CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-584

CHEMISTRY REVIEW(S)

NDA 21-584

depo-subQ provera 104

medroxyprogesterone acetate,
injectable suspension,
for subcutaneous use

Sponsor: Pfizer, Inc.

Chemistry Reviewer:
J. Salemme, Ph.D.
For Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-584

2. REVIEW #: 2

3. REVIEW DATE: 18-Feb-2005

4. REVIEWER: J. Salemme, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION BEING REVIEWED:

Electronic Submissions Reviewed	Document Date
Amendment – response to approvable	27-Jan-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Pharmacia & Upjohn, subsidiary of Pfizer
Address:	7000 Portage Road
Representative:	Kalamazoo, MI 49001-0199
Telephone:	(269) 833-4000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: depo-subQ provera 104
b) Non-Proprietary Name: medroxyprogesterone acetate injectable suspension
c) Code Name/# (ONDC only): PNU 8836

Executive Summary Section

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. INDICATION: for the treatment of endometriosis pain

11. DOSAGE FORM: Sterile aqueous suspension in prefilled syringes

12. STRENGTH/POTENCY: 160 mg/mL (delivered dose 104 mg/0.65 mL per syringe)

13. ROUTE OF ADMINISTRATION: Injection, subcutaneous

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

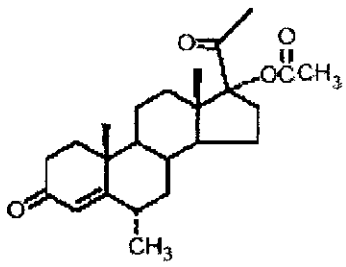
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Medroxyprogesterone acetate; Molecular formula: $C_{24}H_{34}O_4$; Molecular weight: 386
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEWED /Reviewer	COMMENTS
—	II	Pfizer	Drug Substance	1	Adequate	J. Salemme, 8-Mar-2004	Also adequate by Microbiology B. Riley, Jan 2004
—	III			3	Adequate	J. Salemme, 24-May 2004	DMF review is of the — —
—	III			3	Adequate	D. Lewis, 14-Aug-2003	
—	III			3	Adequate	R. Madurawe, 12-May-2004	
—	III			3	Adequate	Y. Yang, 22-Apr 2002	
—	III			3	Adequate	Y. Yang, 26-Sept 2002	
—	III			3	Adequate	Y. Yang, 14-Sept-2001	

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows.

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/Comment
Biometrics	N/A		
Devices (needle)	Acceptable	30-Mar-2004	V. Hibbard
EES	Acceptable	5-Nov-2003	J. Ambrogio
Pharm/Tox	Acceptable	4-Sept-2004	K. Raheja
Biopharmaceutics	Acceptable	1-Jul-2004	M-J Kim
LNC	N/A		
Methods Validation	N/A		The methods, which are the same as those for NDA 20-246, have been previously validated.
DMETS/DDMAC	Tradename of depo-subQ provera 104 is acceptable.		
EA	Categorical exclusion is granted.	22-Mar-2004	J. Salemme
Microbiology	Acceptable	16-Jan-2004 and 10-Feb-2004	B. Riley

Chemistry Review for NDA 21-584

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
From a CMC perspective, NDA 21-584 is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance
The drug product, depo-subQ provera 104 for subcutaneous (SC) injection, is a sterile, aqueous, injectable suspension of medroxyprogesterone acetate that is provided in a single-use, pre-filled syringe. The drug product contains the same active ingredient and excipients present in the approved product, Depo-Provera, a drug product that has been approved for use as a contraceptive for many years. Additionally, the drug product contains three additional excipients compared to Depo-Provera, which are povidone USP, methionine USP, and phosphate— The drug product complies with the current USP monograph for medroxyprogesterone acetate injectable suspension.

The drug product is administered by subcutaneous injection. One injection is effective for a three-month period —

For the treatment of endometriosis pain, the drug product is typically used for a six month period.

The drug product, 104 mg in 0.65mL, is packaged in a single-use syringe with a glass barrel and a coated rubber plunger. The syringe is protected by a device designed to prevent needle-stick injuries. and is packaged with a short needle designed for subcutaneous injection. An expiration date of 36 months is approved for the drug product in the single-use syringe.

The quality of the drug product is adequately controlled by tests for —

The drug substance, medroxyprogesterone acetate, is a white, to almost white powder that is practically insoluble in water.

Medroxyprogesterone acetate is manufactured according to DMF — it is the same drug substance used in the approved product, Depo-Provera, and is controlled by same drug substance specification. The quality of the drug substance is adequately controlled by tests for —

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be given once every three months by subcutaneous injection for the treatment of endometriosis pain.

C. Basis for Approvability or Not-Approval Recommendation

Based on satisfactory CMC information reviewed in Chemistry Review #1 and Chemistry Review #2, NDA 21-584 is recommended for approval with the tradename, "depo-subQ provera 104."

III. Administrative

A. Reviewer's Signature

J. Salemme, Ph.D., Chemistry Reviewer

B. Endorsement Block

ChemistryTeamLeaderName/Date	Moo-Jhong Rhee, Ph.D.
ProjectManagerName/Date	Nenita Crisostomo

C. CC Block

57 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/

Jean Salemme
10/15/04 03:41:37 PM
CHEMIST

Moo-Jhong Rhee
10/15/04 03:54:05 PM
CHEMIST
I concur

NDA 21-584

Tradename Under Review
**(Medroxyprogesterone acetate,
Sterile Injectable Suspension
for subcutaneous injection)**

Sponsor: Pfizer, Inc.

**Chemistry Reviewer:
J. Salemme, Ph.D.
For Reproductive and Urologic Drug Products**

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-584

2. REVIEW #: 1

3. REVIEW DATE: 17-Sept-2004

4. REVIEWER: J. Salemme, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Electronic Submissions Reviewed	Document Date
Original (21-584)	17-Dec-2003
Amendment - samples	23-Feb-2004
Amendment (21-583)- needle information	10-Mar-2004
Amendment - labeling	20-May-2004
Amendment (21-583) – labeling	21-May-2004
Amendment – change in drug substance specification	25-May-2004
Amendment - needle change proposal	15-Jun-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Pharmacia & Upjohn, subsidiary of Pfizer
Address:	7000 Portage Road
Representative:	Kalamazoo, MI 49001-0199

Telephone: (269) 833-4000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename under review
b) Non-Proprietary Name: Medroxyprogesterone acetate injectable suspension
c) Code Name/# (ONDC only): PNU 8836
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. INDICATION: for the treatment of endometriosis pain

11. DOSAGE FORM: Sterile aqueous suspension in prefilled syringes

12. STRENGTH/POTENCY: 160 mg/mL (delivered dose 104 mg/0.65 mL per syringe)

13. ROUTE OF ADMINISTRATION: Injection, subcutaneous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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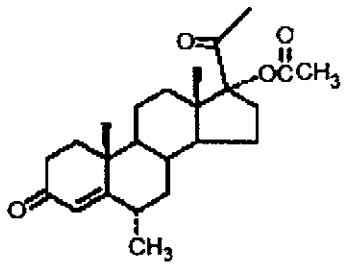
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Medroxyprogesterone acetate
Molecular formula: $C_{24}H_{34}O_4$
Molecular weight: 386

Structure:



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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/Comment
Biometrics	N/A		
Devices (needle)	Acceptable	30-Mar-2004	V. Hibbard
EES	Acceptable	18-Feb-2004	J. D Ambrogio
Pharm/Tox	Acceptable	4-Sept-2004	K. Raheja
Biopharmaceutics	Acceptable	1-Jul-2004	M-J Kim
LNC	N/A		
Methods Validation	N/A		The methods, which are the same as those for NDA 20-246, have been previously validated.
DMETS/DDMAC	Tradename under review		
EA	Categorical exclusion is granted.	22-Mar-2004	J. Salemme
Microbiology	Acceptable	16-Jan-2004 and 10-Feb-2004	B. Riley

The Chemistry Review for NDA 21-584

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
From a CMC perspective, this NDA is recommended for approval once the labeling is finalized.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance
The drug product, medroxyprogesterone acetate, sterile injectable suspension for subcutaneous (SC) injection, is a sterile, aqueous, injectable suspension of medroxyprogesterone acetate that is provided in a single-use, pre-filled syringe. The drug product has slightly different formulation from the approved product, Depo-Provera (3-month contraceptive), in that three additional excipients, povidone USP, methionine USP, and phosphate — are present. The drug product complies with the current USP monograph for medroxyprogesterone acetate injectable suspension.

The drug product is administered by subcutaneous injection. One injection is effective for a three-month period. The duration of action over a three-month period is due to the slow absorption of the relatively insoluble medroxyprogesterone acetate drug substance from the injection site, —

The drug product, 104 mg in 0.65mL, is packaged in a single-use syringe with a glass barrel and a coated rubber plunger. The syringe is protected by a device designed to prevent needle-stick injuries. The syringe is packaged with a short needle designed for subcutaneous injection. An expiration date of — is granted for the drug product in the single-use syringe.

The quality of the drug product is adequately controlled by tests for

The drug substance, medroxyprogesterone acetate, is a white, to almost white powder that is practically insoluble in water.
Medroxyprogesterone acetate is manufactured according to DMF . It is the same drug substance used in Depo-Provera, and is controlled by same drug substance specification. The quality of the drug substance is adequately controlled by tests for

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for treatment of endometriosis pain. A typical length of treatment for this indication is six months.

C. Basis for Approvability or Not-Approval Recommendation

The entire CMC submission for NDA 21-584 is identical to that submitted previously for NDA 21-583. From a CMC perspective, both NDAs can be approved once the labeling for each indication is finalized.

All of the chemistry deficiencies conveyed to the sponsor during the review cycle for NDA 21-583 have been adequately addressed. The Office of Compliance has recommended the manufacturing sites for approval. The manufacturing and controls with regard to sterility assurance have been reviewed by the Microbiologist reviewer and found to be acceptable.

III. Administrative

A. Reviewer's Signature

J. Salemme, Ph.D., Chemistry Reviewer, HFD-580

B. Endorsement Block

ChemistryTeamLeaderName/Date	Moo-Jhong Rhee, Ph.D.
ProjectManagerName/Date	Archana Reddy, MPH

C. CC Block

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

/s/

Jean Salemme
10/15/04 03:41:37 PM
CHEMIST

Moo-Jhong Rhee
10/15/04 03:54:05 PM
CHEMIST
I concur

ENVIRONMENTAL ASSESSMENT
CLAIM FOR A CATEGORICAL EXCLUSION

NDA 21-584

Under the provisions of 21 CFR 25.31(b), action on an NDA is categorically excluded and, therefore, ordinarily does not require the preparation of an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The total planned usage of Depo-Provera (medroxyprogesterone acetate) is estimated to be at levels where the aquatic concentration is estimated to be under a concentration of 1 part per billion. To the best knowledge of Pharmacia & Upjohn, the applicant is not aware of the existence of any extraordinary circumstances that would require the preparation of an Environmental Assessment. Also, Pharmacia & Upjohn do not have any information to indicate that Depo-Provera may be toxic to organisms in the environment at the expected levels of exposure. Pharmacia & Upjohn claim a categorical exclusion to the EA requirements in accordance with 21 CFR 25.31(b).

1. Date
November 25, 2003

2. Name of Applicant

Pharmacia
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Contact: Richard T. Williams
Tel. (860) 441-6287

3. List of Preparers

Richard T. Williams, Ph.D. Asst. Director, Environmental Sciences	Ph.D. in Microbiology with twenty- one years in chemical fate and effect evaluations, EHS, and regulatory compliance.

4. Certification
The undersigned certifies that the information presented is true, accurate, and complete to the best knowledge of Pharmacia & Upjohn.

Richard T. Williams, Ph.D. — 1 December 2003 (Date)

* Pharmacia & Upjohn are a wholly owned subsidiary of Pfizer Inc