

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21945Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

To: CMC Review # 3 of NDA 21-945

From: Donna F. Christner, Ph.D.
CMC Lead/DNDQA II/ONDQA

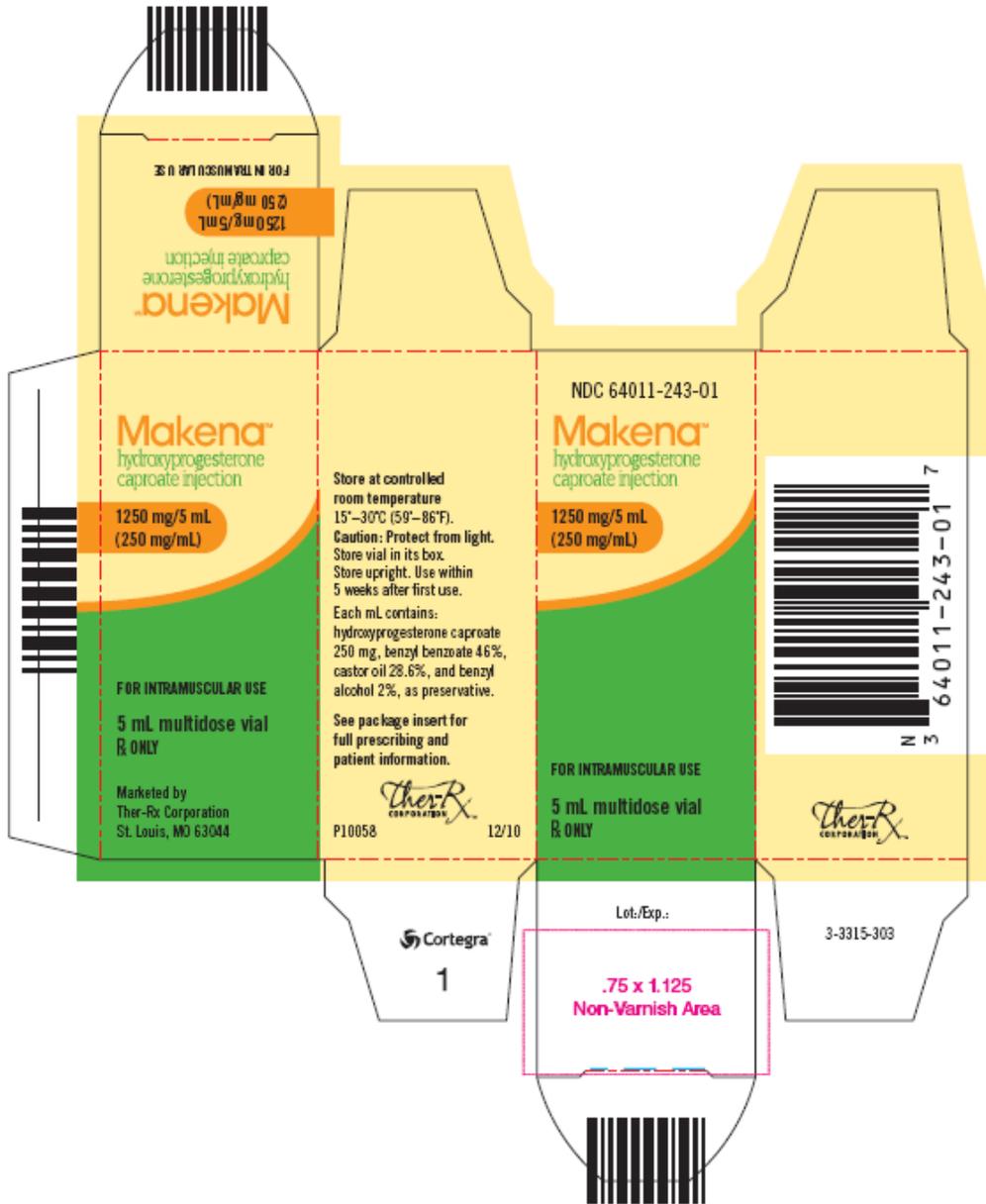
Through: Moo-Jhong Rhee, Ph.D.
Branch Chief/DNDQA II/ONDQA

Date: 31-Jan-2011

Re: Documentation of Final Carton/Container Labeling and Final CMC Recommendation

The previous CMC Review #3 recommended APPROVAL from the CMC standpoint noting that the final TRADENAME had not been agreed to. The sponsor provided the following carton and container labels on 15-Dec-2010. From the CMC standpoint, the labels are acceptable and the NDA is still recommended for APPROVAL.





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/s/

DONNA F CHRISTNER
01/31/2011

MOO JHONG RHEE
01/31/2011
Chief, Branch IV

TERRANCE W OCHELTRIE
01/31/2011

MEMORANDUM

Date: January 7, 2011

To: NDA 21-945

From: Terrance Ocheltree, Ph.D., R. Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 21-945, Hydroxyprogesterone caproate (250 mg/mL) for injection.

I have assessed the ONDQA reviews of NDA 21-945 by Monica Cooper, Ph.D. and Donna Christner, Ph.D. The first ONDQA review for this product was finalized on September 22, 2006 without a recommendation of approval due to unresolved issues related to drug product photosensitivity, particulate matter, expiration dating and labeling changes. A complete response was received on April 25, 2008 followed by a major amendment on August 28, 2008. Following the review of this new information an ONDQA review was entered into DARRTS on December 22, 2008 recommending Approval from an ONDQA perspective. All manufacturing and testing sites were found to be Acceptable, based on the last recommendation in EES dated June 16, 2008. A third ONDQA review was completed and placed in DARRTS on November 22, 2010 following the submission of two amendments, a Complete Response and labeling information. During this period, DMF (b) (4) was also reviewed and found to remain adequate to support this NDA. Review #3 recommends Approval, based on the Review #2 and the additional information. According to EES the manufacturing and testing sites remain Acceptable as of October 26, 2010.

On August 10, 2006 the Microbiology Reviewer entered a review into DARRTS recommending Approval. A second Microbiology review was entered in to DARRTS on June 19, 2008 after it was learned that the applicant had modified the (b) (4) manufacturing process. This review recommends Approval. The status has not changed.

The labeling was reviewed in Review #2 and modified per ONDQA recommendations. Therefore, the labeling is adequate from an ONDQA perspective as of November 22, 2010. The proposed proprietary name, Makena, was conditionally accepted on December 14, 2010.

No post marketing commitments are proposed by ONDQA.

Based on the information in NDA 21945, hydroxyprogesterone caproate injection will be supplied in a multi-dose glass vial. Each vial contains 5 mL of hydroxyprogesterone caproate at a concentration of 250 mg/mL. A 24 months expiration period has been granted when the product is stored at controlled room temperature, protected from light and in an upright position.

I concur with the "Approval" recommendation from an ONDQA perspective and the absence of ONDQA related post marketing commitments.

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/s/

TERRANCE W OCHELTRIE
01/10/2011

NDA 21-945

TRADENAME
(Hydroxyprogesterone caproate) injection

Hologic, Inc

Donna F. Christner, Ph.D.

Branch IV, Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Reproductive and Urologic Products
(HFD-580)

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Chemistry Review Data Sheet

1. NDA 21-945
2. REVIEW #: 3
3. REVIEW DATE: 22-Nov-2010
4. REVIEWER: Donna F. Christner, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
M002 BC	28-Mar-2006
N000	14-Apr-2006
N000 BL	20-Apr-2006
N000 BC	28-Jul-2006
N000 BC	14-Aug-2006
N000 BC	07-Sep-2006
NDA 21-945 Complete Response	25-Apr-2008
Amendment/Response to IR	28-Aug-2008
Amendment/particulate matter	25-Sep-2008
Amendment/updated container labels	02-Oct-2008
Amendment/post-penetration stability	31-Oct-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Labeling PreSubmission (SDN 50)	14-Jun-2010
NDA 21-945 Complete Response (SDN 51)	13-Jul-2010
Amendment/Updated Facility list (SDN 52)	23-Jul-2010
Amendment/Request for Proprietary Name (SDN 56)	15-Oct-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Hologic, Inc
Address:	1240 Elko Drive Sunnyvale, CA 94089-2212
Representative:	Robb Hesley
Telephone:	408-745-5179

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename
b) Non-Proprietary Name (USAN): Hydroxyprogesterone caproate
c) Code Name/# (ONDQA only): 17P
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Prevention of recurrent preterm birth

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: 250 mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Names:

- 17-Hydroxypregn-4-ene-3,20-dione hexanoate
- Pregn-4-ene-3,20-dione, 17-[(1-oxohexyl)oxy]-

Generic Name:

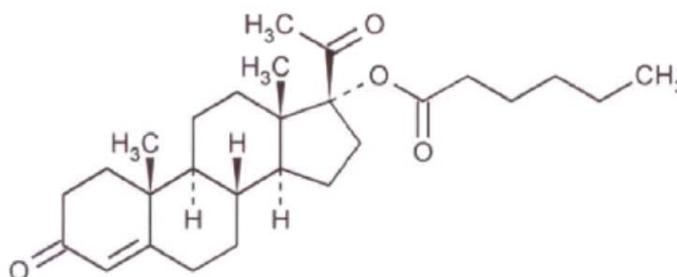
17 α -Hydroxyprogesterone
Caproate

US Adopted Name (USAN):

Hydroxyprogesterone Caproate

International Non-Proprietary Name (INN):

Hydroxyprogesterone (as alcohol)



Chemical Formula:

 $C_{27}H_{40}O_4$

Molecular Weight:

428.60

CAS Registry Number:

630-56-8 (hydroxyprogesterone:
68-96-2)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	10-Sep-2010	
	III			4	N/A		
	III			3	Adequate	24-Dec-2008	Reviewed by D. Ghosh

¹ Action codes for DMF Table:

Chemistry Review Data Sheet

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	53,730	Research IND for 17 α -Hydroxyprogesterone caproate from NICHD
IND	(b) (4)	(b) (4)
NDA	21-945	CMC Review #1 dated 20-Sep-2006 CMC Review # 2 dated Dec-2008

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	26-Oct-2010	A. Inyard
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	To be submitted postapproval as per ONDQA policy		
DMEPA	PENDING but does not impact CMC recommendation		
EA	ACCEPTABLE	20-Sep-2006	M. Cooper, Ph.D.
Microbiology	ACCEPTABLE (manufacturing)	19-Jun-2008	J. Metcalf, Ph.D.
	ACCEPTABLE (post-penetration stability)	18-Dec-2008	J. McVey, Ph.D.

The Chemistry Review for NDA 21-945

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required (the tradename is still under review by DMEPA, but is not a CMC issue). The final overall "Acceptable" recommendation has been made from the Office of Compliance.

Therefore, from a CMC perspective, this NDA is still recommended for APPROVAL as was recommended in Review #2 dated 22-Dec-2008.

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

N/A

II. Summary of Chemistry Assessments

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

The following paragraph has been copied from NDA 21-945 CMC Review # 1 dated 22-Sep-2006 by Monica Cooper, Ph.D.:

Hydroxyprogesterone caproate (also known as 17 α -hydroxyprogesterone caproate or 17-HPC) is a synthetic progestin (progesterone hormone) that is indicated for the prevention of recurrent preterm birth. The drug substance (API) and the drug product are both USP compendial items. 17 α -Hydroxyprogesterone caproate is a synthetic esterified derivative of the naturally-occurring progestin 17 α -hydroxyprogesterone, which has minimal progestational activity. On the other hand, 17 α -hydroxyprogesterone caproate has substantial progestational activity and a prolonged duration of action.

DRUG SUBSTANCE:

Information on the drug substance is contained in DMF (b) (4). See DMF (b) (4) Review # 2 dated 10-Sep-2010 for more detailed information.

Executive Summary Section

DRUG PRODUCT

The following paragraph has been copied from NDA 21-945 CMC Review # 1 dated 22-Sep-2006 by Monica Cooper, Ph.D.:

The drug product, Gestiva™ (hydroxyprogesterone caproate injection), is a clear yellow, viscous, oily solution with an organic odor. It will be supplied in one dosage concentration, 250 mg/mL. All excipients are USP/NF compendial items. The drug product will be provided as a sterile solution in a multi-use 5-mL glass vial (with a (b) (4) stopper) containing five 1-mL injections for intramuscular administration.

Based on the submitted data, **an expiration dating period of 24 months is granted when stored at controlled room temperature. In addition, the contents must be protected from light and stored in the upright position.** Sponsor has adequately addressed all CMC issues.

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

The tradename is still pending as of the date of this review. The following paragraph is taken from NDA 21-945 CMC Review # 1 dated 22-Sep-2006 by Monica Cooper, Ph.D. and refers to the drug product as Gestiva:

Gestiva (hydroxyprogesterone caproate injection) will be supplied in 5-mL multi-use glass vials with (b) (4) stoppers in one dosage concentration – 250 mg/mL. The drug will be dosed as a 1-mL (250 mg) intramuscular injection once per week during pregnancy beginning at week 16 – 20 to week 37 of gestation or until birth (for pregnant women with a prior history of at least one spontaneous preterm birth).

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. The Office of Compliance has issued an overall “ACCEPTABLE” recommendation for all the facilities involved. Labels have required information.

III. Administrative**A. Reviewer’s Signature****B. Endorsement Block**

Donna F. Christner/22-Nov-2010
Moo-Jhong Rhee/Branch Chief/Date
Charlene Williamson, OND PM/Date

C. CC Block

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/s/

DONNA F CHRISTNER
12/01/2010

MOO JHONG RHEE
12/01/2010
Chief, Branch IV

NDA 21-945

**Gestiva
(Hydroxyprogesterone caproate) injection**

Cytoc Corporation

Donna F. Christner, Ph.D.

**Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment**

For

**Division of Reproductive and Urologic Products
(HFD-580)**

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Chemistry Review Data Sheet

1. NDA 21-945
2. REVIEW #: 2
3. REVIEW DATE: 20-Dec-2008
4. REVIEWER: Donna F. Christner, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

M002 BC
N000
N000 BL
N000 BC
N000 BC
N000 BC

Document Date

28-Mar-2006
14-Apr-2006
20-Apr-2006
28-Jul-2006
14-Aug-2006
07-Sep-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA 21-945 Complete Response
Amendment/Response to IR
Amendment/particulate matter
Amendment/updated container labels
Amendment/post-penetration stability

Document Date

25-Apr-2008
28-Aug-2008
25-Sep-2008
02-Oct-2008
31-Oct-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Cytoc Corporation
Address:	1240 Elko Drive Sunnyvale, CA 94089-2212
Representative:	Robb Hesley
Telephone:	408-745-5179

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Gestiva
b) Non-Proprietary Name (USAN): Hydroxyprogesterone caproate
c) Code Name/# (ONDQA only): 17P
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Prevention of recurrent preterm birth

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: 250 mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

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

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Names:

- 17-Hydroxypregn-4-ene-3,20-dione hexanoate
- Pregn-4-ene-3,20-dione, 17-[(1-oxohexyl)oxy]-

Generic Name:

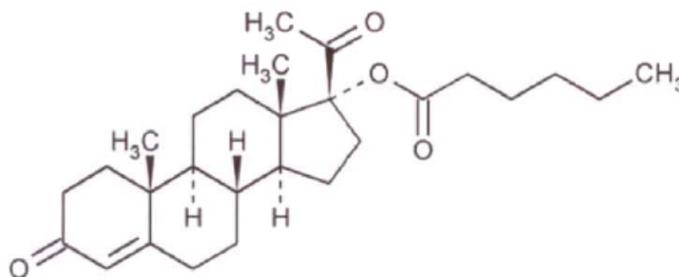
17 α -Hydroxyprogesterone
Caproate

US Adopted Name (USAN):

Hydroxyprogesterone Caproate

International Non-Proprietary Name (INN):

Hydroxyprogesterone (as alcohol)



Chemical Formula:

 $C_{27}H_{40}O_4$

Molecular Weight:

428.60

CAS Registry Number:

630-56-8 (hydroxyprogesterone:
68-96-2)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	20-Sep-2006	Reviewed by M. Cooper
	III			4	N/A		
	III			3	Adequate	19-May-2004	Reviewed by R. Madurawe

Chemistry Review Data Sheet

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	53,730	Research IND for 17 α -Hydroxyprogesterone caproate from NICHD
IND	(b) (4)	Research IND for 17 α -Hydroxyprogesterone caproate from NICHD
NDA	21-945	CMC Review #1 dated 20-Sep-2006

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	16-Jun-2008	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	To be submitted postapproval as per ONDQA policy		
DMETS	ACCEPTABLE	22-Oct-2008	F. Duffy
EA	ACCEPTABLE	20-Sep-2006	M. Cooper, Ph.D.
Microbiology	ACCEPTABLE (manufacturing)	19-Jun-2008	J. Metcalf, Ph.D.
	ACCEPTABLE (post-penetration stability)	18-Dec-2008	J. McVey, Ph.D.

The Chemistry Review for NDA 21-945

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for APPROVAL.

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

N/A

II. Summary of Chemistry Assessments

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

The following paragraph has been copied from NDA 21-945 CMC Review # 1 dated 22-Sep-2006 by Monica Cooper, Ph.D.:

Hydroxyprogesterone caproate (also known as 17 α -hydroxyprogesterone caproate or 17-HPC) is a synthetic progestin (progesterone hormone) that is indicated for the prevention of recurrent preterm birth. The drug substance (API) and the drug product are both USP compendial items. 17 α -Hydroxyprogesterone caproate is a synthetic esterified derivative of the naturally-occurring progestin 17 α -hydroxyprogesterone, which has minimal progestational activity. On the other hand, 17 α -hydroxyprogesterone caproate has substantial progestational activity and a prolonged duration of action.

DRUG SUBSTANCE:

Information on the drug substance is contained in DMF (b)(4). There have been no updates since the last review. See DMF (b)(4) Review # 1 dated 20-Sep-2006 by Monica Cooper, Ph.D. for more detailed information.

Executive Summary Section

DRUG PRODUCT

The following paragraph has been copied from NDA 21-945 CMC Review # 1 dated 22-Sep-2006 by Monica Cooper, Ph.D.:

The drug product, Gestiva™ (hydroxyprogesterone caproate injection), is a clear yellow, viscous, oily solution with an organic odor. It will be supplied in one dosage concentration, 250 mg/mL. All excipients are USP/NF compendial items. The drug product will be provided as a sterile solution in a multi-use 5-mL glass vial (with a (b) (4) stopper) containing five 1-mL injections for intramuscular administration.

Three CMC-related deficiencies were conveyed in the Approvable Letter:

1. *Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.*
2. *Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.*
3. *Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.*

CMC points 1 and 2 were discussed with the company in December 2006 and additional data were submitted for evaluation. It was determined at that time that the additional data were satisfactory and the following agreements were made in a teleconference held on 11-Jan-2007:

1. Analysis of the additional stress light studies indicated that there was no increase in photodegradants and that it was not necessary to develop additional tests.
2. Sponsor will address the photosensitivity of the product with package labeling

For CMC deficiency 3, the sponsor has provided adequate information about the identity of the particulate matter observed in the stability samples held under accelerated conditions. In the Complete Response, they submitted additional long term stability data up to 24 months on the primary stability batches and 12 months of data on process validation batches. Late in the review cycle, the sponsor reported that due to a calculation error, the particulate matter results were reported (b) (4) less than the actual values. Due to the amount of data submitted, the Amendment was coded as a major Amendment, and the review clock was extended. The recalculated and additional data (up to 30 months on the

Executive Summary Section

primary stability batches and 24 months on the process validation batches) were submitted and evaluated. While the particulate matter values were (b) (4), they were well within specifications for this dosage form, and the final evaluation has not changed.

In addition to addressing the CMC issues in the Complete Response, a minor change was made to the solution transfer process to ensure that the product is manufactured in compliance with the Medicine and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom. This change was evaluated by the microbiology reviewer to determine that it did not adversely affect FDA requirements and was found to be adequate.

An issue was raised concerning microbiological stability of the product once the product was penetrated. The issue was consulted to Microbiology, which determined that the data are adequate to support a in-use shelf-life of 5 weeks once the stopper is penetrated by the syringe. This will be reflected in the Dosage and Administration section of the label.

Based on the submitted data, **an expiration dating period of 24 months is granted when stored at controlled room temperature. In addition, the contents must be protected from light and stored in the upright position.** Sponsor has adequately addressed all CMC issues.

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

Gestiva (hydroxyprogesterone caproate injection) will be supplied in 5-mL multi-use glass vials with (b) (4) stoppers in one dosage concentration – 250 mg/mL. The drug will be dosed as a 1-mL (250 mg) intramuscular injection once per week during pregnancy beginning at week 16 – 20 to week 37 of gestation or until birth (for pregnant women with a prior history of at least one spontaneous preterm birth).

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. The Office of Compliance has issued an ACCEPTABLE overall recommendation for all the facilities involved. Labels have required information.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Donna F. Christner/20-Dec-2008
Moo-Jhong Rhee/Branch Chief/Date
Charlene Williamson, OND PM/Date

C. CC Block

30 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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/s/

Donna Christner
12/22/2008 01:21:37 PM
CHEMIST

Made recommended changes

Moo-Jhong Rhee
12/22/2008 01:25:04 PM
CHEMIST
Chief, Branch III

NDA 21-945

**Gestiva™ (proposed)
(hydroxyprogesterone caproate injection)**

**Adeza Biomedical
Division of Reproductive and Urologic Products**

**Monica D. Cooper, Ph.D.
ONDQA Pre-Marketing Assessment
Division II/Branch III**

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S.3 Characterization [Hydroxyprogesterone Caproate, (b) (4)].....	14
S.4 Control of Drug Substance [Hydroxyprogesterone Caproate, (b) (4)].....	14
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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA 21-945
2. REVIEW #: **1**
3. REVIEW DATE: 22-Sep-2006
4. REVIEWER: Monica D. Cooper, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA 21-945 (M002 BC)

NDA 21-945 (N000)

NDA 21-945 (N000 BL)

NDA 21-945 (N000 BC)

NDA 21-945 (N000 BC)

NDA 21-945 (N000 BC)

Document Date

28-Mar-2006

14-Apr-2006

20-Apr-2006

28-Jul-2006

14-Aug-2006

07-Sep-2006

7. NAME & ADDRESS OF APPLICANT:

Name Adeza Biomedical**Address** 1240 Elko Drive
Sunnyvale, CA 94089**Representative** Durlin Hickok, M.D.**Telephone** 408-745-5170

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Gestiva (proposed)
Non-Proprietary Name (USAN)	Hydroxyprogesterone Caproate
Code Name	Drug Substance: 17-HPC Drug Product: 17P
Chemistry Type	5
Submission Priority	P

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

10. PHARMACOL. CATEGORY: Synthetic Progestin / Prevention of recurrent preterm birth

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 250 mg/mL in 5 mL multi-use vial

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Names:

- 17-Hydroxypregn-4-ene-3,20-dione hexanoate
- Pregn-4-ene-3,20-dione, 17-[(1-oxohexyl)oxy]-

Generic Name:

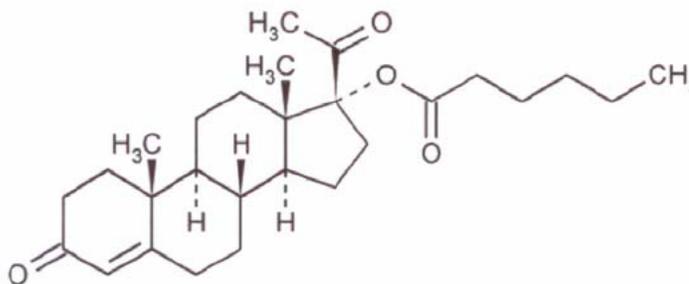
17 α -Hydroxyprogesterone
Caproate

US Adopted Name (USAN):

Hydroxyprogesterone Caproate

International Non-Proprietary Name (INN):

Hydroxyprogesterone (as alcohol)



Chemical Formula:

 $C_{27}H_{40}O_4$

Molecular Weight:

428.60

CAS Registry Number:

630-56-8 (hydroxyprogesterone:
68-96-2)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	20-Sep-2006	Reviewed by M. Cooper
	III			4	N/A		
	III			3	Adequate	19-May-2004	Reviewed by R. Madurawe

Chemistry Review Data Sheet

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	53,730	Research IND for 17 α -Hydroxyprogesterone Caproate from the National Institute of Child Health and Human Development (NICHD)
IND	(b) (4)	(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12-Jul-2006	S. Adams
LNC	N/A	----	----
Methods Validation	<i>To be initiated post-approval</i>	----	----
ODS DMETS	Tradename: <i>Gestiva</i> – Not Acceptable*	13-Sep-2006	F. Duffy
EA	Categorical Exclusion Acceptable	See Review Date Above	M. Cooper
Microbiology	Acceptable	10-Aug-2006	J. Metcalfe

*The tradename *Gestiva* was not acceptable to DMETS due to potential look-alike and sound-alike errors with the drug name Sustiva. This issue will be conveyed to the applicant and further discussions will be conducted. Thus, at this time the tradename is still pending.

The Chemistry Review for NDA 21-945

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (21-945) is **APPROVABLE** from the perspective of chemistry, manufacturing, and controls. Issues regarding drug product photosensitivity and particulate matter, which impact the storage and expiration date for the drug product, remain unresolved.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities.

Labeling issues will be addressed during the second review cycle.

The action letter should state –

- You have not clearly shown that your drug product is photostable. In the validation report for your reverse-phase HPLC method for the determination of 17 α -hydroxyprogesterone caproate content, identity, and purity, on page 37 or 434 of your **Amendment dated 28-Jul-2006**, you stated, “The light stressed drug product sample had significant degradation with a recovery of (b)(4) of label; however, the purity results of (b)(4) did not indicate a corresponding level of impurities.” You did not provide an explanation for this observation. In the revised validation of the HPLC method provided in your **Amendment dated 07-Sep-2006**, you did not indicate the degree of degradation for the stressed samples obtained from the repeated forced degradation studies. It appears the drug product is photosensitive; however, the resulting impurities are not detectable by your HPLC method. ICH Q1B states that analysis of the light-stressed samples should be performed “by a method suitably validated for products likely to arise from photochemical degradation processes.” Since you cannot account for the degradation of the active ingredient under light-stress conditions, you should develop another supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method and a detailed description of the new analytical procedure with appropriate validation should be provided.
- Please revise the drug product labeling to state that the vials should be protected from light. Given the earlier results from your photostability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box)

Executive Summary Section

samples showed decreases in assay from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that your secondary packaging provides adequate light protection for the drug product. Thus, alternative primary and/or secondary packaging should be used. A description of the new packaging system should be submitted, with appropriate letters of authorization.

- Your proposed expiration date of 24 months for the drug product is not acceptable. Based on ICH Q1E guidelines and taking into account the limited stability data provided in the submission and the out-of-specification results for particulate matter observed at accelerated conditions, an expiration date of NMT 10 months would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions and if necessary you should consider a different container closure for storage of your drug product.

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

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

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

Hydroxyprogesterone caproate (also known as 17 α -hydroxyprogesterone caproate or 17-HPC) is a synthetic progestin (progesterone hormone) that is indicated for the prevention of recurrent preterm birth. The drug substance (API) and the drug product are both USP compendial items. 17 α -Hydroxyprogesterone caproate is a synthetic esterified derivative of the naturally-occurring progestin 17 α -hydroxyprogesterone, which has minimal progestational activity. On the other hand, 17 α -hydroxyprogesterone caproate has substantial progestational activity and a prolonged duration of action.

Drug Substance

The drug substance, hydroxyprogesterone caproate (17-HPC), is a crystalline or powdery white to practically white material insoluble in water and soluble in short-chain alcohols (e.g. ethanol and methanol). 17-HPC has multiple chiral centers and an optical rotation of +61° in 1% chloroform ($[\alpha]^{20}_D$). 17-HPC has a melting point of 120 – 124°C and a maximum absorbance at 241 nm in ethanol.

Executive Summary Section

17-HPC is manufactured by (b) (4). The manufacture, testing, and control of 17-HPC is described in (b) (4) Type II DMF (b) (4) – see DMF Review #1 (M.Cooper). The applicant (and DMF holder) proposed a (b) (4) retest date for the bulk drug substance when stored at controlled room temperature based on 60 months of long-term stability data. The (b) (4) retest date is acceptable.

Drug Product

The drug product, Gestiva™ (hydroxyprogesterone caproate injection), is a clear yellow, viscous, oily solution with an organic odor. It will be supplied in one dosage concentration, 250 mg/mL. All excipients are USP/NF compendial items. The drug product will be provided as a sterile solution in a multi-use 5-mL glass vial (with a (b) (4) stopper) containing five 1-mL injections for intramuscular administration.

The formulation of the Gestiva drug product is identical to that of the previously approved Bristol Myers Squibb drug product Delalutin (hydroxyprogesterone caproate injection USP), 250 mg/mL (NDAs 10-347 and 16-911). Gestiva is manufactured using (b) (4) process.

The applicant performed the two photostability studies recommended by ICH Q1B – a forced degradation study and a confirmatory study. The forced degradation study was done in conjunction with the method validation for the HPLC method used to determine the identity, content, and purity of the active (17-HPC) in the drug product. This study revealed that a (b) (4) decrease in assay was obtained after light-stress (250 W/m² for 7 hours) without a corresponding increase in the impurities as detected by the HPLC method. The confirmatory photostability study, which was performed using the ICH conditions of 1.2 million lux hours, showed a (b) (4) decrease in assay for both the fully exposed drug product sample and the drug product sample stored in the secondary packaging (a white chipboard box) as compared to the control sample (wrapped in foil), again without an increase in impurities by HPLC. The applicant claims the drug product is not photosensitive and that the decrease in assay in the confirmatory study should be contributed to analytical variation. However, it appears to this reviewer that the drug product is indeed photosensitive and the HPLC method cannot detect the resulting photodegradants. In addition, it is not clear that the secondary packaging is providing adequate light-protection for the drug product. The applicant should develop a supporting method to detect and quantitate any potential impurities resulting from photodegradation of the drug product. In addition, the applicant should consider using alternative primary and/or secondary packaging (e.g. amber vials or a foil pouch) for the drug product.

The applicant provided updated stability data for three registration (b) (4) pilot-scale) batches out to 6 months in the **Amendment dated 28-Jul-2006 (N000 BC)** and out to 9 months in the **Amendment dated 07-Sep-2006 (N000 BC)** – with data from an additional time point for particulates at (b) (4). Up to 36 months of long-term supportive stability data were also provided. The applicant proposed an expiration date

Executive Summary Section

of 24 months for the drug product when stored at controlled room temperature based on the available data and statistical analysis. However, based on ICH Q1E guidelines and the significant change in particulate matter observed at accelerated conditions, the proposed 24-month expiration date is not acceptable. An expiration date of NMT 10 months would be appropriate for the drug product when stored at controlled room temperature, protected from light.

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

Gestiva (hydroxyprogesterone caproate injection) will be supplied in 5-mL multi-use glass vials with (b) (4) stoppers in one dosage concentration – 250 mg/mL. The drug will be dosed as a 1-mL (250 mg) intramuscular injection once per week during pregnancy beginning at week 16 – 20 to week 37 of gestation or until birth (for pregnant women with a prior history of at least one spontaneous preterm birth).

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (21-945) is **APPROVABLE** from the perspective of chemistry, manufacturing, and controls for the following reasons:

- The drug product appears to be photosensitive and the current packaging does not adequately protect the drug product from light.
- The analytical method (HPLC) for evaluating the purity, identity, and content of the API in the drug product is not validated for the detection of potential photodegradants.

III. Administrative**A. Reviewer's Signature**

/s/ M.D. Cooper, Ph.D.

B. Endorsement Block

CMC Reviewer:	Monica D. Cooper, Ph.D.
Pharmaceutical Assessment Lead:	Donna Christner, Ph.D.
Branch Chief:	Moo-Jhong Rhee, Ph.D.

C. CC Block

Original NDA 21-945
HFD-580 Division File

79 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Monica Cooper
9/22/2006 11:07:28 AM
CHEMIST

Moo-Jhong Rhee
9/22/2006 11:17:52 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 21-945
Applicant: Adeza Biomedical
Stamp Date: 20-Apr-2006 (CMC package received 12-Apr-2006;
NDA first volume received 04-May-2006)
PDUFA Date: 20-Oct-2006 (Priority)
Trademark: Gestiva
Established Name: 17 α -Hydroxyprogesterone Caproate Injection
Dosage Form: Injection
Route of Administration: Intramuscular Injection
Indication: Prevention of recurrent preterm labor

PAL: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	<input type="checkbox"/>
Comments for 74-Day Letter	x	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

The NDA is submitted under a 505(b)(2) New Drug Application. The sponsor did not conduct their own clinical trials, but references published literature and research performed at the National Institute of Child Health and Human Development (NICHD). LOAs to reference the clinical trial information from INDs 53,730 and (b)(4) are provided. This drug product is the subject of a USP monograph and has been manufactured by a number of different companies, but is no longer commercially available. The sponsor compares their drug product to one such product, Delalutin, previously manufactured by Bristol Meyers Squib (BMS). It has been granted a Priority Review because "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."

The 17 α -Hydroxyprogesterone caproate (17P) drug product is a clear, yellow, viscous and oily solution with an organic odor. In addition to the API, the formulation contains benzyl benzoate, USP, benzyl alcohol, NF, and castor oil, USP. It will be supplied in one dosage concentration of 250 mg/mL, as a sterile solution in a (b)(4) stoppered, multi-dose 5 mL glass vial. The dose is 1 mL administered weekly by intramuscular injection. The drug product is (b)(4) processed (b)(4). It should be noted that the Delalutin drug product, in the Approval letter dated 13-Mar-1956 (provided by the sponsor via FOI), states that the drug product is (b)(4).

Information on the drug substance is provided in the referenced DMF, although general information is provided in the NDA for ease of review. The drug substance DMF will require review.

There were extensive interactions with the sponsor during development. The following CMC related meetings/correspondences are captured in DFS, and outlined in the ASSESSMENT NOTES that follow in this document:

- Guidance meeting held on 30-Jan-2004
- Guidance meeting held on 26-Jul-2004
- CMC preNDA meeting held on 18-Apr-2006
- Response to issues raised at preNDA meeting, sent 15-May-2005
- Memo concerning specifications dated 13-Jul-2005

As agreed to by the Division in previous interactions with the sponsor, the compendial test for free caproic acid is not included because a more stringent test for 17- α Hydroxyprogesterone is included in the specification, making the test for free caproic acid redundant. It was also agreed that tests for (b) (4) and Volume Recovery would not be necessary on stability, since these parameters would not be stability-indicating because the packaging would provide adequate protection for the drug product.

A microbiology consult was sent on 28-Apr-2006 for evaluation of the microbiological testing and manufacture of the drug product. An EES request was submitted on 27-Apr-2006 for site inspections. A tradename consult was requested on 02-May-2006.

B. Critical issues for review

Since the critical steps for manufacturing involve assurance of sterility, a microbiology consult was requested on 28-Apr-2006 for their evaluation of the manufacturing steps (b) (4) (b) (4) including packaging and release and stability tests and acceptance criteria. LOAs for two DMFs (b) (4) involving sterile manufacturing are included for their evaluation. It was also requested that the microbiology consult address tests for Bioburden and Endotoxins submitted in the NDA for drug substance. The sponsor states that the holder will add these tests to the DMF, but they were submitted in the NDA for ease of review.

In meetings held prior to NDA submission, the sponsor requested (b) (4) expiry based on historical information on the Delalutin (BMS) product and the clinical drug supplies quality-controlled by (b) (4) which is not the commercial manufacturer (Baxter Pharmaceutical Solutions, LLC) of this product. The sponsor was advised that expiry would be based on their submitted data on drug product manufactured by the commercial manufacturer, with information from (b) (4) as supporting data. The sponsor must also demonstrate that the drug product manufactured by all three manufacturers is pharmaceutically equivalent.

The sponsor has submitted 3 months of stability data on the drug product manufactured by Baxter, and, as agreed with the Division, will submit 6 months of stability data during the review cycle.

C. Comments for 74-Day Letter

There are no comments to convey in the 74-day letter.

D. Recommendation:

This NDA is fileable from a CMC perspective. Because of the exhaustive regulatory guidance provided by the assigned reviewer (Dr. Rajiv Agarwal) to the sponsor prior to NDA submission, there are no comments for the 74-day letter. Due to workload and timeline constraints, the NDA has been reassigned to Dr. Monica Cooper. The primary reviewer will evaluate the application to request any additional information deemed necessary

Because a Priority Review has already been granted, the PDUFA date will be 20-Oct-2006. There will also be an Advisory Committee held during August 2006 for this application. Under the GRMP guidelines, the review will need to be finalized by 20-Aug-2006.

Donna F. Christner, Ph.D.

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
X		On its face, is the section organized adequately?	
X		Is the section indexed and paginated adequately?	
X		On its face, is the section legible?	
X		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	Some CFNs missing
X		Has an environmental assessment report or categorical exclusion been provided?	Categorical exclusion requested as per 21 CFR 25.31(a)

B. Technical Checklists

1. Drug Substance

X		Does the section contain synthetic scheme with in-process parameters?	DMF	(b) (4)
X		Does the section contain structural elucidation data?	DMF	(b) (4)
X		Does the section contain specifications?	DMF	
X		Does the section contain information on impurities?	DMF	
X		Does the section contain validation data for analytical methods?	DMF	
X		Does the section contain container and closure information?	DMF	
X		Does the section contain stability data?	DMF	

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	
X		Does the section contain quality controls of excipients?	
X		Does the section contain information on composition?	
X		Does the section contain specifications?	
X		Does the section contain information on degradation products?	
X		Does the section contain validation data for analytical methods?	
X		Does the section contain information on container and closure systems?	
X		Does the section contain stability data with a proposed expiration date?	
X		Does the section contain information on labels of container and cartons?	
X		Does the section contain tradename and established name?	

C. Review Issues

X		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	X	Is a team review recommended?	
X		Are DMFs adequately referenced?	

DMF LIST

DMF No.	Holder	Description	LOA Included	Status
		(b) (4)	Yes	No review. Submitted on 21-Jan-2004; Annual Report on 30-Jun-2004.
			Yes	Adequate on 12-May-2004 for NDA (b) (4) by R. Madurawe
			Yes	Adequate on 12-Feb-2003 for NDA (b) (4) by L. Rodriguez
			Yes	No review
			Yes	Adequate on 23-Aug-2004 for NDA (b) (4) by J. Metcalfe

ASSESSMENT NOTES

The NDA is submitted under a 505(b)(2) New Drug Application. The sponsor did not conduct their own clinical trials, but references published literature and research performed at NICHD. LOAs to reference the clinical trial information from the Maternal-Fetal Medicine Unit (MFMU) Network of the National Institute of Child Health and Human Development (NICHD) under INDs 53,730 and (b)(4) are provided. This drug product is the subject of a USP monograph and has been manufactured by a number of different companies, but is no longer commercially available. The sponsor compares their drug product to one such product, Delalutin, previously manufactured by Bristol Meyers Squib.

The following CMC-related interactions (captured in DFS) took place between the firm and the FDA under preIND 68,108. The original CMC reviewer was Rajiv Agarwal.

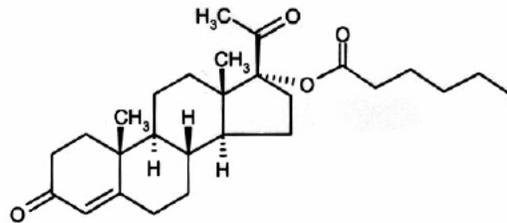
- **Guidance meeting held 30-Jan-2004.** This was a multi-discipline meeting. The Division agreed with the sponsor that FDA's prior findings of safety for Delalutin and current published literature would be sufficient to support an NDA. The following CMC comments were made:
 - Full CMC information on the drug product would need to be submitted in an NDA.
 - If results from the NICHD study are used, pharmaceutical equivalence between the 17 α -Hydroxyprogesterone caproate injection (17P) product used in the study and the to-be-marketed formulation of 17P would need to be demonstrated.
 - It was also recommended that a DMF be opened for drug substance information if the drug substance 17 α -Hydroxyprogesterone caproate (17-HPC) is manufactured by a contractor.
 - The sponsor was further encouraged to submit 12 months of stability data upon submission of the NDA, which would include 12 months of real time data and 6 months accelerated stability on 3 commercial batches.
- **Guidance meeting on 26-Jul-2004.** No specific CMC information was discussed, but the Division advised the sponsor that they could apply for "Fast Track" designation to allow for submission of the NDA on a rolling basis, and that the clock would start upon submission of the last component of the NDA. The sponsor has taken advantage of this, submitting the CMC information on 03-Apr-2006, although the jackets were not delivered until 12-Apr-2006.
- **CMC preNDA meeting held 18-Apr-2005.** The sponsor posed 14 questions:
 - The sponsor asked if the API information could be submitted in a DMF held by (b)(4). The Division agreed, but requested that the physico-chemical properties, specifications and stability data be submitted as part of the NDA, and that the DMF be current.
 - The sponsor asked if the API specifications were adequate. The Division agreed that the specifications were adequate, but adequacy of acceptance criteria would be a review issue. They were advised to submit a COA as part of the NDA.
 - In response to a question on using stability data from one lot of 17P (b)(4) stored in the upright position, the sponsor was advised to provide 3 months real time and accelerated stability data on three primary batches (using at least 2 API batches), stored in the upright and inverted positions using stability-indicating methods and to update with at least 6 months of data 90 days before the PDUFA date. In response to a follow-up question on waiver of the free caproic acid test and use of one batch of API, the sponsor was told to submit the question in writing for a written response.

- The sponsor requested a (b) (4) expiry based on historical data from Delalutin and one batch from (b) (4). The Division did not concur, but stated that expiry would be based on the submitted data. The sponsor was referred to the ICH Q1A(R2) and Q1E guidances.
- Recommendations were made on the stability protocol, with the addition of tests for benzyl alcohol content, volume recovery, free caproic acid content, particulate matter, (b) (4), API degradation products and bacterial endotoxins. Reference was made to the Draft Stability Guidance (June 1998). Upon query from the sponsor for the necessity of volume recovery, particulate matter and (b) (4) on stability, the Agency responded that they are deemed necessary, but this could be reassessed.
- The sponsor was informed that the quantitative and qualitative composition of the clinical study formulation and the to-be-marketed formulation should be submitted to demonstrate the pharmaceutical equivalence, in addition to the information proposed by the sponsor.
- The sponsor was informed that the process validation information including the adequacy and efficacy of the (b) (4) process should be submitted at the time of NDA filing.
- The sponsor was informed that the final product release specifications and analytical methods were acceptable, provided the recommended tests were added. The sponsor was asked to propose new language for the Appearance specification. Reference to the ICH Q2A and Q2B guidances were given.
- The sponsor was informed that three months of accelerated stability data would be adequate to justify the use of an alternate container closure system, along with the relevant DMFs and LOAs.
- The Agency has no objection to the use of alternative HPLC assay methods for drug product release, if it is the same as (b) (4) HPLC method.
- For content of the CMC section of the NDA, the sponsor was referred to the M4Q guidances. They were also advised that if any portion of the NDA was submitted electronically, the whole NDA would be required to be submitted electronically.
- The sponsor was advised that upon submission of the NDA, all sites should be ready for inspection and that all DMFs and LOAs should be provided. DMFs should also be current.
- **IR letter dated 15-May-2005 in response to outstanding issues from CMC preNDA meeting.** There were 5 outstanding issues from the CMC preNDA meeting.
 - The Agency agreed that the three primary stability lots of drug product could be manufactured from (b) (4) drug substance, but that COAs should be provided for the three lots of API used to manufacture the drug product used in the clinical trials.
 - The sponsor was informed that expiry would be based upon review of the submitted stability data.
 - The Agency agreed that the test for free caproic acid would not be necessary because the sponsor will monitor the free 17 α -hydroxyprogesterone on release and stability. It was also agreed that (b) (4) and volume recovery need not be included in the drug product release and stability testing. The release and shelf life specifications should include the test for free 17 α -hydroxyprogesterone.
 - The Agency agreed that the performance of USP <51>, Antimicrobial Testing, at the 6 month time point for the (b) (4) lot 9002244 would be adequate for filing and review of the NDA.
 - The Agency agreed that the Appearance specification of “Clear, yellow color, essentially free from foreign particulate matter, viscous and oily solution with an organic odor,” was adequate, but that a test for particulate matter should be included at release and stability.

- **Memo dated 13-Jul-2005 concerning stability studies.** Guidance was provided on stability studies. Studies will include tests for *Physical examination, Particulate matter, Benzyl alcohol content, Purity, Assay, Antimicrobial Effectiveness Testing, Bacterial endotoxins* and Sterility. Tests in italics were recommended by the Agency at the CMC preNDA meeting. Drug product specifications and testing time intervals for sterility assurance were consulted to Dr. David Hussong and deemed adequate.

DRUG SUBSTANCE

The drug substance is 17 α -Hydroxyprogesterone caproate (17-HPC). It is manufactured by (b) (4) and information is provided in the referenced DMF (b) (4). As requested, physico-chemical properties, specifications, and stability data have been submitted in the NDA. Review of the DMF will be required since it has not been previously reviewed.



17 α -Hydroxyprogesterone Caproate

A general narrative for the manufacture is provided in the NDA. The API is synthesized by the esterification of 17 α -Hydroxyprogesterone (b) (4)

Detailed information is provided in the referenced DMF.

Drug substance manufacturer is :

(b) (4)

The sponsor has provided a specification table for drug substance which compares the USP monograph requirements, the drug product manufacturer's requirements, and the drug substance manufacturer's specifications. The drug product manufacturer uses the USP tests plus tests for Bioburden (as per EP) and Endotoxins. (b) (4) in addition to the USP tests, has a number of stability-indicating methods and assay by HPLC. (b) (4)

Analysis is provided for two lots of drug substance tested by the drug product manufacturer (or contract laboratories). The sponsor states that the first three batches of drug substance will be fully tested according to USP and Fourier Transform Infrared Spectroscopy by the drug product

manufacturer to qualify (b)(4) as a supplier. Subsequent to qualification, drug substance will be accepted as per COA and a mandatory FTIR identity test.

Methods for compendial tests are not provided. All test methods are provided in the referenced DMF. The method and validation for Assay (HPLC) is provided in the NDA because it is used to release finished drug product. Tests for Bioburden and Endotoxins are also included in the submission because the drug substance manufacturer has not submitted them to the DMF at the time of NDA filing. The DMF holder is in the process of updating their DMF to include these tests. Method and validation for the FTIR test is provided.

Table 3.2.S.4-1: Specifications Established by (b)(4) for 17 α -Hydroxyprogesterone Caproate USP

Test Method	USP Requirement	(b)(4)		Acceptance Criteria
Appearance (Visual)	No	No	Yes	Powder
Color (Visual)	No	No	Yes	White to practically white
Visible impurities (Visual)	No	No	Yes	Not present
Identification (USP 29 <197K>; FTIR, BPS SOP 303-08-03-001)	Yes	Yes	Yes	Conforms to reference standard
Identification (TLC)	No	No	Yes	Identical with reference standard
Assay (HPLC)	No	No	Yes	97.0 % to 103.0 %
Assay (USP 29 UV Spectroscopy)	Yes	Yes	Yes	97.0 % to 103.0 %
Free Caproic Acid (USP 29 Titrimetric Assay)	Yes	Yes	Yes	LTE (b)(4)
Melting Point (USP 29 <741> Class Ia)	Yes	Yes	Yes	120°C to 124°C
Related Substances (HPLC) Hydroxyprogesterone 17 α , β -methyl-D-homo compound	No	No	Yes	LTE (b)(4) LTE (b)(4)
Related Substances- total specified and unspecified (HPLC)	No	No	Yes	LTE (b)(4)
Related Substances (Ordinary Impurities)- total (USP 29 <466>TLC)	Yes	Yes	Yes	LTE (b)(4)
(b)(4)	No	No	Yes	LTE (b)(4) LTE (b)(4) LTE (b)(4) LTE (b)(4)
Specific Rotation (USP 29 <781S>; 25°C/1% in chloroform/anhydrous substance)	Yes	Yes	Yes	+58° to +64°
(b)(4)	Yes	Yes	Yes	LTE (b)(4)
(b)(4)	No	No	Yes	LTE (b)(4)
Bioburden [EP 2.6.12; <i>Microbial Examination of Non-Sterile Products (Total Viable Aerobic Count)</i>]	No	Yes	Yes	(b)(4)
Endotoxin (USP 29 <85>; Gel-Clot Limit Test)	No	Yes	Yes	(b)(4)

Stability data on four lots with 60 months of real time data and one lot with 36 months of data are provided. Full information is provided in the DMF.

Comment: The DMF will require review. A microbiology consult was sent on 28-Apr-2006 for evaluation of the microbiological testing. An EES request was submitted on 27-Apr-2006 for site inspection.

DRUG PRODUCT

The 17P drug product is a clear, yellow, viscous and oily solution with an organic odor. It will be supplied in one dosage concentration of 250 mg/mL. It is provided as a sterile solution in a (b) (4) stoppered 5 mL glass vial, which is a multi-dose container, containing five 1-ml doses. It is (b) (4) processed (b) (4). The product is intended to be administered once weekly by intramuscular injection of 1 mL.

The sponsor has provided a comparison of the to-be-marketed formulation, the formulation used in the clinical trials and the discontinued Delalutin drug product, as advised during previous sponsor-FDA interactions.

Table 3.2.P.2-1: Composition of 17P Drug Product Formulations

Component	Adeza 17 Drug Product 250 mg/mL	Study 17P-CT-002 250 mg/mL	Delalutin ² 250 mg/mL
17 α - Hydroxyprogesterone Caproate USP ¹	250 mg/mL 25% (v/v)	250 mg/mL 25% (v/v)	(b) (4)
Benzyl Benzoate USP ¹	(b) (4) 46% (v/v)	(b) (4) 46% (v/v)	(b) (4)
Benzyl Alcohol NF ¹	(b) (4) 2% (v/v)	(b) (4) 2% (v/v)	(b) (4)
Castor Oil USP ¹	(b) (4) 28.6% (v/v)	(b) (4) 28.6% (v/v)	(b) (4)

¹ Formulary designations are for the Adeza 17P drug product and 17P drug product for Study 17P-CT-002 only.

² Delalutin Package Insert (1979). The type of percentage is not reported for the excipients, but assumed to be v/v according to the FDA Chemist Review (1970).

³ Includes a (b) (4) overage.

⁴ It is unknown whether the compounding procedure for the Delalutin product included a (b) (4) overage.

Pharmaceutical Development includes the above comparison of the drug products. It also includes information on the transfer and scale-up studies performed for manufacturing from the site of manufacture of the clinical study supplies for referenced INDs 53,730 and (b) (4). Clinical supplies were manufactured at a (b) (4) scale at (b) (4) (see CMC Review #1 for IND (b) (4) dated 17-Feb-2004). Scale-up was performed to (b) (4) for the exhibit and registration stability batches. Commercial scale will be (b) (4). Manufacturing process development at the commercial manufacturing site also included studies on (b) (4)

The following facilities are involved in production of the drug product. Sites were submitted to EES on 27-Apr-2006.

Manufacturer of drug product, release testing of excipients, drug substance, drug product, and stability testing of drug product

Baxter Pharmaceuticals Solutions LLC
927 South Curry Pike
Bloomington, IN 47403

Contract testing lab to conduct AET and Bacterial Endotoxin testing

(b) (4)
1

Contract testing lab to conduct drug substance USP monograph testing

(b) (4)

Contract testing lab to conduct Photostability testing, Monograph testing of excipients and USP Monograph Ordinary Impurities Testing of drug substance

(b) (4)

Manufacture of the 17P drug product is by (b) (4) . (b) (4)

(b) (4)

Critical parameters for manufacture which are controlled by in-process testing include Assurance of benzyl alcohol and API content, Density of the solution, Prefiltration bioburden, (b) (4) . Since the critical steps for manufacturing involve assurance of sterility, a microbiology consult was requested on 28-Apr-2006 for their evaluation of the manufacturing steps after (b) (4) including packaging and release and stability tests and acceptance criteria. LOAs for two DMFs (b) (4) involving sterile manufacturing are included for their evaluation.

Excipients are controlled by USP/NF compendial testing. An additional test was developed for Benzyl Benzoate Purity by HPLC. It is identical to that for the API purity in drug product and has been validated during validation of the procedure for the API.

The sponsor has established the following specifications based on the guidance given to them in previous FDA/sponsor interactions.

Table 3.2.P.5-1: 17P Drug Product Release Specifications

Finished Product Test	Purpose	Method	Specification	Test Location
Assay (17 alpha-Hydroxyprogesterone Caproate content)	Assurance of API content	RP HPLC SOP No. 303-08-04-002	90 – 110% of label (b) (4)	BPS Chromatography Lab
Identification	Assurance of 17P identity	RP HPLC SOP No. 303-08-04-002	Retention time conforms to RS	
Purity Total 1. 17 alpha-Hydroxyprogesterone 2. Other	Assurance of 17P purity	RP HPLC SOP No. 303-08-04-002	(b) (4)	
Benzyl Alcohol	Assurance of preservative content	RP HPLC SOP No. 303-08-04-001	(b) (4)	
(b) (4)				
Volume Recovery	Assurance of minimum retrieval volume	USP <1> SOP No. 08-02-021	NLT (b) (4) mL per vial	BPS Analytical Lab
Visual Inspection (Appearance)	Assurance that 17P is essentially free of foreign particulate matter	Visual SOP No. 08-02-032	Clear, yellow color, essentially free of foreign particulate matter, viscous and oily solution with an organic odor	
Particulate Matter	Assurance that 17P meets PM criterion for parenteral injections	USP <788> SOP No. 303-08-04-003	(b) (4)	BPS Wet Chemistry Lab
Bacterial Endotoxin	Assurance of safety	Gel Clot USP <85>	(b) (4)	
Sterility	Assurance of sterility	Membrane Filtration USP <71> SOP No. 07-02-003	No growth after 14 days	BPS Microbiology Lab

Since 17P is a USP compendial product, the majority of tests/methods are taken from the USP. In addition to the USP monograph specifications for the drug product, tests were included for API purity by HPLC (monitors impurities from both the API and benzyl alcohol), 17-HPC and benzyl alcohol content by HPLC, and conformance to specifications for USP<1> for injections,

including Particulate Matter, Recovery Volume, Bacterial Endotoxins and Sterility Acceptance Criteria. Antimicrobial Effectiveness Testing has been performed on Lot 901379 (primary stability lot) on release and will be performed at 6 and 36 months. Methods and validation for all noncompendial tests are provided, as is justification for specifications. As agreed to by the Division in previous interactions with the sponsor, the compendial test for free caproic acid is not included because a more stringent test for 17- α Hydroxyprogesterone is included in the specification, making the test for free caproic acid redundant.

The drug product is packaged in 5 ml Type I glass vials with (b) (4) stoppers. All components are covered under referenced DMFs.

STABILITY

On stability, the sponsor tests for Appearance, Particulate Matter, Benzyl Alcohol, Purity, Assay of API, Bacterial Endotoxins, Sterility and Antimicrobial Effectiveness Testing (at 6 and 36 months). The specifications for (b) (4) and Volume Recovery are not included as per agreement with the Division during earlier interactions. Since an (b) (4) would drive the degradation of 17- α Hydroxyprogesterone caproate, any (b) (4) would be captured by a corresponding increase in 17- α Hydroxyprogesterone, making a test for (b) (4) (b) (4) redundant. In addition, because the drug product is packaged in a closed system, it was determined that a change in (b) (4) or volume recovery would not occur, and therefore the tests would not be stability-indicating and were not needed.

The sponsor has not proposed an expiry in the package, but states that they will propose one upon submission of 6 month stability data, including regression analysis, which was agreed to in previous FDA/sponsor interactions. They have submitted 3 months of stability data for product manufactured at the BPS site (vials stored in the upright and inverted positions), and 36 months of supporting stability data on the clinical supplies analyzed by (b) (4) (manufactured at (b) (4) stored in the upright position. The sponsor originally requested (b) (4) months of expiry at the preNDA meeting held on 18-Aug-2005, based on historical data from Delalutin and the data from the (b) (4) samples. The sponsor bases the submission of this application on the previous findings of safety for Delalutin (NDAs 10-347 and 16-911). It should be noted that the Approval letter for NDA 10-347, which the sponsor has requested from FOI and has included in their application (page 5 of Section 3.2 Summary Basis of Approval), states that “ (b) (4)

(b) (4) The drug product used in the clinical trials to support this NDA, and the to-be-marketed supplies, (b) (4)

LABELING

Vial and carton labeling is provided in the CMC section submitted on 12-Apr-2006. Labels are white with black lettering. At the time of submission of this module, the sponsor had not decided on a tradename. The sponsor submitted electronic files dated 14-Apr-2006, and the Physician’s Insert is provided in this submission (Summary Section) with the tradename “Gestiva” and a logo. Color mock-ups for the carton and immediate container labels with the proposed tradename and logo were submitted in an Amendment dated 20-Apr-2006.

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

/s/

Donna Christner
8/1/2006 01:59:25 PM
CHEMIST

Moo-Jhong Rhee
8/1/2006 02:06:56 PM
CHEMIST
Chief, Branch III