

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-778

CHEMISTRY REVIEW(S)

K1.2A



K1.2A

NDA 21-778 - 05-17-05

CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

NDA 21-778

N21778



N21778

REC.
07/12/05
9:16 AM

NDA 21-778

Megace ES

Par Pharmaceutical, Inc.

**John C. Hill, Ph.D., Chemistry Reviewer
ONDC / DNDC II / DMEDP / HFD-510**

Chemistry Review #2



CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

NDA 21-778

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Chemistry Review Data Sheet

1. NDA 21-778
2. REVIEW # 002
3. REVIEW DATE: 06-MAY-2005
4. REVIEWER: John C. Hill, Ph.D., DMEDP, HFM-510
5. PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
CMC Review #1 (redacted) mg/mL strength)	05-APR-2005

6. SUBMISSION(S) BEING REVIEWED:

7.

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	29-JUN-2004
AC amendment (125 mg/ml strength)	07-APR-2005
BL amendment (Revisions)	12-APR-2005
BC amendment (Dissolution test)	15-APR-2005
BL amendment (Revisions)	25-APR-2005
BC amendment (Dissolution data and validation)	10-MAY-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical, Inc.
Address:	One Ram Ridge Road Spring Valley, NY 10977



CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

NDA 21-778

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Representative:	Michelle Bonomi-Huvala, Sr. Dir., Reg. Affairs R&D
Telephone:	(201) 802-4128

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Megace ES
- b) Non-Proprietary Name (USAN): Megestrol Acetate
- c) Code Name/# (ONDC only): NA
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

Listed Drug: Megace (megestrol acetate), Bristol-Myers Squibb

10. PHARMACOL. CATEGORY: Treatment of anorexia, cachexia, or an unexplained significant weight loss in AIDS patients.

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 125 mg/ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product



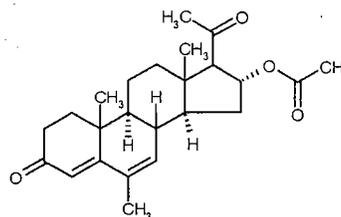
CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

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

BAN: Megestrol Acetate
CAS: 595-33-5
Molecular Formula: $C_{24}H_{32}O_4$
Molecular Weight: 384.52
IUPAC Name: Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
[REDACTED]	II	[REDACTED]		4	Adequate	27-FEB-03	LOA 19-NOV-2003
	II		4	Adequate	22-JUL-2004	LOA 25-NOV-2003	
	II		4	Adequate	03-MAR-2004	LOA 02-MAY-2003	
	IV		4	Adequate	21-AUG-2000	LOA 31-MAR-2004	
	III		4	Adequate	15-SEP-2000	LOA 24-JAN-2002	
	III		4	Adequate	22-APR-2002	LOA 14-AUG-2003	
	III		4	Adequate	22-MAR-2001	LOA 06-JAN-2004	
	III		4	Adequate	03-SEP-1999	LOA 06-JAN-2004	
	III		4	Adequate	06-AUG-2002	LOA 25-JUN-2002	



CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

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NDA 21-778					
	III		4	Adequate	25-OCT-2002 LOA 03-MAR-2000
	III		4	Adequate	25-AUG-1999 LOA 03-MAR-2000
	III		4	Adequate	30-MAR-1999 LOA 28-MAY-2002

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)

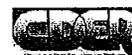
B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,178	Megestrol Acetate Oral Suspension as a treatment of anorexia, cachexia, or unexplained significant weight loss in AIDS patients.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	22-MAR-2005	J. D. Ambrogio
Pharm/Tox			
Biopharm	Change to 125 mg/ml strength	30-MAR-2005	Jim Wei
LNC			
Methods Validation	Not Required		
OPDRA	Comments	01-FEB-2005	
EA	Acceptable	05-APR-2005	John C. Hill, Ph.D., Chemist
Microbiology			



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Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

NDA 21-778

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OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes
 No If no, explain reason(s) below:

**Appears This Way
On Original**



CHEMISTRY REVIEW

Par Pharmaceutical Megace ES
Chemistry Review #2
16-MAY-2005

NDA 21-778

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The Chemistry Review for NDA 21-778

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can be approved from a chemistry point of view. A 24 month dating expiry is granted for the drug product as requested. See labeling comments to be communicated to the firm.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- The applicant agrees to conduct the primary stability study to completion, following the stability protocol; notifying the Agency of the results in a timely manner.
- The applicant agrees to place one batch per year, for each package size, on stability.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

Megace ES will be supplied as a liquid dispersion, 125 mg/ml in strength

This change was made in order to meet bioequivalence to Megace 800 mg/20mL. Megace ES contains Megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone in NanoCrystalline form. Megace ES contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hypromellose, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.

2. Drug Substance

14 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-1

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

/s/

John C. Hill
5/17/05 04:24:49 PM
CHEMIST

Stephen Moore
5/17/05 04:53:22 PM
CHEMIST

04/05/05



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Par Pharmaceutical Megace ES
01-MAR-2005

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NDA 21-778

Megace ES

Par Pharmaceutical, Inc.

**John C. Hill, Ph.D., Chemistry Reviewer
ONDC / DNDC II / DMEDP / HFD-510**

Chemistry Review Data Sheet

1. NDA 21-778
2. REVIEW # 001
3. REVIEW DATE: 01-MAR-2005
4. REVIEWER: John C. Hill, Ph.D., DMEDP, HFM-510
5. PREVIOUS DOCUMENTS

Previous Documents

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

7.

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	29-JUN-2004
BC amendment <u> </u> stability update <u> </u>	20-AUG-2004
BC amendment (Response to filing comments)	20-OCT-2004
BC amendment <u> </u> stability update <u> </u>	04-NOV-2004
BL amendment (Labeling revision)	04-NOV-2004
BC amendment <u> </u> stability update <u> </u>	27-JAN-2005
BC amendment (Response to IR letter)	07-FEB-2005
BL amendment (Labeling revision)	24-FEB-2005
BC amendment (24 month stability update) <u> </u>	25-FEB-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Par Pharmaceutical, Inc.
Address: One Ram Ridge Road
Spring Valley, NY 10977
Representative: Michelle Bonomi-Huvala, Sr. Dir., Reg. Affairs R&D
Telephone: (201) 802-4128



8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Megace ES
b) Non-Proprietary Name (USAN): Megestrol Acetate
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

Listed Drug: Megace (megestrol acetate), Bristol-Myers Squibb

10. PHARMACOL. CATEGORY: Treatment of anorexia, cachexia, or an unexplained significant weight loss in AIDS patients.

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: mg/ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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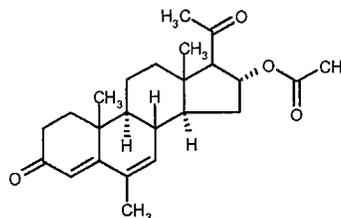
BAN: Megestrol Acetate

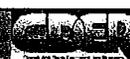
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CHEMISTRY REVIEW



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Par Pharmaceutical Megace ES
01-MAR-2005

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- 5 – Authority to reference not granted
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Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not Required		
OPDRA			
EA	Acceptable	05-APR-2005	John C. Hill, Ph.D., Chemist
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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 No If no, explain reason(s) below:



The Chemistry Review for NDA 21-778

The Executive Summary

I. Recommendations

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1. Drug Product

Megace ES¹ will be supplied as a liquid dispersion, 1 ~~mg~~/ml in strength. Megace ES contains Megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone in NanoCrystalline form. Megace ES contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hypromellose, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.



Studies with Megace in humans have shown that there is a positive food effect on the extent and rate of absorption of megestrol acetate. A ~~mg~~ mg dose of Megace ES provides a C_{max} that is equivalent to (90% confidence interval: ~~) and an AUC that is not greater than (90% confidence interval ~~) that of an 800 mg dose of Megace under fed conditions.~~~~

2. Drug Substance

Megestrol acetate is a synthetic progesterone derivative that is approved for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

¹ Although the Megace ES drug product is supplied as a NanoCrystal Dispersion (NCD), the term "nano" is not used in the name of the drug product



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Par Pharmaceutical Megace ES
01-MAR-2005

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Megestrol acetate is a white, crystalline solid chemically designated as Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate. Megestrol acetate is obtained commercially from either _____ . Both of these DMFs have been reviewed and found to be adequate. Upon receipt of megestrol acetate from the suppliers, the applicant performs acceptance testing against the current USP monograph with the following additional in-house tests: assay and chromatographic purity, particle size, residual solvents, light absorption and related foreign steroids.

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

PAR has developed the NanoCrystalline Dispersion (NCD) formulation of megestrol acetate oral suspension, Megace ES, for the currently approved indications, namely for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of AIDS. Megace ES is supplied as an oral solution containing _____ mg/ml of the Megestrol acetate API. The recommended adult initial dosage of Megace ES is _____ mg/day (5mL/day). In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day of Megace (800 mg equivalent to 575 mg/5 mL of Megace ES) were found to be clinically effective.

C. Basis for Approvability or Not-Approval Recommendation

This application can be approved from a CMC viewpoint. This recommendation is based upon evaluation of the CMC information provided by the applicant. The data contained in this NDA application are substantial and detailed. The applicant has adequately described the manufacturing process and associated process controls of the drug product. Release testing and stability protocols are adequate. Drug product quality, including consistency and stability has been adequately demonstrated. All facilities have an acceptable cGMP status. The labeling comment should be communicated to the applicant (see List of Deficiencies section). This comment is of the type that can be included in the action letter.

III. Administrative

A. Reviewer's Signature: Electronic signature in DFS

See electronic signature page

B. Endorsement Block

ChemistName/Date: John C. Hill, Ph.D. / 01-MAR-2005
ChemistryTeamLeaderName/Date: Stephen K. Moore, Ph.D.
ProjectManagerName/Date : Holly, Wieland , RN

C. CC Block: If applicable in DFS

33 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry- 2

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

/s/

John C. Hill
4/5/05 06:00:52 PM
CHEMIST

Stephen Moore
4/5/05 07:03:12 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21778/000	Action Goal:	
Stamp:	29-JUN-2004	District Goal:	
Regulatory Due:	29-APR-2005	Brand Name:	MEGESTROL ACETATE
ORAL		Estab. Name:	SUSP █████ /ML █████
Applicant:	PAR PHARM	Generic Name:	MEGESTROL ACETATE
ORAL	1 RAM RIDGE RD	Dosage Form:	(SUSPENSION)
	SPRING VALLEY, NY 10977	Strength:	█████ MG/ML
Priority:	5S		
Org Code:	510		

Application Comment:

FDA Contacts: J. HILL (HFD-810) 301-827-6408 , Review C

Overall Recommendation: ACCEPTABLE on 24-AUG-2004 by J. D AMBROGIO (HFD-322)

49

Establishment:



MF No: █████

AADA:

Responsibilities: █████

CSN

OAI Status: NONE

Stab. Comment:



(on 19-AUG-20

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DUCT (on

19-AUG-2004 by E. GALLIERS (HFD-510) 301-827-6429)

Milestone Name ator	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC ADAMSM	19-AUG-2004				
SUBMITTED TO DO RGUSONS	23-AUG-2004	10D			F
DO RECOMMENDATION LFARINA	24-AUG-2004			ACCEPTABLE BASED ON FILE REVIEW	
OC RECOMMENDATION BROGIOJ	24-AUG-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DA

Establishment:

DMF No:

AADA:

Responsibilities:

Profile:

CSN

OAI Status: NONE

Estab. Comment:
1 by E.

(on 19-AUG-20

GALLIERS (HFD-510) 301-827-6429)

Milestone Name ator	Date	Type	Insp. Date	Decision & Reason	C
------------------------	------	------	------------	-------------------	---

SUBMITTED TO OC 19-AUG-2004
ADAMSM.

OC RECOMMENDATION 23-AUG-2004
RGUSONS

ACCEPTABLE

F

BASED ON PROFILE
