

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-716

CHEMISTRY REVIEW(S)



NDA 21-716

HYDASE™ (hyaluronidase, bovine, injection) 150 Units/mL

PRIMAPHARM, INC.

**Libaniel Rodriguez, Ph.D.
Division of Anti-infective and Ophthalmology Products**

HFD-520



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Chemistry Review Data Sheet

1. NDA 21-716
2. REVIEW #: 3
3. REVIEW DATE: 22-Jun-2005
4. REVIEWER: Libaniel Rodriguez
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	15-Oct-2003
BZ	17-Mar-2004
BC	26-Mar-2004
Subject of this review:	
AZ	12-Jan-2005
BC	05-May-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Prima Pharm Inc.
Address: 3443 Tripp Court
San Diego, CA 92121
Representative: Anthony J. Dziabo
Telephone: (858) 259-0717



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: HYDASE™
- b) Non-Proprietary Name (USAN): Hyaluronidase, bovine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzymes: Adjuvant for the dispersion and absorption of other injected drugs.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous; 150 USP units/injection

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:

According to claims in this application, Hyaluronidase is a highly purified protein isolated from bovine testes.

➤ The application claims that the chemical structure of the enzyme is unknown.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Proteomic analysis of the peptide sequences that identify this hyaluronidases as homologous to the PH-20 [Bos-Taurus] hyaluronidase as well as apparent molecular weight of the isozymes are provided in this amendment.

Chemical Name: Hyaluronidase (from Bovine Testes)

Synonyms: Hyaluronidase 4-glycanohydrolase

Hyaluronoglucosaminidase

USAN Name: Hyaluronidase (bovine)

CAS Number: 37326-33-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
157	III	[Handwritten signature]	[Handwritten signature]	3	N/A		
157	III			3	N/A		

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	Apr-22-2005	Office of Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Adequate. M.V. Package not sent for validation by the FDA Laboratory.	Apr-29-2005	Libaniel Rodriguez
OPDRA			
EA	Acceptable	Apr-01-2004	Libaniel Rodriguez
Microbiology	Approvable Approvable Approval	Apr-04-2004 Mar-29-2005 Jun-15-2005	Stephen Languille Stephen Languille Stephen Languille
Viral Clearance	Approvable Approvable Approval	30-Mar-2004 20-Jul-2004 Mar-25-2005	Janice Brown Janice Brown Janice Brown



The Chemistry Review for NDA 21-716

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, this application 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 HYDASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL USP type I, clear glass treated vial, with a

This product was formulated to be the equivalent of the approved and no longer manufactured Wydase® drug product, with the exception that it does not contain the preservative thimerosal. The product contains the active ingredient hyaluronidase, calcium chloride dihydrate, disodium edetate, sodium phosphate monobasic anhydrous, sodium hydroxide and water for injection. Three batches of drug product were manufactured and placed in the stability program in support of this application. The of stability data submitted in this application indicate that the product is stable for the time reported and demonstrates potential for stability at longer periods. Manufacturing of the drug product consists of mixing of all the components in a single compounding vessel followed by of the resulting solution and filling/capping into the sterile container closure. Use of overage to compensate for manufacturing loss is implemented.

The drug substance, bovine hyaluronidase, is extracted from bovine testes. the manufacturer of the drug substance from the bovine testes, provides a Certificate of Origin indicating that the (bovine testes) is obtained in the United States that are certified as Issues concerning in the USA arose during the review cycle of this application. PrimaPharm purchases the hyaluronidase drug substance from

**Executive Summary Section**

addition to the drug product formulation. After the first review cycle, [] changed the bovine source from the U.S. to [] Appropriate certificates of origin were included in the resubmission.

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

Hydase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical 150 USP units. Other than [] the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Hydase. This drug product is administered mixed with the drugs that it will help disperse.

The storage condition for the drug substance is -10°C and the requested and recommended retest period is [] The storage condition for the drug product is refrigeration at 5°C ± 3°C. Based on the stability data submitted the recommended expiry for the drug product is eighteen months.

C. Basis for Approvability or Not-Approval Recommendation

Issues concerning the [] origin of the [], characterization, purity and specification for both drug substance and drug product have been satisfactorily resolved.

See agreement to revise drug substance action limits into acceptance criteria upon collection of a significant body of data for the newly added test in the drug substance specification sheet in the last page of this review.

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

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Review Chemist/22-June-2005
Linda Ng, ChemistryTeamLeader
Mike Puglisi, ProjectManager



Executive Summary Section

C. CC Block

Norman Schmuff, Acting Deputy Division Director DNDCIII
Wiley Chambers, Deputy Division Director HFD-520

18 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-1

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/s/

Libaniel Rodriguez
6/23/05 07:32:18 AM
CHEMIST
AP

Linda Ng
6/23/05 09:00:40 AM
CHEMIST



REVIEW NOTE

NDA 21-716

**Hydase (Hyaluronidase Injection, USP)
Bovine - 150 Units/mL**

Prima Pharm, Inc.

**Janice Brown, HFD-510
Division of Metabolic and Endocrine Drug Products
HFD-510**



REVIEW NOTE

Chemistry Review Data Sheet

- 1. NDA 21-716
- 2. REVIEW #: 3
- 3. REVIEW DATE: 21-Mar-2005
- 4. REVIEWER: Janice Brown, Chemistry Reviewer, ONDC/DNDCII, DMEDP (HFD-510)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-Oct-2003
Amendment	08-Apr-2004

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	12-Jan-2005
Amendment	13-Apr-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Prima Pharm
Address:	3443 Tripp Court San Diego, CA 92121
Representative:	Contact: Anthony Diablo Vice President Regulatory Affairs
Telephone:	858-259-0717

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydase
- b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

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

**REVIEW NOTE**

10. PHARMACOL. CATEGORY: Enzyme; Adjuvant to increase absorption and dispersion of other injected drugs and other indications (see primary chemistry review)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/1 ml

13. ROUTE OF ADMINISTRATION: S.C.

14. Rx/OTC DISPENSED: X Rx OTC

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

X SPOTS product – Form Completed

Not a SPOTS product

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

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

A. DMFs: N/A

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:

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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION



CHEMISTRY REVIEW



REVIEW NOTE

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18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

**REVIEW NOTE****The Chemistry Review for NDA 21-716****Consultative Review for Viral Clearance Studies****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

From this consultative CMC reviewer's viewpoint this application can be APPROVED with respect to the information provided for the viral clearance studies. See primary chemist's review for overall CMC recommendation.

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

This consultative reviewer's recommendation is based on the finding of satisfactory CMC information regarding the viral clearance studies provided by the applicant. See primary chemist's review for basis of overall CMC recommendation.

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

See appended electronic signature sheet

B. Endorsement Block

Chemist Name/Date: Janice Brown, ONDC/DNDCII, DMEDP (HFD-510)
ChemistryTeamLeaderName/Date: Stephen Moore, Ph.D. Chemistry Team
Leader, ONDC/DNDCII, DMEDP (HFD-510)
ProjectManagerName/Date:



REVIEW NOTE

C. CC Block

Linda Ng, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, DAAOPD (HFD-550)

Libaniel Rodriguez, Ph.D., Primary Chemistry Reviewer, ONDC/DNDCIII, DAAOPD (HFD-550)

Lori Gorski, Project Manager, DAAOPD (HFD-550)

9 Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-2

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/s/

Janice Brown
4/20/05 08:27:16 AM
CHEMIST

Stephen Moore
4/20/05 09:54:32 AM
CHEMIST



REVIEW NOTE

NDA 21-716

**Hydase (Hyaluronidase Injection, USP)
Bovine
150 Units/mL**

Prima Pharm, Inc.

**Janice Brown, HFD-510
Division of Metabolic and Endocrine Drug
Products
HFD-510**



REVIEW NOTE

Chemistry Review Data Sheet

1. NDA 21-716
2. REVIEW #: 2
3. REVIEW DATE: 20-Jul-2004
4. REVIEWER: Janice Brown, Chemistry Reviewer, ONDC/DNDCII, DMEDP (HFD-510)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-Oct-2003

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	08-Apr-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Prima Pharm
Address:	3443 Tripp Court San Diego, CA 92121
Representative:	Contact: Anthony Diablo. Vice President Regulatory Affairs
Telephone:	858-259-0717

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydase
- b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P



CHEMISTRY REVIEW



REVIEW NOTE

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

10. PHARMACOL. CATEGORY: Enzyme; Adjuvant to increase absorption and dispersion of other injected drugs and other indications (see primary chemistry review)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/1 ml

13. ROUTE OF ADMINISTRATION: S.C.

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, and 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:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application



CHEMISTRY REVIEW



REVIEW NOTE

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

**REVIEW NOTE**

The Chemistry Review for NDA 21-716

Consultative Review for Viral Clearance Studies

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From this consultative CMC reviewer's viewpoint this application is APPROVABLE (AE) with respect to the information provided for the viral clearance studies. See primary chemist's review for overall CMC recommendation.

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

This consultative reviewer's recommendation is based on the finding of unsatisfactory CMC information regarding the viral clearance studies provided by the Applicant. See Draft Deficiency Letter. See primary chemist's review for basis of overall CMC recommendation.

III. Administrative

A. Reviewer's Signature

See appended electronic signature sheet

B. Endorsement Block

Chemist Name/Date: Janice Brown, ONDC/DNDCII, DMEDP (HFD-510)



CHEMISTRY REVIEW



REVIEW NOTE

ChemistryTeamLeaderName/Date: Stephen Moore, Ph.D. Chemistry Team
Leader, ONDC/DNDCII, DMEDP (HFD-510)
ProjectManagerName/Date:

C. CC Block

Linda Ng, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, DAAOPD (HFD-550)

Libaniel Rodriguez, Ph.D., Primary Chemistry Reviewer, ONDC/DNDCIII,
DAAOPD (HFD-550)

Lori Gorski, Project Manager, DAAOPD (HFD-550)

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Janice Brown
8/4/04 05:13:35 PM
CHEMIST

Stephen Moore
8/4/04 05:37:22 PM
CHEMIST



NDA 21-716

HYDASE™ (hyaluronidase, bovine, injection) 150 Units/mL

PRIMAPHARM, INC.

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

HFD-550



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Chemistry Review Data Sheet

1. NDA 21-716
2. REVIEW #: 2
3. REVIEW DATE: 09-Apr-2004
4. REVIEWER: Libaniel Rodriguez
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	15-Oct-2003
Subject of this review	
BZ	17-Mar-2004
BC	26-Mar-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Prima Pharm Inc.
Address: 3443 Tripp Court
San Diego, CA 92121
Representative: Anthony J. Dziabo
Telephone: (858) 259-0717



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: HYDASE™
- b) Non-Proprietary Name (USAN): Hyaluronidase, bovine
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.

10. PHARMACOL. CATEGORY: Proteolytic enzyme

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous; 150 USP units/injection

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:

According to claims in this application, Hyaluronidase is a highly purified protein isolated from bovine testes

The application claims that the chemical structure of the enzyme is unknown. No molecular, structural or molecular weight information is provided.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemical Name: Hyaluronidase (from Bovine Testes)

Synonyms: Hyaluronidase 4-glycanohydrolase

Hyaluronoglucosaminidase

USAN Name: Hyaluronidase (bovine)

CAS Number: 37326-33-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III			3	N/A		
—	III			3	N/A		

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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:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6343	Wydase referenced through Section 505(b)(2) of the FDA Food , Drug and Cosmetic Act

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending, see p. 21 of this review		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending, see p. 20 of this review		
OPDRA			
EA			
Microbiology	Approvable	March 12, 2004	Stephen Languille
Viral Clearance	Approvable	April 7, 2004	Janice Brown



The Chemistry Review for NDA 21-716

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, this application is recommended as approvable, pending satisfactory resolution of CMC issues.

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 HYDASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL USP type I, clear glass treated vial, with a

This product was formulated to be the equivalent of the approved and no longer manufactured Wydase® drug product, with the exception that it does not contain the preservative thimerosal. The product contains the active ingredient hyaluronidase, calcium chloride dihydrate, disodium edetate, sodium phosphate monobasic anhydrous, sodium hydroxide and water for injection. Three batches of drug product were manufactured and placed in the stability program in support of this application. The of stability data submitted in this application indicate that the product is stable for the time reported and demonstrates potential for stability at longer periods. Manufacturing of the drug product consists of mixing of all the components in a single compounding vessel followed by of the resulting solution and filling/capping into the sterile container closure.

The drug substance, bovine hyaluronidase, is extracted from bovine testes. the manufacturer of the drug substance from the bovine testes, provides a Certificate of Origin indicating that the (bovine testes) is obtained in the United States that are certified as

Issues concerning in the USA arose during the review cycle of this application. PrimaPharm purchases the hyaluronidase drug substance from

**Executive Summary Section**

form, for prompt (less than _____ shelf life) addition to the drug product formulation.

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

Hydase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical 150 USP units. Other than removal of the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Hydase. This drug product is administrated mixed with the drugs that it will help disperse.

The storage condition for the drug substance is -10°C and the requested and recommended retest period is . The storage condition for the drug product is refrigeration at 5°C ± 3°C. Based on the stability data submitted the recommended expiry for the drug product is eighteen months.

C. Basis for Approvability or Not-Approval Recommendation

Issues concerning the characterization, purity and specification for both drug substance and drug product remain to be resolved. The deficiencies below will be conveyed to the applicant in the approvable action letter.

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

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Review Chemist/12-Apr-2004
Linda Ng, ChemistryTeamLeader/12-Apr-2004
Mike Puglisi, ProjectManager/12-Apr-2004

C. CC Block

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

16 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Libaniel Rodriguez
4/13/04 11:46:03 AM
CHEMIST
Review #2 approvable

Linda Ng
4/13/04 12:17:02 PM
CHEMIST
Note comments to be included in letter

NDA 21-716

Hydase (Hyaluronidase Injection, USP)

Bovine

150 Units/mL

Prima Pharm, Inc.

Janice Brown, HFD-510

Division of Metabolic and Endocrine Drug Products

HFD-510



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REVIEW NOTE

Chemistry Review Data Sheet

1. NDA 21-716
2. REVIEW #: 1
3. REVIEW DATE: 30-Mar-2004
4. REVIEWER: Janice Brown, Chemistry Reviewer, ONDC/DNDCII, DMEDP (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

17-Oct-2003

7. NAME & ADDRESS OF APPLICANT:

Name:

Prima Pharm

Address:

3443 Tripp Court
San Diego, CA 92121

Representative:

Contact: Anthony Diablo.
Vice President Regulatory Affairs

Telephone:

858-259-0717

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hydase



REVIEW NOTE

b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine

c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Enzyme; Adjuvant to increase absorption and dispersion of other injected drugs and other indications (see primary chemistry review)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 150 USP Units/1 ml

13. ROUTE OF ADMINISTRATION: S.C.

14. Rx/OTC DISPENSED: X Rx OTC

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

X SPOTS product – Form Completed

Not a SPOTS product

**REVIEW NOTE**

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: See primary chemistry review.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER



REVIEW NOTE

The Chemistry Review for NDA 21-716

Consultative Review for Viral Clearance Studies

The Executive Summary

I. Recommendations

- A. Recommendation and Conclusion on Approvability**
From this consultative CMC reviewer's viewpoint this application is APPROVABLE (AE) with respect to the information provided for the viral clearance studies. See primary chemist's review for overall CMC recommendation.
- 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**

This consultative reviewer's recommendation is based on the finding of unsatisfactory CMC information regarding the viral clearance studies provided by the Applicant. See Draft Deficiency Letter. See primary chemist's review for basis of overall CMC recommendation.

III. Administrative

- A. Reviewer's Signature**
See appended electronic signature sheet
- B. Endorsement Block**

Chemist Name/Date: Janice Brown, ONDC/DNDCII, DMEDP (HFD-510)



CHEMISTRY REVIEW



REVIEW NOTE

ChemistryTeamLeaderName/Date: Stephen Moore, Ph.D. Chemistry Team Leader,
ONDC/DNDCII, DMEDP (HFD-510)

ProjectManagerName/Date:

C. CC Block

Linda Ng, Ph.D., Chemistry Team Leader, ONDC/DNDCIII, DAAOPD (HFD-550)

Libaniel Rodriguez, Ph.D., Primary Chemistry Reviewer, ONDC/DNDCIII, DAAOPD (HFD-550)

Lori Gorski, Project Manager, DAAOPD (HFD-550)

7 Page(s) Withheld

 ✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 5

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

/s/

Janice Brown
4/7/04 11:43:47 AM
CHEMIST

Stephen Moore
4/7/04 11:54:43 AM
CHEMIST



NDA 21-716

**HYDASE™ (hyaluronidase, Bovine, Injection, USP) 150
Units/mL**

PRIMAPHARM, INC.

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

HFD-550



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Chemistry Review Data Sheet

1. NDA 21-716
2. REVIEW #:1
3. REVIEW DATE: 01-Apr-2004
4. REVIEWER: Libaniel Rodriguez
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original

Document Date
15-Oct-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Prima Pharm Inc.
Address: 3443 Tripp Court
San Diego, CA 92121
Representative: Anthony J. Dziabo
Telephone: (858) 259-0717

8. DRUG PRODUCT NAME/CODE/TYPE:



Chemistry Review Data Sheet

- a) Proprietary Name: HYDASE™
b) Non-Proprietary Name (USAN): Hyaluronidase
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)(2), Wydase® Stabilized Solution, 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.
10. PHARMACOL. CATEGORY: Proteolytic enzyme
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 150 USP Units/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous; 150 USP units/injection
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:

According to claims in this application, Hyaluronidase is a highly purified protein isolated from bovine testes

The application claims that the chemical structure of the enzyme is unknown. No molecular, structural or molecular weight information is provided.

Chemical Name: Hyaluronidase (from Bovine Testes)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Synonyms: Hyaluronidase 4-glycanohydrolase

Hyaluronoglucosaminidase

USAN Name: Hyaluronidase (bovine)

CAS Number: 37326-33-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: No DMF numbers or letters of authorization to any DMF are mentioned in this application.

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:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	6343	Wydase referenced through Section 505(b)(2) of the FDA Food, Drug and Cosmetic Act

18. STATUS:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending, see p. 27 of this review		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending, see p. 27 of this review		
OPDRA			
EA			
Microbiology	Approvable	March 12, 2004	Stephen Languille



Executive Summary Section

form for prompt (less than _____ shelf life) addition to the drug product mixture. Issues of purity of the drug substance remain to be resolved.

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

Hydase™ is indicated as an adjuvant to increase the adsorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving the absorption of radiopaque agents. It is supplied as a 1 mL injection in a 2 mL vial. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical 150 USP units. Other than _____ removal of the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Hydase. This drug product is administrated mixed with the drugs that it will help disperse.

The storage condition for the drug substance is -10°C and the requested and recommended retest period is _____. The storage condition for the drug product is refrigeration at 5°C ± 3°C. Based on the stability data submitted the recommended expiry for the drug product is eighteen months.

C. Basis for Approvability or Not-Approval Recommendation

Issues concerning the _____ characterization, purity and specification for both drug substance and drug product remain to be resolved. The deficiencies below and in the next page, were faxed to the applicant on January 30, 2004. The remaining deficiencies will be conveyed in the action letter.

For drug substance:

1. For the description and characterization section (see ICH Q6B), provide apparent molecular weight of the hyaluronidase and its major protein impurities. Provide representative chromatograms or electrophoretograms indicating the relative position and amount of material for each of the identified peaks or bands.
2. The "Certificate of Origin" provided in "Appendix 2" does not provide sufficient information on the origin of the bovine material used to manufacture the raw drug substance. Please provide the following:

• []



Executive Summary Section

3. Provide complete description for the manufacturing process of the drug substance. Alternatively, provide DMF number and letter of authorization for the manufacturing process of hyaluronidase by
4. Establish analytical procedure and acceptance criteria for total protein, hyaluronidase content (mg/mg of protein), protein and non-protein impurities.
5. Provide carbohydrate analysis data for the drug substance.
6. Provide complete description of the Container/Closure System (C/CS) and Provide appropriate references to DMFs with LOAs if available. Indicate whether this C/CS has been appropriately qualified as adequate for contact with food.
7. Conduct and submit results of stress studies according to the ICH Q5C guidance.

For drug product:

1. Correct typo in application form 356h, under "Route of Administration", from "Intravenous" to correct route of administration.
2. Vol. 1, page 3. Provide evidence in support of the equivalence among the USP, TR and IU units.
3. Provide complete description, DMF numbers and LOAs for the Container/Closure System components.
4. Submit compatibility studies of the drug product with the container/closure system to ensure that the solution is free of leachables and loss due to absorption to the components.
5. Overage is permitted to correct for manufacturing loss or for relevant cause with justification. Overage is not permitted for correction of stability loss. Please justify the — overage for the formulation of this drug product with data.
6. Provide certificates of analysis for the excipients.
7. Establish analytical procedure and acceptance criteria for total protein, hyaluronidase content (mg/mg of protein), protein and non-protein impurities.
8. Conduct and submit results of stress studies according to the ICH Q5C guidance.
9. Acceptance criteria for tests should be based on actual long-term stability data. Tighten appropriately and submit the revised specification and stability protocol.

The following deficiencies need to be conveyed to the applicant.



Executive Summary Section

For drug substance:

1. Provide acceptance criteria and tests for the bovine testes
2. Provide data on amounts of starting materials, intermediate and final yields for the PrimaPharm drug substance manufacturing process. Alternatively, provide a sample executed manufacturing batch record for the hyaluronidase drug substance.
3. Certificate of analysis or release data from PrimaPharm for the hyaluronidase drug substance should be provided.
4. Establish acceptance criterion for pH of the drug substance.
5. Please revise and submit specification sheet and stability protocol to reflect amendments to these sections of the drug substance application.

For the Drug product:

6. Revise typo in the drug product specification sheet for the proposed acceptance criterion for Particulate Matter from
7. Convert the Osmolality Test from "For Information Only" to a regular release and stability monitored parameter. Revise specification sheet and stability protocol to reflect this change.
8. The methods validation section of this application needs to be revised to include the validation of the additional analytical methods and acceptance criteria for drug substance and drug product.
9. The "Description" section should include pH and Osmolality ranges for the drug product. The storage statement in the "How Supplied" section should read, Store at 2 to 8 °C (35 to 47°F).



III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist

B. Endorsement Block

Libaniel Rodriguez, Review Chemist/31-Mar-2004

Linda Ng, ChemistryTeamLeader/31-Mar-2004

Mike Puglisi, ProjectManager/31-Mar-2004

C. CC Block

30 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Libaniel Rodriguez
4/7/04 01:45:15 PM
CHEMIST
Review #1 Approvable

Linda Ng
4/7/04 02:01:28 PM
CHEMIST
Note that chem reviews #1 and #2 constitute one
review cycle.