CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-583

CHEMISTRY REVIEW(S)

NDA 21-583

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 21-583

2. REVIEW #: 2

3. REVIEW DATE: 7-Dec-2004

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Electronic Submissions Reviewed	Document Date
Amendment - needle change proposal	15-Jun-2004
Amendment –CMC changes	15-Nov-2004
Amendment – container labels/carton	6-Dec-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: depo-subQ provera 104

Executive Summary Section

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: Prevention of pregnancy

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

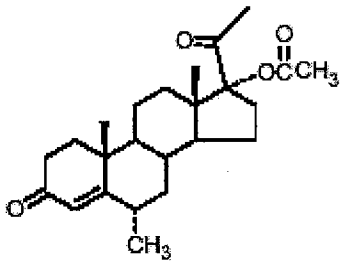
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____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	
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

The Chemistry Review for NDA 21-583

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
From a CMC perspective, NDA 21-583 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, medroxyprogesterone acetate, sterile injectable suspension for subcutaneous (SC) injection, is a stable, sterile, aqueous, injectable suspension of medroxyprogesterone acetate 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 . Additionally, the drug product contains three additional excipients compared to Depo-Provera. These are povidone USP, methionine USP, and phosphate buffer USP.

The drug product is to be administered by subcutaneous injection, in contrast to the approved product, Depo-Provera, which is administered by intramuscular injection. Like Depo-Provera, the drug product is to be administered once every three months for the prevention of pregnancy. For both drug products, the long duration of action is due to the slow absorption of the relatively insoluble medroxyprogesterone acetate drug substance from the injection site. Both the drug product and the IM drug product comply with the current USP monograph for medroxyprogesterone acetate injectable suspension.

The drug product, 104 mg in 0.65mL, is packaged in a single-use syringe with a glass barrel and — 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 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 manufactured according to DMF [redacted] It is the same drug substance used in Depo-Provera, and, thus, is controlled by same specifications, including [redacted] attributes. Medroxyprogesterone acetate is a white, to almost white powder that is practically insoluble in water. It exists in [redacted] form.

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

The drug product is intended for subcutaneous injection to be given once every three months for the prevention of pregnancy.

C. Basis for Approvability or Not-Approval Recommendation

Based on satisfactory CMC information reviewed in Chemistry Review #1, and on satisfactory CMC changes reviewed in Chemistry Review #2, NDA 21-583 is recommended for approval. The tradename for NDA 21-583, "depo-subQ provera 104," has been accepted.

III. Administrative

A. Reviewer's Signature

J. Salemme, Ph.D., Chemistry Reviewer

B. Endorsement Block

ChemistryTeamLeaderName/Date	Moo-Jhong Rhee, Ph.D.
ProjectManagerName/Date	Z. Charlene Williamson

C. CC Block

1 Page(s) Withheld

1 Trade Secret / Confidential

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_____ Deliberative Process

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/s/

Jean Salemme
12/8/04 04:17:58 PM
CHEMIST

Moo-Jhong Rhee
12/9/04 01:27:37 PM
CHEMIST
I concur

NDA 21-583

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 21-583

2. REVIEW #: 1

3. REVIEW DATE: 22-Jul-2004

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Electronic Submissions Reviewed	Document Date
Original	30-Jun-2003
Amendment - samples	23-Feb-2004
Amendment - needle information	10-Mar-2004
Amendment - labeling	20-May-2004
Amendment – labeling	21-May-2004
Amendment – change in ds 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

Executive Summary Section

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: Prevention of pregnancy

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

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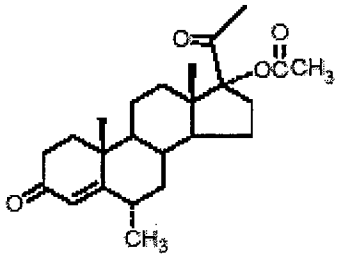

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B. Other Documents: None

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The Chemistry Review for NDA 21-583

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

The drug product is intended for subcutaneous injection to be given once every three months for the prevention of pregnancy.

C. Basis for Approvability or Not-Approval Recommendation

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

III. Administrative

A. Reviewer's Signature

J. Salemme, Ph.D., Chemistry Reviewer

B. Endorsement Block

ChemistryTeamLeaderName/Date	Moo-Jhong Rhee, Ph.D.
ProjectManagerName/Date	Z. Charlene Williamson

C. CC Block

55 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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/s/

Jean Salemme
7/27/04 12:26:54 PM
CHEMIST

Moo-Jhong Rhee
7/29/04 04:40:02 PM
CHEMIST
I concur