

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-640

CHEMISTRY REVIEW(S)

NDA 21-640

**VITRASE®(ovine hyaluronidase) for Injection, 6200 USP
Units/vial**

ISTA Pharmaceuticals, Inc.

**Libaniel Rodriguez, Ph. D.
Division of Anti-inflammatory, Analgesic and Ophthalmic
Drug Products**

HFD-550

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product and Drug Substance.....	8
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative	10
A. Reviewer's Signature	10
B. Endorsement Block	10
C. CC Block	10
Chemistry Assessment	11
I. DRUG SUBSTANCE	11
II. DRUG PRODUCT	11
ATTACHMENT.....	15

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-640
2. REVIEW # 2
3. REVIEW DATE: 12-Apr-2004
4. REVIEWER: Libaniel Rodriguez
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 21-414	30-Sep-2002
NDA 21-640	04-Aug-2003
BC	10-Sep-2003
BC	04-Dec-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC	04-Mar-2004
BZ	12-Mar-2004

7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals, Inc.
Address: 15279 Alton Parkway, Suite 100, Irvine, CA 92618
Representative: Marvin J. Garret
Telephone: 949 788 5303



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VITRASE®
- b) Non-Proprietary Name (USAN): Hyaluronidase, Ovine
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(2) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Proteolytic Enzyme (for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents).

11. DOSAGE FORM: Lyophilized Powder for Injection.

12. STRENGTH/POTENCY: 6200 USP Units/Vial, 50 to 300 USP Units/dose

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

Structural Formula: N/A.

Molecular Formula:

Where; A = Alanine, R = Arginine, N = Asparagine, D = Aspartic Acid, C = Cysteine, E = Glutamic Acid, Q = Glutamine, G = Glycine, H = Histidine, I = Isoleucine, L = Leucine, K = Lysine, M = Methionine, F = Phenylalanine, P = Proline, S = Serine, T = Threonine, W = Tryptophan, Y = Tyrosine and V = Valine.

The drug substance contains two other proteins as impurities, _____ and a fragment of _____ . These two impurities do not interfere with enzyme activity or function.

Chemical Name: Ovine hyaluronidase

Molecular Weight:

CAS Name and Number: None

USAN Name: Hyaluronidase (Ovine)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	_____	_____	1	Adequate	11-Feb-03	Review # 1
—	III	_____	_____	1	Adequate	12-Feb-03	Review # 1
—	III	_____	_____	1	Adequate	12-Feb-03	Review # 1
—	III	_____	_____	3	Adequate	31-Jan-03	

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: IND 49,939



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Approval	04-May-2003	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending. Will be submitted upon receipt of revised package.		
OPDRA			
EA	Categorical exclusion	30-Sep-2002 Original application	
Microbiology	Approval	04-Mar-03	Bryan S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-640

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC viewpoint this NDA is recommended for approval

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

None

II. Summary of Chemistry Assessments

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

The drug product VITRASE® (ovine hyaluronidase) is a sterile, lyophilized powder for injection. It is supplied in a stoppered, 5 mL single-use vial, containing the sterile Vitrase lyophilized powder.

The Vitrase drug product is formulated as a solution containing ovine hyaluronidase, potassium phosphate dibasic, monobasic potassium phosphate, lactose monohydrate and water for injection. The bulk solution is sterile-filtered through _____ filters and the vials are _____ for lyophilization. The



Executive Summary Section

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

The proposed indication for Vitrase is for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Preparations prior to the applications of Vitrase, include aseptic procedures. The drug product is reconstituted with 6.2 mL of 0.9%, sodium chloride injection, USP. The resulting solution is mixed well and examined for clarity and absence of visible particles. 150 μ L (150 USP units) of the reconstituted solution are mixed with the required volume of drug to be dispersed or absorbed and administered subcutaneously where required.



CHEMISTRY REVIEW



Executive Summary Section

The recommended storage period for the reconstituted drug product solution is _____

The proposed eighteen months expiration period for Vitrase drug product is well supported by the twelve months of updated stability data submitted in the amendment of August 1, 2003 for NDA 21-414.

C. Basis for Approvability or Not-Approval Recommendation

All the CMC issues raised during the review cycle were resolved satisfactorily by the applicant. The CMC section of this application is therefore, recommended for approval.

III. Administrative

A. Reviewer's Signature

ChemistName/Date: Libaniel Rodriguez Ph.D./14-Apr2004

B. Endorsement Block

ChemistName/Date: Libaniel Rodriguez Ph.D./14-Apr-2004
ChemistryTeamLeader: Linda Ng Ph.D./14-Apr-2004
ProjectManager: Lori Gorski

C. CC Block

David Lin Acting Director DNDCIII HFD-830
Wiley Chambers, Deputy Director HFD-550

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(b4)

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

/s/

Libaniel Rodriguez
4/19/04 11:45:22 AM
CHEMIST
Approval

Linda Ng
4/19/04 12:15:15 PM
CHEMIST

114 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

NDA 21-640

VITRASE®(ovine hyaluronidase)

ISTA Pharmaceuticals, Inc.

**Libaniel Rodriguez, Ph. D.
Division of Anti-inflammatory, Analgesic and Ophthalmic
Drug Products**

HFD-550



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary	10
I. Recommendations	10
A. Recommendation and Conclusion on Approvability	10
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	10
II. Summary of Chemistry Assessments	10
A. Description of the Drug Product(s) and Drug Substance(s)	10
B. Description of How the Drug Product is Intended to be Used	11
C. Basis for Approvability or Not-Approval Recommendation	12
III. Administrative	12
A. Reviewer's Signature	12
B. Endorsement Block	12
C. CC Block	12
Chemistry Assessment	13
I. DRUG SUBSTANCE	13
1. Description & Characterization	12
a. Description	12
b. Characterization / Proof Of Structure	12
2. Manufacturer	12
3. Synthesis / Method Of Manufacture	12
a. Starting Materials - Specs & Tests.....	12
b. Solvents, Reagents, etc.....	12

c. Flow Chart.....	12
d. Detailed Description.....	12
4. Process Controls.....	12
a. Reaction Completion / Other In-Process Tests.....	12
b. Intermediate Specs & Tests.....	12
5. Reference Standard	12
a. Preparation.....	12
b. Specifications.....	12
6. Regulatory Specifications / Analytical Methods	12
a. Drug Substance Specifications & Tests	12
b. Purity Profile.....	12
c. Microbiology	12
7. Container/Closure System For Drug Substance Storage.....	12
8. Drug Substance Stability.....	12
II. DRUG PRODUCT	13
1. Components/Composition	12
2. Specifications & Methods For Drug Product Ingredients	12
a. Active Ingredient(s).....	12
b. Inactive Ingredients	12
3. Manufacturer	12
4. Methods Of Manufacturing And Packaging	12
a. Production Operations.....	12
b. In-Process Controls & Tests.....	12
c. Reprocessing Operations	12
5. Regulatory Specifications And Methods For Drug Product.....	12
a. Sampling Procedures	12
b. Regulatory Specifications And Methods.....	12
6. Container/Closure System.....	13
7. Microbiology.....	12
8. Drug Product Stability	12
III. INVESTIGATIONAL FORMULATIONS	16

IV. ENVIRONMENTAL ASSESSMENT.....16

V. METHODS VALIDATION16

VI. LABELING16

VII. ESTABLISHMENT INSPECTION17

VIII. DRAFT DEFICIENCY LETTER17

ATTACHMENT.....15

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

1. NDA 21-640
2. REVIEW # 1
3. REVIEW DATE: 23 January, 2004
4. REVIEWER: Libaniel Rodriguez
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 21-414	30-Sep-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 21-640	04-Aug-2003
BC	10-Sep-2003
BC	04-Dec-2003

7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals, Inc.
Address: 15279 Alton Parkway, Suite 100, Irvine, CA 92618
Representative: Marvin J. Garret
Telephone: 949 788 5303

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VITRASE®
- b) Non-Proprietary Name (USAN): Ovine Hyaluronidase
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(2) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Proteolytic Enzyme

11. DOSAGE FORM: Lyophilized Powder for Injection, Solution

12. STRENGTH/POTENCY: — USP Units/Vial (for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents).

* To be determined in review # 2.

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

Structural Formula: N/A.

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Molecular Formula:

Where; A = Alanine, R = Arginine, N = Asparagine, D = Aspartic Acid, C = Cysteine, E = Glutamic Acid, Q = Glutamine, G + Glycine, H = Histidine, I = Isoleucine, L = Leucine, K = Lysine, M = Methionine, F = Phenylalanine, P = Proline, S = Serine, T = Threonine, W = Tryptophan, Y = Tyrosine and V = Valine.

The drug substance contains _____ other proteins as impurities, _____ and a fragment of _____. These _____ impurities do not interfere with enzyme activity or function.

Chemical Name: Ovine hyaluronidase

Molecular Weight:

CAS Name and Number: None

USAN Name: Hyaluronidase. Request has been submitted to USAN to include ovine in the label for this name.

17. RELATED/SUPPORTING DOCUMENTS:

DMF	TYPE	HOLDER	ITEM	CODE ¹	STATUS ²	DATE	COMMENTS
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

#		REFERENCED			REVIEW COMPLETED	
—	III	_____	1	Adequate	11-Feb-03	Review # 1
—	III	_____	1	Adequate	12-Feb-03	Review # 1
—	III	_____	1	Adequate	12-Feb-03	Review # 1
—	III	_____	3	Adequate	31-Jan-03	

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: IND 49,939

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Biometrics			
EES	Approval	04-May-2003	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending. Will be submitted upon receipt of revised package.		
OPDRA			
EA	Categorical exclusion	30-Sep-2002 Original application	
Microbiology	Approval	04-Mar-03	Bryan S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-640

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC viewpoint this NDA is recommended as approvable pending satisfactory resolution of CMC and clinical issues. See "Draft Deficiency Letter" section of this review.

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

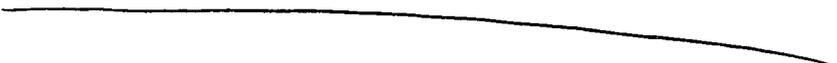
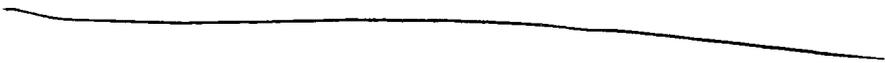
N/A

II. Summary of Chemistry Assessments

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

The drug product VITRASE® (ovine hyaluronidase) is a sterile, lyophilized powder for injection. It is supplied in a stoppered, 5 mL single-use vial, containing the sterile Vitrase lyophilized powder.

The Vitrase drug product is formulated as a solution containing ovine hyaluronidase, potassium phosphate dibasic, monobasic potassium phosphate, lactose monohydrate and water for injection. The bulk solution is sterile-filtered through two  and the vials

Executive Summary Section

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

The proposed indication for Vitrase is for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Preparations prior to the applications of Vitrase, include aseptic procedures. The drug product is reconstituted with _____ mL of 0.9% sodium chloride injection, USP. The resulting solution is mixed well and examined for clarity and absence of visible particles. _____ of the reconstituted solution are mixed with the required volume of drug to be dispersed or absorbed and administered subcutaneously where required.

CHEMISTRY REVIEW

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This 505(b)(2) application cross-references NDA 6-343 (Wydase) without a right of reference, for the clinical, non-clinical, pharmacology and toxicology information. This is permitted, based on the Agency's findings of safety and efficacy for Wydase.

III. Administrative

A. Reviewer's Signature

ChemistName/Date: Libaniel Rodriguez Ph.D./27-Jan-2004

B. Endorsement Block

ChemistName/Date: Libaniel Rodriguez Ph.D.
ChemistryTeamLeader: Linda Ng pH.D.
ProjectManager: Lori Gorski

C. CC Block

Chi-Wan Chen, Director DNDCIII
Wiley Chambers, Deputy Director HFD-550

5 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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Establishment :

DMP No:

AADA

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 71-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMP No:

Responsibilities

Profile : CEX OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-APR-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION



Establishment :

DMP No.

AADA:

Responsibilities

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 21-OCT-02
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

 Establishment : CFN 2022590 FBI : 3003434767
 ISTA PHARMACEUTICALS INC
 15279 ALTON PARKWAY SUITE 100
 IRVINE, CA 92618

DMP No.

AADA:

Responsibilities
 FROM SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 28-MAR-03
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION



Establishment :

DMP No:

Responsibilities:

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 22-OCT-02
 Decision: ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment

DMP No:

Responsibilities:

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 10-OCT-02
 Decision: ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-NOV-02
Decision: ACCEPTABLE
Reason : BASED ON PROFILE

Establish

DMF No:

Responsibilities:

Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-MAY-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

Libaniel Rodriguez
1/27/04 02:16:10 PM
CHEMIST
AE

Linda Ng
1/27/04 03:07:54 PM
CHEMIST
Please convey the CMC deficiency on p. 16 of
review to applicant.

35 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

NDA 21-414

**Vitrase (ovine hyaluronidase)
for intravitreal injection**

ISTA Pharmaceuticals, Inc.

**Stephen Moore, Ph.D.
Division of Metabolic and Endocrine Drug Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
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III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. DRUG SUBSTANCE	
II. DRUG PRODUCT	
III. LABELING & PACKAGE INSERT	
IV. Claim Of Categorical Exclusion	
V. List Of Deficiencies To Be Communicated	

REVIEW NOTE

Chemistry Review Data Sheet

1. NDA 21-414
2. REVIEW #: 1
3. REVIEW DATE: March 17, 2003
4. REVIEWER: Stephen Moore, Ph.D. /ONDC/DNDC2 (HFD-510)
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED: Viral clearance studies only

Submission(s) Reviewed

Document Date

Original Submission

07-OCT-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	ISTA Pharmaceuticals, Inc.
Address:	15279 Alton Parkway, Suite 100 Irvine, CA 92618
Representative:	Marvin Garrett, Vice President
Telephone:	949-788-5303

REVIEW NOTE

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vitrase
- b) Non-Proprietary Name (USAN): Ovine hyaluronidase
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Treatment of vitreous hemorrhage

11. DOSAGE FORM: Intravitreal injection

12. STRENGTH/POTENCY: _____ units/vial

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: X Rx OTC

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

 X SPOTS product – Form Completed

 Not a SPOTS product

CHEMISTRY REVIEW

REVIEW NOTE

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See primary chemistry review.

17. RELATED/SUPPORTING DOCUMENTS: See primary chemistry review.

A. DMFs:

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

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

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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

CHEMISTRY REVIEW

REVIEW NOTE

18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW NOTE

The Chemistry Review for NDA 21-414

Consultative Review for Viral Clearance Studies

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

See primary chemist's review.

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

See primary chemist's review.

C. Basis for Approvability or Not-Approval Recommendation

REVIEW NOTE

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Stephen Moore, Ph.D. , Chemistry Team Leader (HFD-510)

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

C. CC Block

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

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

/s/

Stephen Moore
4/26/04 01:38:15 PM
CHEMIST
Correction of typographical errors

NDA 21-414

VITRASE®(ovine hyaluronidase)

ISTA Pharmaceuticals, Inc.

**Libaniel Rodriguez, Ph. D.
Division of Anti-inflammatory, Analgesic and Ophthalmic
Drug Products**

HFD-550

Table of Contents

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Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	9
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A. Description of the Drug Product(s) and Drug Substance(s)	10
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b. Characterization / Proof Of Structure	13
2. Manufacturer	13
3. Synthesis / Method Of Manufacture	13
a. Starting Materials - Specs & Tests.....	15
b. Solvents, Reagents, etc.....	15

CHEMISTRY REVIEW

c. Flow Chart	15
d. Detailed Description	15
4. Process Controls	15
a. Reaction Completion / Other In-Process Tests	15
b. Intermediate Specs & Tests	15
5. Reference Standard	15
a. Preparation	15
b. Specifications	15
6. Regulatory Specifications / Analytical Methods	16
a. Drug Substance Specifications & Tests	18
b. Purity Profile	19
c. Microbiology	19
7. Container/Closure System For Drug Substance Storage	19
8. Drug Substance Stability	19
II. DRUG PRODUCT	24
1. Components/Composition	24
2. Specifications & Methods For Drug Product Ingredients	22
a. Active Ingredient(s)	22
b. Inactive Ingredients	22
3. Manufacturer	22
4. Methods Of Manufacturing And Packaging	22
a. Production Operations	22
b. In-Process Controls & Tests	22
c. Reprocessing Operations	22
5. Regulatory Specifications And Methods For Drug Product	22
a. Sampling Procedures	22
b. Regulatory Specifications And Methods	22
6. Container/Closure System	26
7. Microbiology	26
8. Drug Product Stability	28
III. INVESTIGATIONAL FORMULATIONS	27

IV. ENVIRONMENTAL ASSESSMENT.....27

V. METHODS VALIDATION.....27

VI. LABELING27

VII. ESTABLISHMENT INSPECTION.....27

VIII. DRAFT DEFICIENCY LETTER.....28

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

1. NDA 21-414
2. REVIEW #: 2
3. REVIEW DATE: January 22, 2004
4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-September-2002
BC	21-October-2002
BC	29-October-2002
BC	27-November-2002
BC	5-February-2003
BC	12-February-2003
BC	28-February-2003
BC	4-March-2003
BC	10-March-2003
BC Review # 1	28 February-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC	August 1, 2003
BC	August 18, 2003
BC	September 23, 2003
BC	October 10, 2003
BC	October 17, 2003

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals, Inc.
Address: 15279 Alton Parkway, Suite 100, Irvine, CA 92618
Representative: Marvin J. Garret
Telephone: 949 788 5303

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VITRASE®
- b) Non-Proprietary Name (USAN): Ovine Hyaluronidase
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Proteolytic Enzyme

11. DOSAGE FORM: Lyophilized Powder for Injection, Solution

12. STRENGTH/POTENCY: — USP Units/Vial

13. ROUTE OF ADMINISTRATION: Subcutaneous injection, — units per injection

14. Rx/OTC DISPENSED: Rx OTC

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

____ Not a SPOTS product

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

Structural Formula: N/A.

Molecular Formula:

Where; A = Alanine, R = Arginine, N = Asparagine, D = Aspartic Acid, C = Cysteine, E = Glutamic Acid, Q = Glutamine, G = Glycine, H = Histidine, I = Isoleucine, L = Leucine, K = Lysine, M = Methionine, F = Phenylalanine, P = Proline, S = Serine, T = Threonine, W = Tryptophan, Y = Tyrosine and V = Valine.

The drug substance contains — other proteins as impurities, _____
_____ These — impurities do not interfere with enzyme activity or function.

Chemical Name: Ovine hyaluronidase

Molecular Weight:

CAS Name and Number: None

CHEMISTRY REVIEW

Chemistry Review Data Sheet

USAN Name: Hyaluronidase. Request has been submitted to USAN to include ovine in the label for this name.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs See review #1. All DMFs are acceptable.

B. Other Documents: NDA 21-640 and documents in review #1.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Approval	04-May-2003	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending. Will be submitted upon receipt of revised package.		
OPDRA			
EA	Categorical exclusion	30-Sep-2002 Original application	
Microbiology	Approval	04-Mar-03	Bryan S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-414

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

None.

II. Summary of Chemistry Assessments

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

The drug product VITRASE® (ovine hyaluronidase) for Ophthalmic _____ Injection, _____ USP Units/vial, is a sterile, lyophilized powder for injection solution. It is supplied in a kit containing a stoppered, _____ single-use vial, containing the sterile Vitrase lyophilized powder, a _____ sterile syringe with needle, a _____ sterile syringe without needle, a sterile _____ filter needle _____, a single sterile _____ gauge needle _____ and a _____ vial of 0.9% Sodium Chloride Injection, USP. The Vitrase drug product is formulated as a solution containing ovine hyaluronidase, potassium phosphate dibasic, monobasic potassium phosphate, lactose monohydrate and water for injection. The bulk solution is sterile-filtered through _____ filters and the vials are _____

⌈

⌋



Executive Summary Section

C

J

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

The proposed indication for Vitrase _____

_____ The proposed dose is a single injection of _____ units (_____ reconstituted drug product). The total volume of the reconstituted drug product in the single-use vial is _____. Preparations prior to the applications of Vitrase, include aseptic procedures. The drug product is reconstituted by transferring _____ from the sodium chloride injection vial into the single-use vial containing the lyophilized drug product. The resulting solution is mixed well and examined for clarity and absence of visible particles. _____ of this solution are withdrawn from the single-use vial through the _____ filter needle into the _____ needle. The filter needle is replaced by the _____ gauge, _____ needle and the syringe is prepared for a _____ injection.

Based on updated stability data submitted for this review, the recommended expiration period for the drug product is eighteen months when stored at 5°C to 8°C. The

CHEMISTRY REVIEW

Executive Summary Section

recommended expiration period for the reconstituted drug product solution is

C. Basis for Approvability or Not-Approval Recommendation

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Linda Ng, Chemistry Team Leader

D. CC Block

Lori Gorski, Project Manager

Chi-Wan Chen, Division Director DNDCIII

Wiley Chambers, Deputy Division Director HFD-550

23 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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 Establishment : _____

DMP No: _____ AADA: _____

Responsibilities: _____

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 21-OCT-02
 Decision : ACCEPTABLE
 Reason: BASED ON PROFILE

 Establishment _____

INF No _____

Responsibilities: _____

Profile : CEX OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 07-APR-03
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

**APPEARS THIS WAY
 ON ORIGINAL**



Establishment : _____

DMP No.

Responsibilities: _____

Profile CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 17 MAR 03
 Decision ACCEPTABLE
 Reason DISTRICT RECOMMENDATION

Establishment : _____

DMP No.

Responsibilities: _____

Profile CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 21-OCT-02
 Decision ACCEPTABLE
 Reason BASED ON PROFILE

**APPEARS THIS WAY
 ON ORIGINAL**

Establishment

DMF No.

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-OCT-07
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment CFN : 2032590 FEI : 100343476
ISTA PHARMACEUTICALS INC
15279 ALTON PARKWAY SUITE 100
IRVINE, CA 92618

DMF No. AADA

Responsibilities: ERCT SUBSTANCE RELEASE: TESTER
FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-MAR-03
Decision: ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Assessment Section

Establishment

DMF No:

Responsibilities:

Profile CTL OAI Status: NONE
Last Milestone: GC RECOMMENDATION
Milestone Date: 27-OCT-02
Decision : ACCEPTABLE
Reason DISTRICT RECOMMENDATION

Establishment

DMF No

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: GC RECOMMENDATION
Milestone Date: 30-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

CHEMISTRY REVIEW

Establishment :

DMP No:

Responsibilities:

Profile : CTI OAI Status NO42
Last Milestone OC RECOMMENDATION
Milestone Date: 05-NOV-02
Decision ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMP No:

Responsibilities:

Profile : SVI OAI Status NO42
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-MAY-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

Libaniel Rodriguez
1/27/04 02:12:35 PM
CHEMIST
AP

Linda Ng
1/27/04 02:50:17 PM
CHEMIST

NDA 21-414

VITRASE®(ovine hyaluronidase)

ISTA Pharmaceuticals, Inc.

**Libaniel Rodriguez, Ph. D.
Division of Anti-inflammatory, Analgesic and Ophthalmic
Drug Products**

HFD-550

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary.....	10
I. Recommendations.....	10
A. Recommendation and Conclusion on Approvability	10
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	10
II. Summary of Chemistry Assessments	10
A. Description of the Drug Product(s) and Drug Substance(s).....	10
B. Description of How the Drug Product is Intended to be Used	11
C. Basis for Approvability or Not-Approval Recommendation	12
III. Administrative	12
A. Reviewer's Signature	12
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. DRUG SUBSTANCE	13
1. Description & Characterization.....	13
a. Description	13
b. Characterization / Proof Of Structure.....	13
2. Manufacturer.....	19
3. Synthesis / Method Of Manufacture.....	20
a. Starting Materials - Specs & Tests	20
b. Solvents, Reagents, etc.	22

CHEMISTRY REVIEW

c. Flow Chart.....	24
d. Detailed Description.....	36
4. Process Controls.....	42
a. Reaction Completion / Other In-Process Tests.....	42
b. Intermediate Specs & Tests.....	42
5. Reference Standard.....	43
a. Preparation.....	44
b. Specifications.....	45
6. Regulatory Specifications / Analytical Methods.....	49
a. Drug Substance Specifications & Tests.....	49
b. Purity Profile.....	60
c. Microbiology.....	60
7. Container/Closure System For Drug Substance Storage.....	61
8. Drug Substance Stability.....	62
II. DRUG PRODUCT.....	64
1. Components/Composition.....	64
2. Specifications & Methods For Drug Product Ingredients.....	65
a. Active Ingredient(s).....	65
b. Inactive Ingredients.....	65
3. Manufacturer.....	65
4. Methods Of Manufacturing And Packaging.....	65
a. Production Operations.....	66
b. In-Process Controls & Tests.....	68
c. Reprocessing Operations.....	68
5. Regulatory Specifications And Methods For Drug Product.....	68
a. Sampling Procedures.....	68
b. Regulatory Specifications And Methods.....	69
6. Container/Closure System.....	78
7. Microbiology.....	81
8. Drug Product Stability.....	81
III. INVESTIGATIONAL FORMULATIONS.....	84

IV. ENVIRONMENTAL ASSESSMENT 87

V. METHODS VALIDATION 87

VI. LABELING..... 87

VII. ESTABLISHMENT INSPECTION..... 87

VIII. DRAFT DEFICIENCY LETTER 88

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

1. NDA 21-414
2. REVIEW #: 1
3. REVIEW DATE: February 28, 2003
4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

BC

BC

BC

BC

BC

BC

BC

BC

Document Date

30-September-2002

21-October-2002

29-October-2002

27-November-2002

5-February-2003

12-February-2003

28-February-2003

4-March-2003

10-March-2003

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals, Inc.
Address: 15279 Alton Parkway, Suite 100, Irvine, CA
92618
Representative: Marvin J. Garret
Telephone: 949 788 5303

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VITRASE®
- b) Non-Proprietary Name (USAN): Ovine Hyaluronidase
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the Food, Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Proteolytic Enzyme

:

11. . DOSAGE FORM: Lyophilized Powder for Injection, Solution

12. STRENGTH/POTENCY: — USP Units/Vial

13. ROUTE OF ADMINISTRATION: — Injection, — per affected Eye.

14. Rx/OTC DISPENSED: X Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

 X SPOTS product – Form Completed

 Not a SPOTS product

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

Structural Formula: N/A.

Molecular Formula:

Where; A = Alanine, R = Arginine, N = Asparagine, D = Aspartic Acid, C = Cysteine, E = Glutamic Acid, Q = Glutamine, G + Glycine, H = Histidine, I = Isoleucine, L = Leucine, K = Lysine, M = Methionine, F = Phenylalanine, P = Proline, S = Serine, T = Threonine, W = Tryptophan, Y = Tyrosine and V = Valine.

The drug substance contains other proteins as impurities, . _____
 These impurities do not interfere with enzyme activity or function.

Chemical Name: OVINE hyaluronidase

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Molecular Weight:

CAS Name and Number: None

USAN Name: None

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	1	Adequate	11-Feb-03	Review # 1
(III	—	—	1	Adequate	12-Feb-03	Review # 1
	III	—	—	1	Adequate	12-Feb-03	Review # 1
—	III	—	—	3	Adequate	31-Jan-03	

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")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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: IND 49,939

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending		
OPDRA			
EA			
Microbiology	Approval	04-Mar-03	Bryan S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-414

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry review perspective, this application is recommended as approvable.

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

None.

II. Summary of Chemistry Assessments

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

The drug product VITRASE® (ovine hyaluronidase) for Ophthalmic — Injection, — USP Units/vial, is a sterile, lyophilized powder for injection solution. It is supplied in a kit containing a

— Sodium Chloride Injection, USP. The Vitrase drug product is formulated as a solution containing ovine hyaluronidase, potassium phosphate dibasic, monobasic potassium phosphate, lactose monohydrate and water for injection. The bulk solution is sterile-filtered

CHEMISTRY REVIEW

Executive Summary Section

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

The proposed indication for Vitrase . _____
_____ The proposed dose is a single
injection of _____ reconstituted drug product). The total volume of the
reconstituted drug product in the single-use vial is _____. Preparations prior to the
applications of Vitrase, include aseptic procedures. The drug product is reconstituted by
transferring _____ from the sodium chloride injection vial into the single-use vial
containing the lyophilized drug product. The resulting solution is mixed well and examined
for clarity and absence of visible particles. _____ of this solution are withdrawn from the
single-use vial through the _____ filter needle into the _____ needle. The filter needle is
replaced by the _____ gauge, _____ needle and the syringe is prepared for a _____ injection.

CHEMISTRY REVIEW

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

7

7

III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Linda Ng, Chemistry Team Leader

D. CC Block

Lori Gorski, Project Manager
Chi-Wan Chen, Division Director DNDCIII
Wiley Chambers, Deputy Division Director HFD-550

77 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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CHEMISTRY REVIEW

Chemistry Assessment Section

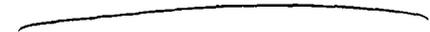
19-MAR-2003

FDA CDER EES

Page 2 of 4

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

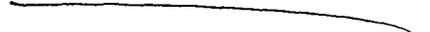
Profile : CEX OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 26-FEB-03
:
:

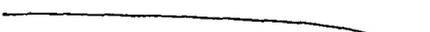
Establishment :


DMF No: 

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-MAR-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :


DMF No: 

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :


DMF No: 

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2032590 FEI : 3003434767
ISTA PHARMACEUTICALS INC
15279 ALTON PARKWAY SUITE 100
IRVINE, CA 92618

DMF No: AADA

CHEMISTRY REVIEW

Chemistry Assessment Section

19-MAR-2003

FDA CDER ERS
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 3 of 4

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 14-MAR-03
:
:

Establishment

DMF No:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment

DMF No:

Responsibilities:

Profile : SVL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 29-OCT-02
:
:

Establishment

DMF No:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment

CHEMISTRY REVIEW

Chemistry Assessment Section

19-MAR-2003

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 4 of 4

DMF No:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

Libaniel Rodriguez
3/21/03 04:18:28 PM
CHEMIST
Review #1, Approvable

Linda Ng
3/21/03 05:19:35 PM
CHEMIST