

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022519Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022519

SUPPL # N/A

HFD # 180

Trade Name Duexis

Generic Name ibuprofen and famotidine

Applicant Name Horizon Pharma, Inc.

Approval Date, If Known April 23, 2011

### 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) NDA

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

3 years

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?

No

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# 017463	Motrin (ibuprofen) tablet, 400mg, 600mg, 800mg
020418	Motrin (ibuprofen) tablet, 100mg
020476	Motrin (ibuprofen) oral suspension drops, 40 mg/mL
019842	Mortin (ibuprofen) oral suspension, 100 mg/5 mL
020135	Motrin (ibuprofen) chewable tablet
018197	IBU (ibuprofen) tablet
019784	IBU (ibuprofen) oral suspension
019012	Nuprin (ibuprofen) tablet
019833	Children's Advil (ibuprofen) oral suspension
020716	Vicoprofen (hydrocodone bitartrate and ibuprofen) tablet
022348	Caldolor (ibuprofen) Injection
021903	Neoprofen (ibuprofen lysine) Injection
021378	Combunox (ibuprofen and oxycodone hydrochloride) tablet
021587	Children's Advil Allergy Sinus (chlorpheniramine maleate, ibuprofen, pseudoephedrine hydrochloride) oral suspension
021441	Advil Allergy Sinus (chlorpheniramine maleate, ibuprofen, pseudoephedrine hydrochloride) tablet
021394	Advil PM (diphenhydramine citrate and ibuprofen) tablet
021393	Advil PM (diphenhydramine hydrochloride and ibuprofen) tablet
021472	Midol Liquid Gels (ibuprofen) capsule
020402	Advil Liquid Gels (ibuprofen) capsule
020603	Children's Motrin (ibuprofen) oral suspension drops
020812	Pediatric Advil (ibuprofen) oral suspension drops
021604	Children's Elixure (ibuprofen) oral suspension
020515	Children's Motrin (ibuprofen) oral suspension
020589	Children's Advil (ibuprofen) oral suspension
020601	Junior Strength Motrin (ibuprofen) chewable tablet
020944	Children's Advil (ibuprofen) chewable tablet

	019012	Motrin IB (ibuprofen) tablet
	020602	Junior Strength Motrin (ibuprofen) tablet
	020267	Junior Strength Advil (ibuprofen) tablet
	018989	Advil (ibuprofen) tablet
	022565	Advil Congestion Relief (ibuprofen and phenylephrine hydrochloride) tablet
	021374	Advil Cold and Sinus (ibuprofen and pseudoephedrine hydrochloride) capsule
	021128	Children's Motrin Cold (ibuprofen and pseudoephedrine hydrochloride) oral suspension
	021373	Children's Advil Cold (ibuprofen and pseudoephedrine hydrochloride) oral suspension
	019899	SINE-AID IB (ibuprofen and pseudoephedrine hydrochloride) tablet
	019771	Advil Cold and Sinus (ibuprofen and pseudoephedrine hydrochloride) tablet
NDA#	019462	Pepcid (famotidine) tablet
	020249	Pepcid Preservative Free in Plastic Container (famotidine) Injection
	019510	Pepcid (famotidine) Injection
	020801	Pepcid AC (famotidine) chewable tablet
	020752	Pepcid RPD (famotidine) orally disintegrating tablet
	021712	Fluxid (famotidine) orally disintegrating tablet
	019527	Pepcid (famotidine) oral suspension
	020958	Pepcid Complete (calcium carbonate, famotidine, magnesium hydroxide) chewable tablet
	020325	Pepcid AC (famotidine) tablet
	020902	Pepcid AC Geltab (famotidine) tablet

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:

N/A

(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:

N/A

(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:

N/A

(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:

HZ-CA-301: A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZT-501 in Subjects Requiring NSAID Treatment

HZ-CA-303: A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZT-501 in Subjects Requiring NSAID Treatment

HZ-CA-304: Double-Blind Follow On Safety Study of HZT-501 in Subject Who Have Completed Participation in Horizon Protocol HZ-CA-301 or Horizon Protocol HZ-CA-303

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:

N/A

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

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

HZ-CA-301: A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZT-501 in Subjects Requiring NSAID Treatment

HZ-CA-303: A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZT-501 in Subjects Requiring NSAID Treatment

HZ-CA-304: Double-Blind Follow On Safety Study of HZT-501 in Subject Who Have Completed Participation in Horizon Protocol HZ-CA-301 or Horizon Protocol HZ-CA-303

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !



IND # 072116      YES       !  
! NO   
! Explain:

Investigation #2  
IND # 072116      YES       !  
! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES       !  
! NO   
Explain:      ! Explain:

Investigation #2  
YES       !  
! NO   
Explain:      ! 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: Jagjit Grewal, M.P.H.  
Title: Senior Regulatory Health Project Manager  
Date: 4/21/11

Name of Office/Division Director signing form: Donna Griebel, M.D.  
Title: Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
04/22/2011

DONNA J GRIEBEL  
04/23/2011

Organization: DGP  
 Appl Type No: NDA 22519  
 Submission Type #: ORIG - 1

Product Name: HZT-501  
 Applicant: HORIZON PHARMA INC  
 Submission Status: PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level	Submission Indication
3/23/2010	TABLET	N	3/23/2010	1/23/2011	TYPE 4	RISK REDUCTION OF DEVELOPMENT OF ULCERS

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
928	DEFERRED	YEARS	2	16	PRODUCT IS READY FOR APPROVAL IN ADULTS	STUDIES IN CHILDREN UNDER THE AGE OF 2 ARE IMPOSSIBLE OR HIGHLY IMPRACTICAL GIVEN LOW INCIDENCE OF JIA IN CHILDREN LESS THAN 2 YEARS OF AGE.	2/27/2015
928	WAIVED	YEARS	0	2	NECESSARY STUDIES ARE NOT FEASIBLE	LOW INCIDENCE OF JIA IN CHILDREN LESS THAN 2 YEARS OF AGE AND INTERMITTENT, SHORT-TERM USE (I.E., LESS THAN 5-10 DAYS) IS NOT LIKELY TO LEAD TO IBUPROFEN-ASSOCIATED, UPPER GASTROINTESTINAL ULCERS.	

**1.3.3 Debarment Certification**

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



\_\_\_\_\_  
Timothy P. Walbert  
President and Chief Executive Officer  
Horizon Therapeutics, Inc.

11/30/09

\_\_\_\_\_  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022519 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Duexis Established/Proper Name: ibuprofen and famotidine Dosage Form: Fixed-dose combination tablet		Applicant: Horizon Pharma, Inc. Agent for Applicant (if applicable): NA
RPM: Jagjit Grewal/Todd Phillips		Division: Gastroenterology and Inborn Errors Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Motrin (ibuprofen) / NDA 017463</p> <p>Pepcid (famotidine) / NDA 019462</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>NDA 022519 provides for a new fixed-dose combination tablet of ibuprofen and famotidine.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 4/22/11</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 23, 2011</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>          Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified



- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, 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 the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>April 29, 2011</p>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s): Approval – April 23, 2011</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>April 22, 2011</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>March 23, 2010</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>N017463 Motrin (ibuprofen): 9/10/07 N019462 Pepcid (famotidine): 3/23/10</p>

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/14/10

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	April 22, 2011
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	March 23, 2010
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	N017463 Motrin (ibuprofen): 9/10/07
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	March 29, 2011
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Conditionally acceptable letter: October 7, 2010 Non-acceptability letter: May 24, 2010  Final review completed: March 9, 2011 Conditionally acceptable review: October 7, 2010 Non-acceptability review: May 24, 2010
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM May 18, 2010 <input checked="" type="checkbox"/> DMEPA November 22, 2010 <input checked="" type="checkbox"/> DRISK March 23, 2011 <input checked="" type="checkbox"/> DDMAC March 22, 2011 <input type="checkbox"/> OSE/DPV <input checked="" type="checkbox"/> Other reviews SEALD: April 22, 2011
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	RPM FR: May 20, 2010
❖ 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2) April 23, 2011
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>December 8, 2010</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 5/14/10

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	April 22, 2011; April 22, 2011; April 21, 2011; April 21, 2011; April 20, 2011; April 20, 2011; April 15, 2011; April 14, 2011; April 6, 2011; April 4, 2011; March 28, 2011; March 17, 2011; January 14, 2011; December 17, 2010; December 7, 2010; October 22, 2010; October 5, 2010; September 24, 2010; September 15, 2010; June 4, 2010; April 5, 2010
❖ Internal memoranda, telecons, etc.	February 14, 2011
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg December 17, 2009
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg March 18, 2008
• Other milestone meetings (Pre-IND)	May 18, 2006; June 13, 2005
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 23, 2011
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 22, 2011
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None April 22, 2011 (4 PMRs)
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	Co-signed clinical review 4/22/11
• Clinical review(s) ( <i>indicate date for each review</i> )	April 22, 2011; May 20, 2010
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

Version: 5/14/10

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See clinical review page 14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None PMHS December 14, 2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested April 8, 2011 DSI Letters to Investigators: March 23, 2011 March 14, 2011 March 2, 2011 February 17, 2011 January 14, 2011
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 22, 2011 co-signed primary review 3/28/11
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 28, 2011; May 13, 2010
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None co-signed primary reviews 4/28/11; 4/22/11; 3/1/11
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 28, 2011 April 22, 2011 March 1, 2011 May 12, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None March 30, 2011 February 25, 2011

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None co-signed primary review 12/7/10
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None December 7, 2010 April 29, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None co-signed primary review 3/3/11
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Product Quality Review: April 7, 2011 March 3, 2011 August 16, 2010 June 16, 2010 May 20, 2010  Biopharmaceutics Review: February 24, 2011
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	December 7, 2010
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: March 31, 2011 (see ONDQA review 4/7/11) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

## Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



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/s/  
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JAGJIT S GREWAL  
04/29/2011

**Grewal, Jagjit**

---

**From:** Jeff Sherman [JSherman@horizonpharma.com]  
**Sent:** Friday, April 22, 2011 1:09 PM  
**To:** Grewal, Jagjit; Tim Walbert; (b) (4) Amy Grahn  
**Subject:** RE: NDA 022519 - FDA revised PI label  
**Importance:** High  
**Attachments:** NDA 22519 - FDA revised PI label 4-22-11\_rev.doc

Thank you Jagjit for the alert. The revisions are acceptable to Horizon. The NDC number is 75987-010-03 and has been inserted into the attachment.

---

Jeffrey W. Sherman, MD, FACP  
Chief Medical Officer  
Executive Vice President, Development  
and Regulatory Affairs

Horizon Pharma, Inc.  
1033 Skokie Blvd, Suite 355  
Northbrook, IL 60062

Office Phone: (224) 383-3000  
Direct Phone: (224) 383-3011  
Cell Phone: (847) 525-8678  
eFax: (847) 939-1576  
E-Mail: jsherman@horizonpharma.com

Website: [www.horizonpharma.com](http://www.horizonpharma.com)

---

**From:** Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]  
**Sent:** Friday, April 22, 2011 12:02 PM  
**To:** Tim Walbert; (b) (4) Jeff Sherman; Amy Grahn  
**Cc:** Grewal, Jagjit  
**Subject:** RE: NDA 022519 - FDA revised PI label

Hello Mr. Walbert,

Upon further review of the package insert label, FDA has additional revisions to conform with the Physician Labeling Rule (PLR) format. Please review the attached revisions and respond with your concurrence.

Please note comment "A2" in the Full Prescribing Information, section 16 "HOW SUPPLIED/STORAGE AND HANDLING."

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone: (301) 796-0846*  
*Fax: (301) 796-9904*  
*Email: Jagjit.Grewal@fda.hhs.gov*

---

**From:** Tim Walbert [mailto:TWalbert@horizonpharma.com]  
**Sent:** Friday, April 22, 2011 11:09 AM  
**To:** Grewal, Jagjit; (b) (4) Jeff Sherman  
**Cc:** Amy Grahn  
**Subject:** RE: NDA 022519 - FDA revised PI label, Med Guide, and PREA PMR dates  
Gagjit,

Confirming Horizon accepts all documents and the PREA.

Best regards,

Tim

---

**Timothy P. Walbert**  
Chairman, President and Chief Executive Officer

*Horizon Pharma, Inc.*  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

(224) 383-3009 - office  
(847) 772-0050 - cell  
(847) 572-1372 - fax  
twalbert@horizonpharma.com

twitter - @horizonpharmceo  
web - www.horizonpharma.com

---

**From:** Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]  
**Sent:** Friday, April 22, 2011 9:59 AM  
**To:** (b) (4) Tim Walbert; Jeff Sherman  
**Cc:** Grewal, Jagjit  
**Subject:** NDA 022519 - FDA revised PI label, Med Guide, and PREA PMR dates

Good Morning,

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to your email correspondences dated April 21, 2011 proposing revisions to the package insert label and Medication Guide.

Please find attached FDA revisions to the proposed package insert label and Medication Guide.

In addition, we have reviewed your submission dated April 21, 2011 which proposed milestone dates for the required pediatric postmarketing studies under PREA. We have revised the milestone dates as follows:

1. Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.

Final Protocol Submission: July 2013  
Study Completion Date: July 2015  
Final Report Submission: March 2016

2. A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as  $C_T$ ,  $C_{max}$ ,  $T_{max}$ ,  $AUC$ ,  $T_{1/2}$ , clearance, and  $Vd_{ss}$ , as applicable.

Final Protocol Submission: July 2016  
Study Completion Date: December 2016

Final Report Submission: March 2017

3. A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.

Final Protocol Submission: October 2011

Study Completion Date: October 2013

Final Report Submission: May 2014

4. A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 9 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 9 years, 11 months.

Final Protocol Submission: January 2016

Study Completion Date: January 2018

Final Report Submission: July 2018

Please review the attached labels and revisions to the PREA studies milestone dates and provide your response today (4/22/11) by 1:00PM EST at latest.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)

18 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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/s/  
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JAGJIT S GREWAL  
04/22/2011

**Grewal, Jagjit**

---

**From:** Grewal, Jagjit  
**Sent:** Thursday, April 21, 2011 2:35 PM  
**To:** (b) (4) Tim Walbert; 'Jeff Sherman'  
**Cc:** Grewal, Jagjit  
**Subject:** NDA 22519 - FDA PI label revisions 4-21-11  
**Importance:** High  
**Attachments:** N22519 - FDA revised PI label 4-21-11.doc

Good Afternoon~

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to your email correspondence dated April 20, 2011 proposing revisions to the package insert (PI) label. Final reference is made to the teleconference scheduled for this afternoon (4/21/11; 3:00PM EST) to discuss the PI label revisions.

Please find attached additional FDA edits on the PI label. Please refer to this most recent version of the PI label during this afternoon's scheduled teleconference discussion.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)

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/s/  
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JAGJIT S GREWAL  
04/21/2011

**Grewal, Jagjit**

---

**From:** Grewal, Jagjit  
**Sent:** Thursday, April 21, 2011 7:57 AM  
**To:** JSherman@horizonpharma.com; TWalbert@horizonpharma.com; (b) (4)  
**Cc:** Grewal, Jagjit  
**Subject:** NDA 022519 - revised PREA PMRs  
**Importance:** High

Good Morning,

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to your submission dated April 14, 2011 providing milestone dates for the PREA postmarketing requirements (PMRs).

We have reviewed your submission and agree with the milestone dates provided for the first 2 PREA PMRs: development of an age-appropriate formulation and a PK study of a new formulation of ibuprofen/famotidine in healthy human subjects.

Per discussion with Dr. Sherman yesterday, it was noted that FDA does not accept (b) (4). Dr. Sherman indicated that it would be challenging for the sponsor to meet the proposed milestone dates for this study if the original age range (2 years to 16 years, 11 months) was maintained due to the need for development of an age-appropriate formulation for younger children, and that additional time may be needed to conduct a study in children less than 10 years of age.

In consideration of these points, FDA is proposing the following revisions to the PK and safety study PREA PMR #3.

**PMR #3:** A study to evaluate the pharmacokinetics (PK) and safety of an age-appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 10 years of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 10 years.

**PMR #4:** A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.

Please provide milestone dates for these PMRs to include the final protocol submission date, study completion date, and final report submission date. Note that PREA PMRs #1 and #2 (development of an age-appropriate formulation and a PK study of a new formulation of ibuprofen/famotidine in healthy human subjects) will remain as sent to you in our correspondence dated March 17, 2011 and will include the milestone dates you provided on April 14, 2011.

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone: (301) 796-0846*

*Fax: (301) 796-9904*

*Email: Jagjit.Grewal@fda.hhs.gov*



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/s/  
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JAGJIT S GREWAL  
04/21/2011

**Grewal, Jagjit**

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**From:** Grewal, Jagjit  
**Sent:** Wednesday, April 20, 2011 5:02 PM  
**To:** (b) (4) TWalbert@horizonpharma.com; JSherman@horizonpharma.com  
**Cc:** Grewal, Jagjit  
**Subject:** NDA 022519 - FDA PI revisions  
**Importance:** High  
**Attachments:** FDA revised PI label 4-20-11.doc

Good Afternoon,

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to the teleconference discussion held this afternoon between FDA and Horizon Pharma to discuss revisions to the proposed package insert (PI) label.

As agreed at during the teleconference, please find FDA's proposed revisions to the package insert label. Please note that our additional edits are limited to the text of section 1 Indications and Usage, section 8.5 Geriatric Use, and section 14 Clinical Studies. Revisions to the tables per the teleconference discussion are not incorporate in the attached proposed PI label.

We look forward to receiving your labeling response later today. I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)

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JAGJIT S GREWAL  
04/20/2011

**Grewal, Jagjit**

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**From:** Grewal, Jagjit  
**Sent:** Wednesday, April 20, 2011 12:47 PM  
**To:** (b) (4)  
**Cc:** TWalbert@horizonpharma.com; JSherman@horizonpharma.com; Grewal, Jagjit  
**Subject:** NDA 022519 - FDA PI label revisions  
**Importance:** High  
**Attachments:** FDA proposed PI label edits 4-20-11.doc

Good Afternoon~

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to FDA's email correspondence dated April 6, 2011 providing edits to your proposed package insert (PI) label, the teleconference with Horizon held on April 7, 2011, and your submission dated April 14, 2011 containing additional revisions to the PI label and Medication Guide. Final reference is made to your submission dated April 18, 2011 which provided your response to the FDA's requests for information dated April 14, 2011 and April 15, 2011.

Please find attached additional FDA edits on the proposed package insert label. Please refer to this most recent version of the PI label during this afternoon's scheduled teleconference discussion.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)

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/s/  
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JAGJIT S GREWAL  
04/20/2011



NDA 022519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We also refer to the April 14, 2011 FDA correspondence, requesting additional information for shift table analyses.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For all shift table analyses requested in the April 14, 2011 FDA correspondence, provide the following additional information:

1. For all patients considered to have developed a change in serum creatinine defined as abnormal in your safety analyses provide the additional information:
  - a. The unique subject ID for each patient
  - b. A list of the patient's concomitant medications, including whether the patient was receiving angiotensin converting enzyme therapy, angiotensin receptor blocker therapy, and or diuretic therapy
  - c. The age of the patient at the time of enrollment
  - d. Whether the patient was  $\geq 65$  years of age, or  $< 65$  years of age at the time of enrollment
  - e. The date and visit number that the increase in serum creatinine occurred
2. For all patients considered to have developed a change in serum creatinine defined as an increase of 20% or more in your safety database, provide the additional information:
  - a. The unique subject ID for each patient

- b. A list of the patient's concomitant medications, including whether the patient was receiving angiotensin converting enzyme therapy, angiotensin receptor blocker therapy, and or diuretic therapy
  - c. The age of the patient at the time of enrollment
  - d. Whether the patient was  $\geq 65$  years of age, or  $< 65$  years of age at the time of enrollment
  - e. The date and visit number that the increase in serum creatinine occurred
3. Provide the date that you informed FDA that the statistical analysis plan for study HZ-CA-301 was changed from the Cochran-Mantel-Haenszel test to a life-table analysis.

Your response to this information request as well as the information request dated April 14, 2011 should be received no later than Monday morning, April 18, 2011.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
04/15/2011





NDA 022519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide shift tables for serum creatinine for all patients enrolled in study HZ-CA-301 and study HZ-CA-303. The table should be designed as follows:

Sample Table

		Study 301		Study 303		
Baseline	Post-Baseline	HZT-501	Ibuprofen	HZT-501	Ibuprofen	Total
Abnormal	Normal					
	Abnormal					
	Not Available					
	Total					

Create a similar table for those patients who had a normal baseline serum creatinine.

You should define what creatinine level was defined in your study as normal, and what change in creatinine was defined as abnormal and provide these definitions with the results.

2. Provide additional shift tables for serum creatinine for all patients enrolled in study HZ-CA-301 and study HZ-CA-303. The table should be designed as follows:

Sample Table

		Study 301		Study 303		
Baseline	Post-Baseline	HZT-501	Ibuprofen	HZT-501	Ibuprofen	Total
Serum creatinine $\leq$ 1.2 mg/dl	Serum creatinine $\leq$ 1.2 mg/dl					
	Increased by 20% or more					
	Not Available					
	Total					

Sample Table

		Study 301		Study 303		
Baseline	Post-Baseline	HZT-501	Ibuprofen	HZT-501	Ibuprofen	Total
Serum creatinine $\geq$ 1.2 mg/dl	Serum creatinine $\geq$ 1.2 mg/dl					
	Increased by 20% or more					
	Not Available					
	Total					

3. Provide data on all patients in both studies who developed a change in serum creatinine and their outcome (i.e., early termination or completed study, and if the patient was terminated early, the reason for early termination).
4. Provide the method used to determine baseline creatinine clearance for study 301 and 303.
5. Provide explanation/rationale for the increase in sample size for study HZ-CA-303 contained in the protocol amendment dated September 15, 2007.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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BRIAN K STRONGIN  
04/14/2011

**Grewal, Jagjit**

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**From:** Grewal, Jagjit  
**Sent:** Wednesday, April 06, 2011 2:27 PM  
**To:** [REDACTED] (b) (4)  
**Cc:** 'Jeff Sherman'; twalbert@horizon-pharma.com; Grewal, Jagjit  
**Subject:** NDA 022519 - FDA PI label revisions  
**Attachments:** N022519 Duexis - FDA revised PI label 4-6-11.doc

Good Afternoon All~

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to FDA's email correspondence dated 4/1/11 providing edits to your proposed package insert label and your response dated 4/4/11. Final reference is made to the teleconference scheduled for 4/7/11 to discuss the labeling revisions and PREA postmarketing requirements.

Please find attached additional FDA revisions on the proposed package insert label. Please refer to this most recent version of the PI label during tomorrow's teleconference discussion.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)

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JAGJIT S GREWAL  
04/06/2011

**Grewal, Jagjit**

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**From:** Grewal, Jagjit  
**Sent:** Friday, April 01, 2011 4:33 PM  
**To:** (b) (4)  
**Cc:** 'Jeff Sherman'; twalbert@horizon-pharma.com; Grewal, Jagjit  
**Subject:** NDA 022519 - FDA PI label and Med Guide revisions  
**Importance:** High  
**Attachments:** N022519 Duexis - FDA revised PI label 4-1-11.doc; N022519 Duexis - FDA revised Med Guide 4-1-11.doc

Hello (b) (4),

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to FDA's correspondence dated March 17, 2011 providing edits to your proposed labeling, and your response dated March 22, 2011.

Please find attached additional FDA revisions/comments on the proposed package insert label and Medication Guide. Please refer to these two documents during the teleconference scheduled for Monday, 4/4/11 to discuss the proposed labeling and PREA postmarketing requirements.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone: (301) 796-0846*

*Fax: (301) 796-9904*

*Email: Jagjit.Grewal@fda.hhs.gov*

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JAGJIT S GREWAL  
04/04/2011

**Grewal, Jagjit**

---

**From:** Grewal, Jagjit  
**Sent:** Monday, March 28, 2011 10:28 AM  
**To:** (b) (4)  
**Cc:** jsherman@horizon-pharma.com; twalbert@horizon-pharma.com; Grewal, Jagjit  
**Subject:** NDA 022519 - FDA container label comments  
**Importance:** High

Hello (b) (4)

Reference is made to your NDA 022519 HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg, dated March 23, 2010. We also refer to FDA's correspondence dated March 17, 2011 providing edits to your proposed labeling, and your response dated March 22, 2011.

Please find below additional FDA comments on your proposed container label:

1. To comply with 21CFR 208.24(d), relocate the Medication Guide Statement to the principle display panel, so that the statement appears in a prominent and conspicuous manner.
2. The proprietary name 'Duexis' should be presented in a consistent font type and size to improve the readability of the name. (b) (4)
3. Revise the presentation of the established name on the side panel to state the following:  
(Ibuprofen and Famotidine) Tablets

We request that you review our comments and submit a response to your application by close of business March 31, 2011.

I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.  
Senior Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/OND/ODE III  
Food & Drug Administration

*Phone:* (301) 796-0846

*Fax:* (301) 796-9904

*Email:* [Jagjit.Grewal@fda.hhs.gov](mailto:Jagjit.Grewal@fda.hhs.gov)



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/s/  
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JAGJIT S GREWAL  
03/28/2011



NDA 22519

**LABELING PMR/PMC DISCUSSION COMMENTS**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your March 23, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We also refer to our December 17, 2010, letter in which we notified you of our target date of March 25, 2011, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2008 THROUGH 2012."

On March 23, 2010, and July 9, 2010, we received your proposed labeling submissions to this application, and have proposed revisions to the package insert and container label which are included as an enclosure. In addition, we have enclosed our proposed Postmarketing Requirements for this application. We request that you review our proposals and submit a response to your application by close of business March 22, 2011.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Attachment:

- (1) DUEXIS Package Insert with FDA Comments (redline)
- (2) FDA Comments on Container Label
- (3) FDA Proposed Postmarketing Requirements

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/s/  
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RICHARD W ISHIHARA  
03/17/2011



Dear Dr. (b) (4)

The purpose of this correspondence is to inform you of a Warning Letter issued by the Food and Drug Administration on February 17, 2011 to Dr. Vaughn Mancha as a result of an inspection conducted between September 7 and September 23, 2010. The inspection was part of FDA's Bioresearch Monitoring Program, which is 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. Your Institutional Review Board was identified by Dr. Mancha as having responsibility for the review and approval of the one clinical study conducted by Dr. Mancha and cited in the Warning Letter. Enclosed for your information is a redacted copy of the Warning Letter.

Should you have any questions or concerns regarding this letter, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief, Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Bldg. 51, Rm. 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Enclosure: Redacted copy of Warning Letter issued to Dr. Vaughn Mancha on February 17, 2011.



**WARNING LETTER**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Vaughn H. Mancha, Jr., M.D.  
339 Saint Lukes Drive  
Montgomery, AL 36117

Ref: 11-HFD-45-02-03

Dear Dr. Mancha:

Between September 7 and September 23, 2010, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol (b) (4), entitled “(b) (4) (b) (4)”) of the investigational drug (b) (4) ((b) (4)), performed for (b) (4).

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated October 4, 2010, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

- 1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**
  - a. Protocol Section 9.5.3.1.5, Reporting and Documenting Serious Adverse Events, specified that “all Serious Adverse Events (SAEs) that occur beginning with the time of administration of the first dose of study medication and continuing until four weeks after administration of the final dose of study medication must be reported.” The protocol further specified that each SAE was to be reported to the Contact Research Organization (CRO) by telephone or via the electronic case report form (CRF) within 24 hours of becoming aware that a subject had experienced an

SAE, and that the investigator must report all SAEs and unexpected problems promptly to the IRB. Also, in Section 9.5.3.1.6, Follow-Up of Adverse Events, the protocol stated that “in the event of an unexplained, treatment-emergent, clinically significant abnormal laboratory test results [*sic*] or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed up until the values have returned to within the reference range or to baseline for that subject.”

(1) Subject #389204 had Week 8 laboratory tests collected on February 18, 2008, and the corresponding laboratory report that was faxed to your site on February 20, 2008, showed that the subject’s creatinine (CR) level measured 3.2 mg/dL. A progress note dated February 20, 2008, stated that subsequent to the review of the Week 8 visit laboratory report, the decision was made to terminate the subject from the study due to the elevated CR level. The progress note further stated that the subject will hold the study drug and proceed with the end of termination visit. The February 20 and 21, 2008, progress notes indicated that your site left messages for the subject to contact your office regarding the abnormal laboratory results. The subject did not contact your site until February 26, 2008, and the end of termination visit was scheduled for February 27, 2008. With respect to this SAE, we note the following:

- (a) In the time period between February 22 and February 26, 2008, when the subject called your site, you had no follow-up with the subject regarding the abnormal laboratory results. The subject’s last dose of study drug was on February 26, 2008.
- (b) You did not report the SAE of acute renal failure to the CRO until February 27, 2008. This was not within the 24-hour reporting period required by the protocol. In addition, the report to the CRO stated that the onset of the SAE and the date your staff was notified of the SAE was February 26, 2008. This is contradictory to your progress note, which stated that your site became aware of the SAE on February 20, 2008.
- (c) Your site did not report the SAE to the IRB until February 27, 2008, even though your progress note indicated that your site was aware of the SAE on February 20, 2008.

You stated that contact was made with the subject immediately by phone message, and that final verbal contact was made within 6 days. You further stated that instructions regarding study medication could not be left on phone message because it would violate HIPAA regulations. To prevent the recurrence of this finding, you indicated that when critical laboratory values are returned for a subject, the subject would be called immediately to report the values, and that the subject would be instructed on what to do regarding the investigational product. You further indicated that if the subject is not reached,

you would leave messages and continue to call the subject daily, and also send a letter via (b) (4) to the subject's address to notify the subject.

Your response is unacceptable. We note that your site sent a Subject Medical Review Form dated June 19, 2008, to the CRO, stating that the "Subject had labs drawn on 20 Feb 2008. They were not accessed in a timely manner. Subject went into renal failure." Thus, your site acknowledged that this SAE was not handled properly. In addition, you provided no detail regarding corrective actions you will take to ensure that reporting of SAEs to the sponsor and to the IRB are within the protocol-specified timeframes. You also failed to describe corrective actions to ensure that the information provided to the sponsor regarding SAEs would be accurate and consistent with the source records.

- (2) Subject 389062 had samples collected on October 9, 2007, and the laboratory results were faxed to your site on October 10, 2007. Records indicate that you did not document your review of the laboratory results until April 22, 2008. Your delayed review of this subject's laboratory results is a violation of Protocol Section 9.5.3.1.6, Follow-up of Adverse Events. Specifically, since your review did not take place until over six months after you received the test results, you did not adequately determine contemporaneously whether the abnormal laboratory results reported were clinically significant and therefore were required to be repeated immediately and followed up until the values were returned to within the reference range or to the baseline for that subject. The fact that these particular samples may not have, in fact, indicated an adverse or serious adverse event is irrelevant because, if they had, they would not have been documented or followed through properly, since your review did not take place until over six months after you received the test results.

Your written response indicated that you originally signed the laboratory result page, crossed out the wrong date, and wrote "reviewed labs on 10/23/07, wrote wrong date." This notation was then initialed and dated "4/10/07." To prevent the recurrence of this finding, you indicated that as laboratory results are received by fax, they will be placed in a basket for the clinical investigator to review and date immediately. You further stated that the basket of faxes is checked regularly throughout the day, and the longest time between receiving the labs and reviewing them is 2 days, when labs are received during the weekend.

Your response is unacceptable. Your written response regarding the dating of the laboratory result could not be verified, because the laboratory report provided during the FDA inspection showed that for the laboratory specimens collected on October 9, 2007, there was only one signature, with a date of review of April 22, 2008. We further note that you provided no corrective actions concerning the review of laboratory reports received when you would not be available.



- b. Protocol Section 9.3.1, Inclusion Criteria, and Protocol Section 9.4.7, Prior and Concomitant Therapy, specified that subjects who had used a nonsteroidal anti-inflammatory drug (NSAID) within the 30 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 6 subjects (389058, 389069, 389080, 389090, 389143, and 389218) had used an NSAID within the 30 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, (b) (4), and in a protocol deviation list submitted to the IRB, you reported that Subjects 389040 and 389111 had taken an NSAID within the 30 days prior to study entry but were enrolled into the study.

Your written response stated that as the study involved two readily available over-the-counter (OTC) medications, it was your observation that subjects often took these medications not realizing that this was a protocol violation, despite your instructing the subject otherwise. You stated that you would work better in the future by asking the subject not to take any OTC medication without notifying you prior to taking it. You indicated that as a corrective action, all subjects would be instructed to bring all concomitant medications to each visit, where they will be reviewed for exclusionary medications, and that the clinical investigator will review the inclusion/exclusion criteria at randomization and will document that the subject is qualified to be randomized.

Your response is unacceptable. FDA's review of the records found that your site was aware that several subjects had taken NSAIDs within the 30 days prior to study entry, but your site continued to enroll the subjects into the study. Your response does not address how a similar situation would be handled in the future. In addition, the worksheet you provided as your corrective action provided no information as to the procedures you would use to verify that subjects met all protocol eligibility criteria.

- c. Protocol Section 9.4.7, Prior and Concomitant Therapy, and Protocol Section 9.3.2, Exclusion Criteria, Subsection 7, specified that subjects who used an acid suppressant agent within 14 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 4 subjects (389086, 389094, 389173, and 389234) had used an acid suppressant agent within 14 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that 4 other randomized subjects (389085, 389092, 389142, and 389247) had taken an acid suppressant agent within 14 days prior to study entry.

Your written response stated that you confirmed that Subjects 389173, 389142, 389092, 389094, and 389234 had used an acid suppressant agent within 14 days prior to study entry. For Subject 389086, you stated that the subject did not notify

your site that she was taking Nexium and Zantac, and this was discovered when her medical records were received from her primary care provider. For Subject 389085, you stated that the subject was prescribed Nexium and Pepcid AC by the primary care provider after the screening visit and prior to randomization, and this was not discovered until the subject had been randomized. You indicated that the corrective action for this was to have a review of the concomitant medications at every visit, and that the investigator would review the excluded medication list with all staff.

Your response is unacceptable. Your corrective actions provided no information as to how your site will verify medical records, if obtainable and received from the primary care provider, prior to enrolling and/or randomizing subjects into the study to verify the subject's concomitant medications. In addition, you provided no corrective actions regarding procedures you will utilize to elicit from subjects all the medications they are currently taking. You also provided no corrective actions or procedures you would utilize to better instruct subjects against taking protocol-specified, excluded medications.

- d. Protocol Section 9.5.3.4, Clinical Laboratory Tests, specified that at the screening visit, blood samples were to be collected from study subjects for on-site testing for serum *H. pylori*. Protocol Section 9.3.2, Exclusion Criteria, Subsection 6, further specified that subjects with a documented current *H. pylori* infection were ineligible for enrollment into the study. Source records indicated that at least 2 subjects (389127 and 389135) were enrolled into the study without documentation of a current negative *H. pylori* test at the screening visit.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that additional subjects, including but not limited to Subjects 389129, 389137, and 389142, were enrolled into the study without documentation of a current negative *H. pylori* test performed at the screening visit.

Your written response stated that this protocol violation was an isolated issue and that the clinical research coordinator (CRC) who inadvertently did not document the results was "re-educated." You also indicated that, as a corrective action, any in-house test to be performed will have the lot number, expiration date, and results documented in the source documents.

Your response is unacceptable. Specifically, your statement that the CRC inadvertently did not document the result implies that the CRC actually performed the testing, but did not record the results in the source records. According to the establishment inspection report, you informed FDA Investigator Smith that while observing this particular CRC's work, you noticed that she was not using any of the supplies needed for the *H. pylori* test but was writing on the source records that she had in fact conducted those tests. Documentation found at your site also stated that the CRC in question either did not conduct any *H. pylori* testing at the screening

visit, or that the testing was questionable because the supplies needed for the test were not used. You further informed FDA Investigator Smith that when you questioned the study coordinator about your discovery and suggested that she would have to undergo training and work under the supervision of other coordinators, she abruptly resigned. Therefore, FDA cannot confirm that the CRC in question was “re-educated,” as you stated in your written response.

- e. In addition to the above protocol violations, in written memos to file, Subject Medical Review Forms submitted to the CRO, and/or protocol deviations sent to the IRB, your site acknowledged numerous protocol deviations, including but not limited to lack of international normalized ratio (INR) testing at the screening visit for subjects on anticoagulant therapy (e.g., 389017 and 389085); dispensing incorrect test articles to subjects (e.g., 389013, 389041, and 389091); study visits not being scheduled according to the protocol (e.g., 389162 and 389040); and failure to conduct screening serum pregnancy tests (e.g., Subjects 389075 and 389211).

In your written response, you confirmed the findings noted above. Your corrective actions included (1) a commitment to reduce human error by having a better understanding of each protocol and all of its procedures, and by total adherence to the protocol; (2) creation of a source document appendix to allow a second coordinator to cross-reference the investigational product (IP) or kit number assigned by the interactive voice recognition system (IVRS) for a particular subject, so that two coordinators can verify that the correct IP is dispensed to the subject; (3) development of a worksheet entitled “Visit Schedule” that includes the projected dates and actual dates of each visit including +/- windows; and (4) development of a new source document to be used at the end of every visit, certifying that the investigator has reviewed the source documents in their entirety for accuracy and correct documentation.

While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here, and that increases our concerns over your approach to ensuring appropriate human subject protection.

**2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

- a. The screening visit source record for Subject 389137 had a signature which appeared to be that of sub-investigator, Dr. <sup>(b) (4)</sup>, documenting that he had performed a physical exam on October 11, 2007. Your records indicated, however, that Dr. <sup>(b) (4)</sup> confirmed that the signature on the screening visit source record was not his and denied performing the examination.

You provided no written response to address this finding.

- b. Source records indicated that Subject 389230 had a physical exam at the screening visit on December 18, 2007. However, you did not sign the source physical exam record until April 21, 2008.

Your written response indicated that the physical exam was done at the screening visit, but that you inadvertently forgot to fill out the source document. Your corrective action to prevent this finding was to have the investigator thoroughly document, sign, and date all of the physical exams in real time.

Your response is inadequate. You provided no information regarding procedures and/or training that you would require to ensure that documents are completed, signed, and dated at the time of the study visit.

- c. Records at your site are discrepant concerning which subject (i.e., 389198 or 389168) had the Week 24 visit out of window. Specifically, your site reported in the Subject Medical Review Form dated May 20, 2008, that Subject 389168 (randomization number 5168) had the Week 24 visit scheduled 3 weeks early. In the upper right-hand corner of this same form, there is a handwritten note stating “#389198.” According to the enrollment log, Subject 389168’s randomization number was not 5168; this randomization number belonged to Subject 389198. In the <sup>(b) (4)</sup> IVRS Deactivation worksheet, you again stated that Subject 389168’s Week 24 visit was out of window.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Sincerely yours,

*{See appended electronic signature page}*

Leslie K. Ball, M.D.  
Director  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LESLIE K BALL  
02/17/2011

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/s/  
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CONSTANCE LEWIN  
03/14/2011

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** February 14, 2011  
**TIME:** 12:00 1:00 pm EST  
**LOCATION:** WO BLD 22 / RM 5201  
**APPLICATION:** NDA 22519  
**DRUG NAME:** HZT-501 (ibuprofen/famotidine)  
**TYPE OF MEETING:** Teleconference

**SUBJECT:** Famotidine Dissolution Method Discussion with Horizon Pharma, Inc.

**FDA ATTENDEES:**

Patrick Marroum, PhD, Biopharmaceutics Lead, Office of New Drug Quality Assessment  
Houda Mahayni, RPh, PhD, Regulatory Review Scientist, Office of New Drug Quality Assessment  
Lynne Yao, MD, Medical Officer Team Leader, Division of Gastroenterology Products  
Ali Niak, MD, Medical Officer, Division of Gastroenterology Products  
Todd Phillips, PharmD, Regulatory Project Manager, Division of Gastroenterology Products

**EXTERNAL CONSTITUENT ATTENDEES:**

Horizon Pharma, Inc

Iain Duncan, Senior Vice President, Manufacturing Operations  
Amy Grahn, Senior Vice President, Clinical Development and Operations  
Jeffrey W. Sherman, M.D., FACP, Chief Medical Officer, Executive Vice President, Development and Regulatory Affairs  
Timothy P. Walbert, Chairman, President and Chief Executive Officer  
Cara Weyker, Vice President, Regulatory Quality and Compliance

Consultants for Horizon Pharma, Inc

(b) (4)



**DISCUSSION POINTS:**

On February 14, 2011, the Agency met with Horizon Pharma, Inc to discuss the Sponsor's February 8, 2011, response to the Agency's January 14, 2011, Information Request letter in which the Agency recommended the Sponsor tighten the famotidine dissolution acceptance criterion to Q (b) (4) at 30 minutes. The Sponsor and the Agency agreed to the following changes:

1. Famotidine dissolution acceptance criterion will be Q (b) (4) at 30 minutes.
2. (b) (4) dissolution testing is not required.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TODD D PHILLIPS  
03/09/2011

## REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM:

Todd Phillips, Regulatory Project Manager  
301-796-4857

CDER/OND/ODE III

Division of Gastroenterology Products

DATE  
March 9, 2011

IND NO.

NDA NO.  
022519

TYPE OF DOCUMENT  
Original NDA submission

DATE OF DOCUMENT  
March 23, 2010

NAME OF DRUG  
Duexis  
(ibuprofen/famotidine)  
Tablet

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
New Combination (non-type  
3)

DESIRED COMPLETION DATE  
March 25, 2011

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

The Division of Gastroenterology Products requests an OSE review of ibuprofen and famotidine post-marketing adverse event data; specifically, DGP would like a list of all post-marketing AEs that have been reported more than once and are not included in the most current ibuprofen and famotidine package inserts.

NDA 22519 was submitted electronically (EDR Location: <\\CDSESUB1\EVSPROD\NDA022519\0000>)

Reference ID: 2915735

SIGNATURE OF REQUESTER Todd Phillips	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TODD D PHILLIPS  
03/09/2011



Timothy P. Walbert  
Chairman, President and Chief Executive Officer  
Horizon Pharma, Inc.  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

The purpose of this correspondence is to inform you of a Warning Letter issued by the Food and Drug Administration on February 17, 2011 to Dr. Vaughn Mancha regarding his conduct of a study sponsored by Horizon Therapeutics, Inc. The Warning Letter was issued as a result of an inspection conducted between September 7 and September 23, 2010. The inspection was 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. Enclosed for your information is a redacted copy of the Warning Letter.

Should you have any questions or concerns regarding this letter, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief, Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Bldg. 51, Rm. 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Enclosure: Redacted copy of Warning Letter issued to Dr. Vaughn Mancha on February 17, 2011.



**WARNING LETTER**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Vaughn H. Mancha, Jr., M.D.  
339 Saint Lukes Drive  
Montgomery, AL 36117

Ref: 11-HFD-45-02-03

Dear Dr. Mancha:

Between September 7 and September 23, 2010, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol (b) (4), entitled “(b) (4) (b) (4)”) of the investigational drug (b) (4) ((b) (4)), performed for (b) (4).

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated October 4, 2010, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

- 1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**
  - a. Protocol Section 9.5.3.1.5, Reporting and Documenting Serious Adverse Events, specified that “all Serious Adverse Events (SAEs) that occur beginning with the time of administration of the first dose of study medication and continuing until four weeks after administration of the final dose of study medication must be reported.” The protocol further specified that each SAE was to be reported to the Contact Research Organization (CRO) by telephone or via the electronic case report form (CRF) within 24 hours of becoming aware that a subject had experienced an

SAE, and that the investigator must report all SAEs and unexpected problems promptly to the IRB. Also, in Section 9.5.3.1.6, Follow-Up of Adverse Events, the protocol stated that “in the event of an unexplained, treatment-emergent, clinically significant abnormal laboratory test results [*sic*] or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed up until the values have returned to within the reference range or to baseline for that subject.”

(1) Subject #389204 had Week 8 laboratory tests collected on February 18, 2008, and the corresponding laboratory report that was faxed to your site on February 20, 2008, showed that the subject’s creatinine (CR) level measured 3.2 mg/dL. A progress note dated February 20, 2008, stated that subsequent to the review of the Week 8 visit laboratory report, the decision was made to terminate the subject from the study due to the elevated CR level. The progress note further stated that the subject will hold the study drug and proceed with the end of termination visit. The February 20 and 21, 2008, progress notes indicated that your site left messages for the subject to contact your office regarding the abnormal laboratory results. The subject did not contact your site until February 26, 2008, and the end of termination visit was scheduled for February 27, 2008. With respect to this SAE, we note the following:

- (a) In the time period between February 22 and February 26, 2008, when the subject called your site, you had no follow-up with the subject regarding the abnormal laboratory results. The subject’s last dose of study drug was on February 26, 2008.
- (b) You did not report the SAE of acute renal failure to the CRO until February 27, 2008. This was not within the 24-hour reporting period required by the protocol. In addition, the report to the CRO stated that the onset of the SAE and the date your staff was notified of the SAE was February 26, 2008. This is contradictory to your progress note, which stated that your site became aware of the SAE on February 20, 2008.
- (c) Your site did not report the SAE to the IRB until February 27, 2008, even though your progress note indicated that your site was aware of the SAE on February 20, 2008.

You stated that contact was made with the subject immediately by phone message, and that final verbal contact was made within 6 days. You further stated that instructions regarding study medication could not be left on phone message because it would violate HIPAA regulations. To prevent the recurrence of this finding, you indicated that when critical laboratory values are returned for a subject, the subject would be called immediately to report the values, and that the subject would be instructed on what to do regarding the investigational product. You further indicated that if the subject is not reached,



you would leave messages and continue to call the subject daily, and also send a letter via (b) (4) to the subject's address to notify the subject.

Your response is unacceptable. We note that your site sent a Subject Medical Review Form dated June 19, 2008, to the CRO, stating that the "Subject had labs drawn on 20 Feb 2008. They were not accessed in a timely manner. Subject went into renal failure." Thus, your site acknowledged that this SAE was not handled properly. In addition, you provided no detail regarding corrective actions you will take to ensure that reporting of SAEs to the sponsor and to the IRB are within the protocol-specified timeframes. You also failed to describe corrective actions to ensure that the information provided to the sponsor regarding SAEs would be accurate and consistent with the source records.

- (2) Subject 389062 had samples collected on October 9, 2007, and the laboratory results were faxed to your site on October 10, 2007. Records indicate that you did not document your review of the laboratory results until April 22, 2008. Your delayed review of this subject's laboratory results is a violation of Protocol Section 9.5.3.1.6, Follow-up of Adverse Events. Specifically, since your review did not take place until over six months after you received the test results, you did not adequately determine contemporaneously whether the abnormal laboratory results reported were clinically significant and therefore were required to be repeated immediately and followed up until the values were returned to within the reference range or to the baseline for that subject. The fact that these particular samples may not have, in fact, indicated an adverse or serious adverse event is irrelevant because, if they had, they would not have been documented or followed through properly, since your review did not take place until over six months after you received the test results.

Your written response indicated that you originally signed the laboratory result page, crossed out the wrong date, and wrote "reviewed labs on 10/23/07, wrote wrong date." This notation was then initialed and dated "4/10/07." To prevent the recurrence of this finding, you indicated that as laboratory results are received by fax, they will be placed in a basket for the clinical investigator to review and date immediately. You further stated that the basket of faxes is checked regularly throughout the day, and the longest time between receiving the labs and reviewing them is 2 days, when labs are received during the weekend.

Your response is unacceptable. Your written response regarding the dating of the laboratory result could not be verified, because the laboratory report provided during the FDA inspection showed that for the laboratory specimens collected on October 9, 2007, there was only one signature, with a date of review of April 22, 2008. We further note that you provided no corrective actions concerning the review of laboratory reports received when you would not be available.

- b. Protocol Section 9.3.1, Inclusion Criteria, and Protocol Section 9.4.7, Prior and Concomitant Therapy, specified that subjects who had used a nonsteroidal anti-inflammatory drug (NSAID) within the 30 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 6 subjects (389058, 389069, 389080, 389090, 389143, and 389218) had used an NSAID within the 30 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, (b) (4), and in a protocol deviation list submitted to the IRB, you reported that Subjects 389040 and 389111 had taken an NSAID within the 30 days prior to study entry but were enrolled into the study.

Your written response stated that as the study involved two readily available over-the-counter (OTC) medications, it was your observation that subjects often took these medications not realizing that this was a protocol violation, despite your instructing the subject otherwise. You stated that you would work better in the future by asking the subject not to take any OTC medication without notifying you prior to taking it. You indicated that as a corrective action, all subjects would be instructed to bring all concomitant medications to each visit, where they will be reviewed for exclusionary medications, and that the clinical investigator will review the inclusion/exclusion criteria at randomization and will document that the subject is qualified to be randomized.

Your response is unacceptable. FDA's review of the records found that your site was aware that several subjects had taken NSAIDs within the 30 days prior to study entry, but your site continued to enroll the subjects into the study. Your response does not address how a similar situation would be handled in the future. In addition, the worksheet you provided as your corrective action provided no information as to the procedures you would use to verify that subjects met all protocol eligibility criteria.

- c. Protocol Section 9.4.7, Prior and Concomitant Therapy, and Protocol Section 9.3.2, Exclusion Criteria, Subsection 7, specified that subjects who used an acid suppressant agent within 14 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 4 subjects (389086, 389094, 389173, and 389234) had used an acid suppressant agent within 14 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that 4 other randomized subjects (389085, 389092, 389142, and 389247) had taken an acid suppressant agent within 14 days prior to study entry.

Your written response stated that you confirmed that Subjects 389173, 389142, 389092, 389094, and 389234 had used an acid suppressant agent within 14 days prior to study entry. For Subject 389086, you stated that the subject did not notify

your site that she was taking Nexium and Zantac, and this was discovered when her medical records were received from her primary care provider. For Subject 389085, you stated that the subject was prescribed Nexium and Pepcid AC by the primary care provider after the screening visit and prior to randomization, and this was not discovered until the subject had been randomized. You indicated that the corrective action for this was to have a review of the concomitant medications at every visit, and that the investigator would review the excluded medication list with all staff.

Your response is unacceptable. Your corrective actions provided no information as to how your site will verify medical records, if obtainable and received from the primary care provider, prior to enrolling and/or randomizing subjects into the study to verify the subject's concomitant medications. In addition, you provided no corrective actions regarding procedures you will utilize to elicit from subjects all the medications they are currently taking. You also provided no corrective actions or procedures you would utilize to better instruct subjects against taking protocol-specified, excluded medications.

- d. Protocol Section 9.5.3.4, Clinical Laboratory Tests, specified that at the screening visit, blood samples were to be collected from study subjects for on-site testing for serum *H. pylori*. Protocol Section 9.3.2, Exclusion Criteria, Subsection 6, further specified that subjects with a documented current *H. pylori* infection were ineligible for enrollment into the study. Source records indicated that at least 2 subjects (389127 and 389135) were enrolled into the study without documentation of a current negative *H. pylori* test at the screening visit.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that additional subjects, including but not limited to Subjects 389129, 389137, and 389142, were enrolled into the study without documentation of a current negative *H. pylori* test performed at the screening visit.

Your written response stated that this protocol violation was an isolated issue and that the clinical research coordinator (CRC) who inadvertently did not document the results was "re-educated." You also indicated that, as a corrective action, any in-house test to be performed will have the lot number, expiration date, and results documented in the source documents.

Your response is unacceptable. Specifically, your statement that the CRC inadvertently did not document the result implies that the CRC actually performed the testing, but did not record the results in the source records. According to the establishment inspection report, you informed FDA Investigator Smith that while observing this particular CRC's work, you noticed that she was not using any of the supplies needed for the *H. pylori* test but was writing on the source records that she had in fact conducted those tests. Documentation found at your site also stated that the CRC in question either did not conduct any *H. pylori* testing at the screening

visit, or that the testing was questionable because the supplies needed for the test were not used. You further informed FDA Investigator Smith that when you questioned the study coordinator about your discovery and suggested that she would have to undergo training and work under the supervision of other coordinators, she abruptly resigned. Therefore, FDA cannot confirm that the CRC in question was “re-educated,” as you stated in your written response.

- e. In addition to the above protocol violations, in written memos to file, Subject Medical Review Forms submitted to the CRO, and/or protocol deviations sent to the IRB, your site acknowledged numerous protocol deviations, including but not limited to lack of international normalized ratio (INR) testing at the screening visit for subjects on anticoagulant therapy (e.g., 389017 and 389085); dispensing incorrect test articles to subjects (e.g., 389013, 389041, and 389091); study visits not being scheduled according to the protocol (e.g., 389162 and 389040); and failure to conduct screening serum pregnancy tests (e.g., Subjects 389075 and 389211).

In your written response, you confirmed the findings noted above. Your corrective actions included (1) a commitment to reduce human error by having a better understanding of each protocol and all of its procedures, and by total adherence to the protocol; (2) creation of a source document appendix to allow a second coordinator to cross-reference the investigational product (IP) or kit number assigned by the interactive voice recognition system (IVRS) for a particular subject, so that two coordinators can verify that the correct IP is dispensed to the subject; (3) development of a worksheet entitled “Visit Schedule” that includes the projected dates and actual dates of each visit including +/- windows; and (4) development of a new source document to be used at the end of every visit, certifying that the investigator has reviewed the source documents in their entirety for accuracy and correct documentation.

While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here, and that increases our concerns over your approach to ensuring appropriate human subject protection.

**2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

- a. The screening visit source record for Subject 389137 had a signature which appeared to be that of sub-investigator, Dr. <sup>(b) (4)</sup>, documenting that he had performed a physical exam on October 11, 2007. Your records indicated, however, that Dr. <sup>(b) (4)</sup> confirmed that the signature on the screening visit source record was not his and denied performing the examination.

You provided no written response to address this finding.

- b. Source records indicated that Subject 389230 had a physical exam at the screening visit on December 18, 2007. However, you did not sign the source physical exam record until April 21, 2008.

Your written response indicated that the physical exam was done at the screening visit, but that you inadvertently forgot to fill out the source document. Your corrective action to prevent this finding was to have the investigator thoroughly document, sign, and date all of the physical exams in real time.

Your response is inadequate. You provided no information regarding procedures and/or training that you would require to ensure that documents are completed, signed, and dated at the time of the study visit.

- c. Records at your site are discrepant concerning which subject (i.e., 389198 or 389168) had the Week 24 visit out of window. Specifically, your site reported in the Subject Medical Review Form dated May 20, 2008, that Subject 389168 (randomization number 5168) had the Week 24 visit scheduled 3 weeks early. In the upper right-hand corner of this same form, there is a handwritten note stating “#389198.” According to the enrollment log, Subject 389168’s randomization number was not 5168; this randomization number belonged to Subject 389198. In the (b) (4) IVRS Deactivation worksheet, you again stated that Subject 389168’s Week 24 visit was out of window.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Sincerely yours,

*{See appended electronic signature page}*

Leslie K. Ball, M.D.  
Director  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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LESLIE K BALL  
02/17/2011

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/s/  
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CONSTANCE LEWIN  
03/02/2011





## WARNING LETTER

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Vaughn H. Mancha, Jr., M.D.  
339 Saint Lukes Drive  
Montgomery, AL 36117

Ref: 11-HFD-45-02-03

Dear Dr. Mancha:

Between September 7 and September 23, 2010, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol HZ-CA-303, entitled "A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZT-501 in Subjects Requiring NSAID Treatment") of the investigational drug HZT-501 (ibuprofen/famotidine), performed for Horizon Therapeutics, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated October 4, 2010, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

- 1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**
  - a. Protocol Section 9.5.3.1.5, Reporting and Documenting Serious Adverse Events, specified that "all Serious Adverse Events (SAEs) that occur beginning with the time of administration of the first dose of study medication and continuing until four weeks after administration of the final dose of study medication must be reported." The protocol further specified that each SAE was to be reported to the Contact Research Organization (CRO) by telephone or via the electronic case report form (CRF) within 24 hours of becoming aware that a subject had experienced an

SAE, and that the investigator must report all SAEs and unexpected problems promptly to the IRB. Also, in Section 9.5.3.1.6, Follow-Up of Adverse Events, the protocol stated that “in the event of an unexplained, treatment-emergent, clinically significant abnormal laboratory test results [*sic*] or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed up until the values have returned to within the reference range or to baseline for that subject.”

(1) Subject #389204 had Week 8 laboratory tests collected on February 18, 2008, and the corresponding laboratory report that was faxed to your site on February 20, 2008, showed that the subject’s creatinine (CR) level measured 3.2 mg/dL. A progress note dated February 20, 2008, stated that subsequent to the review of the Week 8 visit laboratory report, the decision was made to terminate the subject from the study due to the elevated CR level. The progress note further stated that the subject will hold the study drug and proceed with the end of termination visit. The February 20 and 21, 2008, progress notes indicated that your site left messages for the subject to contact your office regarding the abnormal laboratory results. The subject did not contact your site until February 26, 2008, and the end of termination visit was scheduled for February 27, 2008. With respect to this SAE, we note the following:

- (a) In the time period between February 22 and February 26, 2008, when the subject called your site, you had no follow-up with the subject regarding the abnormal laboratory results. The subject’s last dose of study drug was on February 26, 2008.
- (b) You did not report the SAE of acute renal failure to the CRO until February 27, 2008. This was not within the 24-hour reporting period required by the protocol. In addition, the report to the CRO stated that the onset of the SAE and the date your staff was notified of the SAE was February 26, 2008. This is contradictory to your progress note, which stated that your site became aware of the SAE on February 20, 2008.
- (c) Your site did not report the SAE to the IRB until February 27, 2008, even though your progress note indicated that your site was aware of the SAE on February 20, 2008.

You stated that contact was made with the subject immediately by phone message, and that final verbal contact was made within 6 days. You further stated that instructions regarding study medication could not be left on phone message because it would violate HIPAA regulations. To prevent the recurrence of this finding, you indicated that when critical laboratory values are returned for a subject, the subject would be called immediately to report the values, and that the subject would be instructed on what to do regarding the investigational product. You further indicated that if the subject is not reached,

you would leave messages and continue to call the subject daily, and also send a letter via (b) (4) to the subject's address to notify the subject.

Your response is unacceptable. We note that your site sent a Subject Medical Review Form dated June 19, 2008, to the CRO, stating that the "Subject had labs drawn on 20 Feb 2008. They were not accessed in a timely manner. Subject went into renal failure." Thus, your site acknowledged that this SAE was not handled properly. In addition, you provided no detail regarding corrective actions you will take to ensure that reporting of SAEs to the sponsor and to the IRB are within the protocol-specified timeframes. You also failed to describe corrective actions to ensure that the information provided to the sponsor regarding SAEs would be accurate and consistent with the source records.

- (2) Subject 389062 had samples collected on October 9, 2007, and the laboratory results were faxed to your site on October 10, 2007. Records indicate that you did not document your review of the laboratory results until April 22, 2008. Your delayed review of this subject's laboratory results is a violation of Protocol Section 9.5.3.1.6, Follow-up of Adverse Events. Specifically, since your review did not take place until over six months after you received the test results, you did not adequately determine contemporaneously whether the abnormal laboratory results reported were clinically significant and therefore were required to be repeated immediately and followed up until the values were returned to within the reference range or to the baseline for that subject. The fact that these particular samples may not have, in fact, indicated an adverse or serious adverse event is irrelevant because, if they had, they would not have been documented or followed through properly, since your review did not take place until over six months after you received the test results.

Your written response indicated that you originally signed the laboratory result page, crossed out the wrong date, and wrote "reviewed labs on 10/23/07, wrote wrong date." This notation was then initialed and dated "4/10/07." To prevent the recurrence of this finding, you indicated that as laboratory results are received by fax, they will be placed in a basket for the clinical investigator to review and date immediately. You further stated that the basket of faxes is checked regularly throughout the day, and the longest time between receiving the labs and reviewing them is 2 days, when labs are received during the weekend.

Your response is unacceptable. Your written response regarding the dating of the laboratory result could not be verified, because the laboratory report provided during the FDA inspection showed that for the laboratory specimens collected on October 9, 2007, there was only one signature, with a date of review of April 22, 2008. We further note that you provided no corrective actions concerning the review of laboratory reports received when you would not be available.

- b. Protocol Section 9.3.1, Inclusion Criteria, and Protocol Section 9.4.7, Prior and Concomitant Therapy, specified that subjects who had used a nonsteroidal anti-inflammatory drug (NSAID) within the 30 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 6 subjects (389058, 389069, 389080, 389090, 389143, and 389218) had used an NSAID within the 30 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, (b) (4), and in a protocol deviation list submitted to the IRB, you reported that Subjects 389040 and 389111 had taken an NSAID within the 30 days prior to study entry but were enrolled into the study.

Your written response stated that as the study involved two readily available over-the-counter (OTC) medications, it was your observation that subjects often took these medications not realizing that this was a protocol violation, despite your instructing the subject otherwise. You stated that you would work better in the future by asking the subject not to take any OTC medication without notifying you prior to taking it. You indicated that as a corrective action, all subjects would be instructed to bring all concomitant medications to each visit, where they will be reviewed for exclusionary medications, and that the clinical investigator will review the inclusion/exclusion criteria at randomization and will document that the subject is qualified to be randomized.

Your response is unacceptable. FDA's review of the records found that your site was aware that several subjects had taken NSAIDs within the 30 days prior to study entry, but your site continued to enroll the subjects into the study. Your response does not address how a similar situation would be handled in the future. In addition, the worksheet you provided as your corrective action provided no information as to the procedures you would use to verify that subjects met all protocol eligibility criteria.

- c. Protocol Section 9.4.7, Prior and Concomitant Therapy, and Protocol Section 9.3.2, Exclusion Criteria, Subsection 7, specified that subjects who used an acid suppressant agent within 14 days prior to study entry were ineligible for enrollment into the study. FDA's review of your source records indicated that 4 subjects (389086, 389094, 389173, and 389234) had used an acid suppressant agent within 14 days prior to study entry but were enrolled into the study.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that 4 other randomized subjects (389085, 389092, 389142, and 389247) had taken an acid suppressant agent within 14 days prior to study entry.

Your written response stated that you confirmed that Subjects 389173, 389142, 389092, 389094, and 389234 had used an acid suppressant agent within 14 days prior to study entry. For Subject 389086, you stated that the subject did not notify

your site that she was taking Nexium and Zantac, and this was discovered when her medical records were received from her primary care provider. For Subject 389085, you stated that the subject was prescribed Nexium and Pepcid AC by the primary care provider after the screening visit and prior to randomization, and this was not discovered until the subject had been randomized. You indicated that the corrective action for this was to have a review of the concomitant medications at every visit, and that the investigator would review the excluded medication list with all staff.

Your response is unacceptable. Your corrective actions provided no information as to how your site will verify medical records, if obtainable and received from the primary care provider, prior to enrolling and/or randomizing subjects into the study to verify the subject's concomitant medications. In addition, you provided no corrective actions regarding procedures you will utilize to elicit from subjects all the medications they are currently taking. You also provided no corrective actions or procedures you would utilize to better instruct subjects against taking protocol-specified, excluded medications.

- d. Protocol Section 9.5.3.4, Clinical Laboratory Tests, specified that at the screening visit, blood samples were to be collected from study subjects for on-site testing for serum *H. pylori*. Protocol Section 9.3.2, Exclusion Criteria, Subsection 6, further specified that subjects with a documented current *H. pylori* infection were ineligible for enrollment into the study. Source records indicated that at least 2 subjects (389127 and 389135) were enrolled into the study without documentation of a current negative *H. pylori* test at the screening visit.

Furthermore, in Subject Medical Review Forms submitted by your site to the CRO, in a protocol deviation list submitted to the IRB, and/or in memos to files, you reported that additional subjects, including but not limited to Subjects 389129, 389137, and 389142, were enrolled into the study without documentation of a current negative *H. pylori* test performed at the screening visit.

Your written response stated that this protocol violation was an isolated issue and that the clinical research coordinator (CRC) who inadvertently did not document the results was "re-educated." You also indicated that, as a corrective action, any in-house test to be performed will have the lot number, expiration date, and results documented in the source documents.

Your response is unacceptable. Specifically, your statement that the CRC inadvertently did not document the result implies that the CRC actually performed the testing, but did not record the results in the source records. According to the establishment inspection report, you informed FDA Investigator Smith that while observing this particular CRC's work, you noticed that she was not using any of the supplies needed for the *H. pylori* test but was writing on the source records that she had in fact conducted those tests. Documentation found at your site also stated that the CRC in question either did not conduct any *H. pylori* testing at the screening

visit, or that the testing was questionable because the supplies needed for the test were not used. You further informed FDA Investigator Smith that when you questioned the study coordinator about your discovery and suggested that she would have to undergo training and work under the supervision of other coordinators, she abruptly resigned. Therefore, FDA cannot confirm that the CRC in question was “re-educated,” as you stated in your written response.

- e. In addition to the above protocol violations, in written memos to file, Subject Medical Review Forms submitted to the CRO, and/or protocol deviations sent to the IRB, your site acknowledged numerous protocol deviations, including but not limited to lack of international normalized ratio (INR) testing at the screening visit for subjects on anticoagulant therapy (e.g., 389017 and 389085); dispensing incorrect test articles to subjects (e.g., 389013, 389041, and 389091); study visits not being scheduled according to the protocol (e.g., 389162 and 389040); and failure to conduct screening serum pregnancy tests (e.g., Subjects 389075 and 389211).

In your written response, you confirmed the findings noted above. Your corrective actions included (1) a commitment to reduce human error by having a better understanding of each protocol and all of its procedures, and by total adherence to the protocol; (2) creation of a source document appendix to allow a second coordinator to cross-reference the investigational product (IP) or kit number assigned by the interactive voice recognition system (IVRS) for a particular subject, so that two coordinators can verify that the correct IP is dispensed to the subject; (3) development of a worksheet entitled “Visit Schedule” that includes the projected dates and actual dates of each visit including +/- windows; and (4) development of a new source document to be used at the end of every visit, certifying that the investigator has reviewed the source documents in their entirety for accuracy and correct documentation.

While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here, and that increases our concerns over your approach to ensuring appropriate human subject protection.

**2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

- a. The screening visit source record for Subject 389137 had a signature which appeared to be that of sub-investigator, Dr. (b) (4), documenting that he had performed a physical exam on October 11, 2007. Your records indicated, however, that Dr. (b) (4) confirmed that the signature on the screening visit source record was not his and denied performing the examination.

You provided no written response to address this finding.

- b. Source records indicated that Subject 389230 had a physical exam at the screening visit on December 18, 2007. However, you did not sign the source physical exam record until April 21, 2008.

Your written response indicated that the physical exam was done at the screening visit, but that you inadvertently forgot to fill out the source document. Your corrective action to prevent this finding was to have the investigator thoroughly document, sign, and date all of the physical exams in real time.

Your response is inadequate. You provided no information regarding procedures and/or training that you would require to ensure that documents are completed, signed, and dated at the time of the study visit.

- c. Records at your site are discrepant concerning which subject (i.e., 389198 or 389168) had the Week 24 visit out of window. Specifically, your site reported in the Subject Medical Review Form dated May 20, 2008, that Subject 389168 (randomization number 5168) had the Week 24 visit scheduled 3 weeks early. In the upper right-hand corner of this same form, there is a handwritten note stating “#389198.” According to the enrollment log, Subject 389168’s randomization number was not 5168; this randomization number belonged to Subject 389198. In the Horizon IVRS Deactivation worksheet, you again stated that Subject 389168’s Week 24 visit was out of window.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Sincerely yours,

*{See appended electronic signature page}*

Leslie K. Ball, M.D.  
Director  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration



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/s/  
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LESLIE K BALL  
02/17/2011



NDA 22-519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated March 23, 2010, received on March 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The proposed dissolution acceptance criterion of Q <sup>(b) (4)</sup> at 30 minutes for famotidine is not acceptable. We recommend the sponsor to tighten the famotidine dissolution acceptance criterion to Q <sup>(b) (4)</sup> at 30 minutes.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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MOO JHONG RHEE  
01/14/2011  
Chief, Branch IV



NDA 22519

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your March 23, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

On December 16, 2010, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 22, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or post-marketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by March 25, 2011.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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DONNA J GRIEBEL  
12/17/2010



NDA 22519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated March 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg. Additionally, reference is made to our October 5, 2010, Information Request letter.

We are reviewing the Clinical and Biometric sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For study HZ-CA-303, perform a reanalysis of the efficacy data utilizing datasets in which all subjects from Site 389 have been omitted. Additionally, provide updated electronic datasets in which all subjects from Site 389 have been omitted. The results of the reanalysis and the electronic datasets should be presented in the format described in the October 5, 2010, Information Request letter and in the format of the original NDA submission dated March 23, 2010. Submit the revised analysis results, electronic datasets, and define file to the Agency for review.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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RICHARD W ISHIHARA  
12/07/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Pediatric and Maternal Health Staff**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Todd Phillips, Regulatory Project Manager**  
**301-796-4857**  
**CDER/OND/ODE III**  
**Division of Gastroenterology Products**

DATE  
**October 22, 2010**

IND NO.

NDA NO.  
**022519**

TYPE OF DOCUMENT  
**Original NDA submission**

DATE OF DOCUMENT  
**March 23, 2010**

NAME OF DRUG  
**Duexis**  
**(ibuprofen/famotidine)**  
**Tablets, 800 mg/26.6 mg**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**New Combination (non-type 3)**

DESIRED COMPLETION DATE  
**November 22, 2010**

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END OF PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END OF PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN VIVO WAIVER REQUEST     |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The product (HZT-501) in this NDA is a fixed combination NSAID (Ibuprofen, 800 mg)/H2RA (famotadine, 26.6 mg). The sponsor's proposed indication is the risk-reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen (b) (4) (b) (4). On October 18, 2010, OSE completed a Pediatric Drug Use Review that revealed a large number of ibuprofen 800 mg prescriptions written for pediatric patients in the U.S. In pediatric patients aged 12-17 years, approximately (b) (4) prescriptions (3% of total prescriptions) were written in 2009 (see attached OSE consult). Therefore, DGP (b) (4) believes that a deferral for studies in patients 12 years through 16 years 11 months is appropriate. The Division requests PMHS evaluation and comment on the Division's proposal. The Division is scheduled to attend the PeRC on December 8, 2010.



SIGNATURE OF REQUESTOR <b>Todd Phillips</b>	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER



NDA 22519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated March 23, 2010, received March 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

[Redacted] (b) (4)

[Redacted]

[Redacted] (b) (4)

A pediatric plan is a statement of intent that outlines the planned or ongoing pediatric studies you plan to conduct or are conducting. We recommend your pediatric plan include the following items:

1. Timeline for completion of the pediatric study(ies) (i.e. the dates of (1) protocol submission, (2) study completion and (3) submission of study reports);
2. Type of study/study design;
3. Age group and population in which the study(ies) will be performed;
4. Number of patients to be studied or power of study to be achieved;
5. Entry criteria;

6. Clinical endpoints;
7. Timing of assessments;
8. Statistical information (statistical analyses of the data to be performed); and
9. Any comments on drug safety/safety concerns.

There is a possibility that the efficacy of HZT-501 may be extrapolated from adults. Extrapolation of efficacy requires data to support the conclusion that the course of the disease and the effect of treatment are reasonably similar in pediatric and adult patients. We request that you provide data to support that the course of the disease and the effect of treatment are reasonably similar in pediatric and adult patients for the deferred indication (reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen), if you believe that this conclusion is supported by the data. Please note that even if extrapolation of efficacy is possible, studies to support dosing and safety of this product in the pediatric population (b) (4) will be required.

In order to facilitate a timely review of your NDA, please provide a written response by November 12, 2010. While discussion and agreement on waivers and deferrals should occur during the drug development process, they do not become final until the time of NDA approval. Additionally, requests for waivers and deferrals, along with the corresponding pediatric plan(s), must be reviewed by the Pediatric Review Committee (PeRC) prior to approval of the NDA.

Please refer to the *Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, September 2005*.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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RICHARD W ISHIHARA  
10/22/2010



NDA 022519

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Horizon Pharma, Inc  
1033 Skokie Boulevard  
Suite 355  
Northbrook, Illinois 60062

ATTENTION: Timothy P. Walbert  
Chairman, President and Chief Executive Officer

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated March 22, 2010, received March 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Famotidine Tablets, 800 mg/26.6 mg.

We also refer to your July 9, 2010 correspondence, received July 9, 2010, requesting review of your proposed proprietary name, Duexis.

We have completed our review of the proposed proprietary name, Duexis, and have concluded that it is vulnerable to name confusion that could lead to medication errors with a proposed proprietary name for a pending application. Duexis and the pending proprietary name are orthographically and phonetically similar and share overlapping product characteristics. Therefore, at this time, the acceptability of the proposed proprietary name, Duexis, is dependent upon which application is approved first. If Duexis is approved first, we will recommend the second product seek an alternate name. If the second name application is approved prior to your application, then you will be requested to submit another name.

We request that you continue to pursue alternate names in the event the other application is approved first. Additionally, you may withdraw your proposed name and submit an alternate name at this time rather than waiting on approval of the other application.

If you wish to continue to pursue the proposed name Duexis at this time, we will re-review your name 90 days prior to the approval of the NDA. If **any** of the proposed product characteristics as stated in your July 9, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Todd Phillips, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/

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CAROL A HOLQUIST  
10/07/2010



NDA 22519

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated March 23, 2010, received on March 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We are reviewing the Biometric and Clinical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- I. For studies HZ-CA-301 and HZ-CA-303, please provide an electronic dataset for each study (consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*) that includes the following variables:
  - a. Study number;
  - b. Investigator or Site Number;
  - c. Unique Subject Identifier (USUBJID in your submitted data sets);
  - d. Actual Treatment Group (TRTA in your submitted data sets);
  - e. Planned Treatment Group (TRTP in your submitted data sets);
  - f. Primary population flag (Y for yes; N for no);
  - g. Per-protocol population flag (Y for yes; N for no);
  - h. Use of concomitant chemotherapy (Y for yes; N for no);
  - i. Gender;
  - j. Age;
  - k. Race;
  - l. Subject early terminated due to Adverse Event (Y for yes; N for no);
  - m. Subject early terminated due to Lost to Follow-Up (Y for yes; N for no);
  - n. Subject early terminated due to Discretion of Investigator or Sponsor (Y for yes; N for no);
  - o. Subjects who developed an adverse event, or were lost to follow-up, or terminated early by the investigator or sponsor, or developed an Upper Gastrointestinal ulcer, including subjects who were terminated early and did not have a negative



- endoscopy for ulcer within 14 days of the last dose of study drug (Y for yes; N for no);
- p. Subjects who developed an adverse event, or were lost to follow-up, or were terminated early by the investigator or sponsor, or developed a Gastric ulcer, including subjects who were terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (Y for yes; N for no);
  - q. Subjects who developed an adverse event, or were lost to follow-up, or were terminated early by the investigator or sponsor, or developed a Duodenal ulcer, including subjects who were terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (Y for yes; N for no);
  - r. Life Table Interval Upper Ulcer (Gastric/Duodenal);
  - s. Time to Upper Ulcer in Weeks, including subjects who terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (or end of treatment date);  
[Note: For early-terminated subjects who were not re-evaluated during the follow-up window, put the time to Upper Ulcer in Weeks in the nearest follow-up window and put 1 for Upper Ulcer censoring indicator.]
  - t. Censoring indicator for Upper Ulcer (ULC\_INC in your submitted data set);
  - u. Life Table Interval Gastric Ulcer;
  - v. Time to Gastric Ulcer in Weeks, including subjects who terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (or end of treatment date);  
[Note: For early-terminated subjects who were not re-evaluated during the follow-up window, put the time to Upper Ulcer in Weeks in the nearest follow-up window and put 1 for Upper Ulcer censoring indicator.];
  - w. Censoring indicator for Gastric Ulcer (GST\_INC in your submitted data set);
  - x. Life Table Interval - Duodenal Ulcer;
  - y. Time to Duodenal Ulcer in Weeks, including subjects who terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (or end of treatment date);  
[Note: For early-terminated subjects who were not re-evaluated during the follow-up window, put the time to Upper Ulcer in Weeks in the nearest follow-up window and put 1 for Upper Ulcer censoring indicator.]
  - z. Censoring indicator for Duodenal Ulcer (DUO\_INC in your submitted data set).
- II. For studies HZ-CA-301 and HZ-CA-303, perform Life Table analyses on the following three variables: Time to Upper Gastrointestinal Ulcer, Time to Gastric Ulcer, and Time to Duodenal Ulcer. For each of the three analyses, include subjects who terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer as requested in Section I of this document.

Submit the results, datasets, define file, and the associated SAS programs to the Agency for review.

- III. For the three categories of ulcers (Gastrointestinal Ulcer, Gastric Ulcer, and Duodenal Ulcer), perform a Crude Rate analysis using the primary population which includes subjects with Adverse Events, those that were Lost to Follow-Up, terminated early by the investigator or sponsor, and terminated early without a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.

Submit the results, datasets, define file, and the associated SAS programs to the Agency for review.

- IV. For the three categories of ulcers, perform a Crude Rate analysis using the Modified-Intent-to-Treat population which includes subjects with Adverse Events, those that were Lost to Follow-Up, terminated early by the investigator or sponsor, and terminated early without a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.

Submit the results, datasets, define file, and the associated SAS programs to the Agency for review.

- V. The define.xml file for studies HZ-CA-301 and HZ-CA-303 does not provide complete information on specific data columns.
- a. For the ADLB, the definitions for the following were not found in the LBTEST CD HPSTL column: H. pylori, H. pylori Fecal Sample, and H. pylori AG Stool.
- b. For the ADLB data set, the definition for H.pylori is not found.

Provide complete definitions for all abbreviations used in the ADLB dataset in the define.xml file for studies HZ-CA-301 and HZ-CA-303.

- VI. Provide any available information on repeat H. pylori testing in all patients in study HZ-CA-301 and HZ-CA-303 who were terminated from the study due to development of a duodenal ulcer or gastric ulcer at the time the ulcer was diagnosed endoscopically.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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RICHARD W ISHIHARA  
10/05/2010

**MEMORANDUM**

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

**DATE:** September 24, 2010

**FROM:** Todd Phillips, PharmD, Regulatory Project Manager

**SUBJECT:** Clinical Pharmacology Information Request

**APPLICATION/DRUG:** NDA 022519 / HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg

On September 9, 2010, the Division of Gastroenterology (DGP) issued a Clinical Pharmacology Information Request to Horizon Pharma via email. On September 14, 2010, DGP met with the sponsor via teleconference to discuss the Information Request.

**Phillips, Todd D.**

---

**From:** Phillips, Todd D.  
**Sent:** Thursday, September 09, 2010 5:54 PM  
**To:** (b) (4)  
**Cc:** Phillips, Todd D.  
**Subject:** NDA 22519, PK information request

**Attachments:** Sample.xls

Dear Ms. (b) (4)

Good evening. Reference is made to NDA 22519 submitted on 23MAR2010. Please note the following Clinical Pharmacology information requests:

1. For study HZ-CA-015, provide the .xpt files for Tables 9 through 13 from Appendix 16.2.5 (Compliance and/or Drug Concentration Data/Pharmacokinetic Final Report Appendix).
2. For study HZ-CA-010, provide the .xpt files for Tables 3A and 3B.
3. In addition to the tables identified above, all relevant pharmacokinetic data for studies HZ-CA-015 and HZ-CA-010 should be organized in the format specified in the attached Excel spreadsheet and submitted as .xpt files.



Sample.xls (21 KB)

4. For studies HZ-CA-015 and HZ-CA-010, provide the SAS code used in the bioequivalence analyses. If WinNonlin was used to analyze the data (as opposed to SAS), please provide the software version.

The Division would like to schedule a brief teleconference with Horizon early next week to discuss this request. The following Division team members will be in attendance:

1. Jane Bai, PhD, Clinical Pharmacology Reviewer
2. Todd Phillips, PharmD, Project Manager
3. Lynne Yao, MD, Medical Officer Team Leader (tentative)

Thank you and please let me know if you have any questions.

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: [Todd.Phillips@fda.hhs.gov](mailto:Todd.Phillips@fda.hhs.gov)

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/s/

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TODD D PHILLIPS  
09/24/2010



NDA 22-519

**INFORMATION REQUEST**

Horizon Therapeutics, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HZT-501 (ibuprofen and famotidine) Tablet.

We also refer to your March 23, 2010 submission, containing an original New Drug Application for this drug product for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We acknowledge receipt of your amendment dated August 12, 2010, in which you agreed to manufacture and submit data from three additional registration scale batches of product produced by the proposed commercial process employing all of the proposed (b) (4) [redacted]. This amendment was submitted as a follow-up to the August 5, 2010 teleconference with the Agency. The Agency also requested during the teleconference that you submit data concerning (b) (4) [redacted] deficiencies for tablets rejected during the manufacturing process.

In addition, we have the following comments/information requests.

2. Regarding the Uniformity of Dosage Units:
  - Clarify which USP <905> test method is employed for each of the active ingredients.
  - (b) (4) [redacted] report the range, average and %RSD of the assay results in addition to acceptance values for each active ingredient.
3. Please refer to Table 5 in section 3.2.P.5.3.3, Validation of the Method for Measuring Assay/Impurities:



- The summary table for LOD lists famotidine and [REDACTED] (b) (4) in the test column. One of those items appears to be missing from the results column. Please make appropriate corrections.
  - In the evaluated parameters columns, the amount injected into a column (in µg and % nominal sample concentration) is to be evaluated while the results column lists the LOD in ng/mL (concentration) with no % nominal sample concentration provided. The same is true for the LOQ. Please make corrections as appropriate.
4. Regarding the dissolution specification:
- Revise the acceptance criterion for ibuprofen dissolution to Q [REDACTED] (b) (4) at 15 minutes.
5. In your submission, you indicated that the commercial manufacturing process for HZT-501 tablets was evaluated from a design space perspective. However, apparently, no specific design space has been proposed in your application. Please confirm with an amendment that HZT-501 tablets will continue to be produced with the manufacturing parameter settings proposed in the P.3 section and the Master Batch Record; and any changes to these parameters will be subject to the standard regulatory change procedures.
6. [REDACTED] (b) (4) any changes should be subject to the standard regulatory change procedures. Please amend your application with elimination of the statement, [REDACTED] (b) (4) from the Master Batch Sheet.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment IV  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22519

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ORIG-1

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HORIZON PHARMA HZT-501  
INC

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/s/  
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MOO JHONG RHEE  
09/15/2010  
Chief, Branch IV



NDA 022519

**FILING COMMUNICATION**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

Please refer to your new drug application (NDA) dated March 23, 2010, received March 23, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg.

We also refer to your submission dated April 16, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 21, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 17, 2010.

During our filing review of your application, we identified the following potential review issues and request that you respond to the following:

1. Proposed Package Insert (PI):
  - a. Highlights of Prescribing Information
    1. The route of administration should be omitted if it is typical for the dosage form and is commonly understood (e.g., tablets or capsules).

2. The Revision Date is the Month/Year the application is approved. The revision date should be left blank at the time of application submission.
- b. Full Prescribing Information: Contents
1. The same title for the boxed warning that appears in the Highlights of Prescribing Information and Full Prescribing Information sections should also appear at the beginning of the Table of Contents in upper-case letters and bold type.
  2. Periods after the section or subsection numbers should not be used.
  3. Identifying numbers should be presented in bold print and should precede the heading or subheading by at least two squares of the size of the letter “m” in 8 point type.
- c. Full Prescribing Information (FPI)
1. The same title for the boxed warning that appears in the Highlights of Prescribing Information and Table of Contents sections should also appear at the beginning of the Full Prescribing Information.
  2. Periods after the section or subsection numbers should not be used.
  3. For each contraindication, use numbered subsection headings or bullets.
  4. The Medication Guide should not be a subsection under the Patient Counseling Information section.
  5. The Patient Counseling Information section must reference any FDA-approved patient labeling (e.g. Medication Guide or Patient Package Insert). [See 21CFR 201.57(c)(18)] The reference “[see FDA-Approved Patient Labeling or See Medication Guide]” should appear at the beginning of the Patient Counseling Information section.
  6. The statement of the place of business shall include the street address, city, State, and ZIP code. The street address may be omitted if it is shown in a current city directory or telephone directory. [See 21CFR 201.1]
  7. The revision date at the end of the Highlights section replaces the revision date at the end of the labeling. The revision date should not appear in both places.

We request that the revised PI labeling be submitted by August 5, 2010.

## 2. Biometrics

- a. For study HZ-CA-301, we recommend the dataset be modified to comply with all applicable CDISC standards. In addition, we suggest the following variables be included:
  1. Study number;
  2. Investigator or Site Number;
  3. Country Name;
  4. Region;

5. Unique Subject Identifier (USUBJID in your submitted datasets);
6. Actual Treatment Group (TRTA in your submitted datasets);
7. Planned Treatment Group (TRTP in your submitted datasets);
8. Primary population flag (Y for yes; N for no);
9. Per-protocol population flag (Y for yes; N for no);
10. Use of concomitant chemotherapy (Y for yes; N for no);
11. Missing indicator (Y for missing data; N for data not missing);
12. Gender;
13. Age;
14. Race;
15. Life Table Interval Upper Ulcer (Gastric/Duodenal);
16. Time to Upper Ulcer in Weeks;
17. Censoring indicator for Upper Ulcer;
18. Life Table Interval - Duodenal Ulcer;
19. Time to Duodenal Ulcer in Weeks;
20. Censoring indicator for Duodenal Ulcer;
21. Life Table Interval Gastric Ulcer;
22. Time to Gastric Ulcer in Weeks;
23. Censoring indicator for Gastric Ulcer

We request that you modify the existing datasets for HZ-CA-301 as outlined above and submit the datasets to the Agency for review.

Additionally, dataset variables required to create Table 5 in section 11.4.1.1.1, Tables 6 and 7 in section 11.4.1.1.2, Table 8 in section 11.4.1.2.1, Tables 9 and 10 in section 11.4.1.2.2, Table 11 in section 11.4.1.2.3, Table 12 in section 11.4.1.2.4, Table 13 in section 11.4.1.2.6, Table 14 in section 11.4.1.2.7, and Table 15 in section 11.4.1.3, should be included in the modified datasets for HZ-CA-301.

Additionally, we request that you modify the SAS programs used to create Tables 5 through 15 in such a fashion as to be able to input the requested modified dataset described above and submit these modified SAS programs for Agency review.

- b. For study HZ-CA-303, we recommend the dataset be modified to comply with all applicable CDISC standards. In addition, we suggest the following variables be included:
  1. Study number;
  2. Investigator or Site Number;
  3. Country Name;
  4. Region;
  5. Unique Subject Identifier (USUBJID in your submitted datasets);
  6. Actual Treatment Group (TRTA in your submitted datasets);
  7. Planned Treatment Group (TRTP in your submitted datasets);
  8. Primary population flag (Y for yes; N for no);

9. Per-protocol population flag (Y for yes; N for no);
10. Use of concomitant chemotherapy (Y for yes; N for no);
11. Missing indicator (Y for missing data; N for data not missing);
12. Gender;
13. Age;
14. Race;
15. Life Table Interval Upper Ulcer (Gastric/Duodenal);
16. Time to Upper Ulcer in Weeks;
17. Censoring indicator for Upper Ulcer;
18. Life Table Interval - Duodenal Ulcer;
19. Time to Duodenal Ulcer in Weeks;
20. Censoring indicator for Duodenal Ulcer;
21. Life Table Interval Gastric Ulcer;
22. Time to Gastric Ulcer in Weeks;
23. Censoring indicator for Gastric Ulcer

We request that you modify the existing datasets for HZ-CA-303 as outlined above and submit the datasets to the Agency for review.

Additionally, dataset variables required to create Table 6 in section 11.4.1.1.1, Tables 7 and 8 in section 11.4.1.1.2, Table 9 in section 11.4.1.2.1, Tables 10 and 11 in section 11.4.1.2.2, Table 12 in section 11.4.1.2.3, Table 13 in section 11.4.1.2.4, Tables 14 and 15 in section 11.4.1.2.5, Table 16 in section 11.4.1.2.6, Table 17 in section 11.4.1.2.7, and Table 18 in section 11.4.1.3, should be included in the modified datasets for HZ-CA-303.

Additionally, we request that you modify the SAS programs used to create Tables 6 through 18 in such as fashion as to be able to input the requested modified dataset described above and submit these modified SAS programs for Agency review.

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

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/s/

RICHARD W ISHIHARA  
06/04/2010  
Signing for Donna Griebel



## REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

**Division of Medical Error Prevention and Analysis  
(DMEPA)**

FROM:

Todd Phillips, Regulatory Project Manager

301-796-4857

CDER/OND/ODE III

Division of Gastroenterology Products

DATE  
May 10, 2010

IND NO.

NDA NO.  
022519

TYPE OF DOCUMENT  
Original NDA submission

DATE OF DOCUMENT  
March 23, 2010

NAME OF DRUG  
(b) (4)  
(ibuprofen/famotidine)  
Tablet

PRIORITY CONSIDERATION.  
Standard

CLASSIFICATION OF DRUG  
New Combination (non-type  
3)

DESIRED COMPLETION DATE  
December 3, 2010

NAME OF FIRM: Horizon Therapeutics

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

The Division of Gastroenterology requests a DMEPA review of the carton/container and package insert labeling. NDA 22519 was submitted electronically ( EDR Location: <\\CDSESUB1\EVSPROD\NDA022519\0000> )

The sponsor requested review of the proprietary name under IND 072116.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22519

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ORIG-1

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HORIZON PHARMA HZT-501  
INC

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/s/  
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TODD D PHILLIPS  
05/10/2010

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Mail: OSE**

**Division of Risk Management (DRISK)**

FROM:

Todd Phillips, Regulatory Project Manager

301-796-4857

CDER/OND/ODE III

Division of Gastroenterology Products

DATE  
May 10, 2010

IND NO.

NDA NO.  
022519

TYPE OF DOCUMENT  
Original NDA submission

DATE OF DOCUMENT  
March 23, 2010

NAME OF DRUG  
(b) (4)  
(ibuprofen/famotidine)  
Tablet

PRIORITY CONSIDERATION.  
Standard

CLASSIFICATION OF DRUG  
New Combination (non-type  
3)

DESIRED COMPLETION DATE  
December 3, 2010

NAME OF FIRM: Horizon Therapeutics

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

The Division of Gastroenterology requests a DRISK review of the Medication Guide. NDA 22519 was submitted electronically  
( EDR Location: <\\CDSESUB1\EVSPROD\NDA022519\0000> )

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22519

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ORIG-1

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HORIZON PHARMA HZT-501  
INC

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/s/  
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TODD D PHILLIPS  
05/10/2010

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  
**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)  
Todd Phillips, Regulatory Project Manager  
301-796-4857  
CDER/OND/ODE III  
Division of Gastroenterology Products

REQUEST DATE  
May 10, 2010

IND NO.

NDA/BLA NO.  
022519

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

See below

NAME OF DRUG  
(b) (4) (ibuprofen/famotidine)  
Tablet

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
New Combination (non-type 3)

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap up meeting)  
December 3, 2010

NAME OF FIRM:  
Horizon Therapeutics

PDUFA Date: January 21, 2011

## TYPE OF LABEL TO REVIEW

**TYPE OF LABELING:**  
(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**EDR link to submission:**

EDR Location: <\\CDSESUB1\EVSPROD\NDA022519\0000>

**Please Note:** There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

**COMMENTS/SPECIAL INSTRUCTIONS:**

Mid-Cycle Meeting: [Insert Date]: August 31, 2010

Labeling Meetings: [Insert Dates]: 09NOV2010, 30NOV2010, 17DEC2010, 07JAN2011, 13JAN2011, 19JAN2011

Wrap-Up Meeting: [Insert Date]: 10DEC2010

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22519

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ORIG-1

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HORIZON PHARMA HZT-501  
INC

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/s/  
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TODD D PHILLIPS  
05/10/2010





NDA 022519

**NDA ACKNOWLEDGMENT**

Horizon Therapeutics, Inc.  
Attention: Timothy P. Walbert  
President and Chief Executive Officer  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Dear Mr. Walbert:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg

Date of Application: March 23, 2010

Date of Receipt: March 23, 2010

Our Reference Number: NDA 022519

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 22, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22519

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HORIZON  
THERAPEUTICS  
INC

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HZT-501

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/s/  
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TODD D PHILLIPS  
04/05/2010