

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-859

CHEMISTRY REVIEW(S)

NDA 21-859

**Hylenex
Hyaluronidase (rDNA origin) injection**

Halozyme Therapeutics, Inc.

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

Consultative Drug Substance Chemistry Review #2

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Chemistry Review Data Sheet

1. NDA 21-859
2. REVIEW #: Consultative Drug Substance Chemistry Review #2
3. REVIEW DATE: 13-Jul-2005
4. REVIEWER: CDR John C. Hill, Ph.D., MS, ONDC/DNDC II/DMEDP/HFD-510

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA Filing	18-MAR-2005

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Response to Drug Substance IR letter (BC)	17-JUN-2005
Response to Drug Substance T-con (BC)	14-JUL-2005
Drug substance stability update (BC)	12-AUG-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Halozyme Therapeutics, Inc.
Address:	11588 Sorrento Valley Road, #17 San Diego, CA 92121
Representative:	Don Kennard, Vice President Regulatory Affairs
Telephone:	(858) 749-8889 X 208

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: recombinant human hyaluronidase
b) Non-Proprietary Name (USAN): Hylenex
c) Code Name/# (ONDC only): Optiphase, Enhanze SC, Hylenex
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
 - Submission Priority: P

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

LISTED DRUG: Wydase (NDA 6-343), Baxter Healthcare

10. PHARMACOL. CATEGORY: Adjunct to increase the absorption and dispersion of other injected drugs, for hypodermoclysis; as an adjunct in subcutaneous urography for improving the resorption of radiopaque agents.

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 150 USP U/ml

13. ROUTE OF ADMINISTRATION: SC

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:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CAS: 757971-58-7
Molecular formula
Molecular Weight:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1255	II	[]	1	Adequate	24-JUN-2002	LOA: 24-MAR-2005
7	III				Adequate	27-JUL-2004	LOA: 01-APR-2005
7	III				Adequate	15-NOV-2004	LOA: 24-MAR-2005

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	01-AUG-2005	J.D. Ambrogio
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

OGD:

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

19. ORDER OF REVIEW (OGD Only)

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



The Chemistry Review for NDA 21-859

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- Can be approved (AP) for drug substance from a chemistry point of view.
- Based on the provided stability data, a shelf life for the drug substance c _____ when stored at $-30\pm 5^{\circ}\text{C}$ is granted.

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

- The applicant has made an agreement to conduct the primary stability study to completion, following the stability protocol; notifying the Agency of the results in a timely manner.
- The applicant has made an agreement to place one batch per year on stability.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance presented in this NDA is a recombinant human hyaluronidase, rHuPH20. rHuPH20 is the first recombinant human hyaluronidase product marketed in any region of the world. rHuPH20 is a new chemical entity and has been fully characterized by the applicant with respect to its chemical, physical and biological characteristics. This characterization included comparison to the animal derived hyaluronidase products of bovine and ovine origin; demonstrating similar enzymatic activities between the recombinant and natural products.

rHuPH20 is a recombinant protein expressed in a _____ Chinese Hamster Ovary (CHO) cell line.

purity and structural confirmation. Stability studies have been conducted which demonstrate that the drug substance is stable for at least 12 months when stored as a frozen liquid at $-\pm 5^{\circ}\text{C}$.

Drug Product



Executive Summary Section

The drug product is not part of this drug substance consultative review, however the following summary of the Hylenex drug product is provided to put the drug substance review into context.

Hylenex is an injectable liquid formulation that utilizes a recombinant form of human hyaluronidase as the drug substance supplied at a concentration of 150U/mL. This NDA seeks approval based on the Drug Efficacy Study Implementation (DESI 6343)¹ indications. Those indications are:

For enhancing the dispersion and absorption of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography; for improving resorption of radiopaque agents.

Hyaluronidase is a spreading or diffusing enzyme which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid². Hyaluronic acid is a polysaccharide found in the extracellular matrix of connective tissues. rHuPH20 hyaluronidase and other forms of pH20 hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosamidic bond between C₁ of the glucosamine moiety and C₄ of glucuronic acid. This temporarily decreases the viscosity of the extracellular matrix and promotes diffusion of injected fluids thus facilitating their absorption. Reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase occurs within 24 to 48 hours.

Hylenex is an injectable hyaluronidase solution product that has the same dosage form, strength, proposed indications, and proposed route of administration as the Reference Listed Drug, Wydase. Enhanze SC substitutes the active ingredient, rHuPH20, recombinant human hyaluronidase, for the bovine derived active ingredient hyaluronidase in Wydase. Other changes include the absence of a mercury based preservative in Hylenex, and the presence of human serum albumin in Hylenex.

The hyaluronidase drugs previously approved under DESI 6343 include, WydaseB (NDA 6-343), AlidaseB (NDA 6-714), and Hyazymem (NDA 7-933). Each of these drugs were injectable hyaluronidase preparations derived from bovine testes. Commercial bovine hyaluronidase preparations contain the bovine pH20 protein lacking the carboxy-terminal amino acids that mediate attachment to the plasma membrane via a lipid anchor. Halozyme's rHuPH20 also lacks such amino acids in the carboxy terminus giving rise to a soluble, neutral-active enzyme similar to the protein found in bovine testes preparations.



Halozyme Therapeutics, Inc. is relying upon the National Academy of Sciences/National Research Council (NAS/NRC) Report of Safety and Effectiveness of hyaluronidase injectable products, the Federal Register Publications by the Food and Drug Administration that established that hyaluronidase injectable products are safe and effective for the DESI Review indications. Halozyme Therapeutics, Inc. is further relying upon the findings of efficacy and safety as detailed in the Integrated Summary of Efficacy and the Integrated Summary of Efficacy found in files *ise.pdf* and *iss.pdf* respectively. These summaries rely upon published literature and the completion of a Phase I Safety Trial sponsored by Halozyme Therapeutics, Inc.

1. DESI 6343: Drugs for Human Use; Drug Efficacy Study Implementation; Docket No. FDC-D-235; NDA 6343, Fed. Reg., Vol. 35, No. 185-Wednesday, September 23, 1970.

2. The terms hyaluronic acid, and hyaluronate are referred to as hyaluronan in more recent literature.



Executive Summary Section

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

Not part of this consultative review.

C. Basis for Approvability or Not-Approval Recommendation

- All outstanding drug substance CMC issues have been addressed.
- CGMP status of the Avid Bioservices, Inc. contract drug substance manufacturing facility is acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

John C. Hill, Ph.D., Chemist / 23-AUG-2005: See appended electronic signature page
Stephen K. Moore, Ph.D., Team Leader / 23-AUG-2005: See appended electronic signature page

C. CC Block

Allison K. Rodgers, Regulatory Health Project Manager

9 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Chem 2



CHEMISTRY REVIEW



Executive Summary Section

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FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 21859/000 Action Goal:
Stamp: 23-MAR-2005 District Goal: 25-JUL-2005
Regulatory Due: 23-SEP-2005 Brand Name: HYLENEX
Applicant: HALOZYME Estab. Name:
NO CITY, , XX Generic Name: RECOMBINANT HUMAN
1P HYALURONIDASE 150USP
Priority: 520 Dosage Form: (LIQUID)
Org Code: Strength: 150 USP UNITS

Application Comment:

FDA Contacts: A. RODGERS (HFD-550) 301-827-2019 , Project Manager
J. HILL (HFD-810) 301-827-6408 , Review Chemist
S. MOORE (HFD-510) 301-827-6401 , Team Leader

Overall Recommendation: ACCEPTABLE on 01-AUG-2005 by J. D AMBROGIO(HFD-322)301-827-

9049

Establishment: CFN

[

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CHEMISTRY REVIEW



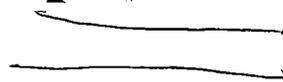
Executive Summary Section



DMF No:

AADA:

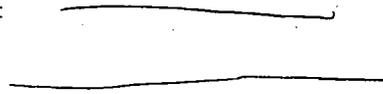
Responsibilities:



Profile: CBI

OAI Status: NONE

Estab. Comment:

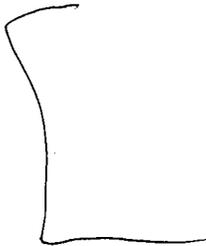


(on 04-APR-2005 by J. HILL (HFD-

810) 301-827-6408)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
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SUBMITTED TO OC	04-APR-2005				HILLJ
SUBMITTED TO DO	04-APR-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	20-APR-2005	PS			CEVERLY
INSPECTION SCHEDULED	12-MAY-2005		12-JUL-2005		CEVERLY
INSPECTION PERFORMED	15-JUL-2005		15-JUL-2005		CEVERLY
INSPECTION PERFORMED	15-JUL-2005		15-JUL-2005		CARYN.MCNAB



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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



CHEMISTRY REVIEW



Executive Summary Section

Establishment: CFN FEI

DMF No:

AADA:

Responsibilities:

Profile: LIQ

OAI Status: NONE

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On Original



CHEMISTRY REVIEW



Executive Summary Section

19-AUG-2005

FDA CDER EES

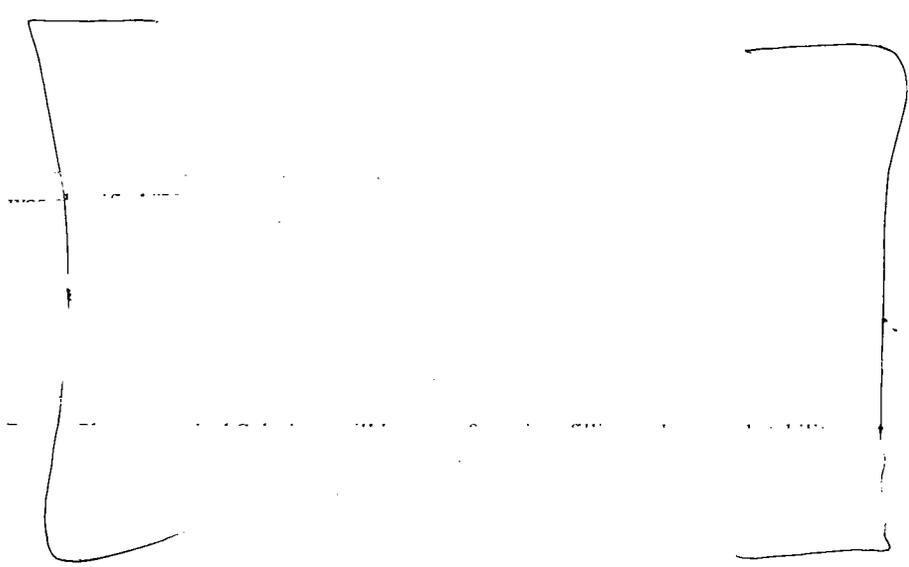
Page 3 of 4

DETAIL REPORT

Estab. Comment: _____

_____ (on 04-APR-2005 by J. HILL (HFD-810) 301-827-6408)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-APR-2005				HILLJ
SUBMITTED TO DO	04-APR-2005	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	05-APR-2005	PS			PDOMINGO
INSPECTION SCHEDULED	01-JUN-2005				PDOMINGO
INSPECTION PERFORMED	09-JUN-2005		09-JUN-2005		LAUSTIN





CHEMISTRY REVIEW



Executive Summary Section



DO RECOMMENDATION 29-JUL-2005 ACCEPTABLE PDOMINGO

INSPECTION

GMP INSPECTION DATED 7/5-22/05 WILL BE CLASSIFIED VAI. DET-DO CONSIDERS THIS FIRM TO BE

ACCEPTABLE.

OC RECOMMENDATION 01-AUG-2005 ACCEPTABLE DAMBROGIOJ

DISTRICT RECOMMENDATION

Establishment: CFN FEI





CHEMISTRY REVIEW



Executive Summary Section

DMF No:

AADA:

Responsibilities:

Profile: CTL

OAI Status: NONE

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Appears This Way
On Original



CHEMISTRY REVIEW



Executive Summary Section

(on 04-APR-2005 by J. HILL (HFD-810) 301-827-6408)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
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SUBMITTED TO OC	04-APR-2005				HILLJ
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OC RECOMMENDATION	04-APR-2005			ACCEPTABLE	DAMBROGIOJ
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BASED ON PROFILE

Establishment: CFN _____ FEI _____

I []

DMF No: _____ AADA: _____

Responsibilities: _____

Profile: CTL OAI Status: NONE

Estab. Comment: _____

(on 04-APR-2005 by J. HILL (HFD-810) 301-827-6408)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
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SUBMITTED TO OC	04-APR-2005				HILLJ
-----------------	-------------	--	--	--	-------

OC RECOMMENDATION	04-APR-2005			ACCEPTABLE	DAMBROGIOJ
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BASED ON PROFILE

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

/s/

John C. Hill
8/23/2005 06:01:08 PM
CHEMIST

Stephen Moore
8/23/2005 06:09:11 PM
CHEMIST



NDA 21-859

**Hylenex
Hyaluronidase (rDNA origin) injection**

Halozyme Therapeutics, Inc.

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

Consultative Drug Substance Chemistry Review #1



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A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used	9
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B. Endorsement Block	9
C. CC Block	9
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Chemistry Review Data Sheet

1. NDA 21-859
2. REVIEW #: Consultative Drug Substance Chemistry Review #1
3. REVIEW DATE: 26-May-2005
4. REVIEWER: CDR John C. Hill, Ph.D., MS, ONDC/DNDC II/DMEDP/HFD-510

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	18-MAR-2005
BZ amendment (DMF authorization letter updates)	06-APR-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Halozyme Therapeutics, Inc.
Address:	11588 Sorrento Valley Road, #17 San Diego, CA 92121
Representative:	Don Kennard, Vice President Regulatory Affairs
Telephone:	(858) 749-8889 X 208

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: recombinant human hyaluronidase
b) Non-Proprietary Name (USAN): Hylenex
c) Code Name/# (ONDC only): Optiphase, Enhanze SC, Hylenex
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: P

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

LISTED DRUG: Wydase (NDA 6-343), Baxter Healthcare

10. PHARMACOL. CATEGORY: Adjunct to increase the absorption and dispersion of other injected drugs, for hypodermoclysis; as an adjunct in subcutaneous urography for improving the resorption of radiopaque agents.

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 150 USP U/ml

13. ROUTE OF ADMINISTRATION: SC

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:



CHEMISTRY REVIEW



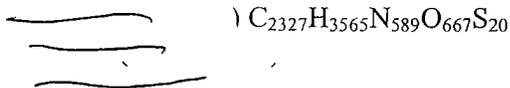
Chemistry Review Data Sheet



CAS: 757971-58-7

Molecular formula

Molecular Weight:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	[Hand-drawn box]	[Hand-drawn box]	1	Adequate	24-JUN-2002	LOA: 24-MAR-2005
—	III			1	Adequate	27-JUL-2004	LOA: 01-APR-2005
—	III			1	Adequate	15-NOV-2004	LOA: 24-MAR-2005

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending Inspection		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

OGD:

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

19. ORDER OF REVIEW (OGD Only)

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



The Chemistry Review for NDA 21-859

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- Approvable (AE) from a chemistry point of view.
- Based on the provided stability data, a shelf life for the drug substance of _____ when stored at $-20\pm 5^{\circ}\text{C}$ is granted.

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

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

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance presented in this NDA is a recombinant human hyaluronidase, rHuPH20. rHuPH20 is the first recombinant human hyaluronidase product marketed in any region of the world. rHuPH20 is a new chemical entity and has been fully characterized by the applicant with respect to its chemical, physical and biological characteristics. This characterization included comparison to the animal derived hyaluronidase products of bovine and ovine origin; demonstrating similar enzymatic activities between the recombinant and natural products.

rHuPH20 is a recombinant protein expressed in a _____ Chinese Hamster Ovary (CHO) cell line.

Stability studies have been conducted which demonstrate that the drug substance is stable for at least _____ when stored as a frozen liquid at $-20\pm 5^{\circ}\text{C}$.

Drug Product



CHEMISTRY REVIEW



Executive Summary Section

The drug product is not part of this drug substance consultative review, however the following summary of the Hylenex drug product is provided to put the drug substance review into context.

Hylenex is an injectable liquid formulation that utilizes a recombinant form of human hyaluronidase as the drug substance supplied at a concentration of 150U/mL. This NDA seeks approval based on the Drug Efficacy Study Implementation (DESI 6343)¹ indications. Those indications are:

For enhancing the dispersion and absorption of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography; for improving resorption of radiopaque agents.

Hyaluronidase is a spreading or diffusing enzyme which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid². Hyaluronic acid is a polysaccharide found in the extracellular matrix of connective tissues. rHuPH20 hyaluronidase and other forms of pH20 hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosamidic bond between C₁ of the glucosamine moiety and C₄ of glucuronic acid. This temporarily decreases the viscosity of the extracellular matrix and promotes diffusion of injected fluids thus facilitating their absorption. Reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase occurs within 24 to 48 hours.

Hylenex is an injectable hyaluronidase solution product that has the same dosage form, strength, proposed indications, and proposed route of administration as the Reference Listed Drug, Wydase. Enhance SC substitutes the active ingredient, rHuPH20, recombinant human hyaluronidase, for the bovine derived active ingredient hyaluronidase in Wydase. Other changes include the absence of a mercury based preservative in Hylenex, and the presence of human serum albumin in Hylenex.

The hyaluronidase drugs previously approved under DESI 6343 include, WydaseB (NDA 6-343), AlidaseB (NDA 6-714), and Hyazymem (NDA 7-933). Each of these drugs were injectable hyaluronidase preparations derived from bovine testes. Commercial bovine hyaluronidase preparations contain the bovine pH20 protein lacking the carboxy-terminal amino acids that mediate attachment to the plasma membrane via a lipid anchor. Halozyme's rHuPH20 also lacks such amino acids in the carboxy terminus giving rise to a soluble, neutral-active enzyme similar to the protein found in bovine testes preparations.



Halozyme Therapeutics, Inc. is relying upon the National Academy of Sciences/National Research Council (NAS/NRC) Report of Safety and Effectiveness of hyaluronidase injectable products, the Federal Register Publications by the Food and Drug Administration that established that hyaluronidase injectable products are safe and effective for the DESI Review indications. Halozyme Therapeutics, Inc. is further relying upon the findings of efficacy and safety as detailed in the Integrated Summary of Efficacy and the Integrated Summary of Efficacy found in files *ise.pdf* and *iss.pdf* respectively. These summaries rely upon published literature and the completion of a Phase I Safety Trial sponsored by Halozyme Therapeutics, Inc.

1. DESI 6343: Drugs for Human Use; Drug Efficacy Study Implementation; Docket No. FDC-D-235; NDA 6343, Fed. Reg., Vol. 35, No. 185-Wednesday, September 23, 1970.

2. The terms hyaluronic acid, and hyaluronate are referred to as hyaluronan in more recent literature.



CHEMISTRY REVIEW

Executive Summary Section

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

Not part of this consultative review.

C. Basis for Approvability or Not-Approval Recommendation

- The applicant should address outstanding CMC issues. See list of deficiencies.
- CGMP status of the Avid Bioservices, Inc. contract drug substance manufacturing facility is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

70 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

John C. Hill
5/26/05 05:37:25 PM
CHEMIST

Stephen Moore
6/1/05 01:15:59 PM
CHEMIST

NDA 21-859

HYLENEX™
hyaluronidase human [rDNA origin]
injection
150 USP Units/mL

Halozyme Therapeutics, Inc.

Allan Fenselau, Ph.D.
Division of Anti-Infective and Ophthalmology Products
(HFD-520)

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II. Summary of Chemistry Assessments	7
A. Description of the Drug Substance and Drug Product.....	7
B. Intended Use of the Drug Product.....	9
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Chemistry Review Data Sheet

1. **NDA 21-859**
2. **REVIEW: # 1**
3. **REVIEW DATE: 01-SEP-2005**
4. **REVIEWER: Allan Fenselau**
5. **PREVIOUS DOCUMENTS: None**
6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	18-MAR-2005
Amendment (BZ)	06-APR-2005
Amendment (BC)	21-APR-2005
Amendment (BC)	20-MAY-2005
Amendment (BC)	01-JUN-2005
Amendment (BC)	01-JUL-2005
Amendment (BC)	14-JUL-2005
Amendment (BC)	28-JUL-2005
Amendment (BC)	03-AUG-2005
Amendment (BC)	12-AUG-2005
Amendment (BC)	15-AUG-2005
Amendment (BC)	23-AUG-2005
Amendment (BC)	26-AUG-2005

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Halozyme Therapeutics, Inc.
Address:	11588 Sorrento Valley Road, #17 San Diego, CA 92121
Representative:	Don Kennard, Vice President Regulatory Affairs
Telephone:	(858) 749-8889 x208

8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) **Proprietary Name:** HYLENEX™
- b) **Non-Proprietary Name (USAN):** Recombinant human hyaluronidase
The Chemical Abstracts Index Name is 36-482-Hyaluronoglucosaminidase PH20 (human).
The CAS Registry Number is [757971-58-7].
USAN name: hyaluronidase (human recombinant)
ONDC name: hyaluronidase human [rDNA origin]
- c) **Code Name/# (ONDC only):** Optiphase, Enhanze SC, Hylenex
- d) **Chem. Type/Submission Priority:** 4/P

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

REFERENCE LISTED DRUG: Wydase (NDA 6-343), Baxter Healthcare

CHEMISTRY REVIEW



LISTING of MANUFACTURING and TESTING SITES USED in the MANUFACTURE of the DRUG PRODUCT, HYLENEX (hyaluronidase human [rDNA origin] injection) 150 USP Units/mL

CFN	HOLDER	DESCRIPTION	Insp. Status	ADDRESS

Abbreviations used: DP, Drug Product; AP, Approval recommended by Office of Compliance. (See Review p. 31 and p. 76)

SUPPORTING DOCUMENTS:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	LOA ¹ DATE	DATE of LAST REVIEW
---	III	[]	[]	Y 12-JUL-2004	Adequate info. provided in NDA
---	III			Y 13-JUL-2004	Adequate info. provided in NDA
---	III			Y 27-AUG-2004	Adequate info. provided in NDA

1. Letter of Authorization; included Yes/No [Y/N]; LOA Date

17. RELATED/SUPPORTING DOCUMENTS:

Documents	Document Date
IND: 66,888	12-NOV-2004
501(k): K042495	Filed 11-SEP-2004
Patents: None listed	-----

18. STATUS: ONDC

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
ONDC/Drug Substance	Acceptable	23-AUG-2005	J.Hill
Biometrics	Not applicable	----	----
EES	Acceptable	01-AUG-2005	J.D'Ambrogio
Pharm/Tox	Acceptable	14-JUN-05	Z.Chen
Biopharm	Not applicable	----	----
LNC	Acceptable	----	S.Moore
Methods Validation	Not applicable	----	----
DDMAC	Acceptable	22-JUN-2005	S.Berkman
EA	Acceptable	01-SEP-2005	A.Fenselau
Microbiology	Acceptable	04-AUG-2005	J.McVey



EXECUTIVE SUMMARY

Chemistry Review for NDA 21-859

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for NDA 21-859, HYLENEX (hyaluronidase human [rDNA origin] injection) 150 USP units/mL based on a consideration of chemistry, manufacturing and controls issues is APPROVAL.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Drug Substance: The drug substance section of this submission has been reviewed by Dr. J. Hill and Dr. S. Moore (Team Leader) in DNDCII, HFD-510. A drug substance issue that would affect drug product quality was identified during review of the drug product. Comparison of the rHuPH20 drug substance specification on the Certificates of Analysis from the drug substance manufacturer _____ with the one proposed by the applicant revealed significant, more tolerant, and inadequately justified limits for the regulatory acceptance criteria for [

]. The toxicological, clinical, and stability studies did not provide justification for the proposed acceptance criteria. These issues were discussed with the applicant and produced an acceptance specification for the drug substance in greater accord with the existing data for lots used in the toxicological, clinical, and stability studies.

Drug Product: The proposed new product contains human albumin _____ for active ingredient), edetate sodium dihydrate _____, calcium chloride dihydrate _____, sodium chloride, _____, sodium phosphate dibasic dihydrate (pH buffer), and sodium hydroxide (for pH adjustment). All of these components are USP/NF compendial grade and tested in accord with pharmacopeial specifications. The compatibility of these excipients with the active ingredient (rHuPH20 hyaluronidase) and with one another was established during formulation development. The product contains no novel excipients or excipients of animal origin.

The manufacturing, packaging, and testing operations are performed at the same facility: Baxter Pharmaceutical Solutions [BPS] (Bloomington, IN). An adequate summary has been provided for the manufacturing process, which requires [

]. Details of a batch manufacturing record have been provided for a primary NDA stability batch (Batch 804419 used in the clinical study). The in-process testing of pH, osmolality, activity, and bioburden is adequate to control product quality. Appropriate controls are in place to assure safe transfer and handling of the drug substance prior to its use in product manufacture. The issue of overage was resolved by retaining the conditions employed in the manufacture of the registration lots.

CHEMISTRY REVIEW

The product specification includes testing for Description, Assay and Identity (by turbidity test), Content of rHuPH20 and impurities/degradants (by HPLC), Particulate Matter, pH, Osmolality, Endotoxin Content, and Sterility. The proposed acceptance criteria are acceptable. With the exception of the turbidity test for enzyme activity and HPLC test for enzyme (and impurity/degradant) content, the analytical procedures are compendial. The Assay has been modified from the USP monograph for "Hyaluronidase Injection" in terms of specific conditions and materials, including the use of a rHuPH20 reference standard [RS] in place of the USP RS. These revisions have been examined to establish the equivalency of the USP and applicant's test methods for determining enzyme activity and the equivalency of the USP and rHuPH20 reference standards. Accordingly, the activity of the rHuPH20 hyaluronidase product is appropriately expressed in terms of USP units.

The HPLC method appears to provide information on the content of rHuPH20 and its impurities/degradants in the HyleneX product but, because of the low levels of rHuPH20 in the product, the method has poor reliability. Furthermore, the content determination does not correlate well with the activity determination. The USP monograph test based on assessing biological activity is considered the relevant and primary test for hyaluronidase products and is the only enzyme-related test required for all other approved hyaluronidase products. In this context, the recommendation is to eliminate the use of the HPLC test or to use it for informational purposes only.

The single cartons are packaged 10 to a carton shelf pack. The container closure system appears adequate to hold the

Batch analyses were provided for the following batches all manufactured by BPS at commercial scale. Primary batches, X804369, 804396, and 804419 (to the approved target potency of) and Support batches, 804570 and 804658 (target potency,) and 804509 (target potency, as a comparator for the batches). Also provided were data for Batches 2004-8-12-3 and 2004-8-12-4 manufactured by Halozyme at the pilot scale (or commercial scale) using a target potency of . At release all batches complied with the product specification.

Stability studies were performed with the primary and support batches employing the following conditions

By completion of this review, months of stability data had been submitted for all product lots. The results of the tests for Description, Particulate Matter, pH, and Osmolality remained within specifications for all lots at all times under all conditions. Endotoxin Content and Sterility testing had been performed at only the initial time point. Considering that the product is contained in a sealed glass vial, sterility after of storage is expected. Nevertheless, real data to support this assumption would have been appreciated. Samples stored at 25°C/60% RH and 30°C/60% RH in

Analysis of product stability using the HPLC test for enzyme content produced equivocal results (primarily due to data scatter) that permit no conclusion concerning product stability. Finally, results from the turbidity test for biological activity (the modified USP method) revealed that two primary lots (X804369 and 804396) reach the 90% USP limit in less than ———. The initial time points were included in this analysis because these data are essential to documenting the unexplained loss in activity during the first month of storage at 5°C. To exclude these data when this phenomenon was inadequately understood would prejudice any judgment about product stability. In light of these observations regarding activity loss during storage at 5°C, an expiry period of ——— for product stored under label conditions (of 2°-8°C) can be justified and is recommended. The proposed post-approval stability protocol and stability commitment are standard statements and acceptable.

Minor CMC-related labeling issues have been identified and will be addressed by the applicant. Two major label issues related to the product name. HYLENEX is similar to a non-prescription product Hylenix (a facial cosmetic product). The USAN established name of “hyaluronidase (human recombinant)” differs from the name “hyaluronidase-human (rDNA)” used with the recombinant products approved by CBER. This matter was resolved by the Office of New Drug Chemistry in recommending the use of “hyaluronidase human [rDNA origin].”

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(b). All manufacturing and testing sites for drug substance and drug product have been recommended for Approval by the Office of Compliance [OC].

B. Intended Use of the Drug Product

Hyaluronidase is a spreading substance that modifies the permeability of connective tissue by hydrolyzing hyaluronan (hyaluronic acid), a polysaccharide found in the intercellular ground substance of connective tissue and certain specialized tissues. The decrease in the viscosity of the cellular cement caused by hydrolysis of hyaluronan promotes diffusion of injected fluids or of localized transudates or exudates and facilitates their absorption. Hylenex (hyaluronidase human [rDNA origin] injection) is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs with use in hypodermoclysis and subcutaneous urography for improving resorption of radiopaque agents.

C. Basis for Approvability or Not-Approval Recommendation

All product quality issues that relate to the safety and efficacy of this drug product have been adequately addressed to support a recommendation to approve this NDA submission. All manufacturing, packaging, and testing sites have undergone inspection and been found to be in compliance with cGMPs. The attributes included in drug product specification-along with their test methods and acceptance criteria-are adequate for assuring drug product quality. Acceptable stability of the product was displayed under stress conditions and normal and accelerated storage conditions, permitting a recommendation of a nine month shelf life for the product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.FENSELAU/Review Chemist/01-SEP-2005: See appended electronic signature page

L.NG/Team Leader/01-SEP-2005: See appended electronic signature page

C. CC Block

HFD-830: N.SCHMUFF/: Acting Division Director

HFD-520: A.RODGERS/: Project Manager

69 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Allan Fenselau
9/1/2005 04:14:07 PM
CHEMIST

Linda Ng
9/1/2005 06:17:00 PM
CHEMIST
CMC recommends approval