# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-665

**CHEMISTRY REVIEW(S)** 



Chemistry Review Data Sheet

# NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.

Division of Anti-inflammatory, Analgesic and Ophthalmic

Drug Products

HFD-550





Chemistry Review Data Sheet

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# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #: 4
- 3. REVIEW DATE: 08-OCT-2004
- 4. REVIEWER: Libaniel Rodriguez
- 5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004
DMETZ Review	29-AUG-2004

#### 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	17-SEP-2004

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

Name: Amphastar Pharmaceuticals Inc.

Address: 11570 6<sup>th</sup> Street

Rancho Cucamonga, CA 91730

Representative: Stephen A. Campbell, Esq.

Telephone: (909) 980-9484 Ext. 2019



#### Chemistry Review Data Sheet

8.	DRUG PRODUCT	NAME/CODE/TYPE:
ο.		THE HILL CONTRACTOR

a) Proprietary Name: AMPHADASE™ b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP c) Code Name/# (ONDC only): N/A d) Chem. Type/Submission Priority (ONDC only): • Chem. Type: 5 • 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: Hyaluronidase injection 12. STRENGTH/POTENCY: 150 USP Units/mL 13. ROUTE OF ADMINISTRATION: Subcutaneous, 150 USP units/injection 14. Rx/OTC DISPENSED: X Rx OTC 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): X SPOTS product – Form Completed

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

\_Not a SPOTS product

Hyaluronidase is a protein — composed of — respectively. Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme at





#### Chemistry Review Data Sheet

#### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III	/		4	N/A	N/A	This product has an NF monograph
	III	~		4	N/A	N/A	
	III	/		4	N/A	N/A	

<sup>&</sup>lt;sup>1</sup> 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")

#### **B.** Other Documents:

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

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





# Chemistry Review Data Sheet

# 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Sent	SEP-15-2004	
OPDRA			
EA	Acceptable	Review #1	L. Rodriguez
	(Categorical Exclusion)	11-DEC-2003	
Microbiology	Approval	18-Nov-2003	Dr. B. Riley



**Executive Summary Section** 

# The Chemistry Review for NDA 21-665

# The Executive Summary

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A. Recommendation and Conclusion on Approvability

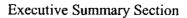
This application is recommended as approval.

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 AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1 mL) is a sterile solution packaged in a 2 mL — glass — vial, with a — rubber stopper and a flip off — aluminum cap. This product was formulated to
be the equivalent of the presently discontinued Wydase®. It contains the enzyme
hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium
chloridethimerosal, monobasic sodium phosphate
oatches of Amphadase. each, were
manufactured for stability studies in support of this application. The components of the
drug product are
· · · · · · · · · · · · · · · · · · ·
- · · · · ·
The drug substance (bovine hyaluronidase) is extracted from — bovine testes. The
testes are obtained from herds  Crude hyaluronidase
is obtained within ten days of collection of the testes and shipped for refinement to the
The crude
material arrives to accompanied by a
CERTIFICATE" issued by the
The certificate states that 1) the hyaluronidase comes from healthy cattle from non-infected areas 2) the cattle is and 3) that the
nealthy cattle from non-infected areas 2) the cattle is and 3) that the
processing facility does not receive, store or process any ruminate material from BSE
countries. Each animal is examined by a veterinarian before slaughter.
The draw substance (best 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
The drug substance (bovine hyaluronidase) is a mixture composed approximately of
proteins and
impurities. The — impurities are: —



determined	from the a	aminoacid sequenc	imed in the application, is e(s). However, further characterization e protein mixture is composed of the di	
substance,			, and approximately	J
impurities.	The appara	ent molecular weig		
-	• •			
-	are	-	•	
	•		The	
impurities o	lo not inte	rfere with the hyali	uronidaze activity as demonstrated by	

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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic  $C_{1-4}$  bond of the glucosamine moiety.

Amphadase<sup>TM</sup> 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 with a grey rubber stopper and an aluminum flip off seal. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical dose of 150 USP units. Other than aseptical removal the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated by mixing with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Based on the long term stability submitted in this amendment, the expiration time recommended for this drug product is 18 months. The recommended retest period for the drug substance remains at \_\_\_\_\_ Amphastar should be able to extend retest and expiry periods based on updated stability data, via annual report.

#### C. Basis for Approvability or Not-Approval Recommendation

A variety of issues and deficiencies raised during the review cycle were resolved satisfactorily by the applicant. Amphastar intends to submit Freeze thaw cycles data for the drug product in the future, with the purpose of removing the "DO NOT FREEZE" warning from all the labeling. Updated stability data will also be submitted for the purpose of extending retest and shelf life expiry.





#### **Executive Summary Section**

#### III. Administrative

#### A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

#### **B. Endorsement Block**

Libaniel Rodriguez, Ph.D., Review Chemist/08-OCT-2004 Linda Ng ,Ph.D., ChemistryTeamLeader/08-OCT-2004 Mike Puglisi, ProjectManager/08-OCT-2004

#### C. CC Block

HFD-550/division file/NDA 21665 Wiley Chambers, M.D./DD/HFD-550 Page(s) Withheld

# 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 10/8/04 12:39:16 PM CHEMIST AP, amendment to extend expiry to 18 months for DP

Linda Ng 10/8/04 01:52:13 PM CHEMIST Complements chem review #3



Chemistry Review Data Sheet

# NDA 21-665

# AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.

Division of Anti-inflammatory, Analgesic and Ophthalmic

Drug Products

HFD-550





Chemistry Review Data Sheet

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III. Administrative	8
A. Reviewer's Signature	8
B. Endorsement Block	9
C. CC Block	9
Chemistry Assessment	10



Chemistry Review Data Sheet

# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #: 3
- 3. REVIEW DATE: 15-SEP-2004
- 4. REVIEWER: Libaniel Rodriguez
- 5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
DMETS Review

Document Date August 29, 2003

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

Name: Amphastar Pharmaceuticals Inc.

Address: 11570 6<sup>th</sup> Street

Rancho Cucamonga, CA 91730

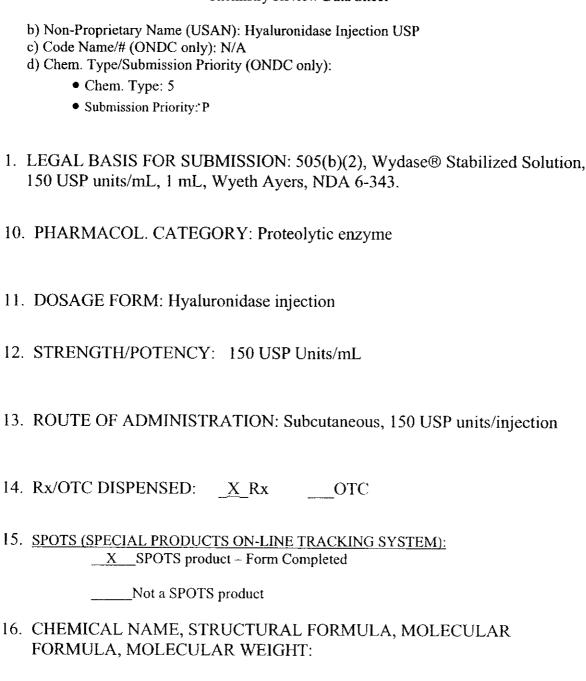
Representative: Stephen A. Campbell, Esq.

Telephone: (909) 980-9484 Ext. 2019

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AMPHADASE™





A. DMFs:

Hyaluronidase is a protein

with apparent molecular weights of

17. RELATED/SUPPORTING DOCUMENTS:

composed of

sequence, the applicant reports the molecular weight of the enzyme at

respectively. Based on the aminoacid





#### Chemistry Review Data Sheet

DMF #	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III		(	4	N/A	N/A	This product has an NF monograph
	III	<del></del>		4	N/A	N/A	
	III		/	4	N/A	N/A	

<sup>&</sup>lt;sup>1</sup> Action codes for DMF Table:

I – 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")

#### **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 RECOMMENDATION	DATE	REVIEWER
	·	

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





# Chemistry Review Data Sheet

RELATED REVIEWS			
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Sent	SEP-15-2004	
OPDRA			
EA	Acceptable	Review #1	L. Rodriguez
	(Categorical Exclusion)	11-DEC-2003	
Microbiology	Approval	18-Nov-2003	Dr. B. Riley



**Executive Summary Section** 

# The Chemistry Review for NDA 21-665

# The Executive Summary

#### I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended as approval.

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

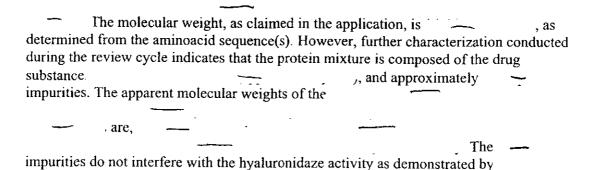
None

# II. Summary of Chemistry Assessments

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

The drug product AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1
mL) is a sterile solution packaged in a 2 mL glass. — vial, with a —
- rubber stopper and a flip off - aluminum cap. This product was formulated to
be the equivalent of the presently discontinued Wydase®. It contains the enzyme
hyaluronidase, 150 USP Units/mL, sodium chloride, edetate disodium — ,calcium
chloride — ,thimerosal, monobasic sodium phosphate
batches of Amphadase — cach, were
manufactured for stability studies in support of this application. The components of the
drug product are
<del>-</del>
The drug substance (bovine hyaluronidase) is extracted from — oovine testes. The
testes are obtained from herds . Crude hyaluronidase
is obtained within ten days of collection of the testes and shipped for refinement to the
The crude
material arrives to accompanied by a
CERTIFICATE" issued by the
· ·
The certificate states that I) the hyaluronidase comes from
healthy cattle from non-infected areas 2) the cattle is of chinese origin only and 3) that the
processing facility does not receive, store or process any ruminate material from BSE
countries. Each animal is examined by a veterinarian before slaughter.
The drug substance (bovine hyaluronidase) is a mixture composed approximately of
proteins
impurities. The impurities are:





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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C<sub>1-4</sub> bond of the glucosamine moiety.

Amphadase™ 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 with a grey rubber stopper and an aluminum flip off seal. The amount of drug supplied is the equivalent of 150 USP units and can accommodate dosages from 50 USP units to the typical dose of 150 USP units. Other than aseptical removal the flip off cap and withdrawal of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated by mixing with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is  $5^{\circ}C \pm 3^{\circ}C$ . Based on the stability data submitted, the retest period for the drug substance is recommended to be twelve months. For the drug product the recommended expiry is twelve months. The retest and expiry periods are less than requested for each by the firm.

## C. Basis for Approvability or Not-Approval Recommendation

A variety of issue satisfactorily by the	es raised durin	ng the review o	cycle were resolved	i
extending retest ar		also be submi	tted for the purpose	e of

This addendum (review # 3) deals with the recommendation issued by DMETS and DDMAC about trade name and labeling.





#### **Executive Summary Section**

#### III. Administrative

## A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

#### **B.** Endorsement Block

Libaniel Rodriguez, Ph.D., Review Chemist/14-SEP-2004 Linda Ng ,Ph.D., ChemistryTeamLeader/14-SEP-2004 Mike Puglisi, ProjectManager/14-SEP-2004

#### C. CC Block

HFD-550/division file/NDA 21665 Wiley Chambers, M.D./DD/HFD-550 Page(s) Withheld

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/s/

Libaniel Rodriguez 9/15/04 11:40:28 AM CHEMIST adendum, labeling consult from DMETS

Linda Ng 9/20/04 03:04:48 PM CHEMIST Chemistry Review Data Sheet

# NDA 21-665

# AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.

Division of Anti-inflammatory, Analgesic and Ophthalmic

Drug Products

HFD-550





Chemistry Review Data Sheet

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II. DRUG PRODUCT17
V. METHODS VALIDATION22
VI. LABELING22
VII. ESTABLISHMENT INSPECTION23
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Chemistry Review Data Sheet

# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #: 2
- 3. REVIEW DATE: 20-AUG-2004
- 4. REVIEWER: Libaniel Rodriguez
- 5. PREVIOUS DOCUMENTS:

Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003

#### 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	13-JAN-2004
BC	05-FEB-2004
BC	15-JUN-2004
BC	21-JUL-2004
BC	30-JUL-2004
BC	12-AUG-2004

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

Name: Amphastar Pharmaceuticals Inc.

11570 6<sup>th</sup> Street

Address: Rancho Cucamonga, CA 91730

Representative: Stephen A. Campbell, Esq.

Telephone: (909) 980-9484 Ext. 2019



# Chemistry Review Data Sheet

_		
Q	DRUG PRODUCT NAME/CODI	C/TVDE.
Ο.	- DICUCLERCHIOCE INFRINGRACION	C/ 1 T F C.

a) Proprietary Name: AMPHADASETM b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP c) Code Name/# (ONDC only): N/A d) Chem. Type/Submission Priority (ONDC only):
• Chem. Type: 5
Submission Priority: P
<ol> <li>LEGAL BASIS FOR SUBMISSION: 505(b)(2), Wydase® Stabilized Solution 150 USP units/mL, 1 mL, Wyeth Ayers, NDA 6-343.</li> </ol>
10. PHARMACOL. CATEGORY: Proteolytic enzyme
11. DOSAGE FORM: Hyaluronidase injection
12. STRENGTH/POTENCY: 150 USP Units/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous, 150 USP units/injection
14. Rx/OTC DISPENSED: X_RxOTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): XSPOTS product – Form Completed
Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Hyaluronidase is a protein — composed of — respectively. Based on the aminoacid sequence, the applicant reports the molecular weight of the enzyme at —





#### **Chemistry Review Data Sheet**

## 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			4	N/A	N/A	This product has an NF monograph
 	III			4	N/A	N/A	
	III	- / /		4	N/A	N/A	

<sup>&</sup>lt;sup>1</sup> Action codes for DMF Table:

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





# Chemistry Review Data Sheet

# 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	JUL-20-2004	OC
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Ready to be sent to the FDA laboratory.		
OPDRA			
EA	Acceptable (Categorical Exclusion)	Review #1 11-DEC-2003	L. Rodriguez
Microbiology	Approval	18-Nov-2003	Dr. B. Riley



**Executive Summary Section** 

# The Chemistry Review for NDA 21-665

# The Executive Summary

T	Reco			4.	4:	
1.	Kec	ımn	1en	ดล	H	ms

A. Recommendation and Conclusion on Approvability

This application is recommended as 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 AMPHADASE™ (hyaluronidase injection USP, 150 USP Units/mL, 1					
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chloride,thimerosal, monobasic sodium phosphate					
patches of Amphadase. — each, were					
manufactured for stability studies in support of this application. The components of the					
drug product are					
en de la companya de La companya de la co					
The drug substance (bovine hyaluronidase) is extracted from bovine testes. The					
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is obtained within ten days of collection of the testes and shipped for refinement to the					
The crude					
material arrives to accompanied by a					
CERTIFICATE" issued by the					
The certificate states that 1) the hyaluronidase comes from					
healthy cattle from non-infected areas 2) the cattle is of chinese origin only and 3) that the					
processing facility does not receive, store or process any ruminate material from BSE					
countries. Each animal is examined by a veterinarian before slaughter.					
The drug substance (bovine hyaluronidase) is a mixture composed approximately of —					
proteins , and					
impurities The impurities are:					



#### **Executive Summary Section**

— The molecular weight, as claimed in the	application, is as
determined from the aminoacid sequence(s). However	ver, further characterization conducted
during the review cycle indicates that the protein m	ixture is composed of the drug
substance.	,, and approximately
impurities. The apparent molecular weights of the	of
, are.	
<u></u>	The
impurities do not interfere with the hyaluronidaze ac	ctivity as demonstrated by -

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

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic C<sub>1-4</sub> bond of the glucosamine moiety.

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# C. Basis for Approvability or Not-Approval Recommendation

A variety of issues and deficiencies raised during the review cycle were resolved satisfactorily by the applicant. Amphastar intends to submit Freeze thaw cycles data for the drug product in the future, with the purpose of removing the "DO NOT FREEZE" warning from all the labeling. Updated stability data will also be submitted for the purpose of extending retest and shelf life expiry.





#### **Executive Summary Section**

#### III. Administrative

#### A. Reviewer's Signature

Libaniel Rodriguez Ph.D., Review Chemist

#### **B.** Endorsement Block

Libaniel Rodriguez, Ph.D., Review Chemist/20-AUG-2004 Linda Ng ,Ph.D., ChemistryTeamLeader/20-AUG-2004 Mike Puglisi, ProjectManager/20-AUG-2004

#### C. CC Block

HFD-550/division file/NDA 21665 Wiley Chambers, M.D./DD/HFD-550 Page(s) Withheld

# 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 8/20/04 11:06:34 AM CHEMIST Amphadase 150 USP units/mL. AP

Linda Ng 8/20/04 11:43:44 AM CHEMIST

# NDA 21-665

# Amphadase<sup>TM</sup> (hyaluronidase injection, USP) Bovine

Amphastar Pharmaceuticals, Inc.

Stephen Moore, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510







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# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #: 2
- 3. REVIEW DATE: July 19, 2004
- 4. REVIEWER: Stephen Moore, Ph.D., Chemistry Team Leader, 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 Amendments

06-JUN-2003 28-OCT-2003 07-NOV-2003 18-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name:

Amphastar Pharmaceuticald, Inc.

11570 6<sup>th</sup> Street Rancho Cucamonga

Address:

CA 91730





#### **REVIEW NOTE**

Representative	
----------------	--

Contact: Stephen A. Campbell, Esq. Senior Vice President Regulatory Affairs

Telephone:

909-980-8296

Q	DRUG	PRODI	ICT N	$\Delta ME$	CODE	TYPE
^	11161111	PR 1 11 11	10 1 10	A IVI I'.		7 I I E C.

- a) Proprietary Name: Amphadase<sup>TM</sup>
- b) Non-Proprietary Name (USAN): Hyaluronidase Injection, USP, Bovine
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1 (New Molecular Entity)
  - Submission Priority: P
- 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
- 10. PHARMACOL. CATEGORY: 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, MOLECULAR WEIGHT: See primary chemistry review.

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

#### A. DMFs:

DMF #	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
			·				

<sup>&</sup>lt;sup>1</sup> 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")





# **REVIEW NOTE**

<sup>2</sup> 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 21-665

# 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 (AP) 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.



## **REVIEW NOTE**

#### III. Administrative

#### A. Reviewer's Signature

#### **B.** Endorsement Block

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

Michael Puglisi, Project Manager, DAAOPD (HFD-550)

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/s/

Stephen Moore 7/19/04 06:56:59 PM CHEMIST

# NDA 21-665

# Amphadase<sup>TM</sup> (hyaluronidase injection, USP) Bovine

Amphastar Pharmaceuticals, Inc.

Stephen Moore, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510





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	I. DRUG SUBSTANCE	

II. DRAFT DEFICIENCY LETTER





#### **REVIEW NOTE**

# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #: 1
- 3. REVIEW DATE: December 19, 2003
- 4. REVIEWER: Stephen Moore, Ph.D., Chemistry Team Leader, 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 Amendments 06-JUN-2003 28-OCT-2003 07-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name:

Amphastar Pharmaceuticald, Inc.

11570 6<sup>th</sup> Street Rancho Cucamonga

Address:





## **REVIEW NOTE**

Representative:	Contact: Stephen A. Campbell, Esq. Senior Vice President Regulatory Affairs
Telephone:	909-980-8296
8. DRUG PRODUCT NAME/CODE/T	YPE:
a) Proprietary Name: Amphadase <sup>TM</sup> b) Non-Proprietary Name (USAN): Hyaluronidase Inject c) Code Name/# (ONDC only) d) Chem. Type/Submission Priority (ONDC only):	tion, USP, Bovine
• Chem. Type: 1 (New Molecular Entity	<b>y</b> )
<ul> <li>Submission Priority: P</li> </ul>	
9. LEGAL BASIS FOR SUBMISSION:	505(b)(2)
10. PHARMACOL. CATEGORY: Adjudispersion of other injected drugs and other review)	avant to increase absorption and ner indications (see primary chemistry
11. DOSAGE FORM: Injection	
12. STRENGTH/POTENCY: 150 USP	Units/1 ml
13. ROUTE OF ADMINISTRATION: S	S.C.

14. Rx/OTC DISPENSED: X\_Rx OTC

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

\_\_\_\_\_Not a SPOTS product

\_\_X\_\_SPOTS product – Form Completed





#### **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 <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
-							-

<sup>&</sup>lt;sup>†</sup>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")





# **REVIEW NOTE**

 $^2$  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 21-665

# **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.





#### **REVIEW NOTE**

#### III. Administrative

#### A. Reviewer's Signature

#### **B.** Endorsement Block

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

Michael Puglisi, Project Manager, DAAOPD (HFD-550)

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/s/

Stephen Moore 12/19/03 04:53:13 PM CHEMIST



# NDA 21-665

AMPHADASE™ (hyaluronidase Injection USP) 150 USP units/mL, 1 mL

Amphastar Pharmaceuticals Inc.

Libaniel Rodriguez, Ph.D.

Division of Anti-inflammatory, Analgesic and Ophthalmic

Drug Products

HFD-550





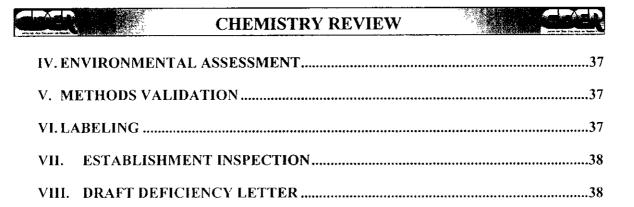
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# **CHEMISTRY REVIEW**

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Chemistry Review Data Sheet

# **Chemistry Review Data Sheet**

- 1. NDA 21-665
- 2. REVIEW #:1
- 3. REVIEW DATE: 11-Dec-2003
- 4. REVIEWER: Libaniel Rodriguez
- 5. PREVIOUS DOCUMENTS: None
- 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	06-JUN-2003
BC	09-SEP-2003
BC	28-OCT-2003
BC	07-NOV-2003

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

Name: Amphastar Pharmaceuticals Inc.

11570 6<sup>th</sup> Street

Address: Rancho Cucamonga, CA 91730

Representative: Stephen A. Campbell, Esq.

Telephone: (909) 980-9484 Ext. 2019



Chemistry Review Data Sheet

	·
8.	DRUG PRODUCT NAME/CODE/TYPE:
	a) Proprietary Name: AMPHADASE™ b) Non-Proprietary Name (USAN): Hyaluronidase Injection USP 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 enzyme
11	. DOSAGE FORM: Hyaluronidase injection
12	. STRENGTH/POTENCY: 150 USP Units/mL
13	ROUTE OF ADMINISTRATION: Subcutaneous; 150 USP units/injection
14.	Rx/OTC DISPENSED: X_RxOTC
15.	SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): XSPOTS product - Form Completed
16.	Not a SPOTS product  CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
	Hyaluronidase is a protein — . composed of — Based on the ammoacid sequence, the applicant reports the molecular weight of the enzyme at





#### Chemistry Review Data Sheet

#### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			4	N/A	N/A	This product has an NF monograph
	III		·	4	N/A	N/A	
-3	III			4	N/A	N/A	

<sup>&</sup>lt;sup>1</sup> 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")

#### **B.** Other Documents:

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

#### 18. STATUS:

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





# Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	pending		
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending		
OPDRA	_		
EA			
Microbiology	Approval	18-Nov-2003	Dr. B. Riley



**Executive Summary Section** 

# The Chemistry Review for NDA 21-665

# The Executive Summary

#### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended as **approvable** upon 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)

mL) is a sterile solution  rubber stopper ar	HADASE <sup>TM</sup> (hyaluronidas packaged in a 2 ml.— nd a flip off—— alumin presently discontinued Wy	glass — vial, um cap. This prod	with a ———————————————————————————————————
	Units/mL, sodium chloriderosal, monobasic sodium		n ,calcium
, <u> </u>	_ batches o	f Amphadase,	each, were
manufactured for stabili	ty studies in support of this	s application. The	components of the
drug product are	~		
testes are obtained from is obtained within ten da material arrives to Issued by the	accompanied by a	es and shipped for	Crude hyaluronidase refinement to the The crude CERTIFICATE"
The	certificate states that 1) the		
cattle from non-infected processing facility does countries.	areas 2) the cattle is not receive store or proces		nd 3) that the terial from BSE
The drug substance (boy proteins	rine hyaluronidase) is a mi		proximately of .— eight, as claimed in





#### **Executive Summary Section**

the application, is		as determined from the aminoacid sequence(s).					
However, further chara	cterization c	onducte	ed duri	ng the review cy	cle indicates	that the	
protein mixture is com	posed of the	drug su	ibstanc	e , , —	<b></b>	_	
and approximatel	у	impı	ırities.	The apparent me	olecular weigl	nts of the	
					-	-	
		<del></del>		are,			
•	~_		/ The	— impurities	s do not interf	ere with the	
hyaluronidaze activity	as demonstra	ated by					

Hyaluronidase act as a spreading agent by hydrolysis of hyaluronic acid found in the intercellular ground substance of connective tissue. Hyaluronic acid, a large polysaccharide, is hydrolyzed by cleavage of the glucosaminidic  $C_{1-4}$  bond of the glucosamine moiety.

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

Amphadase, <sup>TM</sup> 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 aseptically remove the flip off cap and withdrawing of the drug product, there are no unusual preparations prior to the administration of Amphadase. This drug product is administrated mixed with the drug that it will help disperse.

The storage conditions for both drug substance and drug product is  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Based on the stability data submitted, the retest period for the drug substance is recommended to be \_\_\_\_. For the drug product the recommended expiry is \_\_\_\_\_. The retest and expiry periods are less than the firm requested.

#### C. Basis for Approvability or Not-Approval Recommendation

Many information requests were sent to the applicant and some issues were resolved and summarized in this review. Some issues remain outstanding, for example, drug substance composition, drug substance specification, drug substance stability, drug product specification and stability.

#### III. Administrative

A. Reviewer's Signature

Libaniel Rodriguez, Review Chemist





**Executive Summary Section** 

#### **B.** Endorsement Block

Libaniel Rodriguez, Review Chemist/11-DEC-2003 Linda Ng, ChemistryTeamLeader/11-DEC-2003 Mike Puglisi, ProjectManager/11-DEC-2003

#### C. CC Block

<u>34</u> Page(s) Withheld

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/s/

Libaniel Rodriguez 12/16/03 02:23:08 PM CHEMIST approvable

Linda Ng 12/16/03 04:26:00 PM CHEMIST