CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-716

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Lei Zhang, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **3/26/2004**	Related IND No's.:	NDA No. **21-716**	DATE OF DOCUMENT **10/17/2003 and 3/17/2004**	ORM division **HFD-550**
NAME OF DRUG HYDASE™ (Hyaluronidase Injection, USP) 150 Units/mL	PRIORITY CONSIDERATION **Priority**		Date of Formal Consult: **12/1/2003**	Drug Class: **Spreading agent** Indication: **To increase the absorption and dispersion of other injected drugs**

NAME OF THE SPONSOR: [Prima Pharm, Inc., San Diego, CA 92121]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ • BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	• • • IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ • Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ • See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ • See submission cover letter • • • OTHER *(SPECIFY BELOW)*: [Original NDA Review]

REVIEW COMMENT(S)

X NEED TO BE COMMUNICATED TO THE SPONSOR ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

Background

This is a 505(b)(2) application for HYDASE™ (hyaluronidase Injection, USP) 150 USP Units/mL, an enzymatic preparation made from purified bovine testicular hyaluronidase. Hyaluronidase breaks down hyaluronic acid in connective tissue and increases tissue permeability. HYDASE™ 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. Dosing ranges from 75 U for subcutaneous urography

to up to 150 U for use as an adjuvant to increase the absorption and dispersion of other injected drugs and in hypodermoclysis.

Hyaluronidase is considered by the FDA to be a medically necessary drug product. Wydase® (Wydase Lyophilized and Wydase Stabized Solution), the original Wyeth hyaluronidase product (NDA 6-343) was approved in March 1950 and was subject to the Drug Efficacy Study Implementation or DESI review and was found to be effective for the indications in a FR notice published on 9/23/1970 (vol. 35, no. 185, pg. 14800-14801). Hyaluronidase is currently on FDA's list of drug shortages because it is no longer manufactured by Wyeth Laboratories. Ophthalmologists are turning to local compounding pharmacies to obtain hyaluronidase as an alternative to Wydase®. Because of the medical need for hyaluronidase and the unavailability of an approved commercial source of hyaluronidase, the Sponsor (Prima Pharm, Inc.(PPI)) is filing this new NDA (505 (b)(2)) for HYDASE™ (hyaluronidase Injection, 150 USP Units/mL), a similar preparation of hyaluronidase as Wydase® Stabized Solution. The Sponsor will rely on FDA's finding of safety and effectiveness for hyalunonidase.

Drug Substance and Drug Product

The bulk drug substance of hyaluronidase is purchased from [redacted]

[redacted] A Certificate of Origin (volume 1, attachment 2) was provided by [redacted] stating that the hyaluronidase was derived from bovine testes [redacted]

[redacted] The drug substance is then tested to meet established drug substance releasing specifications. The released drug substance is further processed into final drug product by [redacted]

HYDASE™ contains the same "concentration" (150 USP Units/mL) of active ingredient (a purified form of hyaluronidase from bovine testicular protein) as Wydase® Stabized Solution. The exact chemical structure of the enzyme is unknown. The Sponsor does not provide information on approximate molecular weight of the enzyme product and impurity profile. The inactive ingredient of the final product is slightly different from Wydase® Stabized Solution formulation in that no thimerosal (mercury derivative) is added as preservative.

Drug Product Composition

Ingredients	Amount
Hyaluronidase	150 USP unit/mL
Sodium Chloride	8.5 mg/mL
Edetate Disodium	1 mg/mL
Calcium Chloride	0.4 mg/mL
Momobasic Sodium Phosphate	[redacted]
Sodium Hydorxide	pH
Water	QS to 100 mL
[redacted]	[redacted]

The USP hyaluronidase units are equivalent to the turbidity-reducing (TR) unit and to the International Unit.

Waiver Request

The current NDA submission contains no *in vivo* bioavailability information. The Sponsor (PPI) is requesting a waiver of *in vivo* bioavailability/bioequivalence studies based on criteria set in 21CFR320.22(b) in that being a

parenteral solution intended solely for injection, the bioavailability of Hyalase® is self-evident. In addition they claim that their product is a "Me Too" formulation of Wydase® product.

In fact, HYDASE™ does not meet all the requirements of 21CFR320.22(b) because HYDASE™ contains the same active ingredient but slightly different inactive ingredients as Wydase® (an approved drug product) in that no thimerosal (as a preservative) is added in HYDASE™. Furthermore, HYDASE™ is a natural product extracted from bovine testicles by ⊂ ⊐ PPI (different manufacturers as Wydase®). Even the final product has the same enzyme activity ("concentration") of active ingredient as Wydase®, the impurity profile could be different leading to different inactive ingredients.

However, grounds for a waiver do exist in that the exact chemical structure of the enzyme is unknown and there is not a chemical assay for hyaluronidase. The analytical method for hyaluronidase is limited to USP enzyme activity tests. Considering these tests are themselves somewhat non-specific, *in vivo* bioavailability testing would be of little value for the characterization of this product.

Recommendation
Given the fact that this product is considered by the FDA to be a medically necessary drug and that it is indicated for only very special situations at low doses, a waiver of *in vivo* bioavailability studies under the "good cause" provisions of 21CFR320.22(e) can be granted.

SIGNATURE OF REVIEWER: _Lei Zhang_____ **SIGNATURE OF TEAM LEADER:** __E. Dennis Bashaw____	Date ___3/31/2004_____ Date ___3/31/2004_____
CC.: HFD # [880]; TL: [Dennis Bashaw]; **DD:** [John Lazor]; **DDDD** [Arzu Selen]	**Project Manager: Lori Gorski**_____ **Date** _____

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

/s/

Lei Zhang
3/31/04 03:58:05 PM
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Dennis Bashaw
3/31/04 04:06:41 PM
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