CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201923Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Lin Qi

Branch V
Division of New Drug Quality Assessment II
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-923

2. REVIEW #: 5

3. REVIEW DATE: August 3, 2014

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
EOP-2 Meeting Minutes (2-Sep-2008)	02-Jul-2009 (DARRTS)
Pre-NDA Meeting Minutes (04-Mar-2010)	
N-000	28-Jun-2010
BC	08-Jul-2010
BC	09-Jul-2010
BC	13-Jul-2010
IR	21-Jul-2010
BC	23-Jul-2010
IR (biopharm)	04-Aug-2010
BC (biopharm)	12-Aug-2010
BC (stability)	26-Oct-2010
IR	03-Nov-2010
BC	11-Nov-2010
Resubmission	12-May-2011
Amendment	1-June-2011
Amendment	1-July-2011
Resubmission	27-Mar-2013
Amendment	2-Jul-2013

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Resubmission	26-Mar-2014
Amendment	15-Jul-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Alimera Sciences, Inc.
Address:	6120 Windward Parkway, Suite 290 Alpharetta, GA 3005
Representative:	Barbara H. Bauschka
Telephone:	(678) 527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iluvien®
b) Non-Proprietary Name (USAN): fluocinolone acetonide intravitreal insert
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

12. STRENGTH/POTENCY: 0.19 mg

13. ROUTE OF ADMINISTRATION: intravitreal

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

__X____Not a SPOTS product

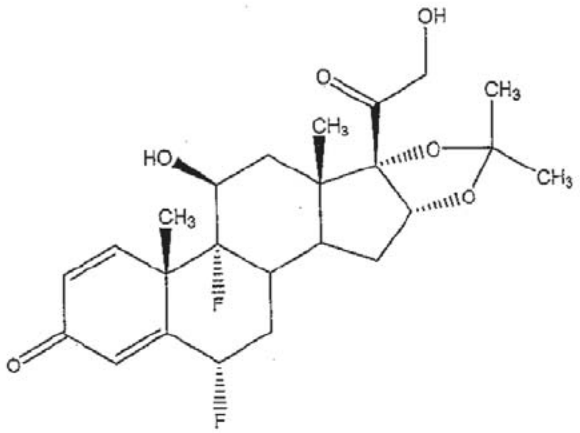
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	

(b) (4)	II	(b) (4)	(b) (4)	4			Information submitted in DMF (b) (4)

[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
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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:

MAF	HOLDER	ITEM	DATE OF LOA
(b) (4)	(b) (4)	(b) (4)	21-Jul-2010

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	7/28/2014	T. Sharp
Pharm/Tox			
Biopharm	Acceptable	9/23/13	Tapash Ghosh
Methods Validation	Acceptable based on CMC review	9/23/13	Lin Qi
DMEPA			
EA	Categorical exemption – acceptable	12/1/10	Dorota Matecka
Microbiology	Acceptable	7/25/11	Steven Fong
CDRH Consult	Issues Resolved	7/28/2014	Nikhil Thakur/Lin Qi

The Chemistry Review for NDA 201-923

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg.

CMC Labeling comments were conveyed to the review team.

Office of Compliance has made an overall recommendation as "Acceptable" for the facilities.

Therefore, from the 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)

Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to insert it into the ocular vitreous chamber.

The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol. [redacted] (b) (4) The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by [redacted]. The proposed commercial manufacturer is [redacted] (b) (4) For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II [redacted] (b) (4) held by [redacted] (b) (4)

See review #1 dated December 1, 2010 by Dr. Dorota Matecka for a detailed description of the drug product and drug substance.

The original NDA dated June 28, 2010 was not approved and a complete response letter (CRL) was sent to the applicant with a list of deficiencies on December 22, 2010. Quality deficiencies identified in the CRL are in CMC review #1, biopharmaceutics review #1, and microbiology review #1. The original NDA also received a site recommendation of "Withhold" from the Office of Compliance.

The NDA resubmission dated May 12, 2011 contains a complete response to CMC deficiencies and the updated quality information. The May 12, 2011 resubmission was found inadequate by this reviewer in CMC review #3 dated September 30, 2011 and deficiencies and additional information requests were listed in the review. One CMC deficiency was sent to the sponsor in the CR letter of November 10, 2011.

The NDA resubmission dated March 27, 2013 contains complete response and supporting documents to the CMC deficiency. Upon request, available stability data, revised description of the drug product analysis procedure, and drug product performance study results were provided in an amendment dated July 2, 2013. The available stability data supports the proposed 24 months expiration dating when stored in the proposed packaging at 15-30°C (59° to 86°F) [redacted] (b) (4)

The new proposed acceptance criteria of [redacted] (b) (4) µg/day for drug product *in-vitro* release rate was found acceptable by Dr. Tapash Ghosh in his review. See biopharmaceutics review dated September 23, 2013 for details.

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

Iluvien® fluocinolone acetonide intravitreal insert (containing 0.19 mg of fluocinolone acetonide) is intended for the treatment of diabetic macular edema. The drug product is to be inserted into the ocular vitreous chamber.

The storage conditions statement recommends the following: "Store at 15-30°C (59° to 86°F) [redacted] (b) (4)". The expiration dating proposed for the product in the original NDA submission is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg. CMC labeling comments were conveyed to the review team during this review cycle (See Attachment 1).

Office of Compliance has made an overall recommendation as "Acceptable" for the facilities on July 28, 2014 (See Attachment 2).

Therefore, from the CMC perspective, this NDA is recommended for **Approval**.

III. Administrative

A. Reviewer's Signature:

Lin Qi, Ph.D., Product Quality Reviewer, Branch V/Div II, ONDQA
{*See electronic signature page*}

B. Endorsement Block

Balajee Shanmugam, Ph.D., CMC Lead, Branch V/Div II, ONDQA
{*See electronic signature page*}

Rapti Madurawe, Ph.D., Branch Chief, Branch V/Div II, ONDQA
{*See electronic signature page*}

C. CC Block

{*Listed in DARRTS*}

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/s/

LIN QI
08/03/2014

BALAJEE SHANMUGAM
08/04/2014

RAPTI D MADURAWE
08/06/2014

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Lin Qi

Branch V
Division of New Drug Quality Assessment II
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-923

2. REVIEW #: 4-Addendum #1

3. REVIEW DATE: October 15, 2013

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
EOP-2 Meeting Minutes (2-Sep-2008)	02-Jul-2009 (DARRTS)
Pre-NDA Meeting Minutes (04-Mar-2010)	
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Amendment	2-Jul-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Alimera Sciences, Inc.
Address:	6120 Windward Parkway, Suite 290 Alpharetta, GA 3005
Representative:	Barbara H. Bauschka
Telephone:	(678) 527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iluvien®
b) Non-Proprietary Name (USAN): fluocinolone acetonide intravitreal insert
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

12. STRENGTH/POTENCY: 0.19 mg

13. ROUTE OF ADMINISTRATION: intravitreal

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

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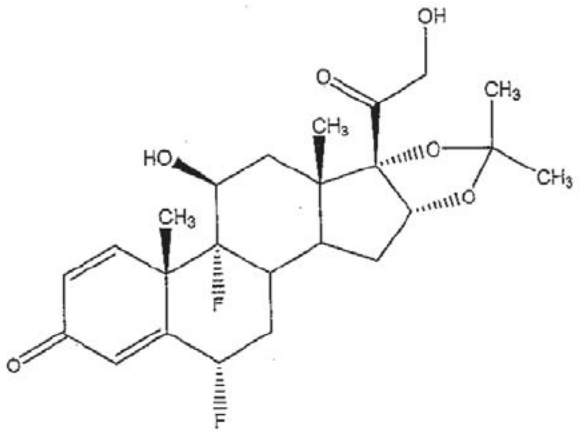
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	

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B. Other Documents:

MAF	HOLDER	ITEM	DATE OF LOA
(b) (4)	(b) (4)	(b) (4)	21-Jul-2010

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	10/11/13	Juandria Williams
Pharm/Tox			
Biopharm	Acceptable	9/23/13	Tapash Ghosh
Methods Validation	Acceptable based on CMC review	9/23/13	Lin Qi
DMEPA			
EA	Categorical exemption – acceptable	12/1/10	Dorota Matecka
Microbiology	Acceptable	7/25/11	Steven Fong
CDRH Consult	Unacceptable		Nikhil Thakur

The Chemistry Review for NDA 201-923

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I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg.

Labeling discussions are pending a team review.

Office of Compliance has made a determination as "Withhold" on the acceptability of the facilities.

Therefore, from the CMC perspective, this NDA is not 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)

Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to insert it into the ocular vitreous chamber.

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The new proposed acceptance criteria of (b) (4) µg/day for drug product *in-vitro* release rate was found acceptable by Dr. Tapash Ghosh in his review. See biopharmaceutics review dated September 23, 2013 for details.

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

Iluvien® fluocinolone acetonide intravitreal insert (containing 0.19 mg of fluocinolone acetonide) is intended for the treatment of diabetic macular edema. The drug product is to be inserted into the ocular vitreous chamber.

The storage conditions statement recommends the following: "Store at 15-30°C (59° to 86°F) (b) (4)". The expiration dating proposed for the product in the original NDA submission is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg. Labeling discussions are pending a team review.

Office of Compliance has made a determination as "Withhold" on the acceptability of the facilities on October 11, 2013 (See Attached EES Report).

Therefore, from the CMC perspective, this NDA is not recommended for approval.

III. Administrative

A. Reviewer's Signature:

Lin Qi, Ph.D., Product Quality Reviewer
{*See electronic signature page*}

B. Endorsement Block

BalajeeShanmugam, Ph.D., CMC Lead
{*See electronic signature page*}

C. CC Block

{*Listed in DARRTS*}

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/s/

LIN QI
10/15/2013

BALAJEE SHANMUGAM
10/15/2013

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Lin Qi

Branch V
Division of New Drug Quality Assessment II
ONDQA

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1. NDA 201-923

2. REVIEW #: 4

3. REVIEW DATE: September 24, 2013

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
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c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

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13. ROUTE OF ADMINISTRATION: intravitreal

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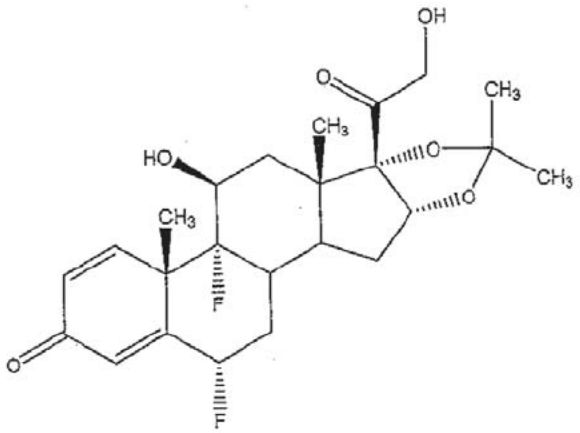

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A. DMFs:

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(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	

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18. STATUS:

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I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg.

Labeling discussions are pending a team review.

Office of Compliance has not made a determination on the acceptability of the facilities as of September 24, 2013.

Therefore, from CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the Office of Compliance.

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)

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The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg. Labeling discussions are pending a team review.

Office of Compliance has not yet made a determination on the acceptability of the facilities.

Therefore, from the CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the Office of Compliance.

III. Administrative

A. Reviewer's Signature:

Lin Qi, Ph.D., Product Quality Reviewer
{*See electronic signature page*}

B. Endorsement Block

Balajee Shanmugam, Ph.D., CMC Lead
{*See electronic signature page*}

C. CC Block

{*Listed in DARRTS*}

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/s/

LIN QI
09/24/2013

BALAJEE SHANMUGAM
09/24/2013

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Lin Qi

Branch V
Division of New Drug Quality Assessment II
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-923

2. REVIEW #: 3

3. REVIEW DATE: Sept 28, 2011

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
EOP-2 Meeting Minutes (2-Sep-2008)	02-Jul-2009 (DARRTS)
Pre-NDA Meeting Minutes (04-Mar-2010)	
N-000	28-Jun-2010
BC	08-Jul-2010
BC	09-Jul-2010
BC	13-Jul-2010
IR	21-Jul-2010
BC	23-Jul-2010
IR (biopharm)	04-Aug-2010
BC (biopharm)	12-Aug-2010
BC (stability)	26-Oct-2010
IR	03-Nov-2010
BC	11-Nov-2010

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Resubmission Amendment Amendment	12-May-2011 1-June-2011 1-July-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Alimera Sciences, Inc.
Address:	6120 Windward Parkway, Suite 290 Alpharetta, GA 3005
Representative:	Barbara H. Bauschka
Telephone:	(678) 527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iluvien®
b) Non-Proprietary Name (USAN): fluocinolone acetonide intravitreal insert
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

12. STRENGTH/POTENCY: 0.19 mg

13. ROUTE OF ADMINISTRATION: intravitreal

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

__X____Not a SPOTS product

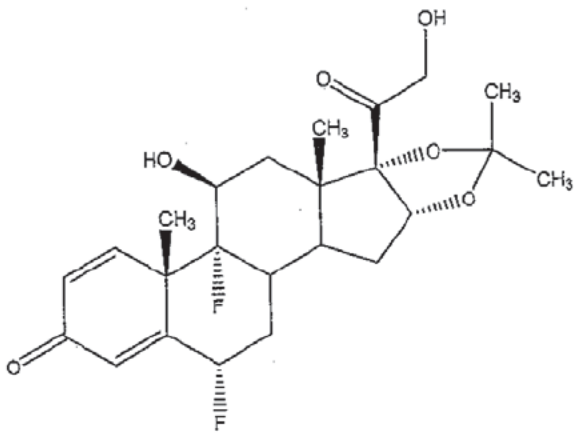
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	
	II		(b) (4)	4			Information submitted in DMF (b) (4)

[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:

MAF	HOLDER	ITEM	DATE OF LOA
(b) (4)	(b) (4)	(b) (4)	21-Jul-2010

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	7/11/2011	EES Report
Pharm/Tox	Informal (excipients and impurities) – acceptable		Conrad Chen
Biopharm	Unacceptable	6/28/11	Tapash Ghosh
Methods Validation	Unacceptable. MV should be sent to FDA Lab the next cycle for evaluation.		Lin Qi
DMEPA	Acceptable		
EA	Categorical exemption – acceptable		Dorota Matecka
Microbiology	Acceptable	7/25/11	Steven Fong
CDRH Consult	Unacceptable		Nikhil Thakur

The Chemistry Review for NDA 201-923

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA viewpoint, NDA 201-923 is not recommended for approval. As of the date of this review, the site recommendation from the Office of Compliance has not been made. There are outstanding CMC and biopharmaceutics deficiencies. In addition, labeling was not addressed in this review cycle. The issues identified above need to be resolved before this NDA can be approved.

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)

Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to insert it into the ocular vitreous chamber.

The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol. [redacted] (b) (4) The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by [redacted]. The proposed commercial manufacturer is [redacted] (b) (4) For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II [redacted] (b) (4) held by [redacted] (b) (4)

See review #1 dated December 1, 2010 by Dr. Dorota Matecka for a detailed description of the drug product and drug substance.

The original NDA dated June 28, 2010 was not approved and a complete response letter (CRL) was sent to the applicant with a list of deficiencies on December 22, 2010. Quality deficiencies identified in the CRL are in CMC review #1, biopharmaceutics review #1, and microbiology

review #1. The original NDA also received a site recommendation of "Withhold" from the Office of Compliance.

The NDA resubmission dated May 12, 2011 contains a complete response to CMC deficiencies and the updated quality information. The May 12, 2011 resubmission was found inadequate by this reviewer in CMC review #2 dated July 22, 2011 and deficiencies and additional information requests were listed in that review. The product quality microbiology deficiency cited therein is now resolved and "NDA Approval" is recommended from a product quality microbiological perspective in the quality microbiology review #2 dated July 25, 2011. The remaining deficiencies and information requests are outstanding. The overall site recommendation is still pending. All facilities are required to be found acceptable by the Office of Compliance for NDA approval.

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

Iluvien® fluocinolone acetonide intravitreal insert (containing 0.19 mg of fluocinolone acetonide) is intended for the treatment of diabetic macular edema. The drug product is to be inserted into the ocular vitreous chamber. Fluocinolone acetonide is released (b) (4)

The storage conditions statement recommends the following: "Store at 15-30°C (59° to 86°F) (b) (4)". The expiration dating proposed for the product in the original NDA submission is 24 months (*currently under consideration*).

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not recommended for approval because of outstanding ONDQA quality issues. These are listed below. CDRH deficiencies and information requirements were identified and listed in CMC review #2 dated July 22, 2011. The site recommendation on a new testing facility has not been made for this application by the Office of Compliance as of the date of this review. In addition, labeling review is pending.

Quality Deficiencies:

1. Without the data and clarification as requested in Comment #3 below, we cannot make any final recommendation regarding the acceptability of the proposed specification range for the *in-vitro* release rate. Provide the release rates of the batches that were tested in the clinical studies to justify your proposed *in-vitro* release rate. We consider that the proposed range (b) (4) We suggest that the estimation of the range for the release rate be based on mean data and 90% confidence intervals around the mean. Note that the proposed release rate specification range should (b) (4)

2. You have not provided the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA.

a. Provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ([redacted] method if applicable), operation procedures, and quantitative analysis.
b. Provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

Non-deficiency comments to be addressed in the next resubmission:

3. Your protocol for the *in vitro* drug release rate test specifies the collection of samples [redacted] It is not clear from the data submitted in your May 12, 2011 submission, specifically "*Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured* [redacted]" and "*Table 3: Release Rates* [redacted] *from Study 10123*," at what time points these samples were collected. This needs to be clarified. In addition, it is not clear how many samples from each batch were tested. A detailed raw data sheet (preferably in electronic format) describing all the data used to generate the *in-vitro* release rates in the Tables 2 and 3 needs to be submitted.

4. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

5. Because the resubmission dated May 12, 2011 provided updated analytical procedures and method validation reports for the drug product, provide the following updates and information:

   a. List under specified impurities, each degradant reported in the drug product specification identified by its name or relative retention tim [redacted].

   b. Specify how impurities [redacted] are to be "combined reported" in the drug product specification.

   c. The method transfer report-08202 recommends [redacted] Update CTM - 200501 to include the [redacted] information.

   d. Explain the [redacted] RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).

e. For the in-vitro drug release test, we recommend you maintain a record of the visual checks being performed as part of the protocol.

6. No updated stability data were submitted in the resubmission. Provide all available stability data.

III. Administrative

A. Reviewer's Signature:

Lin Qi, Ph.D.
{*See electronic signature page*}

B. Endorsement Block

Rapti D. Madurawe, Ph.D., Branch Chief
{*See electronic signature page*}

C. CC Block

{*Listed in DARRTS*}

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/s/

LIN QI
09/30/2011

RAPTI D MADURAWE
09/30/2011

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Lin Qi

Branch V
Division of New Drug Quality Assessment II
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-923

2. REVIEW #: 2

3. REVIEW DATE: July 14, 2011

4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
EOP-2 Meeting Minutes (2-Sep-2008)	02-Jul-2009 (DARRTS)
Pre-NDA Meeting Minutes (04-Mar-2010)	
N-000	28-Jun-2010
BC	08-Jul-2010
BC	09-Jul-2010
BC	13-Jul-2010
IR	21-Jul-2010
BC	23-Jul-2010
IR (biopharm)	04-Aug-2010
BC (biopharm)	12-Aug-2010
BC (stability)	26-Oct-2010
IR	03-Nov-2010
BC	11-Nov-2010

6. SUBMISSION(S) BEING REVIEWED:

Previous Documents	Document Date
Resubmission Amendment Amendment	12-May-2011 1-June-2011 1-July-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Alimera Sciences, Inc.
Address:	6120 Windward Parkway, Suite 290 Alpharetta, GA 3005
Representative:	Barbara H. Bauschka
Telephone:	(678) 527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iluvien®
b) Non-Proprietary Name (USAN): fluocinolone acetonide intravitreal insert
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

12. STRENGTH/POTENCY: 0.19 mg

13. ROUTE OF ADMINISTRATION: intravitreal

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

__X____Not a SPOTS product

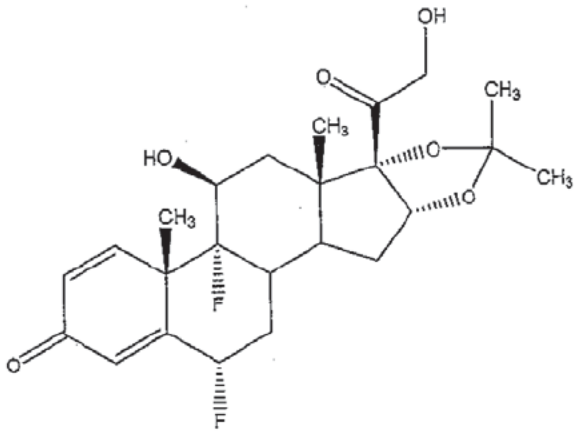
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	
	II		(b) (4)	4			Information submitted in DMF (b) (4)

[1] Action codes for DMF Table:
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6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

MAF	HOLDER	ITEM	DATE OF LOA
(b) (4)	(b) (4)	(b) (4)	21-Jul-2010

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Informal (excipients and impurities) – acceptable		Conrad Chen
Biopharm	Unacceptable	6/28/11	Tapash Ghosh
Methods Validation	Unacceptable. MV should be sent to FDA Lab the next cycle for evaluation.		Lin Qi
DMEPA	Acceptable		
EA	Categorical exemption – acceptable		Dorota Matecka
Microbiology	Unacceptable		Steven Fong
CDRH Consult	Unacceptable		Nikhil Thakur

The Chemistry Review for NDA 201-923

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA viewpoint, NDA 201-923 is not recommended for approval. As of the date of this review, the site recommendation from the Office of Compliance has not been made and the product quality microbiology review is pending. There are outstanding CMC and biopharmaceutics deficiencies. These are listed in section II.C of the Executive Summary. Several deficiencies were identified in the CDRH device consult as listed in section II.C. In addition, labeling was not addressed in this review cycle. The issues identified above need to be resolved before this NDA can be approved.

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)

Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to insert it into the ocular vitreous chamber.

The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol. [redacted] (b) (4) The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by [redacted]. The proposed commercial manufacturer is [redacted] (b) (4) For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II [redacted] (b) (4) held by [redacted] (b) (4)

See review #1 dated December 1, 2010 by Dr. Dorota Matecka for a detailed description of the drug product and drug substance.

The original NDA dated June 28, 2010 was not approved and a complete response letter (CRL) was sent to the applicant with a list of deficiencies on December 22, 2010. Quality deficiencies identified in the CRL are in CMC review #1, biopharmaceutics review #1, and microbiology review #1. The original NDA also received a site recommendation of "Withhold" from the Office of Compliance.

The NDA resubmission dated May 12, 2011 contains a complete response to the CMC deficiencies identified in the CRL and updated quality information. Subsequently, quality amendments were submitted in June 1, 2011 and July 1, 2011. The updated CMC information is evaluated in three sections of this review: A. Responses to CMC deficiencies (Page 14); B. Updated information for the drug substance (Page 18); and C. Updated information for the drug product (Page 27).

The applicant's response to two of the three CMC deficiencies, deficiency A and C, are acceptable and these are now resolved. The response to the third deficiency, deficiency B, remains inadequate, since the polymorph testing method is not provided for (b) (4) the proposed testing facility. The adequacy of the proposed acceptance criteria for the drug substance polymorph testing cannot be determined at this time, since the analytical procedure and the method validation are not provided.

Two new facilities were added in the response to deficiency A and B. The overall site recommendation is still pending. All facilities are required to be found acceptable by OC for NDA approval.

Sections S.4 and P.5 (Control of Drug Product) contain major CMC changes. Additional information is required on drug product specification and analytical procedure. Refer to the Biopharmaceutics review for deficiencies identified on the drug release test.

CMC and biopharmaceutics deficiencies and additional information required are listed in section II.C below. The method validation should be sent to the FDA Lab for evaluation in the next review cycle.

Product quality microbiology issues are not resolved as the review is still pending.

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

Iluvien® fluocinolone acetonide intravitreal insert (containing 0.19 mg of fluocinolone acetonide) is intended for the treatment of diabetic macular edema. The drug product is to be inserted into the ocular vitreous chamber. Fluocinolone acetonide is released (b) (4)

The storage conditions statement recommends the following: "Store at 15-30°C (59° to 86°F) (b) (4)". The expiration dating proposed for the product in the original NDA submission is 24 months (*currently under consideration*).

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not recommended for approval because of outstanding quality issues. ONDQA and CDRH deficiencies and information requirements identified during this review are listed below. The site recommendation on the new testing facilities has not been made for this application by the Office of Compliance as of the date of this review. Refer to microbiology review #2 for the adequacy of the resubmitted microbiological updates. In addition, labeling review is pending.

List of ONDQA Deficiencies and additional comments to be sent to the applicant:

Deficiencies:

1. CMC: You have not provided the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA.
   a. Provide the polymorph testing method in 3.2.S.4.2 of the NDA. Provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ((b) (4) method if applicable), operation procedures, and quantitative analysis.
   b. Provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA.

2. Biopharmaceutics: With regards to the in-vitro drug release test, no final concurrence can be made without appropriate clarification of the data provided in 3.2.P5 Tables 2 and 3 of the NDA resubmission dated May 12, 2011. Provide a detailed raw data sheet (preferably in electronic format) describing all the data used to generate the in-vitro release rates, the exact time points at which data were collected and the number of samples tested from each batch. The proposed drug release rate specification range ((b) (4) µg/day) should (b) (4)

Additional comments:

3. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

4. Because the resubmission dated May 12, 2011 provided updated analytical procedures and method validation reports for the drug product, provide the following updates and information:
   a. List under specified impurities, each degradant reported in the drug product specification identified by its name or relative retention time (b) (4)
   b. Specify how impurities (b) (4) are to be "combined reported" in the drug product specification.
   c. The method transfer report-08202 recommends (b) (4) Update CTM-200501 to include the (b) (4) information.

d. Explain the (b) (4) RSD results observed on accuracy, precision, and intermediate precision for assay in the validation report (DP2006-156) compared to those in the method transfer report (08202).
e. For the in-vitro drug release test, we recommend you maintain a record of the visual checks being performed as part of the protocol.

The following are deficiencies from CDRH device consult review to be sent to the applicant:

We have reviewed the information provided in your original submission for NDA 201923 (June 2010) and the 24 Amendments and supplements that have been submitted to CDER as a result of the interactive review process for NDA 201923. Unfortunately, aside from the engineering drawings provided in the Original Submission (Section 3.2.P.7), and the pictures of the assembled device (Section 1.14.1.1), there was no additional testing to demonstrate that device functionality, biocompatibility and Human Factors had been assessed. Please provide the following information in order to facilitate a thorough assessment of the safety and effectiveness of the Iluvien Intravitreal Insert (b) (4)

Device Performance

1) Please demonstrate that the length of the (b) (4) needle has been designed specifically for intravitreal implantation of the Iluvien implan (b) (4)

2) Regarding the slider mechanism, please demonstrate through performance testing that the mechanism does not inadvertently disengage during the Iluvien implant insertion process, and (b) (4) from the implant site.

3) It is unclear whether the manual slider mechanism (which the clinician utilizes to (b) (4) facilitate delivery of the device), can be manually retracted, or whether there is any type of sharps injury prevention feature on the device to prevent inadvertent needle sticks to the user upon device activation. If the device contains a manual retraction mechanism (passive sharps injury prevention feature) or an automatic needle retraction mechanism (active feature), please perform the appropriate testing to demonstrate the operation of the sharps injury prevention feature to a 99% confidence interval. Please review FDA's Guidance Document Medical Devices with Sharps Injury Prevention Features (August 9, 2005) located at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf.

Device Biocompatibility

4) We acknowledge that you have performed stability testing on the drug product, have characterized the impurities, and have performed the pK/pD studies on the drug product. We also acknowledge that you have provided the MSDS's and testing (b) (4) used to manufacture the final finished device. Unfortunately, this does not meet CDRH's threshold for demonstrating that the biocompatibility concerns regarding this device have been adequately assessed. CDRH relies on ISO 10993 to demonstrate that leachables / extractables and the characterization / quantification of the impurities have been assessed. Please perform the appropriate irritation, sensitization and cytotoxicity studies to meet the

recommendations within ISO 10993. It is important to note that you should perform these tests on the final / finished components of the device (b) (4)

Sterilization

5) We have reviewed the information regarding the sterilization validation you provided in your original submission (June 28, 2010) and Amendments 9 (August 12, 2010), 17 (November 11, 2010), and 22 (May 12, 2011). Your validation reports state that your validation was conducted per the (b) (4) method described (b) (4) However, your product specifications (provided in the original Submission, Section 3.2.P.5.1, and in subsequent Amendments) state that your validation was performed per (b) (4) Therefore, please clarify which documents were used for your validation, and provide a rationale on how your sterilization validation meets the recommendations stated (b) (4)

Human Factors

6) You have not provided any testing to demonstrate that the use-related risks associated with your product have been appropriately characterized and assessed. We recommend that you perform a comprehensive Human Factors study to assess the use-related risks and to ensure that these risks have been appropriately mitigated through testing. Please refer to FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000) located at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

CDRH offers to provide comments to your Human Factors protocol prior to its execution, to ensure that your approach is aligned with the requirements of our Guidance, and to the principles regarding Human Factors studies. If you would like CDRH's comments, please provide a draft protocol through CDER.

To ensure that you understand CDRH's perspective with regard to this Guidance, we have provided general Human Factors considerations below.

Human Factors General Considerations

7) The purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including

instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions, including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

a. Devices and Labeling Used
For design validation, the devices used in your testing should represent the final design, including the labeling.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

b. User Tasks and Training
FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you provide and how it corresponded to realistic training levels.

c. Use Environment and Conditions
You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us to determine it they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels) will use your device, you should include 15 from each group.

Regardless of the number of groups you test, please provide a rationale that these groups adequately represent the overall population of users for your device. Note that study participants should not be your own employees.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

III. Administrative

A. Reviewer's Signature:

Lin Qi, Ph.D.
{*See electronic signature page*}

B. Endorsement Block

Rapti D. Madurawe, Ph.D., Branch Chief
{*See electronic signature page*}

C. CC Block

{*Listed in DARRTS*}

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/s/

LIN QI
07/22/2011

RAPTI D MADURAWE
07/22/2011
I concur with the primary reviewer's assessment.

NDA 201-923

Iluvien® (fluocinolone acetonide intravitreal insert), 0.19 mg

Alimera Sciences, Inc.

Dorota Matecka
ONDQA,
Division of New Drug Quality Assessment II,
Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-903

2. REVIEW #: 1

3. REVIEW DATE: 30-Nov-2010

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Meeting Minutes (27-Sep-2006)	06-Nov-2006 (DARRTS)
EOP-2 Meeting Minutes (2-Sep-2008)	02-Jul-2009 (DARRTS)
Pre-NDA Meeting Minutes (04-Mar-2010)	?
N-000	28-Jun-2010
BC	08-Jul-2010
BC	09-Jul-2010
BC	13-Jul-2010
IR	21-Jul-2010
BC	23-Jul-2010
IR (biopharm)	04-Aug-2010
BC (biopharm)	12-Aug-2010
BC (stability)	26-Oct-2010
IR	03-Nov-2010
BC	11-Nov-2010

6. SUBMISSION(S) BEING REVIEWED:

Chemistry Review Data Sheet

Previous Documents	Document Date
N-000	28-Jun-2010
BC	08-Jul-2010
BC	09-Jul-2010
BC	13-Jul-2010
BC	23-Jul-2010
BC (stability)	26-Oct-2010
BC	11-Nov-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Alimera Sciences, Inc.
Address:	6120 Windward Parkway, Suite 290 Alpharetta, GA 3005
Representative:	Barbara H. Bauschka
Telephone:	(678) 527-1330

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iluvien®
b) Non-Proprietary Name (USAN): fluocinolone acetonide intravitreal insert
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: (505)(b)(1)

10. PHARMACOL. CATEGORY: Ophthalmic (treatment of diabetic macular edema)

11. DOSAGE FORM: intravitreal insert

12. STRENGTH/POTENCY: 0.19 mg

13. ROUTE OF ADMINISTRATION: intravitreal

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

__X____Not a SPOTS product

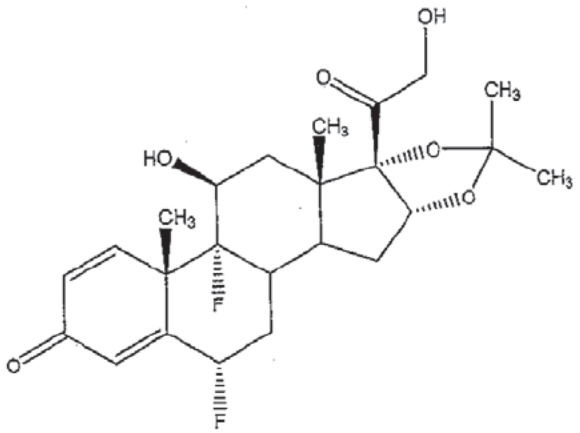
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone

Molecular Formula: $C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Fluocinolone Acetonide	3	Adequate	29-Nov-2010 in DARRTS (D. Matecka)	
	II		(b) (4)	7	N/A	N/A	Information submitted in DMF (b) (4)

[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:

MAF	HOLDER	ITEM	DATE OF LOA
(b) (4)	(b) (4)	(b) (4)	21-Jul-2010

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Informal (excipients and impurities) – acceptable		Dr. Conrad Chen
Biopharm	Pending		
Methods Validation	NA		
DMEPA	Acceptable		
EA	Categorical exemption – acceptable		D. Matecka
Microbiology	Pending		Dr. Steven Fong
CDRH Consult			?

The Chemistry Review for NDA 201-923

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, this NDA is not recommended for approval. The site recommendation from the Office of Compliance has not been made as of the date of this review and there are several outstanding CMC issues for this NDA (listed in the end of this review) including biopharmaceutics deficiencies (as identified by the Biopharmaceutics Reviewer of this application). In addition, the microbiology review, the CDRH device consult, and the labeling review are pending. These issues need to be resolved before this NDA can be approved.

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)

This NDA provides for fluocinolone acetonide intravitreal insert to be used for the treatment of diabetic macular edema.

Iluvien®, (fluocinolone acetonide intravitreal insert) 0.19 mg, is a novel, sterile, sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide into the ocular vitreous chamber. The drug substance (0.19 mg) is mixed with polyvinyl alcohol and this mixture is contained in a tube made of polyimide, which is a non-biodegradable polymer. The empty tube measures 3.5 mm x 0.37 mm OD and weighs approximately 0.1 mg. This tiny insert is preloaded in a especially designed inserter, which allows the specialized clinician to conveniently insert it into the ocular vitreous chamber.

Iluvien is manufactured by mixing fluocinolone acetonide with (b) (4) polyvinyl alcohol (b) (4) The inserter is placed into a tray, sealed with a (b) (4) lid and placed into a carton (b) (4). The inserter has a 25 gauge extra-thin wall needle attached, which allows the physician to place the insert through the sclera into the vitreous of the eye.

[redacted] The applicant is seeking marketing authorization on the Iluvien Low Dose.

The sustained drug delivery technology used by Iluvien was developed by pSivida Corp. and licensed to Alimera Sciences. The clinical supplies were manufactured [redacted]; the proposed commercial manufacturer is [redacted]

The proposed specification for the drug product include appearance, identification, assay, related substances, release rate, endotoxins, and sterility. [redacted]

The primary stability data submitted in the initial NDA submission, updated via the 26-Oct-2010 amendment include 12 months of long-term (25°C/75% RH) and 6-month of accelerated (40°C/75% RH) results for three batches of the product manufactured at the proposed commercial manufacturing. The proposed expiration dating of 24 months is under review.

The drug substance, fluocinolone acetonide (FA), is compendial (USP, Ph.Eur., JP) grade. It has been used in a variety of established, marketed pharmaceutical products in the United States, EU member States, and Japan. Fluocinolone acetonide is a corticosteroid known for its use as an anti-inflammatory agent in the treatment of skin diseases. Corticosteroids have been shown to repress inflammatory symptoms in ocular diseases affecting the posterior segment of the eye, including posterior uveitis.

The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol. [redacted]

The fluocinolone acetonide drug substance used in clinical trials for this NDA was supplied by [redacted] The proposed commercial manufacturer is [redacted] For the chemistry manufacturing and controls information for fluocinolone acetonide drug substance, the reference is made to DMF type II [redacted] held by [redacted]

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

Iluvien® fluocinolone acetonide intravitreal insert (containing 0.19 mg of fluocinolone acetonide) is intended for the treatment of diabetic macular edema and it is supposed to be inserted into the ocular vitreous chamber [redacted]

(b) (4)

The storage conditions statement recommends the following: "Store at 15-30°C (59° to 86°F) [see USP controlled Room Temperature]". The expiration dating proposed for the product in the original NDA submission is 24 months (*currently under consideration*).

C. Basis for Approvability or Not-Approval Recommendation

From the CMC perspective, this NDA is currently not recommended for approval.

There are several pending quality issues for this NDA. Several outstanding CMC comments are listed in the end of this review. That includes lack of information for the facilities conducting the polymorph testing (b) (4) (if applicable) of the fluocinolone drug substance. In addition, the biopharmaceutics review of the proposed release method for the drug product could not be performed due to the lack of the necessary information such as: 1) full development and validation report for the in-vitro release method (justifying choice of method parameters, e.g, choice of release medium, medium volume, temperature, agitation speed, maintenance of sink condition, discriminatory power etc.); 2) in-vitro release profiles generated for different batches and associated data set used to generate the in-vitro release profiles; and 3) full report of the calculation involved (f2 etc.) to qualify different formulations, manufacturing sites etc. Therefore, this application is not recommended for approval form the biopharmaceutics perspective (refer to the Biopharmaceutics Review of this NDA).

The site recommendation has not been made for this application by the Office of Compliance as of the date of this review. Also, the microbiology review has not been located in DARRTS at the time of this review, and the consult review from CDRH has not been completed . In addition, there are labeling issues that will need to be resolved before this application can be approved (labeling review is pending).

III. Administrative

A. Reviewer's Signature:

Dorota Matecka
{*see electronic signature page*}

B. Endorsement Block

Stephen P. Miller, Ph.D., Branch Chief
{*see electronic signature page*}

C. CC Block

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/s/

DOROTA M MATECKA
11/30/2010

STEPHEN P MILLER
12/01/2010
I concur - an approval recommendation cannot be made at this time, from the CMC perspective.

Initial Quality Assessment
Branch __IV__
Pre-Marketing Assessment Division __II__

OND Division:	Division of Anti-Infective and Ophthalmology Produ
NDA:	201-923
Applicant:	Alimera Sciences Inc
Stamp Date:	June 28, 2010
PDUFA Date:	December 28, 2010
Trademark:	Iluvien
Established Name:	(fluocincolone acetonide intravitreal insert) 0.19 mg
Dosage Form:	Intravitreal insert
Route of Administration:	
Indication:	Treatment of diabetic macular edema
PAL:	Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

Summary

This NDA, 5P, dated June 28, 2010, is a 505(b)(1) NDA, submitted in eCTD format and was accepted for priority review. The product is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide for the treatment of diabetic macular edema (DME), a leading cause of blindness associated with diabetic retinopathy. The standard of care is laser photocoagulation. The IND related to this NDA is IND 72,056.

A microbiology consult was submitted by the OND PM, Raphael Rodriguez/Jane Dean, and Dr. Stephen Fong was assigned. The trade name consult was sent directly from the applicant to OSE. The EES request was submitted by ONDQA PM, Ms. Altheo Cuff who confirmed sites with the applicant and finalized the request with me. A CDRH consult dated August 9, 2010 was submitted by Altheo Cuff for evaluation of compatibility, functionality, and reliability of the inserter device for use with the fluocinolone acetonide insert. CDRH was also asked for inspection of the device site as appropriate.

The drug substance, fluocinolone acetonide is manufactured by [redacted]. Fluocinolone acetonide is a synthetic glucocorticoid. An LOA dated August 25, 2009 was submitted, referencing the synthesis, controls and stability information in DMF [redacted] (b) (4). Only the drug substance is described in a USP monograph. The USP reference standard is used for testing.

The drug product is formulated by mixing fluocinolone acetonide with [redacted] (b) (4) polyvinyl alcohol [redacted] (b) (4)

(b) (4)

Each insert is placed in an inserter device containing a 25 gauge needle. The inserter device is manufactured (b) (4) The drug product is manufactured, packaged, labeled, and release tested at (b) (4)

A 3 cycle freeze-thaw study was performed.

The stability data were generated using 3 batches at each low and high strength with release rate of 0.25 µg/day and 0.5 µg/day respectively. In addition, stability data for 3 batches, of each strength, for 36 months were collected for the clinical batches. Storage room temperature stability conditions were 25°C±2°C/60%±5% RH and accelerated conditions at 40°C±2°C/75%±5% RH. Only the low strength product will be marketed. No professional sample size is proposed. An expiry of 24 months is claimed. Product is claimed to be stored between 15 to 30ºC.

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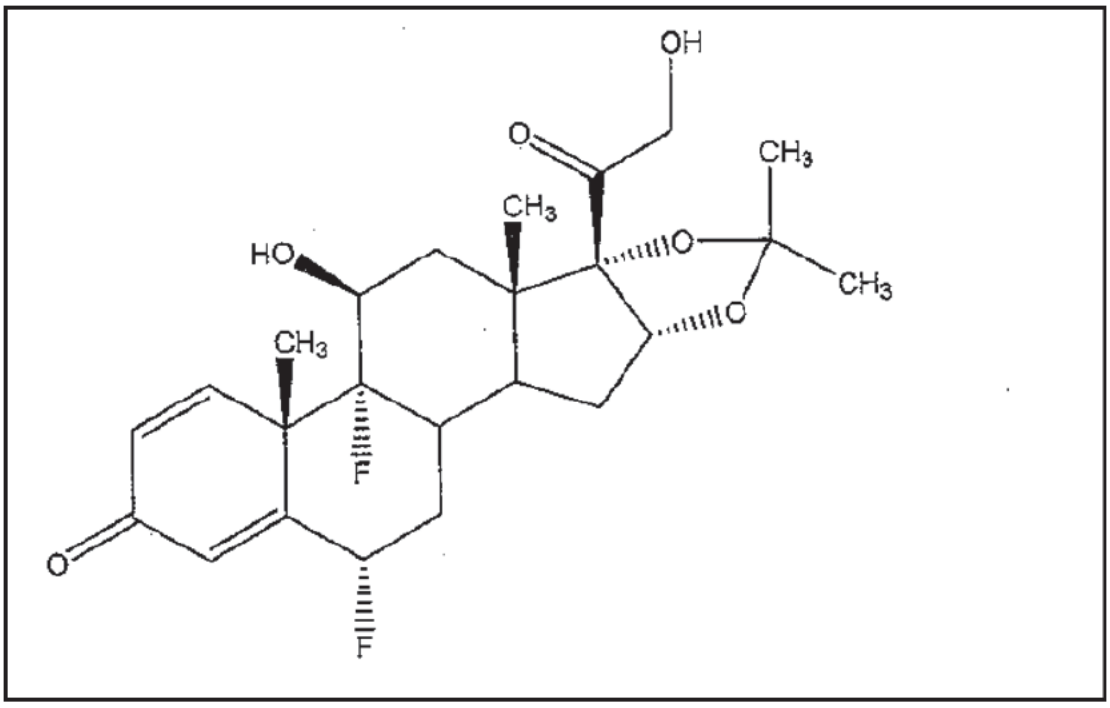

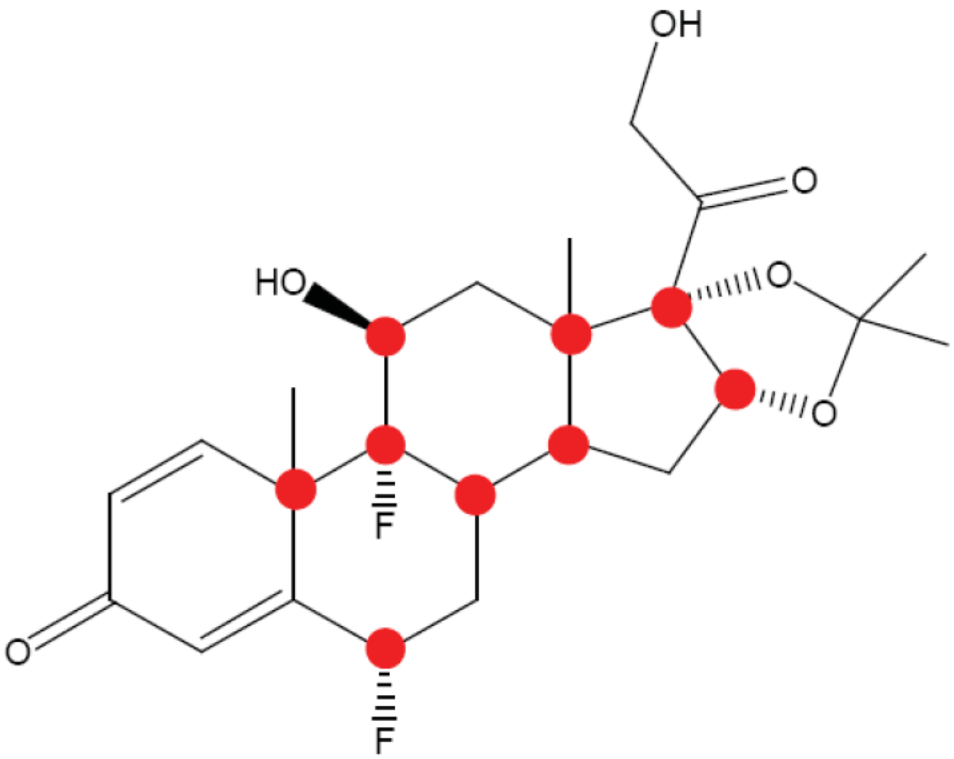

Fluocinolone acetonide

● - centers of chirality

Molecular Formula:

$C_{24}H_{30}F_2O_6$

Molecular Weight: 452.49

Critical issues for review

- DMF (b) (4) contains (b) (4) The applicant was asked to provide (b) (4) either in a DMF or to the NDA. LOA to a DMF was submitted and will need to be evaluated.
- The drug substance has 9 centers of chirality. Some assurance of the correct chiral compound for consistent use in the drug product may be needed.
- (b) (4) Even though a statement was made (b) (4) it does not appear to have any supporting data to confirm that statement.

- All tests should be evaluated for meaningful conditions and acceptance criteria for both drug substance and drug product.
- In the drug substance specification, residual solvents should be minimized because the sustained release drug product will be injected into the vitreous of the eye. Reviewer should evaluate actual values vs. acceptance criteria for residual solvents and tighten as appropriate.
- The particle size acceptance criteria are recommended to be evaluated. Meaningful criteria, e.g., propose values at 10, 50 and 90 percentile may be more useful.
- In the drug product specification, the impurities testing should contain a criterion for Any individual unspecified to be set at NMT [redacted] %. Testing content uniformity of dose for delivery should be included unless justified. Reviewer should consider.
- It is not clear if the polyimide tubes are light brown in color. The drug substance is white crystals. Reviewer should evaluate source of color.
- The amount of material packed in each insert is different between the clinical batches and the commercial batches, i.e., [redacted] (b) (4) mg vs. 0.19 mg respectively [redacted] (b) (4) If the rate of release through delivery is [redacted] (b) (4) biopharm should evaluate.
- In the drug product specification, any individual unspecified impurity should be set at NMT [redacted] %.
- In the impurities testing procedure, a sensitivity standard is prepared but not clear how it is used. In general, all impurity tests should include a standard at the quantitation limit as part of the system suitability test to ensure detectability of impurities down to that level at time of analysis.
- Not clear what the batch size is. The Master Batch Record mentioned using [redacted] (b) (4) drug substance [redacted] (b) (4) The applicant should define what a commercial batch size is.
- The applicant claims parametric release in the stability protocol for sterility. Reviewer and evaluate with Micro the validity of their claim.
- The stability protocol's statement on informing the Agency with OOS is inadequate. In addition to informing the Division, applicant should include a reference to the CFR for reporting.
- Not clear which stability batches for extending expiry. May need to follow up.
- The applicant refers [redacted] (b) (4) Reviewer Dorota had pointed out the naming issue.
- Storage temperature is normally claimed at 15 to 25ºC. Reviewer should evaluate temperature claim in labeling.

- Comments for 74-Day Letter

CMC comments, included in the CMC Filing review were sent to the applicant on July 21, 2010. Responses dated July 23, 2010 in amendment have been received.

D. Review, Comments and Recommendation:

Acceptable for filing. Dr. Dorota Matecka has been assigned to review this NDA.

_____Linda Ng, Ph.D._____ _____
Pharmaceutical Assessment Lead Date

___Stephen Miller, Ph.D._____ _____
Acting Branch Chief Date

Cc: OND PM RRodriguez
OND PM JDean
ONDQA PM ACuff

Appendix 1. Composition of the Drug Product

Table 1: Composition of Iluvien

Amount per Insert	Component	Function	Quality Standard
0.19 mg	Fluocinolone Acetonide	Active Ingredient	USP, Ph. Eur.
(b) (4)	Polyvinyl Alcohol	(b) (4)	Manufacturer's specifications
	Water for Injection		USP, Ph. Eur.
			(b) (4)

(b) (4)

Table 2:

Amount per Insert	Component	Function	Quality Standard
Not Applicable[a]	Polyimide Tubing	(b) (4)	Manufacturer's specification
(b) (4)	Silicone Adhesive		Manufacturer's specification
			(b) (4)

Appendix 2. Drug Substance Specification

Table 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
Identification by HPLC	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4),	CTM-200500
Related Substances		
(b) (4)	Not more than (b) (4)	CTM-200500
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Table 1: Specification for Fluocinolone Acetonide (cont'd)

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
(b) (4)	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4)	Not less than (b) (4)	(b) (4) MGR051FLU011
Particle	Not less than	
Particle	Not less than	
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than (b) (4)	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
		(b) (4)

Appendix 3. Drug Product Specification

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4) %.	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4)	CTM-200502
Endotoxin		MTM-200033
Sterility		
Release	(b) (4	(b) (4)
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

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/s/

LINDA L NG
09/24/2010

STEPHEN P MILLER
10/06/2010