

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022519Orig1s000

CHEMISTRY REVIEW(S)

Memorandum:

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

Date: April 6, 2011

From: Gene W. Holbert, Ph.D. Review Chemist,
Branch IV
Division of New Drug Quality Assessment II/
ONDQA

Through: Moo-Jhong Rhee, Ph.D. Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 22-519

Subject: Final Recommendation

When CMC review #1 was submitted, there were two issues pending: one was the Establishment Evaluation, and the other was the issues of CMC labels and labeling. On March 31, 2011, the Office of Compliance issued an overall "Acceptable" recommendation for all facilities involved in the manufacture and testing of the drug substance and drug product (see the EER Summary Report, Attachment II),

Revised container label (see the Attachment I) and labeling sections ("Description" and "How Supplied") are acceptable from the CMC perspective.

Therefore, approval of this application is now recommended from the CMC perspective.

Attachment I

(b) (4)



Attachment II

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22519/000	Sponsor:	HORIZON PHARMA
Org. Code:	180		1033 SKOKIE BLVD STE 355
Priority:	4		NORTHBROOK, IL 60062
Stamp Date:	23-MAR-2010	Brand Name:	HZT-501
PDUFA Date:	23-JAN-2011	Estab. Name:	
Action Goal:		Generic Name:	IBUPROFEN
District Goal:	24-NOV-2010	Product Number; Dosage Form; Ingredient; Strengths	
			001; TABLET; IBUPROFEN; 800MG
			001; TABLET; FAMOTIDINE; 26.8MG
FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 301-796-3877
	G. HOLBERT	Review Chemist	301-796-1368
	M. KOWBLANSKY	Team Leader	301-796-1390

Overall Recommendation:	ACCEPTABLE	on 31-MAR-2011	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 28-MAR-2011	by EES_PROD		
	WITHHOLD	on 24-JAN-2011	by EES_PROD		
	WITHHOLD	on 13-JAN-2011	by EES_PROD		
	WITHHOLD	on 13-JAN-2011	by EES_PROD		

Establishment:	(b) (4)
DMF No:	(b) (4)
Responsibilities:	(b) (4)
Profile:	(b) (4)
Last Milestone:	(b) (4)
Milestone Date:	(b) (4)
Decision:	(b) (4)
Reason:	(b) (4)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

(b) (4)

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DMF No:

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Profile:

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Establishment:

DMF No:

Responsibilities:

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Milestone Date:

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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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Milestone Date:	
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Reason:	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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(b) (4)

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Profile:

Last Milestone:

Milestone Date:

Decision:

Reason:

Establishment:

DMF No:

Responsibilities:

Profile:

Last Milestone:

Milestone Date:

Decision:

Reason:

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/s/

GENE W HOLBERT
04/06/2011

MOO JHONG RHEE
04/07/2011
Chief, Branch IV

NDA 22-519

DUEXIS
(ibuprofen and famotidine)
800 mg/26.6 mg

Horizon Therapeutics, Inc.

Division of Gastroenterology Products

Gene W. Holbert, Ph.D.
(Lead CMC Review)

Yubing Tang, Ph.D.
(Manufacturing Process Review)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

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Chemistry Review Data Sheet

1. NDA 22-519
2. REVIEW #: 1
3. REVIEW DATE: 31-JAN-2011
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment (BL)

Amendment (QR)

Amendment (BH)

Amendment (QR)

Amendment (BH)

Amendment (QR)

Amendment (QR)

Document Date

23-MAR-2010

09-JUL-2010

12-AUG-2010

13-AUG-2010

24-SEP-2010

18-OCT-2010

08-FEB-2011

15-FEB-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Horizon Therapeutics, Inc.
Address: 1033 Skokie Boulevard, Suite 355
Northbrook, IL 60062

Representative: Timothy P. Walbert
President and Chief Executive Officer
Telephone: (224) 383-3009

As of April 1, 2010, the applicant has merged with the Swiss company Nitec Pharma AG to form a new firm, Horizon Pharma, Inc.

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: DUEXIS (proposed)
b) Non-Proprietary Name (USAN): Ibuprofen and famotidine
c) Code Name/#: HZT-501
d) Chem. Type/Submission Priority:
- Chem. Type: 4
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-inflammatory/antiulcerative

11. DOSAGE FORM: Tablet

CODE: 500

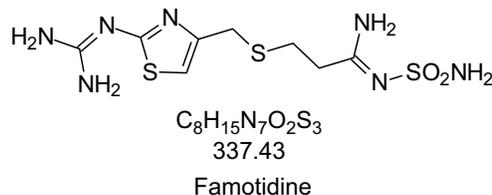
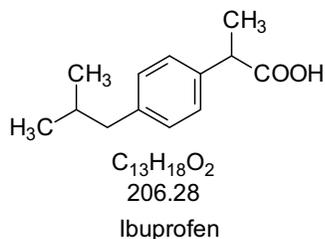
12. STRENGTH/POTENCY: 800 mg ibuprofen/26.6 mg famotidine

13. ROUTE OF ADMINISTRATION: Oral

CODE: 001

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product Form Completed Not a SPOTS product

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



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Ibuprofen	3	Adequate	18 FEB 2009 S. Dhanesar	LOA: 06 JUL 2009
	II	(b) (4)	(b) (4)	3	Adequate	23 APR 2010 G. Holbert	LOA: 06 JUL 2009
	II	(b) (4)	Famotidine	3	Adequate	08 SEP 2009 K. Bernard	LOA: 16 JUN 2009
	IV	(b) (4)	(b) (4)	3	Adequate	01 NOV 2005 S. Pope	LOA: 15 JUN 2009
	IV	(b) (4)	(b) (4)	1	Adequate	16 APR 2010 G. Holbert	LOA: 16 JUN 2009
	III	(b) (4)	(b) (4)	3	Adequate	15 SEP 2000 D. Kline	LOA: 21 JUL 2009
	III	(b) (4)	(b) (4)	3	Adequate	06 DEC 2004 R. Madurawe	LOA: 06 AUG 2009
	III	(b) (4)	(b) (4)	3	Adequate	20 APR 2004 S. Pope	LOA: 18 SEP 2009
	III	(b) (4)	(b) (4)	3	Adequate	27 JUL 2004 S. Pope	LOA: 21 JUL 2009
	III	(b) (4)	(b) (4)	3	Adequate	25 NOV 1997 G. Kang	LOA: 06 AUG 2009
	III	(b) (4)	(b) (4)	3	Adequate	20 AUG 2007 R. Agarwal	LOA: 15 SEP 2009
	III	(b) (4)	(b) (4)	3	Adequate	30 JAN 2007 A. Shaw	LOA: 17 JUL 2009

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT
IND

APPLICATION NUMBER
72,116

DESCRIPTION
HZT-501 (ibuprofen and famotidine) tablets

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	REVIEW DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	24-JAN-2011	A. Inyard
Pharmacology/Toxicology	N/A		
Biopharmaceutics	Issues resolved in teleconference 14-FEB-2011	17-FEB-2011	H. Mahayni
LNC	N/A		
Methods Validation	N/A		
DMEPA	Revision of presentation of strength and other items; pending	22-NOV-2010	Y. Maslov
EA	Categorical exclusion	07-DEC-2010	G. Holbert
Microbiology	N/A		

The Chemistry Review for NDA 22-519

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity and quality of the drug product. However, labeling issues are still pending. A site recommendation of “Withhold” has been issued by the Office of Compliance. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

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

None.

II. Summary of Chemistry Assessments

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

DUEXIS™ (ibuprofen and famotidine) Tablets are light blue, round, biconvex tablets debossed with “HZT” on one side.” DUEXIS is supplied as a tablet for oral administration and combines the nonsteroidal anti-inflammatory agent, ibuprofen, and the histamine H₂-receptor antagonist, famotidine.

Each DUEXIS tablet contains ibuprofen, USP (800 mg) and famotidine, USP (26.6 mg) and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water, povidone, titanium dioxide, polyethylene glycol, polysorbate 80, polyvinyl alcohol, talc, FD&C Blue #2/Indigo Carmine Aluminum Lake and FD&C Blue #1/Brilliant Blue FDF Aluminum Lake. With the exception of the colorants all excipients are of compendial grade. The colorants meet applicable FDA requirements.

The product is packaged in 250-cc, white, opaque HDPE bottles with child-resistant (b) (4) closures and induction seal liners. Each bottle contains 90 tablets.

DUEXIS™ Tablets are manufactured by Pharmaceuticals International, Inc. (Pii), Hunt Valley, MD.

DUEXIS is an immediate release (b) (4) formulation containing 800 mg of ibuprofen, USP and 26.6 mg of famotidine, USP. (b) (4)

Executive Summary Section

(b) (4)

There were some initial concerns about the adequacy of the manufacturing process. (b) (4)

(b) (4)

These and other modifications to the manufacturing equipment have minimized the probability of generating a defective HZT-501 tablet.

The drug product specification includes tests for Appearance, Ibuprofen Identity and Assay, Famotidine Identity and Assay, Related Substances for each active ingredient, Unspecified/Unknown Degradants related to each active ingredient, Total Degradants/Unspecified Peaks for each active ingredient, Uniformity of Dosage Units for each active ingredient, Water Content, Dissolution for each active ingredient and Microbiological Quality.

As amended, the application contains 12 months of long term stability data on three full scale registration batches and nine months of data on a fourth batch manufactured by Pharmaceuticals International, Inc. There were no significant changes in any of the lots stored at the long term, intermediate or accelerated condition. The applicant has proposed an 24 month expiration dating period when stored at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

Labeling negotiations are still in progress as of the date of this review. Manufacturing facilities inspections have been completed, and the Office of Compliance issued an overall recommendation of "Withhold" on January 24, 2011.

The active drug substances are ibuprofen and famotidine. Ibuprofen, a white to almost white powder or crystals with a characteristic odor, is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and anti-pyretic properties. Ibuprofen is supplied (b) (4)

Famotidine USP is a white to pale yellowish white crystalline powder with antiulcerative and histamine H₂ receptor antagonist properties. (b) (4)

Executive Summary Section

(b) (4)

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

DUEXIS is indicated for the reduction of the risk of development of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen. The recommended daily dose of DUEXIS is one tablet (800 mg ibuprofen and 26.6 mg famotidine) administered orally three time a day. DUEXIS may be taken without regard to food. The tablets should be swallowed whole.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls. The drug product specification is adequate for assuring consistent quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure the identity, strength, purity and quality of the drug product during the expiration dating period.

As of the date of this review, all manufacturing facilities do not have an "Acceptable" recommendation form the Office of Compliance, and labeling issues are not completely resolved.

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

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert, Ph.D. 31-JAN-2011
Yubing Tang, Ph.D. 03-MAR-2011
Moo-Jhong Rhee, Ph.D. 03-MAR-2011

C. cc:

Regulatory Project Manager: Todd Phillips
Product Quality Review Lead: Marie Kowblansky
Project Manager for Quality: Jeannie David

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/s/

GENE W HOLBERT
03/03/2011

YUBING TANG
03/03/2011

MOO JHONG RHEE
03/03/2011
Chief, Branch IV

DATE: 04-Aug.-2010

REFERENCE: NDA 22-519 Ibuprofen (800mg) /famotidine (26.6 mg) tablet.

FROM: Yubing Tang (yubing.tang@fda.hhs.gov, tel.: 301-796-2457) on behalf of CMC Review Team

THROUGH: Christine Moore, Ph.D.

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for Inspections (CFI) Memo

Horizon Therapeutics, Inc. (Horizon) is submitting this 505(b)(2) original New Drug Application (NDA) for HZT-501 (ibuprofen and famotidine) tablets for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal (GI) ulcers in patients who require use of ibuprofen.

HZT-501 is a fixed-dose combination, immediate release, solid oral dosage form containing 800 mg of ibuprofen and 26.6 mg of famotidine. One tablet of HZT-501 is administered orally three times per day (TID) without regard to food. The HZT-501 drug product is a (b) (4) formulation, (b) (4)

(b) (4) The diagram of the (b) (4) formulation of HZT-501 is shown below.

(b) (4)

(b) (4)

The manufacturing site below is responsible for drug product manufacturing and drug product release and stability testing.

Pharmaceuticals International, Inc. (Pii)
10819 Gilroy Road
Hunt Valley, MD 21031
CFN No.: 1124535

This memo includes:

- An overview of drug product manufacturing
- Discussion of QbD elements incorporated in DP development
- Reviewer's assessment of risk
- CMC perspective on areas of consideration for pre-approval and follow-up inspections

Overview of DP manufacturing

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

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/s/

DON L HENRY
08/16/2010

YUBING TANG
08/16/2010

MOO JHONG RHEE
08/16/2010
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 22-519
Applicant: Horizon Therapeutics
Stamp Date: 3/23/2010
Review Date: 6/14/2010
PDUFA Date: 1/23/2010
Filing Meeting: 5/3/2010
Proposed Trademark: (b) (4)
Established Name: ibuprofen and famotidine
Dosage Form: tablets
Route of Administration: oral
Indication: Reduce risk of ibuprofen-associated ulcers

PAL: Marie Kowblansky, PhD

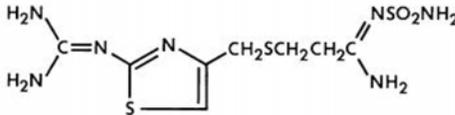
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

The proposed product, (b) (4) is an immediate release combination tablet, containing 800 mg ibuprofen and 26.6 mg of famotidine. It is intended for oral administration 3 times daily to reduce the risk of developing ibuprofen-associated gastrointestinal ulcers. The product has been developed under IND 72,116 and is being filed as a 505(b)(2) application, with Motrin (ibuprofen, NDA 17-463) and Pepcid (famotidine, NDA 19-462) as the reference listed drugs. Since the product contains currently approved drugs that have not been previously marketed in combination, this NDA is classified as a type 4 application under the Chemical Classification Code, MAPP 7500.3.

Drug Substances

Famotidine

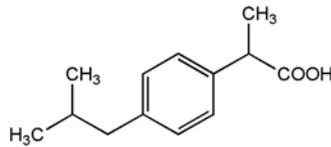


will be manufactured by (b) (4) to conform to all USP requirements. The specification includes all testing required in the USP monograph, with additional testing to control organic solvents, (b) (4), particle size, and bulk density. The material is (b) (4)

The applicant claims that the (b) (4) does not affect product performance, but the specified range is what is supplied by (b) (4). Since Phase 3 trials, bioequivalence trials, and stability studies were done with drug substance containing (b) (4), consideration should be given to revising the (b) (4) limits in the specification to reflect levels that were actually present in batches used in clinical studies. In addition, since the USP monograph requires only a TLC test for related compounds, at FDA's request, the applicant has added HPLC testing (with ICH limits) for related compounds.

Complete CMC information regarding the manufacture and characterization of this drug substance is referenced to (b) (4)

The racemic form of ibuprofen



will be used in the product. It will be supplied by (b) (4) which is a formulated form of the drug substance consisting of (b) (4)

The ibuprofen will conform to USP monograph requirements but the company has added residual solvent testing to the (b) (4) specification, as well as an HPLC assay for related substances, since the USP monograph only requires TLC testing for this purpose. (b) (4) are respectively referenced for complete CMC information regarding the ibuprofen and (b) (4)

Drug Product

The proposed commercial drug product is an immediate release (b) (4) formulation containing 26.6 mg of famotidine and 800 mg of ibuprofen, (b) (4)

(b) (4)

(b) (4) all of the excipients are tested and conform to their respective United States Pharmacopoeia (USP)/National Formulary (NF) monographs. The tablet will be debossed with the letters "HZT" on one side and packaged into 90-count containers.

(b) (4)

Consequently, bioequivalence and dissolution data have been submitted to link the commercial and phase 3 formulations. This linking information will be reviewed by ONDQA's Biopharm group.

The commercial manufacturing process for this product (b) (4)

(b) (4)

(b) (4) Registration lots (b) (4) that were manufactured with this equipment met all release specifications. However, two lots were found to have the following (b) (4) (as described by the applicant):

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

(b) (4)

(b) (4)

The commercial manufacturing process was evaluated from a design space perspective, whereby process parameters were evaluated for impact on overall product quality. However, the design space has not been well defined since interactions among parameters were only evaluated within unit operations (b) (4) but not between unit operations. The design of experiment studies (DOE) were performed within the individual unit operations in the process and then in step-wise fashion (b) (4)

(b) (4) From the DOE studies, the applicant has “concluded that the proposed commercial process was operating within the design space”, but despite the submitted DOE studies, the applicant has defined only fixed or narrow operating ranges for most of the manufacturing variables (b) (4)

(b) (4). The applicant relies on extensive standard in-process testing for control of the manufacturing process, not on information from the DOEs. The applicant does not ask for any regulatory relief based on the inclusion of DOE data in the submission.

The drug product will conform to the following specification

Test	Acceptance Criteria	method
Appearance	Blue oval tablet, debossed with “HZT”	visual
Identification ibuprofen/famotidine	Conforms to standard	HPLC

Test	Acceptance Criteria	method
Assay (HPLC) Ibuprofen famotidine	(b) (4) of label claim of label claim	HPLC with UV detection HPLC with UV detection
Impurities -- ibuprofen-related	(b) (4)	HPLC
Impurities – famotidine-related	(b) (4)	HPLC
Dissolution ibuprofen famotidine	(b) (4) (Q) at 30 min (Q) at 30 min	HPLC
Content uniformity ibuprofen famotidine	Conforms to USP Conforms to USP	USP<905> USP<905>
Water content	(b) (4)	
Microbial count: <i>Salmonell</i> , <i>E.coli</i> , <i>S. aureus</i> , <i>P aeruginosa</i> (performed on 1 lot per year)	absent	USP <62>

Impurity limits for ibuprofen-related impurities conform to ICH recommendations. Famotidine-related impurities exceed ICH limits, but are the same or lower than USP monograph requirements and are, therefore, considered acceptable. Dissolution testing, which is conducted at pH 7.2, involves simultaneous testing for ibuprofen and famotidine. Dissolution curves that are provided indicate that both drug substances are approximately (b) (4) dissolved in 10 – 15 minutes, suggesting that the dissolution acceptance criteria proposed above may be too liberal and may need to be tightened.

With a request for an (b) (4) expiration dating period, the applicant has submitted a very complicated stability data package that makes interpretation of the data difficult:

- Six months of long-term, intermediate, and accelerated stability data are provided for three registration batches of the product stored in the commercial packaging configuration. Additional stability data will be provided while the NDA is under review (FDA agreed to this at the end of phase 2 meeting).
- Three months of stability data are provided for one batch of tablets debossed with “HZT”, indicating that the primary stability batches are not debossed.

- (b) (4)
- (b) (4)

In accordance with 21 CFR 25.31(a), the firm requests a claim for categorical exclusion from an environmental assessment because approval of this New Drug Application will not increase the use of either active moiety.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Established name: The applicant proposes to use [REDACTED] (b) (4) as the established name. To be in accord with the format of established names used for other combination products, the established name should be: *(ibuprofen and famotidine) tablets*.

B. Critical issues for review

The following issues will require closer scrutiny during the course of the full review of this application:

- consideration should be given to revising the [REDACTED] (b) (4) limits in the famotidine specification to reflect levels that were actually present in batches used in clinical studies.
- the medical risks associated with [REDACTED] (b) (4) need to be evaluated.
- It is essential to determine if sufficient controls are in place, [REDACTED] (b) (4)
- In view of the numerous variations of the product on stability testing (as described above) a greater effort than usual will need to be expended to evaluate this data and thereby ensure acceptable stability for the commercial product.
- A reviewer should be assigned to evaluate the DOE information.

This NDA has been assigned to Houda Mahayni, Ph.D. for biopharmaceutics review.

C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

6/15/2010
Date

Moo-Jhong Rhee, PhD
Branch Chief

Manufacturing Sites

Famotidine

Facility Name and Address	Responsibility
(b) (4)	Manufacturing, release testing, storage and distribution

Ibuprofen

Facility Name and Address	Responsibility
(b) (4)	Ibuprofen manufacturing, including release testing and storage
(b) (4)	

FEI = FDA Establishment Identifier

Drug product:

Manufacturer Information	Operations
(b) (4)	Incoming materials and drug product release microbiological testing
(b) (4)	
Pharmaceutics International, Inc. (Pii) 10819 Gilroy Road Hunt Valley, MD 21031 FEI No. 1124535 QA Contacts: Kim Potter or Alex McClung Tel: (410) 584-0001 Email: kpotter@pharm-int.com ameclung@pharm-int.com	Incoming materials testing, drug product manufacturing, and drug product release and stability testing
(b) (4)	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

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/s/

MARIE KOWBLANSKY
06/15/2010

MOO JHONG RHEE
06/16/2010
Chief, Branch IV

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2
FILING CHECKLIST

NDA 22-519

NDA Number: 22-519 **Supplement Number and Type:** original **Established/Proper Name:** Ibuprofen and famotidine

Applicant: Horizon Therapeutics **Letter Date:** March 23, 2010 **Stamp Date:**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		√	Referenced to DMFs
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to DMFs
14.	Does the section contain information regarding the characterization of the DS?		√	Referenced to DMFs
15.	Does the section contain controls for the DS?		√	Referenced to DMFs
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to DMFs
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		Phase 3 and commercial formulation are different. Bioequivalence and dissolution data are provided as linkage
23.	Have any biowaivers been requested?		√	Not needed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		√	Although no separate validation package has been submitted, there appears to be sufficient methods validation information in the body of the submission

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not needed

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2		(b) (4)		
(b) (4)	2		(b) (4)		
(b) (4)	2		(b) (4)		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		√	No issues for inclusion in the 74-day letter

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
 CMC Lead
 Division of Pre-Marketing Assessment #2
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Branch Chief
 Division of Pre-Marketing Assessment #2
 Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

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/s/

MARIE KOWBLANSKY
05/20/2010

MOO JHONG RHEE
05/20/2010
Chief, Branch IV