

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-859

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

NDA 21-859

NAME OF APPLICANT / NDA HOLDER

Halozyme Therapeutics Inc

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Enhanze SC

ACTIVE INGREDIENT(S)

recombinant human hyaluronidase, rHuPH20

STRENGTH(S)

150 U/mL

DOSAGE FORM

1 mL non-preserved injectable liquid

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

2,795,529

b. Issue Date of Patent

6/11/1957

c. Expiration Date of Patent

6/11/1974

d. Name of Patent Owner

Patent Expired

(owned upon issuance in 1957 by

American Home Products Corporation)

Address (of Patent Owner)

City/State

New York, NY (Note: Corporation subsequently Wyeth, Madison, NJ)

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

[unknown, n/a]

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
3/21/2005



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Halozyme Therapeutics, Inc.

Address
11588 Sorrento Valley Road, #17

City/State
San Diego, CA

ZIP Code
92121

Telephone Number
858-794-8889

FAX Number (if available)
858-259-2539

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21,859

SUPPL #

HFD # 520

Trade Name Hylenex

Generic Name hyaluronidase (human recombinant) injection

Applicant Name Halozyme Therapeutics

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Alison Rodgers

Title: Project Manager

Date: 7/27/05

Name of Office/Division Director signing form: Wiley A. Chambers

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05



March 11, 2005

Department of Health and Human Services
Food and Drug Administration

RE: Debarment Certification for NDA 21-859, Enhance SC™ (recombinant human hyaluronidase injection)

Halozyme Therapeutics Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sincerely,

A handwritten signature in black ink, appearing to read 'D. Kennard', is written over a light blue horizontal line.

Don Kennard
Vice President
Regulatory Affairs & Quality Assurance

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-859 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: March 23, 2005 Action Date: September 23, 2005

HFD 520

Trade and generic names/dosage form: Hylenex (hyaluronidase (human recombinant) injection) 150 IU/mL

Applicant: Halozyme Therapeutics Therapeutic Class: 5

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indication #1:

An adjuvant to increase the absorption and dispersion of other injected drugs

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- X NO:** Please check all that apply: ___ Partial Waiver ___ Deferred **X** Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: Hyaluronidase was permitted in 1947 and efficacy was re-confirmed in 1970 in a DESI review for several indications, including for use in neonates for hypodermoclysis. More information is included in the clinical review.

Indication #2:

For hypodermoclysis

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- X NO:** Please check all that apply: ___ Partial Waiver ___ Deferred **X** Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section D: Completed Studies

Age/weight range of completed studies:

NDA 21-859

Page 2

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: Hyaluronidase was permitted in 1947 and efficacy was re-confirmed in 1970 in a DESI review for several indications, including for use in neonates for hypodermoclysis. More information is included in the clinical review.

Indication #3:

An adjunct in subcutaneous urography for improving resorption of radiopaque agents

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- X Disease/condition does not exist in children**
- Too few children with disease to study
- There are safety concerns
- Other: _____

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-859
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Alison Rodgers
12/5/2005 01:46:53 PM

Deputy Division Director's Memorandum
NDA 21-859

Name: HYLENEX recombinant (hyaluronidase human injection)

Applicant: Halozyme Therapeutics, Inc.
11588 Sorrento Valley Road, Suite 17, San Diego, CA 92121

Indication: Indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

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Recommendation on Regulatory Action

Hylenex™ is recommended for approval with the labeling submitted on September 15, 2005. This recommendation is supported by the Medical, Chemistry/Manufacturing, and Pharmacology/Toxicology reviews.

Regulatory Background

Halozyme Therapeutics submitted NDA 21-859 for Hylenex™ recombinant (hyaluronidase human injection) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Halozyme seeks approval to market Hylenex for the currently approved drug uses of hyaluronidase: as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Halozyme listed Wydase® (hyaluronidase injection) (NDA 6-343) as the reference listed drug. There are no pending patents or marketing exclusivities for Wydase.

Summary

Due to a combination of factors summarized in this memorandum, clinical safety of new hyaluronidase products can be supported by allergenicity studies and efficacy can be supported by using an *in vitro* surrogate, the United States Pharmacopoeia (USP) monograph test for hyaluronidase. These same factors, as well as, additional considerations based on the recombinant nature of the hyaluronidase enzyme in the Halozyme product, support approval of Hylenex without any additional clinical data requirements.

The hyaluronidases are a class of enzymes, the members of which share a common ability to depolymerize sodium hyaluronate. This activity correlates to the efficacy of hyaluronidase products for their currently approved drug uses. Because a USP *in vitro* assay can reliably show whether an enzyme exhibits this activity, additional product-specific clinical trials are not needed to support the efficacy of hyaluronidase products for their currently approved drug uses. This assay has been used to support approval of several hyaluronidase products. The Hylenex product has been shown to have appropriate activity in this assay.

There are several reasons that the historical information on hyaluronidase together with the product specific allergenicity study is sufficient to support the safety of a new hyaluronidase product for its currently approved uses. The route of administration and the pharmacological effect of these hyaluronidase products are local, and the drug product is rapidly inactivated and metabolized. Consequently, there are no safety issues related to distribution of the drug product, retention of the drug, or the drug's sustained or long-term effects. Adverse event information from the long marketing history of hyaluronidases (>50 years) shows that these products have not exhibited any significant safety risks except risks related to allergic reactions, a lack of efficacy on the part of the hyaluronidase, or a potentiation of the pharmacologic effects of the co-administered product. In addition, doses of hyaluronidase products over 1000 times the entire vial size proposed for marketing for Hylenex have been administered systemically without causing any significant adverse events.

A clinical allergenicity study is now required for each hyaluronidase drug product approval because the risk of allergenicity relates to the purity of the specific drug product. The allergenicity study of Hylenex showed that the product has an acceptable allergenicity profile.

Previously approved hyaluronidase products have been naturally sourced from mammalian testicular material and have not been fully characterized. Based on available information, marketed products appear to have been principally sourced from bovine or ovine sources. Hylenex is the first human hyaluronidase product. Hylenex also is the first recombinant hyaluronidase product. The methodology used to produce Hylenex is well established. Hyaluronidase produced using this process raises no questions of efficacy or safety requiring any clinical data not required for previously approved hyaluronidase products.

In summary, the applicant has provided adequate information to support the safety and efficacy of Hylenex recombinant (hyaluronidase human injection) for its proposed uses.

Background

Naturally sourced mammalian testicular hyaluronidase drug products have been legally marketed for over 50 years for their three currently approved indications: as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. The safety and efficacy of hyaluronidase products for these indications are supported by: a USP *in vitro* test of their ability to depolymerize sodium hyaluronate; and the Agency's evaluation of the National Academy of Sciences-National Research Council, and Drug Efficacy Study Implementation (DESI) reports on hyaluronidase (DESI 6343, 6714, 7933). The conclusions from the Agency's evaluation of the DESI report were published in the Federal Register on September 23, 1970 (35 FR 14800-1). The regulatory history of these hyaluronidase products is discussed in considerable detail in FDA's May 5, 2004, response to a Citizen Petition from Baxter Healthcare (Docket 2003P-0494). Wydase, the reference listed drug cited in the Hylenex NDA, was one of the hyaluronidase products for which efficacy was established as part of the DESI review.

Hyaluronidase products are an unusual set of drug products. Hyaluronidase is a term for a family of protein enzymes (1-4 glucosaminidases) that depolymerize hyaluronic acid (HA) and chondroitin sulfate. They were named for their ability to depolymerize HA.

Neither Wydase nor any other approved naturally-sourced hyaluronidase product has ever been fully characterized. Full characterization of hyaluronidase has never been necessary because minor variations in the amino acid sequence have been frequently noted and, after adjustments for potency based on the USP monograph test variations, have not affected the safety or efficacy of hyaluronidase.

Hyaluronidase polymorphism has been demonstrated in human, mouse, rat, hamster and dog sera.¹ For example, six paralogous human hyaluronidase genes clustered on chromosomes 3p21 and 7q31 have been reported.^{3,2}

The hyaluronidases' unifying feature has been the ability to depolymerize HA, regardless of differences in chemical structure, in species source, in tissue sources, or in the batches of drug product sourced from the same species and tissue. They are unusual in the fact that their activity is the same (except for potency) in spite of having different structures. The USP monograph addresses all hyaluronidase drug substances derived from mammalian testes together; it does not distinguish species source.

1 Fiszler-Szafarz B, Litnska A, Zou L. Human hyaluronidases: electrophoretic multiple forms in somatic tissues and body fluids. Evidence for conserved hyaluronidase potential N-glycosylation sites in different mammalian species. J Biochem Biophys Methods. 2000; 45:103-116.

2 Csoka AB, Frost GI, Stern F. The six hyaluronidase-like genes in the human and mouse genomes. Matrix Biology. 2001; 20:499-508.

As noted above, the ability to depolymerize HA can be measured by a USP monograph test for hyaluronidase, and this test has been used as a surrogate for establishing efficacy for the three DESI indications. It is an unusually predictive surrogate because the test measures depolymerization of a substance (HA) *in vitro* that hyaluronidase would depolymerize in the body. Since the effect is a local effect for the DESI indications and the product is administered locally, there are no issues of bioavailability or distribution through the body. The USP test is also used to adjust for differences in potency and establish an equivalent measure of activity as described by the number of hyaluronidase units.

Hyaluronidase is administered locally because it is inactivated and/or degraded in minutes by hyaluronidase inhibitors in mammalian serum. Even at large doses, no significant effects with the exception of fluid dispersion have been observed. Several large clinical studies have been performed administering intravenous hyaluronidase at doses of up to 500 units per kilogram every 6 hours for 48 hours (greater than 1,000 times the proposed average dose for NDA 21-859).^{3,4} There were no significant adverse events attributable to hyaluronidase in these studies; nor were there any benefits.

As noted above, Wydase and several other naturally sourced hyaluronidase drug products were included in the DESI review and found to be effective for the DESI review indications (the three indications listed above). These products were known to have differences in their amino acid structure, but none were ever fully characterized. The long history of use of activity assays instead of structure identification for hyaluronidase is relatively unusual, but it has generated evidence to support the approval of safe and effective products. Although none of these products was characterized other than to specify its source and ability to depolymerize HA, safety and efficacy have been supported by information derived from millions of uses, information on adverse events from over 50 years of safe marketing, and the results of hundreds of published studies including adequate and well controlled studies of their use.

In the human body, hyaluronidase is found both in organs (testes, spleen, skin, eye, liver, kidney, uterus and placenta) and body liquids (tears, blood and sperma).⁵ A human plasma hyaluronidase has been purified, cloned and expressed.^{1,6,7} The amino acid sequence obtained matched a cDNA which was used to clone the plasma hyaluronidase gene, Hyal-1.^{1,2} This gene codes for a protein of amino acids that is approximately 40% identical to the PH-20 gene thought to code for sperm-specific hyaluronidase.^{1,2,3}

3 Roberts et al. Effect of hyaluronidase on mortality and morbidity in patients with early peaking of plasma creatine kinase MB and non-transmural ischaemia. *Br Heart J.* 1988; 60(4):290-8.

4 Julian DG et al. A controlled trial of GL enzyme in the treatment of acute myocardial infarction. *Cardiology.* 1988; 75(3): 177-83.

5 Menzel EJ and Farr C. Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses. *Cancer Letters.* 1998; 131:3-11.

6 Csoka TB et al. Purification and microsequencing of hyaluronidase isozymes from human urine. *FEBS Letters.* 1997; 417:307-310.

7 Frost GI et al. Purification, Cloning and Expression of Human Plasma Hyaluronidase. *Biochemical and Biophysical Research Communications.* 1997; 236:10-15.

Halozyme's hyaluronidase product, Hylenex, contains a recombinant human testicular hyaluronidase. It is the first human testicular hyaluronidase drug product and the first recombinant hyaluronidase drug product. However, the Center for Devices and Radiological Health has cleared a 510(k) application for an *in vitro* fertilization device, Cumulase, that contains this same recombinant hyaluronidase in a different formulation.

Multiple structural and functional comparisons have been performed between naturally sourced mammalian hyaluronidase and PH-20 cDNA clones from humans and other mammals. The PH-20 gene is the gene used for the recombinant product in NDA 21-859; however the recombinant drug product is a 447 amino acid truncated version of the full protein encoded by the PH-20 gene. Structural similarities with respect to amino acid sequences rarely exceed 60% in any comparison. Functional comparisons show Hylenex's activity is very similar to that of previously approved hyaluronidase products. This information is consistent with the clinical findings during the past 50 years that regardless of the source of the hyaluronidase, the clinical safety and efficacy of units of hyaluronidase are equivalent. We are not aware of clinical studies (except for allergenicity testing) that have been conducted with human recombinant hyaluronidase.

Currently Approved Hyaluronidase Products for DESI Indications

There are four naturally sourced hyaluronidase products currently approved for the hyaluronidase DESI review indications:

Wydase (hyaluronidase injection) bovine source, NDA 6-343
Vitrase (hyaluronidase injection) ovine source, NDA 21-640
Amphadase (hyaluronidase injection) bovine source, NDA 21-665
Hydase (hyaluronidase injection) bovine source, NDA 21-716

Vitrase, Amphadase, and Hydase are currently marketed. Wydase is not.

Prior NDAs for Hyaluronidase in the United States

The following hyaluronidase drug products were legally marketed in the past:

NDA 6-392	Hyronase (Schering)
NDA 6-714	Alidase (Searle)
NDA 6-809	Diffusin (Ortho)
NDA 7-933	Hyazyme (Abbott)
NDA 8-619	Enzodase (Squibb)
NDA 8-985	Infiltrase (Armour)
NDA 9-082	Haruadase (Harvey)
NDA 9-201	Hyaluronidase (Cudahy)
NDA 9-380	Hyaluronidase (Worthington)

Local effect

Hyaluronidase, when used for the DESI indications, is administered locally and has its entire effect locally. Hyaluronidase is inactivated and metabolized locally in minutes and has not been noted to have systemic or long term effects. Its rapid (minutes) inactivation and metabolism when it enters the blood stream precludes a realistic ability to perform comparable biodistribution studies between products. It also minimizes any potential systemic safety concerns because the drug product cannot act at distant sites. As noted above, several large clinical studies have been performed administering intravenous hyaluronidase at doses greater than 1,000 times the proposed average dose for NDA 21-859.^{6,7} Consistent with the lack of activity at distant sites, there were no significant adverse events attributable to hyaluronidase in these studies; nor were there any benefits.

Safety Profile

The safety profile for hyaluronidase products is remarkably favorable. After millions of uses, the vast majority of reported adverse experiences fall into one of the following three categories: 1) the product has no effect; 2) the product enhances the side effects of any co-administered products; or 3) the product causes an allergic reaction. The first two categories are expected due to the pharmacological action of the product (or lack thereof due to rapid inactivation and metabolism). The frequency of the third (allergic reaction) has historically been dependent on the quality of the purification process. Relatively simple purifications have reduced the allergic reaction rate from greater than 10% to less than 0.1%. Beginning in 2004, the Agency required a product specific, clinical study to verify that the purification process was sufficient to preclude the unacceptable allergic reaction rate seen with unpurified products.

In attempts to establish efficacy for other indications, hyaluronidase has been repeatedly administered intravenously at doses greater than 1000 times the 150 unit recommended dose. Clinical studies at these doses reported no significant clinical effects (beneficial or negative)^{6,7}.

Hyaluronidase human injection

Hylenex™ recombinant (hyaluronidase human injection) is a 150 USP enzymatic unit formulation composed of a protein enzyme that is prepared from a recombinant human form of hyaluronidase, rHuPH20. It is administered as a local injection; it is not for intravenous use.

NDA 21-859 for Hylenex™ recombinant (hyaluronidase human injection) was submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Wydase® (hyaluronidase injection) (NDA 6-343) was listed as the reference listed drug. The approval of Wydase was based upon the DESI findings.

The drug product for which this application (NDA 21-859) has been submitted is different from the products in previously submitted hyaluronidase applications because it is a human hyaluronidase and it is manufactured through a recombinant process in which the specific amino acid sequence of the product is known. The amino acid sequence for this product is not

necessarily the same amino acid sequence as that of any enzyme in a previously approved hyaluronidase products. Based on the differences in hyaluronidases observed between species alone, the hyaluronidase in Hylenex is unlikely to have exactly the same sequence as any hyaluronidase in a previously approved drug product.

Direct comparisons of the structure of the Halozyme hyaluronidase have not been made with Wydase. While hyaluronidases have been partially characterized, neither Wydase nor any other approved hyaluronidase product has ever been sufficiently characterized to enable such comparisons. As discussed above, more complete characterization of hyaluronidase has never been considered necessary because hyaluronidases can be adequately identified by their activity.

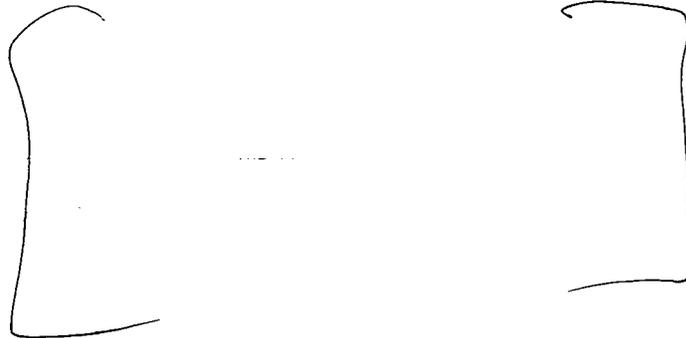
The particular sequence used for Hylenex recombinant is based on the human gene (PH-20) obtained from an NIH_MGC human testis cDNA library. The human PH-20 gene is the one thought to be responsible for testicular hyaluronidase and is one of several hyaluronidase genes in the body.⁵



Chemistry/Manufacturing

The drug substance in Hylenex is a recombinant human hyaluronidase, rHuPH20. The following description is taken directly from the Chemistry/Manufacturing review for rHuPH20:

The amino acid sequence is as follows:



Since Hylenex is recombinant, the manufacturing processes for it differs in significant respects from those for naturally sourced hyaluronidases. However, the manufacturing methodology used for Hylenex is consistent with well established processes for producing recombinant proteins. Hylenex is manufactured in chemically defined media that does not include animal derived ingredients and therefore should theoretically have a decreased potential risk of disease transmission from animal pathogenic agents. There is nothing about the methodology used to produce Hylenex that raises distinct concerns warranting clinical data requirements in addition to the requirement for allergenicity data that has been applied to hyaluronidase products previously approved for these uses.

Biological Activity

The enzymatic activity of the 1.0 mg/mL API solution is measured using an *in vitro* method derived from the USP method. This assay is based on the formation of an insoluble precipitate when hyaluronan binds with a quaternary amine.



The USP hyaluronidase test has been used to set the number of USP units to be consistent with other hyaluronidase products. CMC test methods for the drug substance and the drug product were developed as part of the Hylenex development program to meet the criteria given by the Division. Minor modifications to the description and methods of the USP test have been made in this application to tighten permissible ranges and provide improved consistency in the testing.

These methods demonstrate the hyaluronidase activity of the recombinant human hyaluronidase (rHuPH20) drug substance. These methods also demonstrate the hyaluronidase activity of rHuPH20 in the Hylenex™ drug product and utilize the USP Reference Standard in determining enzymatic activity values.

Allergenicity

To support product safety, NDA 21-859 relies upon several types of evidence. It relies on: the published literature for hyaluronidase products, including analysis of the consistency in activity between all hyaluronidase products; the USP monograph test for hyaluronidase units; safety information derived from more than 50 years of marketing history for other hyaluronidase products; and a Phase I Safety Trial (R04-0851) sponsored by Halozyme Therapeutics, Inc. The objective of the study was to evaluate the allergic sensitivity of subjects to Hylenex™ and to determine whether less than 10% of subjects would have a positive test reaction to Hylenex™. None of the 100 subjects in the trial exhibited a positive skin test result, establishing that the allergic reaction rate would be less than 10% (95% confidence interval suggests the rate is less than 3%). As discussed above, there are no new safety concerns or relevant adverse events that have not previously been included in other hyaluronidase labeling. The most serious labeled adverse events for this family of products have been hypersensitivity (allergic) reactions including anaphylactic-like reactions. These events vary in severity. In several large published studies, the frequency of reported events has been less than 0.1%. The more severe events occur even less frequently.

Name of drug product

The applicant has selected "HYLENEX recombinant" as their trademark name. The USP has a monograph (hyaluronidase injection) for hyaluronidase derived from mammalian testicular sources. There is disagreement among the reviewers with respect to the most appropriate established name. There is a common desire among the reviewers to have the product clearly identified as a human recombinant form of hyaluronidase as opposed to bovine or ovine sourced product. While there are no known differences with respect to the safety or efficacy of this product compared to other hyaluronidase products, this distinction is suggested because there are theoretical potential risks from the use of animal sourced products which would not be associated with the recombinant form. In reviewing the names of recombinant insulin products in the USP, the structure used for those names is "insulin human injection." Until such time as the USP establishes a monograph for this product and adopts a specific established name, the established name for this product has been listed as "hyaluronidase human injection."

Recommendation on Postmarketing Actions (Risk Management Activity)

No postmarketing risk management activity is recommended given the reported event profile of hyaluronidase over the past 50 years. There are no recommended Phase 4 commitments or recommendations for postmarketing studies beyond the routine collection of data on potential adverse events.

Dosing Regimen and Administration

Established dosing has been in the range of 30 to 300 units administered concurrently or in combination with another drug product as needed for the indication. The most typical dose is 150 units.

Drug-Drug Interactions

No drug-drug interaction analyses were performed for this product. Furosemide, the benzodiazepines and phenytoin have been found to be incompatible with hyaluronidase. Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs because of the potential enhancement of their pharmacologic effects.

Special Populations

Although there have been suggestions in the literature of differences due to age (>75 years old) and racial factors, the differences have never been supported by the data in clinical studies. There are no known differences in dose response due to age, gender, racial or ethnic factors. Studies of hyaluronidase supporting the proposed indications have been conducted in pediatric patients including premature infants.

Conclusion

NDA 21-859 for Hylenex™ recombinant (hyaluronidase human injection) is recommended for approval with the labeling submitted on September 15, 2005.

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On Original**

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/s/

Wiley Chambers
12/2/2005 02:56:09 PM
MEDICAL OFFICER

Edward Cox
12/2/2005 03:08:01 PM
MEDICAL OFFICER
I concur with Dr. Chambers' memorandum.

MEMORANDUM

From: John K. Jenkins, M.D.
Director, Office of New Drugs

To: NDA 21-859

Re: Approval of NDA 21-859/Hylenex (recombinant human hyaluronidase)

Date: December 2, 2005

The Division of Anti-infective and Ophthalmic Products has for approval an application for Halozyme Therapeutics' Hylenex, a recombinant human hyaluronidase injection for use (1) as an adjuvant to increase the absorption and dispersion of other injected drugs, (2) for hypodermoclysis, and (3) as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. These are indications for which the DESI review process found mammalian testicular hyaluronidase to be effective in 1970. This will be FDA's first approval of a recombinant hyaluronidase drug product. We have already approved numerous naturally-sourced mammalian testicular hyaluronidase drug products. The Center for Devices and Radiological Health has cleared a 510(k) application for an in vitro fertilization device, Cumulase, that contains, in a different formulation, the same recombinant hyaluronidase as is proposed in Hylenex. The recombinant hyaluronidase in Hylenex is a 447 amino acid protein.

We have specifically been asked by the sponsor of an approved naturally-sourced hyaluronidase drug product to require of recombinant hyaluronidase products clinical data comparable to those for other recombinant products. In my role as the Director of the Office of New Drugs, I have management responsibility for all new drug applications reviewed in the Center for Drug Evaluation and Research and familiarity with the major policy issues associated with 505(b)(2) applications. Because of this responsibility and expertise, I have been asked for my opinion on whether the Division's decision to approve the Hylenex NDA is consistent with CDER's actions with regard to other 505(b)(2) applications for recombinant products.

FDA has recently had a number of occasions in which to consider the issue of data requirements for 505(b)(2) applications seeking approval for recombinant drug products. In August 2005, we approved Fortical, a recombinant salmon calcitonin nasal spray for the prevention and treatment of osteoporosis, which relied for approval in part upon our finding of safety and effectiveness for Miacalcin, a synthetic salmon calcitonin nasal spray for the same indication, and in part on clinical data specific to Fortical. We also have been considering the data requirements for

[

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I have reviewed the Deputy Division Director's memorandum detailing and analyzing the data submitted to support the Hylenex application and recommending approval. I have also considered the August 12, 2005, FDA response to a citizen petition from Buc & Beardsley regarding the approval of Fortical. Finally, I am aware of the issues raised in _____ regarding our review of the Omnitrope 505(b)(2) application for recombinant

human growth hormone. Based upon consideration of this information, I concur with the Division's conclusion that the Hylenex NDA contains adequate data to support the safety and effectiveness of Hylenex to treat the above-referenced indications.

As elaborated upon in Dr. Chambers' memorandum, hyaluronidase products for the DESI indications identified above are relatively unusual in that their activity can be demonstrated through an in vitro assay. This activity correlates with efficacy for the currently approved uses; and a substantial body of safety information exists supporting the safety of hyaluronidases for these uses. In addition, the route of administration and the pharmacological effect of these hyaluronidase products are local, and the drug product is rapidly inactivated and metabolized. These characteristics permit approval of a recombinant hyaluronidase product in reliance on data derived from a USP in vitro assay of activity, CMC data, conclusions from a DESI review and confirming literature, safety information derived from marketing history, and a clinical safety trial submitted by the sponsor that was designed to establish that Hylenex has an acceptable allergenicity profile. Approval for these indications does not require that the sponsor undertake a structural or clinical comparison of recombinant human hyaluronidase with reference to approved naturally-derived mammalian testicular hyaluronidase products.

These drug product characteristics distinguish hyaluronidase drug products from other recombinant drug products for which the applicant may submit, in a 505(b)(2) application, substantial chemistry data to support the sameness or comparability of the active ingredients, and/or clinical data to support the identity of the active ingredient and the safety and effectiveness of the drug to treat the specific indications for which approval is sought. Such data may be submitted in other cases because of the nature of the drug product at issue or the specific indications for which approval is sought. For example, Fortical, the recombinant salmon calcitonin nasal spray, was approved to prevent and treat osteoporosis, a use that requires chronic, systemic treatment. The Fortical NDA contained evidence of the sameness of the primary, secondary, and tertiary chemical structures of the 32 amino acid peptide that is the active ingredient in the synthetic and recombinant salmon calcitonins. It also contained data from a clinical study demonstrating that the pharmacodynamic effects of Fortical were comparable to those for the synthetic salmon calcitonin for which a safety and effectiveness finding had been made by the agency. The sponsor also submitted bioequivalence information and pharmacokinetic data. The data in the Fortical NDA established a basis for the Fortical NDA to rely for approval on safety and effectiveness finding made for Miacalcin.

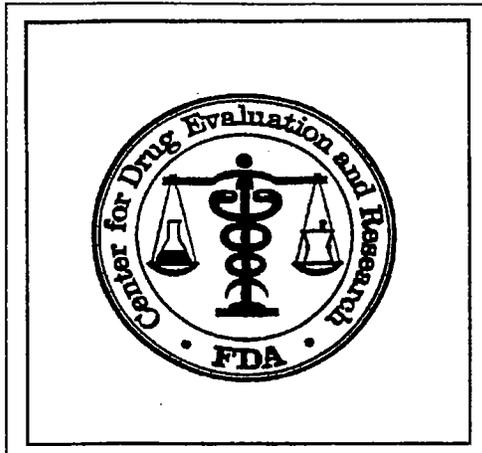
The Omnitrope NDA, for a 191 amino acid recombinant human growth hormone, also includes substantial chemistry and clinical data intended to justify reliance, in part, on the agency's finding of safety and effectiveness for another 191 amino acid recombinant human growth hormone. Although we are still completing our review of the Omnitrope NDA, we believe the Hylenex NDA is distinguishable from the Omnitrope NDA because of the unique characteristics of the hyaluronidase products described above.

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/s/

John Jenkins
12/2/2005 03:19:32 PM
MEDICAL OFFICER

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: August 26, 2005

To: Name Don Kennard
Company Halozyme Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 2

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 31-AUG-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

26-AUG-2005

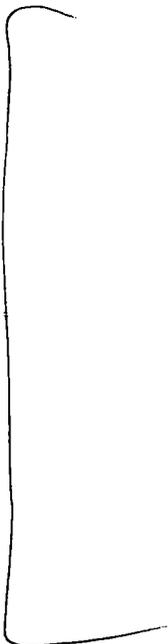
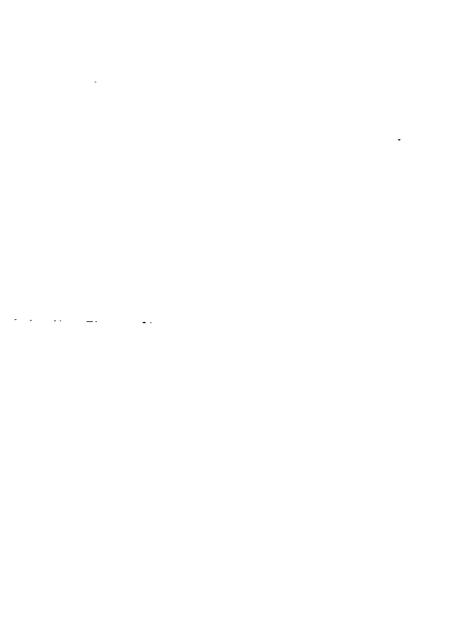
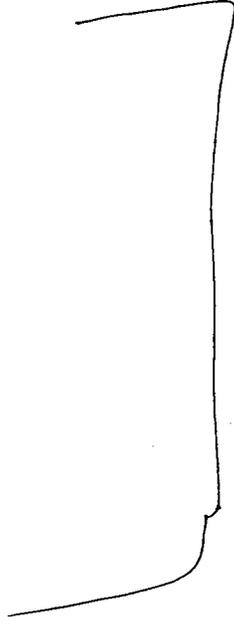
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NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In your cover letter refer to the date on which this information was requested.

Chemist's Concerns

1. Confirm that the following specification for rHuPH20 drug substance is acceptable.

REVISED (23-AUG-2005): rHuPH20 Hyaluronidase Drug Substance Specification

Test	Acceptance Criteria	Method
		

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/s/

Allan Fenselau
8/26/2005 02:27:14 PM
CHEMIST

Linda Ng
8/26/2005 02:48:58 PM
CHEMIST

Memorandum

Review NDA 21-859

To: Alison Rodgers
From: Zhou Chen, Ph.D.
Through: Bob Osterberg, Ph.D.
Date: August 22, 2005
Re: NDA 21-859
Enhanze (rHuPH20)
Action: No action indicated

This is a response to reviewing chemist's comments regarding impurity issues for rHuPH20. The sponsor proposed a drug substance specification level of _____ while the reviewing chemist recommended an acceptance criterion of _____

rHuPH20, a recombinant human hyaluronidase, is a biological product. The impurity is mostly the _____ A criterion of _____ is higher than some marketed hyaluronidase products. If the _____ applies only to active drug substance, then from a pharmacological/toxicological standpoint it is acceptable because of the relatively less pure marketed hyaluronidase products available for human use and apparent difficulty in improving purity levels for these products.

cc:

NDA 21-859
HFD-520 Div. File

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/s/

Zhou Chen
8/22/2005 03:03:07 PM
PHARMACOLOGIST

Robert Osterberg
8/22/2005 03:06:06 PM
PHARMACOLOGIST

Lillian Gavrilovich
8/23/2005 12:05:42 PM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: August 19, 2005

To: Don Kennard	From: Alison Rodgers
Company: Halozyme Therapeutics, Inc.	Division of Anti-Infective and Ophthalmology Products
Fax number: 858-259-2539	Fax number: 301-827-2531
Phone number: 858-794-8889 x 208	Phone number: 301-827-2019
Subject: NDA 21-859 Hylenex Label	

Total no. of pages including cover: 10

Comments:

Hi Don,

Please find attached the draft label for Hylenex. If it is acceptable to you, please send back a clean copy along with a note stating that the label is acceptable. If you want to make changes, please send the changes with a justification for them. Please respond by Thursday, August 25, 2005. Please submit all correspondence officially as well. Thank you!
Alison Rodgers

Document to be mailed: • YES NO

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Attachment

9 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

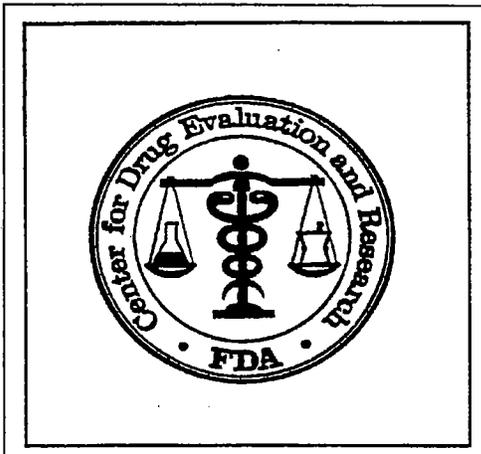
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/s/

Alison Rodgers
8/22/2005 09:44:41 AM
CSO

FACSIMILE TRANSMISSION
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From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: August 18, 2005

To: Name Don Kennard
Company Halozyme Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 25-AUG-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In your cover letter refer to the date on which this information was requested.

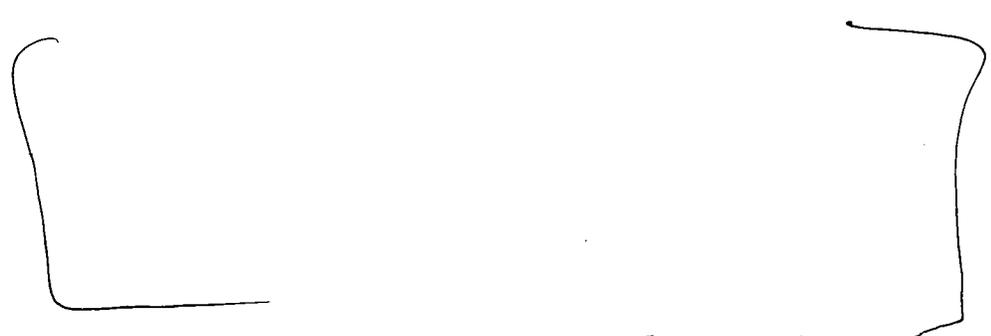
Chemist's Concerns

- 1. Revise the acceptance criteria listed for "Purity by HPLC" such that 1) the term "purity" refers only to the species identified as "rHuPH20" and 2) the total %purity cannot exceed 100%. The recommended changes in the acceptance criteria for "Purity by HPLC" are:

rHuPH20 (by area normalization),	NLT	}
Individual specified impurity/degradant,*	NMT	
Any individual unspecified impurity/degradant,	NMT	
Total impurities/degradants,	NMT	

* Specified based on name or relative retention time [RRT]

- 2. A putative _____ increase in the EU limit for the Endotoxin Content test in the drug substance specification may have consequences beyond the safety considerations discussed in your amendment dated 12-AUG-2005.



- 3. Confirm your agreement that a Hylanex lot that satisfies the acceptance criteria for Protein Content at _____ and Assay at _____ will be out-of-specification for the Specific Activity attribute.

- 4. Confirm your agreement to employ an expiry period of _____ for all Hylanex lots manufactured at a target activity of _____ for storage at 2°-8°C.

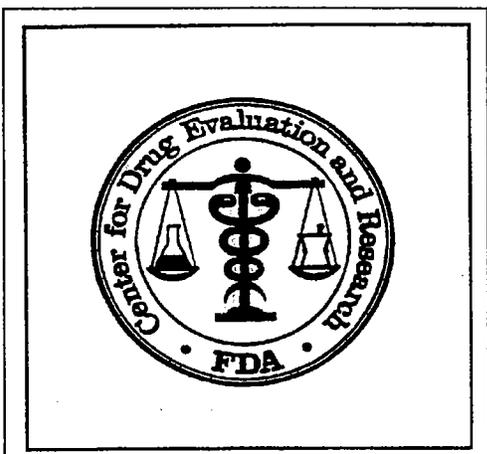
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/s/

Allan Fenselau
8/18/2005 03:06:38 PM
CHEMIST

Linda Ng
8/18/2005 04:28:58 PM
CHEMIST

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: August 9, 2005

To: Name Don Kennard
Company Halozyne Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 16-AUG-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

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NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In your cover letter refer to the date on which this information was requested.

Chemist's Concerns

1. Clarify the differences between the vial specified for commercial use _____ and the vial used in the stability program _____ (see Section 3.2.P.7: Container Closure System). Discuss the possible effects of these differences on product _____ to the glass container (referred to in your amendment dated 21-APR-2005).
2. Provide a description of the acceptance testing performed on the container closure components.
3. Revise the Post-approval Stability Protocol and Stability Commitment (Section 3.2.P.8.2) for Hylenex drug product in accord with the following recommendations:
 - a) Specify that at least one new commercial lot of the product per year will be added to the stability program.
 - b) Correct storage temperature to "5° ± 3°C."
 - c) Specify that the sample vials will be stored in the _____
 - d) Indicate that the Assay will be tested in triplicate.
 - e) State that the tests to be performed at each time point are Description, Assay, pH, Osmolality, and Particulate Matter.
 - f) Perform Sterility and Bacterial Endotoxin testing initially and at or beyond shelf life.
 - g) Continue to perform the HPLC test for rHuPH20 content and impurities/related substances on a "Report results" basis.
 - h) Indicate that additional testing at _____ intervals will be performed for the purpose of extending expiry dating. Pursuant to the provisions of 21 CFR 314.70(d)(5), expiry dating will be extended based upon full shelf-life data obtained from full-scale stability batches under this protocol. After approval of the NDA, extension of expiry dating with additional data will be submitted in the Annual Report.
 - i) In the event that a batch of drug product fails to meet the specification during stability testing, the change or deterioration will be reported to the U.S. Food and Drug Administration under 21 CFR 314.81(b)(1)(ii). All deviations will be promptly discussed with the reviewing division of the FDA. If the deviation from the specification could affect product safety or efficacy, the batch of drug product will be promptly withdrawn from the market. Otherwise, justification for continued distribution of the batch will be discussed with the reviewing division.

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

09-AUG-2005

4. Confirm that the acceptance criterion for the Assay test in the product specification is _____ as stated in Report R05052: Interim Stability Report for Hylenex Registration Stability Lots at the _____ Stability Interval (submitted in the amendment dated 28-JUL-2005)].

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/s/

Allan Fenselau
8/9/05 02:57:12 PM
CHEMIST

Linda Ng
8/9/05 03:15:34 PM
CHEMIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

AUG - 4 2005

Food and Drug Administration
Rockville MD 20857

Rachel A. Bittker, M.D.
15222-B Avenue of Science
PRACS Dermatology, LLC
San Diego, California 92128

Dear Dr. Bittker:

Between June 13 and June 16, 2005, Mr. Robert Sweeton, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # R04-0851 entitled "Evaluation of Sensitivity to Enhanze SC™ (Hyaluronidase) Injection") of the investigational drug Enhanze™, performed for Halozyme Therapeutics. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Sweeton during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Leslie K. Ball, M.D.

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-520 Doc.Rm. NDA#21-859

HFD-520 Soreth Review Div.Dir.

HFD-520 Lloyd MO

HFD-520 Rodgers PM

HFD-46/47c/r/s/ GCP File #11578

HFD-46/47 GCP Tesch Reviewer

HFD-47 Ball Branch Chief

HFD-46/47 CS

HFR-PA252 Maxwell DIB

HFR-PA2565 Koller Bimo Monitor

HFR-PA2535 Sweeton Field Investigator

GCF-1 Seth Ray

r/d: DT 7/25/05
reviewed: LKB: 7/25/05
f/t: (REVIEWER)

o:\Tesch\letters\Dr. Bittker

Reviewer Note to Rev. Div. M.O.

This was a routine PDUFA related inspection of the operations of Dr. Rachel Bittker. This was the first inspection of Dr. Bittker. The inspector found the site to be in compliance with federal regulations governing the conduct of clinical trials. The only deficiency noted was a failure by the firm to keep the test article in a refrigerated environment that was not consistently monitored for temperature. No other deficiencies were noted. No form 483 was issued. The inspection was classified NAI. Data are acceptable for consideration in the NDA.

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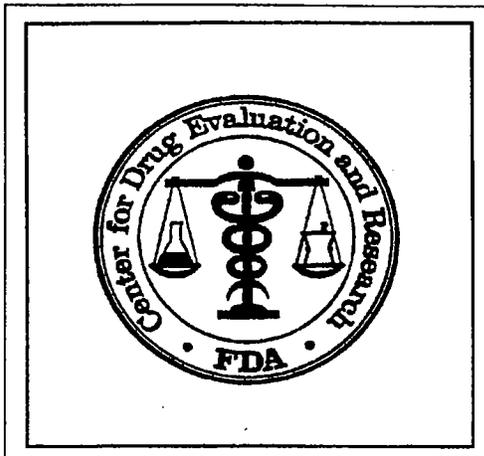
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/s/

Leslie Ball

9/2/2005 09:28:46 AM

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From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: August 2, 2005

To: Name Don Kennard
Company Halozyne Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 3

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 15-AUG-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

2-AUG-2005

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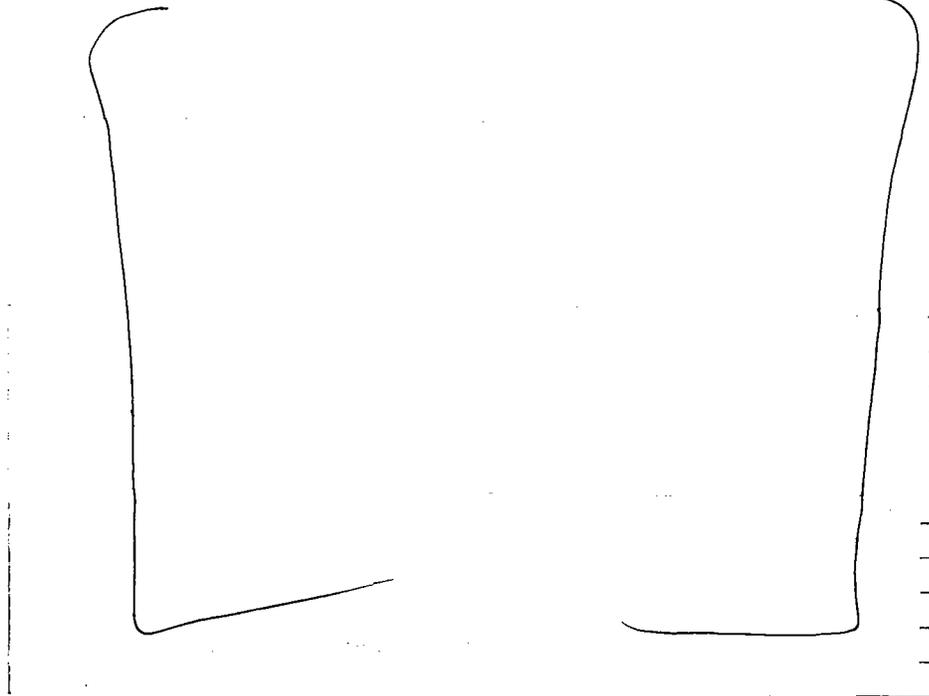
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Information Request

Comparison of the — drug substance (DS) specification with the proposed Halozyme's acceptance specification reveals differences in the acceptance criteria for various critical quantitative tests (see the following table).

rHuPH20 Drug Substance Specifications

Test	Halozyme NDA 21-859
------	---------------------



NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

2-AUG-2005

When drug substance rHuPH20 [DS] Lot HUA0410CA (manufacture date: 15-JUL-2004) was used to manufacture drug product Hylenex [DP] Lot 804419 used in the clinical studies (manufacture date: 24-AUG-2004), the Assay value approximated _____ (reported in stability studies as _____). The reported values for Protein Concentration _____) and Purity (including content of impurities/degradants) by HPLC _____ and _____ also indicated no changes in the first _____ months after _____ manufacture. Lot quality for the clinical studies appears to be considerably superior to a lot that would satisfy the minimum conditions listed in the acceptance specification.

If the _____ specification provides for an adequately controlled manufacturing process, then two major considerations for setting acceptance criteria remain: 1) the tests and acceptance criteria assuring that the quality of future drug substance lots will be equivalent to the lots used in the preclinical and clinical studies and 2) drug substance stability during long-term storage. Of particular interest are studies examining the potential effect of elevated levels of denatured aggregates on immunogenicity or hypersensitivity.

Please address the following:

1. Justify or revise the acceptance specification to reflect _____ specification for Protein Concentration, Assay, and Purity (including content of impurities/degradants) by HPLC _____
2. Provide information on the submitted toxicology studies that identify the rHuPH20 lots used in the studies. Identify the impurities/degradants contained in these lots and their amounts.
3. Discuss the basis for setting limits for _____
Please provide supporting data to justify the limits.
4. Increasing the acceptance criterion for Endotoxin Content from _____ is not acceptable. Please revise or justify accordingly.
5. Provide a copy of the revised acceptance specification for the drug substance rHuPH20.
6. Provide an update on the ongoing drug substance stability studies.
7. Explain the observation that the Certificates of Analysis for all product lots are dated _____ whereas these lots had been manufactured more than _____ (during _____
[Refer to your amendment dated _____

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/s/

Allan Fenselau
8/4/05 06:54:21 AM
CHEMIST

Linda Ng
8/4/05 10:15:24 AM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 29, 2005

TO: File

FROM: Alison Rodgers, HFD-520

SUBJECT: **Pre-Approval Safety Conference**
NDA 21-859, Hylanex (hyaluronidase (human recombinant))
injection

Ron Wassel, RPh, of the Office of Drug Safety, advised Alison Rodgers, Project Manager, Division of Anti-Infective and Ophthalmology Products, that a pre-approval safety conference would not be required for NDA 21-859 because there were no safety issues identified by the medical officer.

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/s/

Alison Rodgers
7/29/05 12:45:26 PM
CSO

Rhea Lloyd
7/29/05 01:24:59 PM
MEDICAL OFFICER

Wiley Chambers
7/29/05 04:09:57 PM
MEDICAL OFFICER

Janice Soreth
8/12/05 03:48:25 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: July 25, 2005

APPLICATION NUMBER: NDA 21859

BETWEEN:

Name: Don Kennard
Phone: 858-794-8889
Representing: Halozyme Therapeutics

AND

Name: Dr. Linda Ng
Alison Rodgers
Division of Anti-Infective and Ophthalmology Products, HFD-520

SUBJECT: CMC Issues

We discussed the issue of submitting data close to the PDUFA date to support a revised manufacturing batch of $\frac{1}{2}$ USP units per mL.

FDA's Comments:

- With the CDER move to White Oak and the PDUFA date for this application of September 23, 2005, mid-September is too late for the Division to receive Halozyme's release data from the $\frac{1}{2}$ USP unit manufacturing batch.
- If Halozyme would go with the originally proposed activity label claim of 150 with a manufacturing target at $\frac{1}{2}$ an expiry of $\frac{1}{2}$ will be given.
- Halozyme could come in with supporting data for the $\frac{1}{2}$ USP unit batch, or a higher manufacturing target with justification, when they are ready.

Halozyme's Comments:

- Halozyme will need to confirm with Baxter that $\frac{1}{2}$ expiry is acceptable. Don Kennard will respond to the Agency regarding this proposal as soon as possible.
- The data are not available before mid September due to scheduling.

Linda Ng, PhD
Chemistry Team Leader for the
Division of Anti-Infective and Ophthalmology

Products

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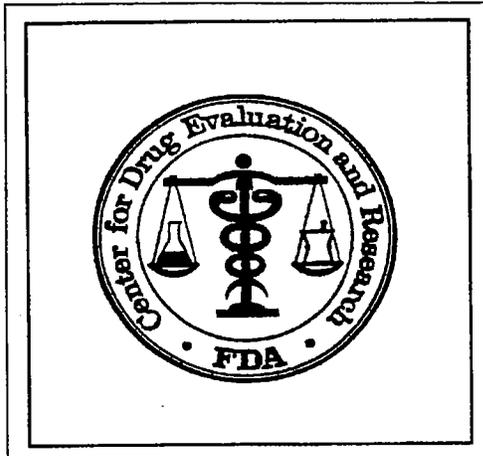
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/s/

Alison Rodgers
8/1/05 01:02:09 PM
CSO

Linda Ng
8/1/05 02:39:44 PM
CHEMIST

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RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: July 22, 2005

To: Name Don Kennard
Company Halozyne Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 2

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 08-AUG-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859
Drug Name: HYLENEX (hyaluronidase injection)

Applicant: Halozyme Therapeutics
22-JUL-2005

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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Chemist's Concerns

1. The test for enzyme activity _____ and the hyaluronidase reference standard that are employed in your determination of units of activity are not the same as those listed in the USP monographs for "Hyaluronidase Injection" and "Hyaluronidase for Injection." Submit the complete report(s) of the studies that prove the equivalency of the test results obtained using _____ and the USP Assay with reference standards of rHuPH20 hyaluronidase and USP hyaluronidase.

[NOTE: A "complete report" is not simply a collection of data (such as you provided in your amendment dated 01-JUL-2005 to Item 7 in our Information Request dated 13-JUN-2005). A "complete report" specifies the protocol that was followed by the study, the materials used for the study, details on the treatment of these materials, the data obtained as a consequence of these treatments, and a statement of the conclusions drawn from the analyses of these data.]

2. The studies comparing enzyme potency with enzyme content (reported in your amendment dated 01-JUL-2005 to Item 5 in our Information Request dated 13-JUN-2005) display a coincidence of data points for the rHuPH20 hyaluronidase working reference standard [RS] and the USP RS. Provide an explanation for this finding. Include the details for preparing and treating the USP RS sample(s). If relevant, provide information on the determination of the protein content of the USP RS sample(s). If relevant, provide information on the specific activities of the two RS hyaluronidases at the assay pH of 6.3
3. The studies comparing enzyme potency with enzyme content _____

_____. Explain. Provide details for the _____ treatment used in the reported study as well as in the HPLC method validation report (RP Validation Report PDR 233-103-01; p. 9). Appropriate information to submit includes (but is not limited to) the amount of _____ medium and pH, temperature, length of treatment. Discuss these observations in the context of the credibility of the two test methods as stability-indicating assays for hyaluronidase.

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/s/

Allan Fenselau
7/28/05 07:14:52 AM
CHEMIST

Linda Ng
7/29/05 09:27:15 AM
CHEMIST

MEMORANDUM OF TELECON

DATE: July 21, 2005

APPLICATION NUMBER: NDA 21-859

BETWEEN:

Name: Don Kennard, Regulatory
Carolyn Renard
Dan Vaughn, CMC
Mary Wilhelm, Regulatory
Phone: 858-794-8889
Representing: Halozyme Therapeutics

AND

Name: Linda Ng, PhD
Allan Fenselau, PhD
Alison Rodgers
Division of Anti-Infective and Ophthalmology Products, HFD-520

SUBJECT: CMC Issues

The Agency called the sponsor, Halozyme Therapeutics, to discuss outstanding CMC issues, as follows:

FDA Comments:

- 1) There are 3 options for manufacturing the commercial batches:
 - a) Manufacturing target of --- units/mL* and change label claim to --- USP units/mL.
 - b) Manufacturing target of --- units/mL with label claim of 150 USP units/mL.
 - c) Manufacturing target of --- units/mL with label claim of 150 units/mL.
- * Halozyme would need to manufacture another batch and provide more information on manufacturing losses.
- 2) For the --- USP units/mL batch size:
 - a) Submit release data and justification for manufacturing loss as soon as possible.
 - b) The Agency does not need to have data on the additional two batches by the time of the action. This release and stability data should be submitted in the Annual Reports.
- 3) Halozyme's product must meet the USP monograph. This decision has been made by the medical team.

- 4) The modified USP test method and the in-house reference standard (of human rHuPH20 hyaluronidase) must provide results equivalent to USP units. Halozyme must reference studies that prove equivalency of hyaluronidase injection and the USP monograph. (See CMC Information Request faxed July 22, 2005.)

Halozyme has provided raw data, but should provide a report to include the experimental conditions, etc., before we can call its product USP.

- 5) Inconsistencies in the information provided should be addressed. For example, do Halozyme's reference standard and the USP standard have the same specific activity? Also, Halozyme needs to explain inconsistencies in the results of _____ of both recombinant human and bovine enzymes. Halozyme should provide more information on the conditions used to generate this data. Also, discuss the credibility of these two methods as stability indicating tests for Hylenex. (See CMC Information Request faxed July 22, 2005.)
- 6) Microbiology needs to know the identification of the filling line and the building number that are being used for product manufacture.
- 8) Send all requested information via fax or email to Dr. Fenselau as it becomes available and then send it in an amendment.
- 9) Up-to-date results from ongoing stability studies should be submitted.

Linda Ng, PhD
Chemistry Team Leader for the
Division of Anti-Infective and Ophthalmology
Products

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/s/

Alison Rodgers
8/5/05 12:55:01 PM
CSO

Linda Ng
8/9/05 03:12:50 PM
CHEMIST

MEMORANDUM OF TELECON

DATE: July 18, 2005

APPLICATION NUMBER: NDA 21-859

BETWEEN:

Name: Don Kennard, Regulatory
Carolyn Renard, CMC
Don Vaughn, CMC
Phone: 858-794-8889
Representing: Halozyme Therapeutics

AND

Name: Linda Ng, PhD
Allan Fenselau, PhD
Alison Rodgers
Division of Anti-Infective and Ophthalmology Products, HFD-520

SUBJECT: Clarification of Agency's Request for CMC Information

Halozyme requested discussion of items listed as the Agency's Chemistry Concerns in a facsimile dated July 14, 2005. For ease of reference, the facsimile is listed here followed by the discussion.

FDA 07-14-05 IR:

The four product lots manufactured at a target concentration of _____ (Batches X804369, 804396, 804419, and 804509) provide a mean value for the Assay value at release of 150 U/mL, which indicates a manufacturing loss of _____. [NOTE: The two lots manufactured at _____ indicate _____ manufacturing losses, which underscores the need to evaluate more data on the actual losses incurred during manufacture and the place in the process where the losses occur.] The validation studies performed on the Assay provide a measure of the method's accuracy in terms of the _____ value of approximately _____. Combining these two observations, a justifiable target for the Assay in formulating product is:

Target Activity =

Activity Label Claim (150 U/mL) + 150 U/mL x _____

If this recommended target of _____ for formulating product is acceptable, the following commitments should be met:

- a. Determination of the extent and location of manufacturing losses in hyaluronidase activity during the manufacture of one commercial size batch of drug product at

- the target activity.
- b. Release data for at least one commercial size batch of drug product manufactured at the target activity.

The information from the requests of Items 1a and 1b should be submitted as an amendment to the NDA by August 1, 2005, or by a date to be negotiated.

- c. Accelerated stability data obtained during the first six months after batch manufacture should be obtained for at least one commercial size batch of drug product manufactured at the target activity.
- d. The long-term stability studies should be performed on the first three commercial size batches in accord with the approved stability protocol.

The information in response to the requests of Items 1c and 1d should be submitted in the Annual Reports.

Halozyme Question: Does the NDA approval depend on the information needed by 8/1/05? It is going to be difficult for Baxter to schedule by 8/1/05. Is it acceptable to work at _____ level and work at specifications proposed earlier?

FDA Response: One batch of release data is absolutely essential. We want to know that Halozyme is in control of the manufacturing process. Some of the stability data for lots manufactured at the _____ target are approaching the limit of NLT _____ by the _____ month of storage at 5°C. We may need to give the product a shorter shelf life than the _____

Halozyme Comments: Hylenex is not a monograph product.

FDA Response: Recombinant human hyaluronidase is a mammalian enzyme and, consequently, is covered by the monograph.

Halozyme Comments: Halozyme expects to have the data to : _____

Baxter will need to be consulted about their manufacturing schedule for production of any new product lots. It could take 6 – 8 weeks to get data related to product release.

Halozyme will send a manufacturing schedule and a schedule for sending responses to the Agency's information request of July 14, 2005, via fax as soon as possible.

FDA's Comments on Stability Protocol:

Regarding FDA July 14, 2005 IR, item c, long term stability is carried out at 5°C, accelerated storage conditions employ 25°C. Time points should be 1, 2, 3, and 6 months for accelerated stability studies.

Only 1 batch is required for accelerated stability data.

Regarding FDA July 14, 2005, IR, item d, provide information at _____ on 3
batches stored at 5° C.

There are a lot of mistakes in the protocol that need to be resolved before taking action on the submission. For example, long-term storage at 25° C should be corrected to 2° – 8°C.

FDA's General Comments:

Please note that all primary reviews undergo secondary review as well. While the secondary reviews are not as extensive, issues can still be raised.

Linda Ng, PhD
Chemistry Team Leader for the Division of Anti-
Infective and Ophthalmology Products

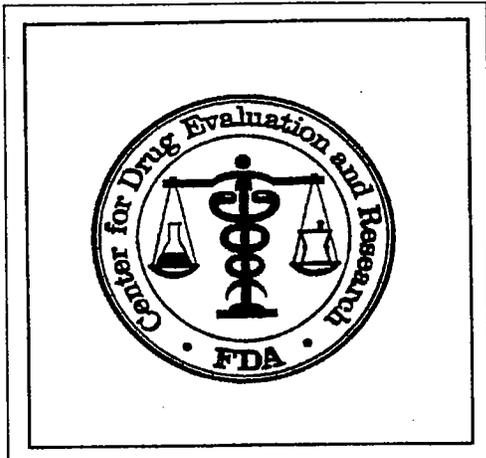
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/s/

Alison Rodgers
7/26/05 10:37:47 AM
CSO

Linda Ng
7/26/05 10:54:47 AM
CHEMIST

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RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: July 15, 2005

To: Name Don Kennard
Company Halozyne Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 2

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Mr. Kennard:

NDA 21-859

The following response provides a recommendation for your request for an Assay target to use in formulating the drug product Hylenex (hyaluronidase injection). If this recommendation and the conditions for its immediate implementation are acceptable to you, please provide written confirmation to this effect. If you have any questions about this response, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

14-JUL-2005

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NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In your cover letter refer to the date on which this information was requested.

Chemist's Concerns

1. The four product lots manufactured at a target concentration of _____ (Batches X804369, 804396, 804419, and 804509) provide a mean value for the Assay value at release of 150 U/mL, which indicates a manufacturing loss of _____ [NOTE: The two lots manufactured at _____ indicate _____ manufacturing losses, which underscores the need to evaluate more data on the actual losses incurred during manufacture and the place in the process where the losses occur.] The validation studies performed on the Assay provide a measure of the method's accuracy in terms of the _____ value of approximately _____. Combining these two observations, a justifiable target for the Assay in formulating product is:

$$\text{Target Activity} = \frac{\text{Activity Label Claim (150 U/mL)} + 150 \text{ U/mL} \times [\text{Manufacturing Losses} + \text{Assay Accuracy}]}{\text{_____}}$$

If this recommended target of _____ for formulating product is acceptable, the following commitments should be met:

- a. Determination of the extent and location of manufacturing losses in hyaluronidase activity during the manufacture of one commercial size batch of drug product at the target activity.
- b. Release data for at least one commercial size batch of drug product manufactured at the target activity.

The information from the requests of Items 1a and 1b should be submitted as an amendment to the NDA by August 1, 2005, or by a date to be negotiated.

- c. Accelerated stability data obtained during the first six months after batch manufacture should be obtained for at least one commercial size batch of drug product manufactured at the target activity.
- d. The long-term stability studies should be performed on the first three commercial size batches in accord with the approved stability protocol.

The information in response to the requests of Items 1c and 1d should be submitted in the Annual Reports.

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/s/

Allan Fenselau
7/28/05 07:12:49 AM
CHEMIST

Linda Ng
7/29/05 09:20:15 AM
CHEMIST



Food and Drug Administration
CDER/ONDC/DNDC II/DMEDP/HFM-510
5600 Fishers Ln.
Parklawn, RM 14B48
Rockville, Maryland 20852
(301) 827-6408
(301) 594-6071 (FAX)

Teleconference Minutes

DATE: 13-JUL-2005
FROM: John C. Hill, Ph.D., Review Chemist
RE: 13-JUL-2005 T-con with Halozyme, rHuPG20 drug substance
THROUGH: Allison K. Rodgers, Regulatory Health Project Manager
THROUGH: Linda Ng, Ph.D., Team Leader
TO: NDA 21-859 File

The consultative drug substance CMC review was finished on 18-MAR-2005 and several Information Request (IR) comments were communicated to the Applicant.

A complete response to the IR comments was received from the applicant on 17-JUN-2005. After review of these responses, clarification/discussion with the applicant about two of the IR comments was deemed necessary.

A T-con was held between representatives from CDER and Halozyme at 1:00pm (EST) on 13-JUL-2005.

The attendees from CDER included:

Linda Ng, Ph.D., Team Leader
John Hill, Ph.D., Drug Substance Reviewer
Alison Rodgers, Regulatory Health Project Manager

The attendees from Halozyme Therapeutics included:

Don Kennard, Vice President, Regulatory Affairs
Don Vaughn, Analytical CMC
Mary Wilhelm, Senior Manager, Regulatory Affairs

The first item discussed was the applicant's response to the request to tighten lot release acceptance criteria for drug substance. The applicant has tightened the proposed acceptance criteria based on commercial (n-3) and development lots. The proposed acceptance criteria are OK; however they are inadequate for a recombinant protein. This fact was discussed with the applicant at length. Dr. Hill indicated that the applicant could either agree to a post-marketing commitment to tighten the drug substance lot release acceptance criteria or that they could agree to re-evaluate and tighten the release acceptance criteria based on a statistically meaningful sampling (commercial scale drug substance lots). Dr. Ng from CDER indicated that the applicant should set acceptable acceptance criteria and thus avoid future regulatory supplements. At this point Dr. Hill suggested a HPLC purity acceptance criteria of _____ and not _____. The applicant indicated that it might be possible to meet this _____ acceptance criteria if

1 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

John C. Hill
7/20/05 04:07:28 PM
CHEMIST

Linda Ng
7/20/05 05:40:29 PM
CHEMIST

Signing as the attending TL to vouch that the
Telcon reflects the discussion. The acceptability of any
agreements is between the primary and secondary reviewers.

MEMORANDUM OF TELECON

DATE: June 14, 2005

APPLICATION NUMBER: NDA 21-859

BETWEEN:

Name: Don Kennard, Regulatory
Don Vaughn, Analytical CMC
Phone: 858-794-8889
Representing: Halozyme Therapeutics

AND

Name: Linda Ng, PhD
Allan Fenselau, PhD
Alison Rodgers
Division of Anti-Infective and Ophthalmology Products, HFD-520

SUBJECT: Clarification of Agency's Request for CMC Information

Halozyme requested clarification of item numbers 2, 5, and 11, listed in the Agency's request for information dated June 13, 2005, as follows:

FDA IR Item #2:

Confirm that HPLC Method _____ has not been validated for use in determining enzyme activity, i.e., the method has never provided an absolute correlation between enzyme/protein content and eluted enzyme activity. If this is correct, revise the validation report to reflect that the method monitors only protein content and not enzyme activity.

[]

Halozyme Comment: Halozyme concurred with the observation that enzyme activity and protein content are not both measurable by this method. Only enzyme/protein content can be determined.

FDA Response: Provide the information requested in Item #3. Specify the units of content. Clean up the validation report. Be clear that this procedure is used for content (and not enzyme activity).

FDA IR Item #5:

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

USP states that nothing less than 90% is acceptable; therefore, as a minimum, the specification should be changed to reflect this. In order to be approved, you need to meet the USP. However, there is a movement to allow a range around the label claim.

We will allow some overages, but need to see data supporting them.

Linda Ng, PhD
Chemistry Team Leader for the Division of Anti-
Infective and Ophthalmology Products

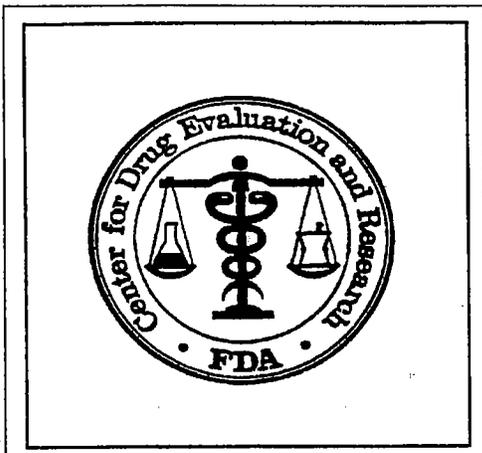
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/s/

Alison Rodgers
7/28/05 07:54:21 AM
CSO

Linda Ng
7/29/05 03:27:45 PM
CHEMIST

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: June 14, 2005

To: Name Don Kennard
Company Halozyme Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 05-JUL-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

14-JUN-2005

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In your cover letter refer to the date on which this information was requested.

Chemist's Concerns

1. Provide results from the use of the Assay _____ in stress testing the drug product. The conditions should include those employed in the analogous studies performed with the method for determining enzyme content _____. In addition, provide information of the photostability of the drug product.
2. Provide the release test results for drug product batches formulated in accord with "Enhanze, _____" and "Enhanze, _____" —both of which target _____. If stability studies were performed with these batches, submit the results.
3. Provide information on the degradant(s) detected by the HPLC method _____ at all storage temperatures (5°C, 25°C, and 30°C). Indicate the retention time relative to rHuPH20, area%, and, if known, identity of the degradant.

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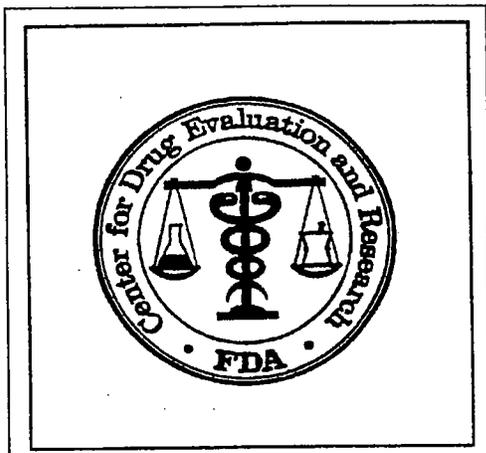
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/s/

Allan Fenselau
6/14/05 02:28:55 PM
CHEMIST

Linda Ng
6/16/05 10:51:20 AM
CHEMIST
No action needed by PM

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Infective and Ophthalmic
Products, HFD-520

Phone 301-827-2050

Fax 301-827-2531

Date: June 13, 2005

To: Name Don Kennard
Company Halozyne Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 3

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 05-JUL-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

2 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

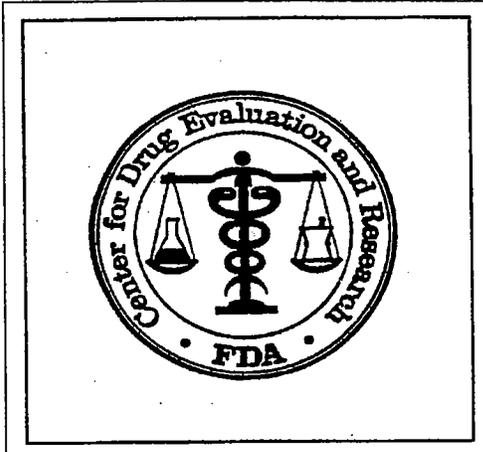
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/s/

Allan Fenselau
6/13/05 03:24:40 PM
CHEMIST

Linda Ng
6/13/05 03:45:26 PM
CHEMIST

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2050

Fax 301-827-2531

Date: May 26, 2005

To: Name Don Kennard
Company Halozyme Therapeutics
City San Diego State CA

Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 3

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 13-JUN-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYELENEX (hyaluronidase injection)

26-JUN-2005

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission.

Chemist's Concerns

The following issues relate to information provided in the drug product Stability Section [3.2.P.8] of the NDA.

1. Provide release data on all product lots manufactured using a target for enzyme activity equal to _____. If available, provide Assay results from stability studies that employ the recommended storage condition (of 2-8°C) and were obtained at a later time point (preferably at one month). Also, include general information, such as the information included in the table on p. 7.
2. Explain the apparent increase in rHuPH20 content noted on p. 28 during stability studies with the drug product stored at 5°C. These results are opposite to those obtained at higher storage temperatures, e.g., those reported on pp. 12, 17, and 22.
3. Explain the plot of rHuPH20 content at 5°C (presented on p. 28) that displays a decrease in content that is inconsistent with the data presented in the preceding table.
4. Explain the apparent disproportionate decrease in the rHuPH20 content over time for product batches containing initially higher levels of enzyme activity. The batches containing approximately _____ more activity _____ display monthly decreases in rHuPH20 content that are _____ greater than the product batches with less activity (150 U/mL) [see table on p. 12].
5. Provide updated stability data for all _____ product lots included in the Stability section of the submission. Before the end of this review cycle (in September 2005), nine months of data should be available for these lots (listed on p. 7), the last of which was manufactured on 17-SEP-2004.
6. Provide stability study plots for all storage conditions that compare changes in the drug product Relative Potency in terms of % of release activity and % of label claim for activity.
7. Provide stability study plots for all storage conditions that correlate the changes in drug product rHuPH20 potency and content.

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/s/

Allan Fenselau
5/26/05 11:08:37 AM
CHEMIST

Linda Ng
5/27/05 01:59:22 PM
CHEMIST



FILING COMMUNICATION

NDA 21-859

Halozyme Therapeutics, Inc.
Attention: Don Kennard
Vice President, Regulatory Affairs & Quality Assurance
11588 Sorrento Valley Road, Suite 17
San Diego, CA 92121

Dear Mr. Kennard:

Please refer to your March 18, 2005, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hylenex (recombinant human hyaluronidase).

We also refer to your submissions dated April 6 and 21, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on May 20, 2005, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 827-2019.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and
Ophthalmological Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Janice Soreth
5/26/05 08:43:18 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-859 Supplement # Efficacy Supplement Type SE-

Trade Name: Hylenex
Established Name: (hyaluronidase injection) human recombinant
Strengths: 150 USP Units

Applicant: Halozyme Therapeutics, Inc.
Agent for Applicant: Don Kennard

Date of Application: March 18, 2005
Date of Receipt: March 23, 2005
Date clock started after UN: N/A
Date of Filing Meeting: April 13, 2005
Filing Date: May 22, 2005
Action Goal Date (optional): September 23, 2005 User Fee Goal Date: September 23, 2005

Indication(s) requested: As an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication

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for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO

If yes, explain: Recent approvals of Hyaluronidase

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO

If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

If no, explain: Missing Clinical Pharmacology waiver request.

- If an electronic NDA, does it follow the Guidance? N/A YES NO

If an electronic NDA, all forms and certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? All parts except for the administrative forms that required signatures.

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO

If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 66,888
- End-of-Phase 2 Meeting(s) Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) Date(s) March 8, 2005 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: April 13, 2005

BACKGROUND: Hylenex is an injectable non-preserved formulation that contains recombinant human hyaluronidase as the drug substance. Halozyme Therapeutics has named Wydase (NDA 6-343) as the reference listed drug.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Wiley Chambers, MD, Deputy Division Director, DAAODP
Jennifer Harris, MD, Medical Officer, DAAODP
Lucious Lim, MD, Medical Officer, DAAODP
Rhea Lloyd, MD, Medical Officer, DAAODP
Martin Nevitt, MD, Medical Officer, DAAODP
Linda Ng, PhD, Chemistry Team Leader
Allan Fenselau, PhD, Chemistry Reviewer (drug product)
Zhou Chen, PhD, Pharm/Tox Reviewer
James McVey, PhD, Microbiology Reviewer
John Hill, PhD, Chemistry Reviewer (drug substance)
Lori Gorski, Project Manager, DAAODP
Michael Puglisi, Project Manager, DAAODP
Raphael Rodriguez, Project Manager, DAAODP
Carmen DeBellis, RPh, Chief Project Manager, DAAODP
Alison Rodgers, Project Manager, DAAODP

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Rhea Lloyd
Secondary Medical:	N/A
Statistical:	Yongman Kim
Pharmacology:	Zhou Chen
Statistical Pharmacology:	N/A
Chemistry:	Allan Fenselau/ John Hill
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Dennis Bashaw
Microbiology, sterility:	James McVey
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
Regulatory Project Management:	Alison Rodgers
Other Consults:	DDMAC, DMETS

Per reviewers, are all parts in English or English translation?
If no, explain:

YES NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
 N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY N/A FILE REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Alison Rodgers
Regulatory Project Manager, HFD-550

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Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Wydase/NDA #6-343

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). Provides for a recombinant form of hyaluronidase.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s): 2,795,529

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 66,888 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

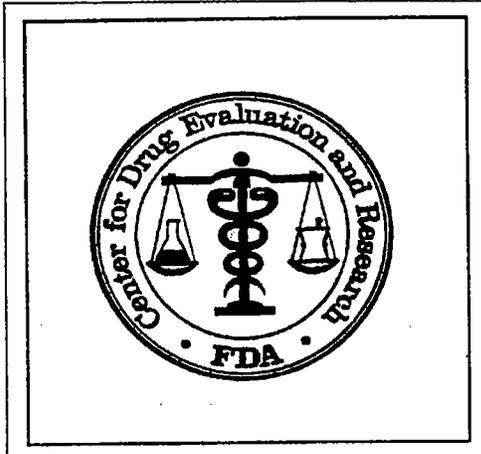
YES NO

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/s/

Alison Rodgers
8/22/2005 11:06:50 AM
CSO

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From: Allan Fenselau, Ph.D.

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2050

Fax 301-827-2531

Date: April 12, 2005

To: Name Don Kennard
Company Halozyme Therapeutics
City San Diego State CA
Phone # 858-794-8889 x208 or 858-353-1541

FAX # 858-259-2539

Number of Pages (INCLUDING COVER PAGE) 3

Please telephone (301) 827-2040 IMMEDIATELY if re-transmission is necessary.

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Mr. Kennard:

NDA 21-859

The following questions came up in reviewing the CMC issues regarding your NDA submission. A response by 02-MAY-05 would be greatly appreciated. Please let us know if this deadline cannot be met. If you have any questions about specific items in the list or any other points in need of clarification, just call Alison Rodgers (301-827-2020) or me (301-827-2050).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYLENEX (hyaluronidase injection)

12-APR-2005

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an amendment to the submission.

Chemist's Concerns

1. Specify the site(s) that perform the testing listed in the drug product specification. For each site, provide the facility name, address, and contact person (with phone and fax numbers).
2. Clarify the formulation process. The use of two tables is recommended: one table to describe vehicle formulation; the other, final product formulation. Make clear the basis for determining the final batch size. Indicate the basis for making any adjustments in batch size. [Make clear the relationship between batch size, weight of drug substance solution, and units of enzyme activity needed to manufacture the batch. Eliminate confusion such as exists in the executed batch record for Batch 804419, in which the Formulation Summary indicates the need for _____ of drug substance, but the actual amount used was _____.]
3. Provide a flow diagram for product manufacture that is appropriate for the proposed commercial batch size (presumed to be _____ as given in the submitted diagram). Correct the calculation used to determine the amount of rHuPH20 [API] that needs to be added.
4. Describe the process by which drug substance rHuPH20 is transferred from the supplier _____ to the drug product manufacturer (Baxter Pharmaceutical Solutions, Bloomington, IN). Provide documentation on all drug substance batches that have been transferred to date in order to verify control of the transfer process.
5. Indicate the acceptance testing that is performed on the drug substance received by the drug product manufacturer. Provide a table for the batches transferred from _____ to Baxter Pharmaceutical Solutions that compares the results of Baxter acceptance testing with those from _____ release testing.

NDA Number: 21-859

Applicant: Halozyme Therapeutics

Drug Name: HYELENEX (hyaluronidase injection)

12-APR-2005

6. Describe the procedures followed during product manufacture for transferring rHuPH20 from the _____ storage vials to the commercial batch. Indicate controls employed in performing this transfer, e.g., the temperature conditions and rate at which the frozen protein solution is thawed.
7. Justification for a manufacturing overage cannot be based on _____ drug product. [The use of a target concentration of _____ in product formulation is unacceptable.]
8. Explain the apparent decrease of _____ in enzyme activity during the first month after product release.
9. Provide a comparison of results obtained using the same number of units of USP Hyaluronidase Reference Standard [RS] in the original USP method and in the modified USP method [TM011].
10. Describe the process by which the activity of the rHuPH20 Reference Standard for hyaluronidase as determined by _____ is converted to "USP units" of hyaluronidase activity.
11. Provide copies of the Certificates of Analysis for all batches of drug product manufactured to date.

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

/s/

Allan Fenselau
4/12/05 12:56:01 PM
CHEMIST

Linda Ng
4/12/05 02:34:12 PM
CHEMIST
No activity by PM needed

DRAFT MEETING MINUTES TO THE SPONSOR
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

Meeting Date: March 8, 2005

Time: 11:00 AM EST

Application: IND 66,888/NDA 21-859

Meeting Type: Pre-NDA meeting

Drug: Enhanze SC recombinant hyaluronidase

Sponsor: Halozyme

These draft comments are being given to as a courtesy prior to our formal meeting on March 8. If you understand our responses and feel they warrant no further discussion, the meeting could be cancelled. If you do wish to still have the meeting, please remember we will not entertain any new questions or documentation for that meeting. If you wish to discuss any new information another meeting request should be submitted.

QUESTIONS

a) Halozyme is developing a recombinant human form of hyaluronidase injection. Halozyme has been previously informed by the agency that this product is eligible for a 505(b)(2) route of submission. Halozyme proposes referencing the Baxter NDA 6-343 for Wydase® as the Reference Listed Drug in the Enhanze SCT™ submission. Is this reference appropriate?

Response: Yes. (RL)

b) The CDER web site (<http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>) as of 2005/01/03, lists the following hyaluronidase products with NDA approval and New Chemical Entity designations and associated exclusivities:

Product	Active Ingredient	NDA #	Dosage	Exclusivity Expiration
Amphadase®	bovine extract	21-665	Liquid	Oct 26, 2009
Vitrace®	ovine extract	21-640	Multiple presentations	May 5, 2009

Recombinant human hyaluronidase (rHuPH20) does not contain bovine or ovine extracted proteins and thus is distinctly different from both the bovine derived and ovine derived materials. We believe rHuPH20 is also a New Chemical Entity. We request clarification regarding the following questions on this subject:

b.1) Will Enhanze SCT™ be designated a New Chemical Entity?

Response: Yes. (RL)

b.2) Will the exclusivities held by Amphadase® or Vitrace® block the acceptance of a NDA submission for Enhanze SCT™?

Response: *Unlikely to block the acceptance.*

b.3) Will the exclusivities held by Amphadase® or Vitrase® delay the approval of a NDA submission for Enhanze SC™?

Response: *Not from the Division's prospective or time frame.*

c) We anticipate filing Enhanze SC™ NDA 21-859 as a combination of paper documents and electronic media. We propose providing three copies of the paper documentation and one copy of the electronic documentation. We will utilize Guidance for Industry: Providing Regulatory Submissions in Electronic Format –General Considerations January 1999 for constructing the submission. Are there any unique requirements or preferences that the Division needs in the electronic formatting?

Response: *No. (RL)*

d) The proposed labeling for Enhanze SC™ will designate the product as Enhanze SC™, recombinant human hyaluronidase. We believe this is appropriate to differentiate the recombinant human product from the ovine and bovine hyaluronidase products. Is this appropriate?

Response: *The labeling may differentiate the product, but the established name should follow the USP monograph.*

The phrase "(rDNA origin)" is customarily added to the established name for all recombinant DNA products. In this case, the established name would be hyaluronidase injection (rDNA origin).

e) Halozyme proposes submitting the case report tabulations and data sets from the clinical study and not submitting copies of the executed case report forms. Is this acceptable?

Response: *Submission of the case report tabulations and data sets is acceptable. However, the case report forms for any discontinued subjects, regardless of cause, should be submitted.*

f) The December 14, 2004 letter from FDA included the following remark (#8):



However, the USP — excludes small volume injectables such as Enhanze SC™ intended for subcutaneous injection. Although historically US — was required for both large and small-volume injections, USP has been revised. USP 28 includes the language:

“All large-volume injections for single-dose infusion and those small-volume injections for which the monographs specify such requirements are subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph. Excluded from the requirements of this chapter are injections intended solely for intramuscular and subcutaneous administration.”

The existing monographs for testes-derived hyaluronidase do not specify particulate matter requirements. (Although Enhanze SC™ is not a testes-derived product, the existing monographs may be used as guidelines.) Also, Enhanze SC™ is intended for intramuscular and subcutaneous administration, further exempting the product from the particulate matter requirements. To comply with the most current USP, Halozyme proposes to not include particulate matter in the drug product specification. Is this acceptable?

Response: *The particulate matter test should be included in the drug product specification. Hyaluronidase is not intended solely for intramuscular and subcutaneous administration (e.g., retrobulbar injection) (WAC).*

Additional comment:

Please establish a purity test in the drug product specification in order to determine any impurities generated or increased during manufacture and/or storage of the drug product. And set the acceptance criteria according to the actual long term stability data. Also refer to ICH Q6B for the requirements on drug product specification (LQ).

g) The December 14, 2004 letter from FDA included the following question (#17):

“Please establish a specification for _____ as part of routine release testing of drug substance, unless a justification can be provided for omission of such a specification.”

Halozyme will include a test for _____ in response to this question. The proposed specification is a total monosaccharides mole ratio range of _____ based on quantitation by _____. Is this acceptable?

Response: *The response is acceptable. The agency recommends that the sponsor consider moving towards characterization of the _____ as a more general characterization method than the proposed _____ analysis.*

h) The December 14, 2004 letter from FDA included the following question (#18):

“As part of the drug substance stability program the sponsor should set an expiry date. Extension of the expiry date can then be made in accordance with the drug substance stability protocol.”

Response: The response is acceptable.

i) At the time of filing, Halozyme will include a retest date for drug substance, is this acceptable?

Response: The response is acceptable.

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The comments below are from ODS

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

RiskMAPs

2.5.5 Overview of Safety with appropriate cross references to section

2.7.4 Summary of Clinical Safety

and any other relevant sections of the Common Technical Document for the NDA/BLA application.

Pharmacovigilance plans

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or BLA Clinical Data Section (21 CFR 601.25(b)(3)) and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/guidance/5766dft.pdf> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc>.
- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

MEMORANDUM OF TELECON

DATE: March 28, 2005

APPLICATION NUMBER: NDA 21-859

BETWEEN:

Name: Don Kennard
Phone: 858-353-1541
Representing: Halozyme Therapeutics, Inc.

AND

Name: Dennis Bashaw, PharmD, Biopharm Team Leader
Carmen DeBellas, RPh, Chief Project Manager
Alison Rodgers, Project Manager
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug
Products, HFD-550

SUBJECT: PK/Clinical Pharmacology Section in Submission of NDA 21-859

Dr. Bashaw explained that since a PK/clinical pharmacology section was not included in the submission, a written request for a waiver must be provided. He explained that the metabolic fate of a recombinant product needs to be addressed. Dr. Bashaw referred Mr. Kennard to the regulation, 21CFR320.21 (a), where this issue is explicitly addressed.

Mr. Kennard stated that much of the information regarding PK/clinical pharmacology is in the document, but he will pull it all together and make a compelling justification for the waiver.

In addition, Mr. DeBellas explained that a filing meeting has been set up and the sponsor will receive a letter within 74 days. If any outstanding issues are identified during the meeting, they will be included in the letter.

SIGNER'S NAME
TITLE

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

/s/

Alison Rodgers
4/18/05 11:07:52 AM
CSO

Alison Rodgers
4/26/05 08:56:45 AM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 03/31/05

DESIRED COMPLETION DATE: 06/29/05

ODS CONSULT #:

DATE OF DOCUMENT: 03/18/05

PDUFA DATE: 08/23/05

05-0084

TO: Janice Soreth, M.D.
Director, Division of Anti-Infective and Ophthalmology Drug Products
HFD-520

THROUGH: Alison Rodgers
Project Manager
HFD-520

PRODUCT NAME:

Hylanex (Hyaluronidase Injection)
150 units/mL

NDA#: 21-859

NDA SPONSOR:

Halozyme Therapeutics, Inc.

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Hylanex, provided that **only one name**, Hylanex (NDA 21-859) or _____ is approved. The acceptability of the proposed proprietary name Hylanex depends on which application, Hylanex or _____, receives approval first, as these two names may not coexist in the U.S. market due to their similarities (see section II.C.3).

This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Hylanex acceptable from a promotional perspective.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol A. Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

*** Name pending approval. Not FOI releasable.

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 04/25/05
NDA#: 21-859
NAME OF DRUG: Hylenex (Hyaluronidase Injection)
150 units/mL
NDA HOLDER: Halozyme Therapeutics, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Drug Products (HFD-520), for a review of the proprietary name, "Hylenex", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

Hylenex was previously reviewed by DMETS (Consult # 04-0114) for the same product in the 150 units/mL and 1500 units/10 mL strengths and found acceptable. The sponsor, Baxter, subsequently sold the name to Halozyme Therapeutics, Inc., who are now submitting an application for the 150 units/mL strength only.

PRODUCT INFORMATION

Hylenex is a highly purified preparation of recombinant human hyaluronidase, a protein enzyme. Hylenex is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hylenex is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Absorption and dispersion of other injected drugs may be enhanced by adding 150 units hyaluronidase to the injection solution. For hypodermoclysis, insert the needle with aseptic precautions, then inject Hylenex into rubber tubing close to the needle. An alternate method is to inject Hylenex under skin prior to clysis. One hundred and fifty units will facilitate absorption of 1,000 mL or more of solution. The subcutaneous route of administration of urographic contrast media is indicated when intravenous administration cannot be successfully accomplished, particularly in infants and small children. When the patient is prone, 75 units of Hylenex is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites. Hylenex will be supplied sterile as 150 units of recombinant human hyaluronidase per mL in a 2 mL glass vial.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Hylenex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS did not repeat the prescription studies since the name was already reviewed for the same active ingredient and proprietary name (ODS Consult # 04-0114) under the NDA 6-343/S-014.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Hylenex. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Hylenex acceptable from a promotional perspective.
2. Since the name review conducted on June 10, 2004, the Expert Panel identified four additional proprietary names that were thought to have the potential for confusion with Hylenex. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

Appears This Way
On Original

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Hylenex	Hyaluronidase Injection 150 units/mL	For absorption and dispersion of other injected drugs and hypodermoclysis: 150 units As an adjunct in subcutaneous urography for improving resorption of radiopaque agents: 75 units over each scapula, followed by injection of the contrast medium or the same sites.	
Buprenex	Buprenorphine Hydrochloride Injection 0.3 mg/mL	0.3 to 0.6 mg IV/IM every 6 to 8 hours as needed.	LA
Hydromox	Quinethazone Tablets 50 mg	25 mg to 100 mg daily. Max: 200 mg daily.	LA
Myleran	Busulfan Tablets 2 mg	4 to 8 mg daily or 60 mcg/kg/day.	LA
Synvisc	Hylan polymers Solution 16 mg hylan polymers (hylan G-F 20)/2 mL ³	Give a total of 3 injections/treatment cycle using an 18 to 22 gauge needle. Remove synovial fluid or effusion before each injection.	LA
Mycelex	Clotrimazole Cream, 1%	Apply twice daily.	S/A/LA
	Clotrimazole Troche, 10 mg	Dissolve 1 troche 5x/day for 14 days.	
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Name pending approval. Not FOI releasable.			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Hylenex were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Hylenex, the primary concerns related to look-alike and sound-alike confusion with Buprenex, Hydromox, Myleran, Synvisc, []***, and Mycelex. Upon further review of the names gathered from EPD, independent analysis, and POCA, the names Buprenex and Synvisc were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Hylenex in addition to numerous differentiating product characteristics such as the strength, indication for use, frequency of administration, route of administration and dosage form.

1. Hydromox and Hylenex have look-alike similarities when scripted. Hydromox is a thiazide diuretic used for hypertension and controlling edema due to congestive heart failure or renal dysfunction. Oral doses for hypertension are 25 to 100 mg/day, with titration to doses as high as 200 mg/day for severe edema. Hydromox and Hylenex share the first two letters, Hy-, and the "d" in Hydromox has an upstroke characteristic which resembles the upstroke "l" in Hylenex. Their endings, "-nex" vs. "-mox", resemble each other because "n" can look like "m" and the "x" is distinct and present in both names (see below). Individually, the letters may be distinct, but formulated together, the letters in each name have the potential to be mistaken for each other. Despite these orthographic similarities, Hydromox and Hylenex have many product differences. They differ in dosage form (tablet vs. injection), route of administration (oral vs. subcutaneous or intramuscular), dosage strength (50 mg vs. 150 units/mL), and frequency of administration (daily vs. as per procedure). Hydromox would most likely be taken as a maintenance medication as opposed to Hylenex which would be utilized for a surgical procedure. Data from Thomson & Thomson's SAEGIS™ Online Service⁵ indicates that sales usage during 1998 was low. Given that the usage of Hydromox is low, in addition to other dissimilarities, there is insufficient evidence at this time to conclude that the proposed drug would be confused with Hylenex.

Hydromox
Hylenex

2. Myleran was found to have look-alike similarity to Hylenex. Myleran (busulfan) is a bifunctional alkylating agent that is not cell cycle specific. Myleran is indicated for use in the palliative treatment of chronic myelogenous leukemia (CML). Myleran is given 4 to 8 mg daily or 6 mcg/kg/day. The "Myl-" prefix resembles the "Hyl-" prefix (see below) and the suffixes ("-ran" vs. "-nex") may resemble each other if not precisely scripted. Despite these similarities, Myleran and Hylenex have many product differences. They differ in dosage form (tablet vs. injection), route of administration (oral vs. subcutaneous or intramuscular), dosage strength (2 mg vs. 150 units/mL), and frequency of administration (daily vs. per procedure). Myleran would most likely be taken as a maintenance medication as opposed to Hylenex which would be utilized for a surgical procedure. Additionally, because Myleran is a chemotherapeutic agent, specific strengths and frequency of administration must be present when ordering the medication. Therefore, despite some orthographic similarities, for the aforementioned reasons, DMETS believes the likelihood for confusion to be minimal.

Myleran
Hylenex

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

3.



4. Mycelex and Hylenex have potential for sound-alike and look-alike confusion. Mycelex (clotrimazole) is an imidazole antifungal drug used for prophylaxis and treatment of oropharyngeal candidiasis and is also effective in the treatment of superficial dermatomycosis. Mycelex is available in as a troche or topical cream. The usual dose of clotrimazole oral troches is 1 troche dissolved slowly in the mouth 5 times per day for 14 days. Topical clotrimazole is applied twice daily. Mycelex and Hylenex share the "y" sound in the prefix, and the "ex" ending. The remaining letters ("c" vs. "l" and "l" vs. "n" sounds) are distinct enough that the two names may be differentiated from one another phonetically. When scripted, the "M" and "H" resemble each other (see page 7). In addition, the "l" in Hylenex, if not prominently scripted, may resemble the "c" in Mycelex. Similarly, the

*** Pending approval; proprietary and confidential information that should not be released to the public.

“-elex” in Mycelex resembles the “-nex” if not precisely written. Mycelex and Hylenex differ in route of administration (oral or topical vs. intramuscular or subcutaneous), dosage form (tablet or cream vs. injection), strength (1% and 10 mg vs. 150 units/mL), and dosage administration (twice daily to five times daily vs. per procedure). Despite some orthographic and phonetic similarities, their product differences help minimize the potential for confusion.

Mycelex
Hylenex

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Hylenex, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1.



2.

3.



B. CARTON LABELING

See CONTAINER LABEL comments.

C. INSERT LABELING

No comments.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Hylenex, provided that **only one name**, Hylenex (NDA 21-859) or [REDACTED] (IND [REDACTED]), is approved. The acceptability of the proposed proprietary name Hylenex depends on which application, Hylenex or [REDACTED], receives approval first, as these two names may not coexist in the U.S. market due to their similarities.

This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Hylenex acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-3242.

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina R. Mahmud, R.Ph., M.S.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

*** Name pending approval. Not FOI releasable.

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

/s/

Jinhee Jahng
7/20/05 09:38:35 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/20/05 10:26:06 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/20/05 11:03:34 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/20/05 11:15:07 AM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-859

Halozyme Therapeutics, Inc.
Attention: Don Kennard
Vice President Regulatory Affairs
11588 Sorrento Valley Road, #17
San Diego, CA 92121

Dear Mr. Kennard:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Enhanze SC 1 mL non preserved injectable solution
Review Priority Classification:	Priority (P)
Date of Application:	March 18, 2005
Date of Receipt:	March 23, 2005
Our Reference Number:	NDA 21-859

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 20, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be September 23, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

NDA 21-859

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Attention: Document Room N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 827-2019.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, RPh
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Carmen DeBellas
3/29/05 03:18:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG
USER FEE COVER SHEET**

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Halozyme Therapeutics Inc.
11588 Sorrento Valley Road, #17
San Diego, CA 92121

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-859

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(858) 794-8889x208

3. PRODUCT NAME

Enhance SC (recombinant human hyaluronidase injection)

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Don Kennard

DATE

03/11/2005



Department of Health and Human Services

Public Health Service

Food and Drug Administration

Rockville, MD 20857

FEB 7 2005

Don Kennard
Vice President, Regulatory Affairs & Quality Assurance
Halozyme Therapeutics, Inc.
11588 Sorrento Valley Road, Suite # 17
San Diego, CA 92121

**RE: Halozyme Therapeutics, Inc., Small Business Waiver Request # 2005.025 for
NDA 21-859, Enhanze SC Injectable**

Dear Mr. Kennard:

This responds to your November 1, 2004, letter requesting a waiver of the human drug application fee for new drug application (NDA) 21-859, Enhanze SC Injectable, under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request # 2005.025). For the reasons described below, the Food and Drug Administration (FDA) grants the Halozyme Therapeutics, Inc. (Halozyme) request for a small business waiver of the application fee for NDA 21-859.

According to your letter, Halozyme has fewer than 500 employees and has no affiliated corporations or divisions. You also stated NDA 21-859 is the first NDA submitted by Halozyme and is scheduled for submission in February 2005.²

Under section 736(d)(3) of the Act,³ a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate⁴ submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Halozyme's request for a small business waiver for its NDA for Enhanze SC is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated December 8, 2004, that Halozyme and its affiliates, DeliaTroph Pharmaceuticals (DeliaTroph), Global Yacht Services (Global), and Halozyme Acquisition Corporation (HAC), have fewer than 500

¹ 21 U.S.C. 379h(d)(1)(D).

² In your telephone conversation of January 12, 2005, with Beverly Friedman of my staff, you noted that the application is now scheduled for submission in mid-March 2005.

³ 21 U.S.C. 379h(d)(3).

⁴ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

Halozyme Therapeutics, Inc.
Waiver Request # 2005.025
Page 2

employees. Second, according to FDA records, the marketing application for NDA 21-859 is the first human drug application, within the meaning of the Act, to be submitted to FDA by Halozyme or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-859, Enhanze SC, is granted, provided that FDA receives the marketing application no later than December 8, 2005, 1 year after the effective date of the size determination made by SBA. Please include a copy of this letter with your application.

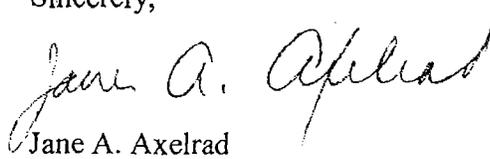
We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for Halozyme's NDA 21-859. FDA records show that Halozyme has not yet submitted NDA 21-859, Enhanze SC Injection.

If FDA refuses to file the application or Halozyme withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Halozyme should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 21-859

Submission Type: N/A (pilot)

Serial Number: N/A (pilot)

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
	Gender	Males	All Females	Females >50		
Age:	0-≤1 Mo.		>1 Mo.- ≤2Year		>2-≤12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	
	Other					

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?

If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

Age-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?

If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

Race-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?

If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

NDA 21-859 Hylenex™ (hyaluronidase (human recombinant) injection) is submitted under Section 505 (b) (2) of the Food Drug and Cosmetics Act. Wydase® (NDA 6-343) designated as the reference listed drug. The indications in the proposed labeling in this review are supported by the Agency's evaluation of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's reports on hyaluronidase (DESI 6343, 6714, 7933) as well as other available evidence.

Gender effects have been investigated. No significant differences have been observed. Differences based on race have been proposed; however, the data in controlled studies has not supported any differences based on age, gender, race or ethnicity.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-859	Efficacy Supplement Type SE-	Supplement Number
Drug: Hylenex		Applicant: Halozyme Therapeutics, Inc.
RPM: Alison Rodgers		HFD-520 Phone # 301-796-0797
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Wydase</p>	
❖ Application Classifications:		
<input type="checkbox"/> Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<input type="checkbox"/> Chem class (NDAs only)		1
<input type="checkbox"/> Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		September 23, 2005
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<input type="checkbox"/> User Fee		<input type="checkbox"/> Paid UF ID number
<input type="checkbox"/> User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<input type="checkbox"/> User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<input type="checkbox"/> Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<p><input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No</p>
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Project Manager: 8-22-05

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	Submitted 9-14-05
• Original applicant-proposed labeling	Submitted 3-18-05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC: 6-22-05, DMETS: 7-20-05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	Submitted 3-18-05
• Reviews	See Clinical reviews 9-14-05, 9-21-05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In package
❖ Memoranda and Telecons	In package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	March 8, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A (See memo 7-29-05 in package)
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	OND Director: 12-2-05 Deputy Division Director: 12-2-05
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9-14-05, 9-21-05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	8-4-05
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical review 9-21-05
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	12-05-05
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	7-5-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	7-25-05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	Drug Substance: 5-26-05, 7-13-05 Drug Product: 9-1-05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	5-26-05
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	5-26-05
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	8-4-05
❖ Facilities inspection (provide EER report)	Date completed: 8-19-05 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed 5-26-05 () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	6-15-05, 8-22-05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).