisa Soule, M.D., Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Myong-Jin Kim, Pharm.D., Clinical Pharmacology/Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)

Pfizer, Inc.:
Daniel Chirby, M.Sc., Associate Director, Regulatory Affairs
Barry Jones, Senior Director/*In-Vitro* Sciences
Lynn Purkins, Clinical Kineticist

Meeting Objective:
The sponsor requested this teleconference to discuss the pending Phase 4 commitment for NDA 21-583 and for NDA 21-584. The sponsor was requested to undertake an *in-vitro* metabolism study as a Phase 4 commitment. The sponsor submitted additional review of the literature pertaining to the potential effect of drug inducers on medroxyprogesterone following subcutaneous injection.

Discussion:

Clinical Pharmacology and Biopharmaceutics Comments:

- The sponsor was advised to characterize the metabolic pathways of medroxyprogesterone and address the drug interaction potential in the label. On July 15, 2004, the sponsor had agreed to undertake an *in-vitro* metabolism study as a Phase 4 commitment.
- However, the sponsor requested the Agency to reconsider this commitment by submitting the additional review of literature pertaining to potential effect of drug inducers on medroxyprogesterone following subcutaneous injection.
- The sponsor provided the literature data to suggest that CYP3A4 appears to be one of the metabolic pathways of medroxyprogesterone. The sponsor also provided documentation to support that the induction of medroxyprogesterone is more likely with oral administration and less likely with subcutaneous administration.
- Although we agree with this scientific basis, drug interaction potential will be appropriately addressed in the label. Once this justification is submitted to NDA 21-583 and NDA 21-584, the Phase 4 commitment will be satisfied and no further studies will be recommended.

Other Comments:
A general discussion of the labeling took place. The sponsor intends to pursue a combined label for endometriosis and contraception.

Decision Reached:
The sponsor will submit the literature information to NDA 21-583 and cross-reference NDA 21-584 for medroxyprogesterone acetate, in order to satisfy the Phase 4 commitment.

Signature: Meeting Chair
See appended electronic signature page
Ameeta Parekh, Ph.D.

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

/s/

Archana Reddy
10/18/04 12:30:04 PM
CSO

Ameeta Parekh
10/18/04 03:35:24 PM
BIOPHARMACEUTICS

6 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 8, 2004

To: Daniel Chirby, M.Sc. Associate Director, Worldwide Regulatory Strategy	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 734-622-2856	**Fax number:** 301-827-4267
Phone number: 734-622-3750	**Phone number:** 301-827-7514

Subject: Fax of information requests for your pending NDA 21-584 (DMPA)

Total no. of pages including cover: 2

Comments:

Mr. Chirby,

Please respond to the attached information requests. If there are any questions, you can call me at 301-827-7514.

Archana Reddy

Document to be mailed: • YES ☑ NO

NDA: 21-584
Drug: Depot Medroxyprogesterone Acetate
Sponsor: Pfizer, Inc.

To facilitate our review of your NDA 21-584, we request that you provide the following information.

1. A list of foreign countries in which medroxyprogesterone acetate is approved for endometriosis.
2. The dose, route of administration, and duration of treatment for this indication.
3. A copy of an English-language label for one of these countries where DMPA is approved for endometriosis.

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

/s/

Archana Reddy
9/8/04 02:00:45 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: August 20, 2004

To: Daniel Chirby, M.Sc. Associate Director, Worldwide Regulatory Strategy	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 734-622-2856	**Fax number:** 301-827-4267
Phone number: 734-622-3750	**Phone number:** 301-827-7514

Subject: Fax of clinical information requests for your pending NDA 21-584 (DMPA)

Total no. of pages including cover: 4

Comments:

Mr. Chirby,

Please respond to the attached clinical information requests by August 27, 2004. If there are any questions, you can call me at 301-827-7514.

Archana Reddy

Document to be mailed: • YES ☑ NO

NDA: 21-584
Drug: Depot Medroxyprogesterone Acetate
Sponsor: Pfizer, Inc.

To facilitate our review of your NDA 21-584, we request that you provide the following information no later than August 27, 2004.

1. Efficacy Analyses and Populations Analyzed

   We note that the criteria for demonstrating non-inferiority of DMPA-SC compared to leuprolide are not met in Study 268 when the analysis is based on the ITT-LOCF population. This finding is discrepant with the finding based on the ITT-OC population, and with the findings in Study 270. The initial statistical analysis plan for Study 268 noted that the ITT-LOCF would be the primary analysis; an amendment from March 2001 notes that both ITT-LOCF and ITT-OC analyses would be conducted and consistency between the analyses would be explored. The statistical analysis plan for Study 270 continues to describe the ITT-LOCF population as that to be used in the primary analysis.

   Provide the following information regarding the efficacy analyses and populations analyzed:
   a. Your explanation for the difference in outcomes in Study 268 when the primary efficacy analysis is based on the ITT-LOCF and the IT-OC populations, respectively.
   b. Your justification for using the ITT-OC population for the primary efficacy analysis in Study 268.
   c. The documentation (e.g., protocol amendments, communications/agreements with the Division) supporting your using the ITT-OC population for the primary efficacy analyses in Study 268.
   d. The rationale for what appears to be a difference in your selection of the primary efficacy population for Study 268 (ITT-OC population) and Study 270 (ITT-LOCF population).

2. Change in (Serious Adverse Event) SAE Count and Treatment-Relatedness

   In the updated study report for Study 268 dated February 27, 2004, we note two changes in the SAE section:
   a. Subject 264 is no longer counted as experiencing SAEs in both the treatment and follow-up phases; she is counted only in the follow-up period. Since her initial evaluation for the event occurred at the 6-month visit, provide justification for removing her from the treatment-phase SAEs.
   b. Subject 167 was initially reported to have a treatment-related SAE; in the updated report, the same narrative ends with the conclusion that her SAE is not related to the study medication. Please justify this change.

3. Adverse Events (AEs) Occurring in the Follow-Up Period in Study 268

   In the updated report for Study 268, follow-up AEs (those occurring after the EOT visit) appear to be reported only for those subjects who completed the entire follow-up period. Provide data and analyses, as was done for Study 270, based on all AEs occurring after the EOT visit, regardless of whether the subjects completed the full 12 months of follow-up.

4. Injection Site Reactions

   Provide a more detailed summary/analysis of the adverse events categorized as "injection site reactions" in both studies using a more precise description of the event or a lower level

category term. Also, provide separate analyses of the PSQ results for subjects who reported, and those who did not report, injection site reactions.

5. Lack of Linkage to Tables T16.3.1-T16.3.3

In the updated report for Study 270, the tables reporting results for the PSQ do not appear to be hyperlinked to the body of the report and do not appear to be included in the Final Tables section. Although we anticipate that these tables would remain unchanged from those in the initial study report, we request that you provide these tables in the updated study report.

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

/s/

Archana Reddy
8/20/04 12:07:04 PM
CSO

6 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

4 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-583
NDA 21-584

ADVICE LETTER

Pfizer, Inc.
Attention: Daniel Chirby, M.Sc.
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Mr. Chirby:

Please refer to your June 30, 2003 and December 17, 2003, new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for medroxyprogesterone acetate injectable suspension, USP.

We also refer to your submission dated May 20, 2004, proposing two proprietary names, "Depo-— and "Depo- —

The Division of Medication Errors and Technical Support (DMETS) has reviewed your submission and recommends against the use of either of the proposed proprietary names because

1) the use of "Depo" has been previously reserved for the intramuscular route of administration and
2) the potential for misinterpretation of the modifier —

The Division of Reproductive and Urologic Drug Products (DRUDP) also recommends against use of the modifier — because the incidence of adverse events (e.g., weight gain and decrease in bone mineral density) is not significantly lower than that observed with Depo-Provera Intramuscular Injection.

However, DRUDP is not opposed to your use of the modifier "Depo" and suggests that "Depo-SubQ-Provera (medroxyprogesterone acetate injectable suspension, USP) Injection" would be an acceptable alternative proprietary name for this product.

We are willing to discuss this further, if needed. If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Jennifer L. Mercier
7/14/04 04:35:16 PM
for Margaret Kober

Stephen Gordon, M.D.
Comprehensive NeuroScience Inc.
6065 Roswell Road, Suite 820
Atlanta, Georgia 30328

Dear Dr. Gordon:

Between May 12 and May 17, 2004, Ms. Chateryl Washington, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation:

> Protocol #839-FEH-0012-268 entitled: "Phase III Study of Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC) in Women with Endometriosis in the United States and Canada", conducted for Pharmacia & Upjohn.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Washington during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004488538
Field Classification: NAI

Headquarters Classification:
__x__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-580/Doc.Rm./NDA 21-584
HFD-580/MO/Willett
HFD-580/PM/Reddy
HFD-46/c/r/s/ GCP File # 0814
HFD-46/Blay
HFD-46/Khin
HFR-CE750/DIB/Todd-Murrell
HFR-CE750/BIMO Monitor/Hubbard
HFR-SE150/Field Investigator/Washington
GCF-1 Seth Ray

r/d:rab/

c:\data\royblay\nai letters\gordon.doc
O:\blay\gordon.doc

Reviewer's Note to Review Division's Medical Officer

66 subjects were screened for this study, 53 subjects were screen failures, 13 subjects were enrolled, 11 discontinued prematurely, and two subjects completed the study. The FDA investigator did not issue a Form 483 to the clinical investigator. The inspection report did note that four subjects did not sign consent forms in a timely manner. Review of the various versions of the consent forms revealed that changes to the consent form were minor and would have had little, if any, impact on the willingness of the subjects to consent to the study. The inspection report also noted that diaries were missing for four subjects. For one subject, the diaries for the entire six-month treatment were missing while diaries were missing for specific time intervals for other subjects. The FDA investigator was informed that the diaries were maintained at a firm in Europe and could be shipped for arrival at the site on May 18, 2004; however, the investigator closed the inspection on May 17, 2004, and these diaries were not reviewed. The FDA investigator stated that she reviewed 100% of the source records and compared them with the CRFs. The investigator reviewed all consent forms, adverse event reports, and concomitant medications.

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

/s/

Khin U
7/1/04 03:57:33 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Drug Marketing, Advertising and Communications, HFD-42
Michael Brony, Reviewer

FROM: Archana Reddy, M.P.H., Regulatory Project Manager
DRUDP/HFD-580

DATE: June 22, 2004	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: Revised Labeling	DATE OF DOCUMENT: May 20, 2004 June 3, 2004
NAME OF DRUG: Depo- —— medroxyprogesterone acetate)	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: July 30, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW).

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Request for DDMAC review of the labeling for NDA 21-584 — medroxyprogesterone acetate). The labeling can be found electronically on the EDR. The sponsor is proposing Depo — as the primary tradename and Depo — as the alternate tradename. The PDUFA goal date is October 18, 2004.

Thanks,
Archana Reddy
7-7514

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM: Archana Reddy, M.P.H., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

DATE: June 21, 2004	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: Labeling	DATE OF DOCUMENT: May 20, 2004, June 3, 2004
NAME OF DRUG: Depo — medroxyprogesterone acetate) Depot-Provera Lo SubQ	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: August 20, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Request for Tradename Review
The tradenames — and Depo — ere both rejected by DMETS, and the sponsor has submitted an alternate proposal for tradenames.
The primary proposed tradename is Depo — and the proposed back-up tradename is Depo- —
Please note that the same tradenames are being proposed as for NDA 21-583, which is currently under review by the Division for the contraception indication.
The labeling for this e-CTD NDA application can be found on the EDR. The May 20, 2004 correspondence, containing a proposal for new tradenames, is attached for your review.
PDUFA DATE: October 18, 2004
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 21-584
HFD-580/Division File
HFD-580/Reddy/Rhee/Salemme/Raheja/Reid/Monroe/Willett/Soule/Parekh/Kim/Meaker/Kober/Griebel

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

9 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2004

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Archana Reddy, M.P.H., Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for [TRADEMARK]
(medroxyprogesterone acetate injectable suspension, USP),
NDA 21-584

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for [TRADEMARK] (medroxyprogesterone acetate injectable suspension, USP),
NDA 21-584. We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on labeling dated December 17, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please call us if you have any questions.

5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Jeanine Best
6/14/04 03:31:50 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/14/04 04:13:10 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-583
NDA 21-584

INFORMATION REQUEST LETTER

Pfizer, Inc.
Attention: Daniel Chirby, M.Sc.
Associate Director
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Mr. Chirby:

Please refer to your June 30, and December 17, 2003, new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for medroxyprogesterone acetate injectable suspension.

We also refer to your submission dated January 6, 2004.

The following comments and recommendations regarding your proposed proprietary name are those of the FDA's Division of Medication Errors and Technical Support (DMETS).

Tradename Comments

1. It is not recommended to use the proprietary names "Depo- — and "Depo- — . The primary concerns relate to confusion when spoken and also look similar when written to Depo-Provera® Contraceptive Injection.
2. The names Depo- — and Depo — are phonetically identical except for the — modifier. This modifier might mislead a user into thinking that a lower dose is the only difference between the new Depo-Provera formulation and the old formulation.
3. The new products are intended for an entirely different route of administration. Because of the potential for misinterpretation of the modifying text, ' — , has all of the concerns expressed above regarding the proposed proprietary name, Depo- —

General Labeling Comments

1. Our review of the labeling from a safety perspective has identified several areas of possible improvements that might minimize potential user error. The draft labels and labeling submitted do not include the artwork and font sizes that will be used in the final printed labels and labeling. Therefore, it is not possible to fully assess the safety of the labels and labeling based upon this draft labeling.

2. Due to concerns about confusion between the intramuscular and subcutaneous routes of administration for medroxyprogesterone acetate suspension products in the marketplace, it is recommended that this product be differentiated from Depo-Provera in the following ways.

    - The provision of a short needle intended for subcutaneous administration of the proposed product and additional labeling recommendations may prevent risk of intramuscular administration.
    - Prepare and submit plans for an education campaign to alert practitioners of the new route of administration and new indications.

Container Label (104 mg/0.65ml)

1. Include the product strength in association with the volume (104mg/0.65 ml), beneath the established name on the principal display panel. To prevent confusion of this product with products available for administration by the intramuscular route of administration, it is requested that the route of administration of this product appear with exaggerated prominence on the label.

Carton Label (individual and 24's)

1. Include required labeling information on more than one carton panel. We refer you to 21 CFR 201.15(a)(2) for guidance.

2. It is noted that you have proposed a package size of [redacted]. This size represents a [redacted] supply of the product and therefore would be considered unsuitable for dispensing as such. There may be situations where a package of [redacted], without individual cartons may be warranted, (e.g., a clinic or hospital where the syringes are used "in-house"). However, the availability of this packaging configuration increases the risk that the syringes will be dispensed without adequate patient information. Since the container label itself provides insufficient information, verify that each of the [redacted] will be individually cartooned.

Physician Package Insert

General Comment

The physician package insert submitted for review of NDA 21-584 includes both the endometriosis indication and the contraception indication while labeling submitted for NDA 21-583 includes only the contraception indication. Unless otherwise specified, the comments apply to both version of the insert labeling.

DOSAGE AND ADMINISTRATION section

1. Revise the text, "Instructions for [redacted]" to appear with the same prominence as other subsection headings.

2. Although the instructions for use of this product refer to [redacted]. Please revise and/or comment.

3. Include information regarding injection at a [redacted] angle and the depth of the injection.

4. Provide specific instructions regarding the proper disposal of this device.

5. Include the following statement: "[redacted] should be inspected visually for particulate matter and discoloration prior to administration. [redacted]."

HOW SUPPLIED section

1. We note that this product will be in pre-filled syringes that have been pre-assembled with UltraSafe Passive Needle Guard devices. Assure that the syringe label is in no way obscured by this device and that the label can be easily read.

2. It is noted that [redacted]

3. Include the established name and strength of this product in this section.

If you have any questions, call Charlene Williamson or Archana Reddy, M.Ph., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Jennifer L. Mercier
4/9/04 12:07:40 PM
for Margaret Kober

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-584

Pfizer, Inc.
Attention: Daniel Chirby, M.Sc.
Associate Director
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Chirby:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depot Medroxyprogesterone Acetate Subcutaneous Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 13, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Potential clinical review issues:

   a. There appear to be differences between the relative efficacy of Depot Medroxy Progesterone Acetate-Subcutaneous Injection (DMPA-SC) compared to leuprolide in Study 270 (non-US study) and that in Study 268 (US/Canada). DMPA-SC may not be statistically equivalent to leuprolide for several of the signs/symptoms of endometriosis in one or more analyses in Study 268.

   b. In Study 268 (US/Canada), the percentage of patients who withdrew before completing the 6-month treatment period was higher in the DMPA-SC group (35.3%, 48/136) than in the leuprolide group (26.1%, 36/138).

2. Potential clinical pharmacology and biopharmaceutics review issues:

   a. The accumulation of medroxyprogesterone acetate (MPA) following multi-dose administration.

   b. The effect of injection site (anterior thigh versus abdomen), race, and body weight on the pharmacokinetics of MPA.

c. The relevance of dose-finding studies conducted with any formulation (e.g, Depo-Provera intramuscular formulation given subcutaneously).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. For subjects who terminated prematurely from the Phase 3 clinical trials because of the reason "withdrawal of consent," no additional information was provided in the NDA. Because "withdrawal of consent" is a vague reason and can be due to a variety of underlying reasons, we request that you provide additional information concerning the underlying reason(s) for "withdrawal of consent" for all of these subjects. We recognize that this may require your reviewing source documents to obtain this information because it was not obtained on the Termination Case Report Form (CRF).

2. For each subject who terminated prematurely because of 'withdrawal of consent," provide a listing by subject of all on-going adverse events at the time of their termination from the clinical trial.

3. Provide a copy of the written instructions for completing the study CRFs that were given to the Investigators.

4. Provide the reference for the Hailperin-Ruger adjustment method used for multiple endpoints in Studies 268 and 270 (Section 6.7.1.5 of the Study Report).

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call, Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827 - 4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margaret Kober
2/20/04 03:37:33 PM
Chief, Project Management Staff

NDA: 21-584 (Depo

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	x		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	x		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	x		The dosing selection was based on the appropriate level for ovulation suppression. This dosing level is acceptable clinically for the endometriosis indication.
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	x		Two phase III pivotal trials were performed
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	x		
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	x		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	x		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x	No rationale was submitted. The efficacy appears better in the foreign data This will be a review issue
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division		x	It appears that CRFs for discontinuations for non-serious adverse events were not included. Individual CRFs may be needed as per review.
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	x		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	x		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	x		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	x		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	x		

ITEM	YES	NO	COMMENT
17) Reasons for refusal to file:			

NDA 21-584: Filing Meeting Clinical Comments

Drug: Depo (depo-medroxyprogesterone acetate subcutaneous)
Sponsor: Pharmacia & Upjohn (Pfizer)
Date of submission: December 17, 2003
Dosage: 104mg depo-medroxyprogesterone acetate (subcutaneous injection or DMPA-SC) once every three months
Indication: Management of endometriosis-associated pain

Background:

Medroxyprogesterone acetate is found in a number of approved products for contraception, endometrial protection in combination therapy for menopausal therapy, secondary amenorrhea, dysfunctional uterine bleeding, and adjunctive/palliative treatment for endometrial and renal carcinoma. The dosage forms include both oral tablets and intramuscular injections. This NDA submission is one part of the sponsor's development program for a subcutaneous injection form. The sponsor is seeking both contraceptive and endometriosis indications for this product. The NDA for contraception is 21-583, which was submitted on June 30, 2003.

Medroxyprogesterone acetate has been used off label for endometriosis for over thirty years. One of the standard gynecologic texts stated that it is often the first choice for medical treatment of endometriosis. Side effects include weight gain, fluid retention, breakthrough bleeding and slow return to ovulation.

Priority Review

The sponsor provides the following rationale for its priority review request:

Rationale Summary
The request for priority review of NDA 21-584 is being submitted on the basis that depot medroxyprogesterone acetate subcutaneous injection (DMPA-SC) provides a significant improvement in therapeutic value compared to leuprolide for the treatment of endometriosis -associated pair — The sponsor claims that:

- DMPA-SC for the treatment of endometriosis clinically equivalent to leuprolide and also provides persistent symptomatic relief following treatment. The therapeutic value of DMFA-SC as compared to leuprolide is enhanced due to the fact that it has a safety profile that is superior to leuprolide.

- DMPA-SC is superior to leuprolide with respect to minimizing bone mineral density (BMD) loss, representing a substantial reduction of a treatment-limiting drug reaction without compromising the efficacy in relieving symptoms of endometriosis.

- The tolerability of DMPA-SC is superior to leuprolide in the incidence of hypoestrogenemic symptoms as measured by the Kupperman Index, and in the incidence and severity of reported moderate or severe hot flushes.

- The drug substance MPA has a long history of clinical experience in oral and intramuscular formulations, with a well-established safety profile. DMPA-SC meets an unmet medical need by offering an effective treatment for endometriosis–associated pain — — . DMPA-SC therefore represents a significant advance in the treatment options for this serious gynecologic condition.

- In addition, it is anticipated that FDA's review and assessment will already be completed for the Quality (Module 3) and Nonclinical (Module 4) sections of NDA 21-584, based on the fact that these same data were previously submitted for review under NDA 21-583. This provides additional justification that a more expedited review of NDA 21-584 could be completed.

MAPP 6020.3 defines priority review in the following manner:

> The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased

effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.

Medical officer's comments:* Of *the four components in the MAPP definition, the sponsor's rationale for priority review only pertains to number 2 (elimination or substantial reduction of a treatment-limiting drug reaction). The treatment limiting drug reaction for leuprolide alone pertains to bone loss associated with GnRH agonists. This bone loss restricted use of these products to 6 months of use. However, Lupron with norethindrone acetate 5mg daily (NDA 20-708/s011) is also indicated for initial management of endometriosis and management of recurrence of symptoms. The norethindrone acetate was found to be effective in significantly reducing the loss of bone mineral density associated with Lupron alone.

In NDA 20-708/s011 there was also evidence that norethindrone acetate add-back will decrease the number of vasomotor symptoms induced by Lupron alone.

The sponsor did not compare their product to Lupron plus norethindrone but rather to Lupron alone. In their rationale they do not even specifically mention norethindrone add-back (only mentioned daily oral estrogen add-back). It is this reviewer's opinion that approved treatment regimen of Lupron plus add-back provides similar benefits to DMPA-SC and is presently available to clinicians and their patients.

In the sponsor's rationale presentation following the bulleted items (listed above) they go on to discuss off label use of oral contraceptives for endometriosis. They failed to mention the off label use of oral and intramuscular medroxyprogesterone acetate for endometriosis which has been used for over thirty years. In reality there will be many patients treated with intramuscular or oral medroxyprogesterone off label throughout 2004 for endometriosis. Prioritizing this review on a 6-month clock will not hold back a critically needed product or deprive women of a significant new therapy for endometriosis. Theoretically there is no reason to suspect that the subcutaneous formulation will act significantly better than the current off label practice use of medroxyprogesterone acetate for endometriosis.

Although some of the modules for review (nonclinical) overlap with the previously submitted NDA-583 (DMPA-SC for contraception) there is a significant amount of follow-up data (an additional 6 months of efficacy and safety) which is being submitted at the time of the 4-month safety update. These submissions will require additional review time.

Division of Scientific Investigation (DSI) Consult:

On initial review of the sponsor's study sites, one site in Brazil (Dr. Filho) showed better efficacy in regard to pelvic pain and had a very low number of adverse events compared to

another site in Brazil with an equal number of patients (Dr. Tadini site). DSI was informed of this discrepancy. Dr. Blay from DSI will suggest these two Brazilian sites for inspection along with two US sites (Dr. Sundwall & Dr. Gordon). The US sites recommended were primarily because of the number of subjects studied and their status in regard to prior inspections.

Financial Disclosure

In the financial disclosure Dr. — has the following section checked

7b. Any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

Dr. — , site enrolled two patients and had the average number of edits.

No other potential financial conflicts of interest were noted by the sponsor for the pivotal studies (268 and 270)

Pediatric Waiver:

Endometriosis is not considered a pediatric problem. A full waiver can be granted.

Anticipated review issues:

In the pivotal study #268 (US/Canada) the percentage of patients who withdrew from the study before completing the 6-month treatment period was higher in the DMPA-SC group (35.3%, 48/136) than in the leuprolide group (26.1%, 36/138). In the DMPA-SC group, the most common reason for discontinuation of study medication was withdrawal of consent, which led to discontinuation of treatment in 15.4% (21/136) of patients in the DMPA-SC group and 5.8% (8/138) of patients in the leuprolide group.

Medical officer's comments: The Treatment Termination Report form in CRF does not specify the reason for withdrawal of consent. The sponsor could be asked to submit all the adverse events recorded for those individuals who withdrew consent.

The treatment groups were similar with respect to all baseline and demographic characteristics with the exception of age, which was lower in the DMPA-SC group (mean ± SD, 29.2 ± 6.3 years) than in the leuprolide group (mean ± SD, 32.1 ± 6.6 years). The majority (>80%) of patients were white.

Medical officer's comments: It is possible that with a 4 year age difference the Lupron group could have more women with longer histories of endometriosis

Efficacy Study #268 (US/Canada)

Analysis Group	Results
ITT	Treatment with DMPA-SC was statistically equivalent ($p<0.02$) to treatment with leuprolide at month 6 (end of treatment [EOT]) for the reduction of **4 of the 5** signs/symptoms of endometriosis (dysmenorrhea, dyspareunia, pelvic pain, and pelvic tenderness).
Evaluable patient population	Treatment with DMPA-SC was statistically equivalent ($p<0.02$) to treatment with leuprolide at month 6 (EOT) in the evaluable patient population for the reduction of **3 of the 5** signs/symptoms of endometriosis: dysmenorrhea, pelvic pain, and pelvic tenderness.
ITT (LOCF)	Treatment with DMPA-SC was statistically equivalent ($p<0.02$) to treatment with leuprolide at month 6 (EOT) for the **reduction of pelvic tenderness.** The discrepancy between the results of the ITT and ITT-LOCF analyses may be due to the relatively large number of patients in both treatment groups who withdrew from the study before completing the 6-month treatment period, a larger proportion of which occurred in the DMPA-SC group. The slower time to amenorrhea (and thus, the slower time to improvement in dysmenorrhea) in the DMPA-SC group may also be a contributing factor.

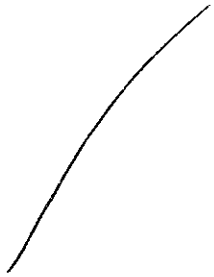
Efficacy Study #270 (Latin America, Europe, Asia)

Analysis Group	Results
ITT Evaluable patient population ITT (LOCF)	**Efficacy Results:** For the ITT population, treatment with DMPA-SC was statistically equivalent ($p<0.02$) to treatment with leuprolide at month 6 in each of the 5 signs/symptoms of endometriosis: dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. The results of the evaluable patient population and ITT-LOCF analyses also demonstrated the equivalence of DMPA-SC and leuprolide.

Medical officer's comments: There will be review issues to evaluate the differences within the analysis groups for study 268 and for the efficacy difference between study 268 and study 270.

Anticipated labeling issues:

After initial review it is felt that the following clinical sections of the label may require deletion or revision:



Endometriosis
[TRADEMARK] is indicated for management of endometriosis-associated pain

Comments to be conveyed to the sponsor in the 74-day letter.

The following items should be conveyed to the sponsor as requested information:

- For subjects who terminated prematurely from the Phase 3 clinical trials because of the reason "withdrawal of consent", no additional information was provided in the NDA. Because "withdrawal of consent" is a vague reason and can be due to a variety of underlying reasons, we request that you provide additional information concerning the underlying reason(s) for "withdrawal of consent" for all of these subjects. We recognize that this may require your reviewing source documents to obtain this information since it was not obtained on the Termination CRF.

- For each subject who terminated prematurely because of 'withdrawal of consent", provide a listing by subject of all on-going adverse events at the time of their termination from the clinical trial.

- Provide a copy of the written instructions for completing the study CRFs that were given to the Investigators.

The following should be conveyed to the sponsor as potential review issues:

- There appears to be a differences between the relative efficacy of DMPA-SC compared to Lupron in Study 270 (non-US study) and that in Study 268 (US study). DMPA-SC may not have been statistically equivalent to Lupron for several of the signs/symptoms of endometriosis in one or more analyses in Study 268.

- In pivotal Study 268 (US/Canada) the percentage of patients who withdrew from the study before completing the 6-month treatment period was higher in the DMPA-SC group (35.3%, 48/136) than in the leuprolide group (26.1%, 36/138).

Gerald Willett MD / 12-10-03
Reviewing Medical Officer

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

/s/

Gerald Willett
2/17/04 02:37:14 PM
MEDICAL OFFICER

Scott Monroe
2/17/04 03:59:19 PM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-584

Pfizer, Inc.
Attention: Daniel Chirby, M.Sc.
Associate Director
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Chirby:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Medroxyprogesterone Acetate Injectable suspension, USP (104 mg/0.65 mL)
Review Priority Classification:	Standard
Date of Application:	December 17, 2003
Date of Receipt:	December 18, 2003
Our Reference Number:	NDA 21-584

You have requested priority review of this application. We are denying your request for priority review. An approved regimen for endometriosis is available which protects against excessive bone loss and other hypoestrogenic symptoms. Therefore, the user fee goal date is October 18, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are, however, waiving the requirement for pediatric studies for this application.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review

but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, 8B-45
Rockville, Maryland 20857

If you have any questions, call, Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827 - 4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margaret Kober
2/17/04 02:30:40 PM
Chief, Project Management Staff

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM: Archana Reddy, M.P.H., Regulatory Project Manager
DRUDP/HFD-580

DATE	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: Original NDA Submission	DATE OF DOCUMENT: December 17, 2003
February 10, 2004				

NAME OF DRUG: Depot Medroxyprogesterone acetate	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: August 15, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Request for review of the patient package insert and physician insert for NDA 21-584.
The primary proposed tradename is Depo- ⌣ and the proposed back-up tradename is Depo ⌣
Please note that the same tradenames are being proposed as for NDA 21-583, which is currently under review by the Division for the contraception indication.
The labeling for this e-CTD NDA application can be found on the EDR.
PDUFA DATE: October 18, 2004
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 21-584
HFD-580/Division File
HFD-580/Reddy
HFD-580/Rhee/Salemme/Raheja/Reid/Monroe/Willett/Parekh/Kim/Meaker/Kober/Griebel/Shames

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DDMAC
Lisa Stockbridge, Ph.D.

FROM: Archana Reddy, M.P.H., Regulatory Project Manager
DRUDP/HFD-580

DATE: February 9, 2004	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: Original NDA Submission	DATE OF DOCUMENT: December 17, 2003
NAME OF DRUG: Depo — (depot medroxyprogesterone acetate)	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: August 15, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Request for DDMAC review of the package insert for NDA 21-584 (depot medroxyprogesterone acetate). The labeling can be found electronically on the EDR. The sponsor is proposing Depo— as the primary tradename and Depo— as the alternate tradename. The PDUFA goal date is October 18, 2004.

Thanks,
Archana Reddy
7-7514

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM: Archana Reddy, M.P.H., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

DATE: February 6, 2004	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: Original NDA	DATE OF DOCUMENT: December 17, 2003
NAME OF DRUG: Depo- ⌣ (depot medroxyprogesterone acetate) ⌣	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: August 15, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ *DRUG ADVERTISING*
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ *SAFETY/EFFICACY*
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIFIC INSTRUCTIONS:

Request for Tradename Review *- On January 9, 2004, Pfizer submitted their proposed tradenames for NDA 21-584 (A hard copy of this correspondence will be provided with the consult.)*
The primary proposed tradename is Depo — and the proposed back-up tradename is Depo —
Please note that the same tradenames are being proposed as for NDA 21-583, which is currently under review by the Division for the contraception indication.
The labeling for this e-CTD NDA application can be found on the EDR.
PDUFA DATE: October 18, 2004
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 21-584
HFD-580/Division File
HFD-580/Reddy
HFD-580/Rhee/Salemme/Raheja/Reid/Monroe/Willett/Parekh/Kim/Meaker/Kober/Griebel/Shames

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Archana Reddy
2/6/04 03:33:05 PM

Memo to the file

NDA 21-584

Subject: 45 Day NDA Filing

NDA 21-584 (Medroxyprogesterone acetate injectable suspension) is similar in formulation and dosage as NDA 21-583. The only difference is that the present NDA 21-584 is indicated for the management of endometriosis-associated pain while NDA 21-583 is indicated for contraception. All the P/T data submitted for the present NDA 21-584 is cross-referenced to NDA 21-583. As such NDA 21-584 is filable from the P/T prospective.

Krishan Raheja
P/T reviewer

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

/s/

Lynnda Reid
2/4/04 01:27:32 PM
PHARMACOLOGIST

4 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

__✓__ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

NDA FILEABILITY CHECKLIST

NDA Number: 21-584 **Applicant:** Pharmacia & Upjohn, subsidiary of Pfizer

Stamp Date: 17-Dec-2003

Filing Meeting: 2-Feb-2004

Drug Name: Medroxyprogesterone acetate, subcutaneous injection [Sterile aqueous suspension]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review, but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Electronic NDA in CTD format – NDA 21-583 is identical to NDA 21-584 with regard to CMC information. Most of the sections of the e-NDA for 21-584 have a statement to refer to the e-NDA for 21-583 for the information.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Most of the CMC information is provided in DMF —
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		— f data have been provided; a 36-month expiry is requested.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	A micro consult will be required. A separate micro section is not necessary.
16	Is a separate Device section included?		X	Syringe to be used is equivalent to ones in use.

THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

Review Chemist HFD-580, Date J. Salemme, Ph.D, 30-Jan-2004

Team Leader, HFD-580 Moo-Jhong Rhee, Ph.D.

COMMENTS

NDA 21-583 and 21-584 are identical with regard to CMC information. The following CMC comments apply to both NDAs.

Drug Product Composition

Medroxyprogesterone Acetate-SC (MPA-SC) contains the active ingredient Medroxyprogesterone Acetate (MPA). The drug product is presented as a pre-filled, single-use glass syringe, which delivers 104 mg of MPA in 0.65 mL. The drug product is a sterile aqueous suspension.

The sponsor states the formulation of MPA-SC has been slightly modified from the approved formulation for Depo-Provera. The proposed formulation for MPA-SC and the formulation for Depo-Provera are shown below in the table:

Table 3.2.P.2.1-3: Comparison of DMPA-SC and Marketed DEPO-PROVERA® IM formulations. Composition as % w/v

	DMPA - SC	Marketed DEPO-PROVERA ® IM (1)
Medroxyprogesterone Acetate (MPA)		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol		
Polysorbate 80		
Monobasic Sodium Phosphate monohydrate		
Dibasic Sodium Phosphate dodecahydra		
Methionine		
Povidone		
Sodium Hydroxide or Hydrochloric Acid	QS	QS
Water for Injection	QS to	QS to

(1) US formula

The drug product and drug substance manufacturing will be reviewed by the Microbiology Reviewer for an assessment of sterility assurance. A consult was sent February 2004.

The drug substance and drug product manufacturing sites for NDA 21-583 are "Acceptable" based on a recent assessment by the Office of Compliance.

Screening of New NDA
Division of Biometrics II

Date: 1/30/04

NDA #: 21-584

Priority Classification: S

Trade Name:

Applicant: Pfizer

Date of Submission: 12/18/03

Generic Name: Medoxyprogesterone acetate
injectable suspension, USP

Indication: management of endometriosis-associated pain

No. of Controlled Studies: 2

User Fee Goal Date: 10/18/04

Date of 45-Day Meeting: 2/2/04

Medical Officer: Jerry Willett, M.D. (HFD-580)

Project Manager: Archana Reddy (HFD-580)

Screened by: Kate Meaker, M.S. (HFD-715)

Volume numbers in statistical section: \\CDSESUB1\N21584\N_000\2003-12-30

Anticipated Review Completion Date: 9/1/04

Comments:

1. This NDA is fileable.

2. Please request the sponsor submit the reference for the Hailperin-Ruger adjustment method used for multiple endpoints in Studies 268 and 270 (Section 6.7.1.5 of Study report).

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**Yes (Efficacy endpoint at 6 months completed; On-going for follow-up)**
Appropriate references included for novel statistical methodology (if present)	**No – see comments for request to sponsor**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Data from primary studies on diskettes and/or edr submitted	**Yes - edr**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for ~~gender~~, racial, and ~~geriatric~~ subgroups investigated (BMI also)	**Yes**

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS
(or attach relevant table from summary volume of NDA)

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
268	50 sites (US, Canada)	DMPA-SC (n=136) Leuprolide (n=138)	Active (leuprolide)	Randomized, Multicenter, Evaluator-blind, Parallel Arm	6 mos on treatment; 12 mos follow-up
270	37 sites 12 countries (Europe, Asia Latin America)	DMPA-SC (n=153) Leuprolide (n=146)	Active (leuprolide)	Randomized, Multicenter, Evaluator-blind, Parallel Arm	6 mos on treatment; 12 mos follow-up

Katherine B. Meaker, M.S.
Statistical Reviewer

Concur: Dr. Welch

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

/s/

Katherine Meaker
2/10/04 08:50:14 AM
BIOMETRICS

Mike Welch
2/10/04 12:17:39 PM
BIOMETRICS

21 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-584

Pfizer, Inc.
Attention: Daniel Chirby, M.Sc.
Associate Director
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Chirby:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Medroxyprogesterone Acetate Injectable suspension, USP (104 mg/0.65 mL)
Date of Application:	December 17, 2003
Date of Receipt:	December 18, 2003
Our Reference Number:	NDA 21-584

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2004, in accordance with 21 CFR 314.101(a). You have requested priority review of this application. We are considering your request, and you will be notified of our decision in a subsequent correspondence.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products

Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, 8B-45
Rockville, Maryland 20857

If you have any questions, call, Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827 - 4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margaret Kober
12/30/03 02:02:45 PM
Chief, Project Management Staff

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Microbiology
Peter Cooney, Ph.D.

FROM: Archana Reddy, MPH
Regulatory Project Manager
DRUDP/HFD-580

DATE: December 29, 2003	IND NO.	NDA NO. 21-584	TYPE OF DOCUMENT: NEW NDA	DATE OF DOCUMENT: December 17, 2003
NAME OF DRUG: Depot Medroxyprogesterone Acetate Subcutaneous Injection	PRIORITY CONSIDERATION: Priority		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: May 30, 2004

NAME OF FIRM: Pfizer, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please let me know who the reviewer assigned to this NDA will be. This is a new electronic NDA submission in CTD format and is available on the EDR.

The goal date will be 6-18-04 or 10-18-04 depending on whether the NDA receives priority review status or not.

Thank you,
Archana

PLEASE ASSIGN REVIEWER FOR THIS NEW NDA

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Archana Reddy
12/29/03 11:39:54 AM

PPG Regulatory Library
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 4595 Fax 212 309 4331

Pfizer Pharmaceuticals Group

December 5, 2003

Food Drug Administration
Mellon Client Services Center
Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

Re: Prescription Drug User Fees

Dear Sir or Madam:

As required by the Prescription Drug User Fee Act of 2003, enclosed is the application fee in the amount of $573,500 for Pfizer's New Drug Application for Depot Medroxyprogesterone Acetate Subcutaneous Injection (DMPA-SC). The NDA number for this submission is 21-584 and has been assigned User Fee ID Number 4673. This submission will be filed to the Food and Drug Administration on or about December 17, 2003.

If you require further assistance, please contact me at 212-573-1246.

Sincerely,

Marianne Kopelman

Marianne Kopelman
Senior Manager
Project Tracking and Administration

cc: D. Chirby
B. Ginch
R. Hernandez
R. Wittich
User Fee File

000091
P1221222

FOR INQUIRIES CONCERNING THIS PAYMENT
TELEPHONE (901) 215-1111

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Vendor #	Voucher #	Invoice #	Invoice Date	Invoice Amount	Discount	Net Amount
0000199426	006016339	11-25-03	11/25/03	573,500.00	0.00	573,500.00
	UFN 4673					

Stop waiting by the mailbox for your check. You may be eligible to receive payments directly into your bank account. Call (901) 215-1191 or email ACH@Pfizer.com to find out more about Pfizer's Electronic Payment (ACH) program.

Page 0001 of 0001

NY01 003347896	573,500.00	0.00	573,500.00

Pfizer

NY01 003347896

Pfizer Inc 66-49
New York, NY 10017-5755 531

Wachovia Bank N.A.
Charlotte, NC

Mo	Day	Year	
12	03	03	Pay Exactly: Five Hundred Seventy-Three Thousand Five Hundred and NO/100 Dollars

Amount ******573,500.00

To the Order of FOOD AND DRUG ADMINISTRATION
[redacted] RM 670
003347896 MELLON CLIENT SERVICE CENTER
500 ROSS STREET
PITTSBURGH PA 19529-0001

Pfizer Inc

Richard A. Burns

Authorized Corporate Signatory

VOID

⑈00334789⑈ ⑆053100494⑆013569 069491⑈

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

PHARMACIA & UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

2. TELEPHONE NUMBER *(Include Area Code)*

(269) 833-9411

3. PRODUCT NAME

Dept Medroxyprogesterone Acetate Subcutaneous Injection

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-584

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4673

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☑ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Daniel G. Chirby, M. Sc, Associate Director	12/04/2003

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-6690 EF

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form 3397 should be placed in the first volume of the application with the application form.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval
Applications (including supplements) for:

- Products for further manufacturing only
- Whole Blood or Blood Component for Transfusion
- Bovine Blood Product for Topical Application Licensed before September 1, 1992
- A crude Allergenic Extract Product
- An *In-Vitro* diagnostic biological product licensed under section 351 of the PHS Act

ITEM NO.: **INSTRUCTIONS**

1-2. **Self-explanatory**

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **BLA STN / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the 6-digit Biologics License Application STN if known.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: N099999.

5. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on CDER's web site: http://www.fda.gov/cder/pdufa/default.htm.

6. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210. Questions regarding the CDER User Fee I.D. Number should be directed to CDER's User Fee Staff at (301) 594-2041.

FOR BIOLOGIC PRODUCTS - The User Fee I.D. Number is the applicant's four digit U.S. License Number, followed by a sequential number for each fee paying submission from the applicant; starting with number 1. If the firm is unlicensed, a number may be obtained by calling CBER's Regulatory Information Management Staff (RIMS) at (301) 827-3503. Questions regarding the CBER User Fee I.D. number should also be directed to RIMS.

EXAMPLE: For U.S. License Number 0222, the fifth submission would be given the User Fee I.D. Number: 0222-5.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. *A copy of the official FDA notification that the waiver has been granted must be provided with the submission.*

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-584 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Depo —
Generic Name: depot medroxyprogesterone acetate subcutaneous injection
Strengths: 104 mg/0.65 mL

Applicant: Pfizer, Inc.

Date of Application: December 17, 2003
Date of Receipt: December 18, 2003
Date clock started after UN: N/A
Date of Filing Meeting: February 2, 2004
Filing Date: February 13, 2004
Action Goal Date (optional): User Fee Goal Date: October 18, 2004

Indication(s) requested: Endometriosis

Type of Original NDA: (b)(1) X (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S X P _____
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A
Chemical Classification: (1,2,3 etc.) 5s
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid X Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # 4673
Clinical data? YES X NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  The entire New Drug Application has been submitted in e-CTD format.

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Yes, this is a completely electronic NDA in CTD format.

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure forms included with authorized signature? YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 61,389

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2004

BACKGROUND:
Pfizer, Inc. submitted a New Drug Application for Depo — on December 18, 2003. This is a New Drug Application for a new route of administration, Depot Medroxyprogesterone Acetate-Subcutaneous Injection (DMPA-SC), pursuant to 505(b)(l) of the Federal Food, Drug, and Cosmetic Act. The proposed indications are for the management of endometriosis-associated pain — — . The sponsor is requesting priority review of this application, in accordance with the FDA Manual of Policies and Procedures (MAPP) Priority and Review Policy (6020.3).

On June 30, 2003, Pfizer, Inc. submitted NDA 21-583 for DMPA-SC for the proposed indication of contraception in women of childbearing potential. For NDA 21-584, the formulation, dosage regimen and route of administration of DMPA-SC are exactly the same as that described in NDA 21-583. It is the sponsor's intention to have both the contraception and endometriosis indications included in one label for this subcutaneous injectable formulation of DMPA.

ATTENDEES:
Scott Monroe, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Jerry Willett, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Martin Kaufman, D.P.M., M.B.A., Project Manager, DRUDP (HFD-580)
Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jean Salemme, Ph.D., Review Chemist, DNDC II @ DRUDP (HFD-580)
Myong-Jin Kim, Pharm.D., Clinical Pharmacology/Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sandhya Apparaju, Ph.D., Clinical Pharmacology/Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division of Biometrics II (DB II) @ DRUDP (HFD-580)

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Gerald Willett, M.D.
econdary Medical:	Scott Monroe, M.D.
tatistical:	Kate Meaker, M.S.
armacology:	Krishan Raheja, D.V.M., Ph.D.
atistical Pharmacology:	N/A
emistry:	Jean Salemme, Ph.D.

n: 9/25/03

Environmental Assessment (if needed):	Jean Salemme, Ph.D.
Biopharmaceutical:	Myong Jin-Kim, Pharm.D.
Microbiology, sterility:	Bryan Riley, Ph.D.
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Roy Blay, Ph.D.
Regulatory Project Management:	Archana Reddy, M.P.H.
Other Consults:	Archana Reddy, M.P.H.

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA ___X___ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X___ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__X__ Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Archana Reddy, M.P.H.
Regulatory Project Manager, HFD-580

9/25/03

Teleconference Meeting Minutes

Date: October 2, 2000 **Time:** 10:30 –12:00 PM **Location:** Conference Room "C"

NDA 20-246 **Drug:** —
(medroxyprogesterone acetate injectable suspension)

Indication: Contraception

Sponsor: Pharmacia & Upjohn

Type of Meeting: Clinical Guidance

FDA Attendees:
Susan Allen, M.D. – Director, Division of Reproductive and Urologic Drug Products (*DRUDP*; HFD-580)
Gerald Willett, M.D. – Acting Team Leader, DRUDP (HFD-580)
Lesley Furlong, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. – Statistics Reviewer, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Shala Farr, M.S. – Statistics Reviewer, DBII @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, *DRUDP* (HFD-580)

External Attendees:
Emil C. Berro – Senior Project Manager, Project Management
Fred R. Bode, M.D. – Clinical Program Leader, Clinical Development – US
Michael D. Burdick – Associate Director, Global Regulatory Affairs
Daniel G. Chirby – Regulatory Manager, Global Regulatory Affairs
Dan Fagan, Ph.D. – Vice President, Product Development
Henk de KoningGans, M.D. – Therapeutic Area Vice President, Women's Health Urology
Roger J. Garceau, M.D. – Director, General Medicine, Clinical Research
Cindy A. Greenwald – Senior Statistician – Math Analyst, Clinical Biostatistics
Carol W. Johnson, DVM, Ph.D., DACVP – Senior Scientist, Investigative Toxicology

Mohamad H. Rahimy, Ph.D. – Senior Research Scientist/Clinical Pharmacology
Charles P. Wajszczuk, M.D. – Associate Director/Clinical Research

Meeting Objective: To discuss clinical development program to support the new indication and formulation for MPA.

Discussion Points:
Contraceptive Trials

1. Are these two studies, and other existing data showing efficacy/safety of active ingredient, sufficient for registration of DMPA-SC for the contraception indication?

   - efficacy will be evaluated on the women who are 35 years old or less at the start of therapy, therefore, the sponsor must have adequate numbers of subjects completing 1 year of therapy to give meaningful efficacy numbers; the Division recommends a minimum of 200 women 35 years and younger completing 13 cycles of use
   - bleeding diaries should be kept and analyzed for a full year; it is unclear from the material presented whether this is intended or not
   - the sample sizes and proposed trial designs would appear to support filing of an application for contraception, but safety and efficacy of this product would be a review issue

2. Given our experience with DMPA-IM, does FDA agree that no comparator arm is needed in the two contraceptive trials?

   - the Division agrees that no comparator arm is needed for this study

3. Would FDA require further PK/PD studies or other data to support the proposed regimens?

   - the sponsor will submit additional data to complete the PK/PD information before initiating the Phase 3 clinical trials
   - the sponsor should clarify if they are seeking the use of the same dose for endometriosis as contraception because many endometriosis patients need contraception
   - the sponsor has indicated that there is no PK profiles available on the subcutaneous route of product administration

4. Do these safety evaluations and follow-up plans conform to FDA requirements?
   - there are no follow-up plans presented in the meeting package
   - follow-up and outcome information on all exposed pregnancies for outcome information is recommended
   - follow-up on a subset (approximately 30 – 40 subjects) for return to menstruation and ovulation is recommended since this is an issue for some women with the DMPA-IM formulation

General Comments for Contraceptive Trial:

- the sponsor should submit complete protocols for Division review before the study is initiated
- the Division would like the sponsor to conduct a PK/PD analysis by weight, if possible
- the sponsor should include a 2-month washout period for any volunteers using hormonal oral contraceptive or implant contraceptive products
- the Division would like the sponsor to encourage women to self-inject in the clinical setting or at home if the sponsor is seeking approval for such use
- exclude women with T-scores less than –1 at baseline from the bone density for safety reasons; this comment applies to both contraception and endometriosis trials

Endometriosis Trials

1. Are these two studies, and other existing data showing efficacy/safety of active ingredient, sufficient for registration of DMPA-SC for the endometriosis indication?

   - two studies with appropriate trial design would most likely support filing of an application for this indication; the Division will need to review the modified Biberoglu and Behrman scales proposed for use, including associated references

2. Does FDA agree with P&U's follow-up plans and total length of study time of 6 months for bone mineral density studies with the one-year data form the US contraception study as specifically being supportive of the endometriosis filing?

   - there are no follow-up plans presented in the meeting package
   - the Division recommends that the sponsor collect data 6 months and 1 year after the 25-27 week visit, at least for the primary endpoint
   -

3. Does FDA agree with the plan for only one diagnostic laparoscopy, the chosen primary endpoint of pain reduction, and the proposed target population?

   - the Division agrees with the single laparoscopy proposed, but the sponsor should add gonorrhea and chlamydia cultures to baseline screening, as well as pelvic sonograms for all women who had their laparoscopic diagnosis of endometriosis more than 3 months prior to study initiation
   - with regard to the endpoint for these trials, the sponsor should propose a priori an amount of reduction in summary pain scores that would be clinically significant
   - individual symptom scores and summary scores should be evaluated as primary endpoints
   - pre and post treatment differences between the summary scores and the individual pain parameter scores should be measured
   - the proposed target population should be women with at least a moderate score (2 or greater) in each of the 3 symptoms, and therefore, a summary score of at least 6

4. Is the comparator, leuprolide, and the regimen adequate to gain approval for the endometriosis indication?

   - the Division agrees with the use of leuprolide as the comparator
   - adequacy for approval depends on review of submitted data

5. Do these safety evaluations and follow-up plans conform to FDA requirements?

   - follow-up should be performed for 6 and 12 months following treatment completion
   - return of symptoms should be assessed at 6 and 12 months post-treatment
   - pregnancy testing should be performed at regular intervals (every 3 months) throughout the trial
   - the specific sites for measurement of BMD and the type of measurement planned should be described in a detailed protocol submitted to the Division for review prior to trial initiation
   - the Division suggests that the sponsor add breast cancer, thromboembolic disease and breastfeeding as exclusion criteria as these are contraindications to DMPA-IM and Lupron

General Comments for Endometriosis Trial:

- the sponsor should submit a detailed protocol for these studies to the Division for review prior to trial initiation
- the sponsor needs to address the blinding of the investigator in the final protocol
- the Division would like the sponsor to conduct a PK/PD analysis by weight, if possible
- the sponsor needs to clarify the scoring system for the endometriosis study
- the sponsor should plan to have patients maintain a diary for recording bleeding patterns and pain

Discussion of Proposed studies:
General Comments:

- the Division is interested in seeing the two-year data regarding — — in the contraception trials
- the sponsor needs to justify excluding patients on lipid lowering agents
- the bone mineral density will be measured from the hip and spine in those studies assessing BMD changes

Action Items:

- the sponsor should separate IND into two INDs, one for each indication
- fax meeting minutes to the sponsor within 30 days

Jennifer J Mercier
Minutes Preparer

Susan Alte, MD
Concurrence, Chair

Note: These minutes the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.