

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202880Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202880

SUPPL # n/a

HFD # 170

Trade Name: Zohydro ER

Generic Name: hydrocodone bitartrate extended-release capsules

Applicant Name: Zogenix Inc.

Approval Date, If Known: October 25, 2013

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

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

505(b)(2)

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

YES NO

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

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?

n/a

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# 020716 Vicoprofen
NDA# 022439 Zutripro
NDA# 022442 Rezira
NDA# 204307 Vituz

In addition to the above approved NDAs for hydrocodone-containing products listed in the Orange Book, there are many ANDAs for hydrocodone-containing products listed in the Orange Book (see the attached list).

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.)

n/a YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

to PART II, Question 1 or 2 was "yes."

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

YES NO

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

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

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

YES NO

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

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

YES NO

[The applicant states: "Zogenix certifies that a thorough search of the scientific literature has been conducted and no published studies or reports that provide a sufficient basis for approval of the conditions for which Zogenix is seeking approval were found."]

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

ZX002-0801- A Randomized Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy, Tolerability and Safety of Hydrocodone Bitartrate Extended-Release Capsules in Opioid-Experienced Subjects with Moderate to Severe Chronic Low Back Pain

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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"):

ZX002-0801- A Randomized Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy, Tolerability and Safety of Hydrocodone Bitartrate Extended-Release Capsules in Opioid-Experienced Subjects with Moderate to Severe Chronic Low Back Pain

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 # 065111 YES ! NO
! Explain:

Investigation #2
IND # 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?

n/a

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: ***Dominic Chiapperino, Ph.D.***

Title: ***Senior Regulatory Health Project Manager***

Date: ***October 25, 2013***

Name of Office/Division Director signing form: ***Bob A. Rappaport, M.D.***

Title: ***Division Director, Division of Anesthesia, Analgesia, and Addiction Products***

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DOMINIC CHIAPPERINO
10/25/2013

BOB A RAPPAPORT
10/25/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202880	NDA Supplement #: Not applicable (N/A), original NDA	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Zohydro ER Established/Proper Name: hydrocodone bitartrate Dosage Form: extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg strengths		Applicant: Zogenix Inc. Agent for Applicant (if applicable): N/A
RPM: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager		Division: Division of Anesthesia, Analgesia, and Addiction Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>NDA 020716, Vicoprofen (hydrocodone bitartrate/ibuprofen) tablets, 7.5 mg/ 200 mg</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product is an extended-release, versus immediate-release, formulation of hydrocodone bitartrate as single active ingredient, i.e., it does not contain ibuprofen or acetaminophen as other approved (combination) hydrocodone-containing products contain.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		

¹ 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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA 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> 	<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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).

- [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

<p><i>paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “No,” continue with question (5).</i></p> <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 checked="" type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	10/28/13
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Officer/Employee List

❖ 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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approval, 10/25/13
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	<p>10/25/13</p> <p>5/1/12</p> <p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<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"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	10/25/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5/1/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color 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"> • Most-recent draft labeling 	10/25/13
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	D. Baugh; L. Merchant; Updated review confirming name still acceptable, 7/2/13; C. Holquist, letter accepting proposed name, 9/12/12; D. Baugh; L. Merchant; C. Holquist, original review, 9/12/12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM D. Chiapperino, SRPI Review, 10/11/12 <input checked="" type="checkbox"/> DMEPA D. Baugh; L. Merchant; C. Holquist; Review, 10/5/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) S. Mills; B. Fuller; L. Griffiths; Review, 2/8/13; Consult Request form, D. Chiapperino, 8/2/12 <input checked="" type="checkbox"/> ODPD (DDMAC) E.H. Chung-Davies, Review, 2/13/13; L.S. Toombs, Review, 2/12/13, D. Chiapperino, Consult Request form, 8/2/12 <input checked="" type="checkbox"/> SEALD A. Adebawale; L. Burke, 9/24/13 <input type="checkbox"/> CSS (see CSS review, "Clinical" tab)
Administrative / Regulatory Documents	

<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁵/Memo of Filing Meeting) (indicate date of each review) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date) 	<p>505(b)(2) Assessment, D. Chiapperino 10/25/13 (cleared by committee 2/6/13, and confirmed as still acceptable on 9/17/13) <u>Filing reviews:</u> D. Chiapperino, 10/11/12 K. Meaker, 10/12/12 R. Levin; F. Pucino, 8/10/12 E. Bolan; D. Mellon, 6/26/12 D. Christodoulou; P. Peri, 6/22/12 D.J. Lee; Y. Xu, 6/18/12 A. Khairuzzaman; A. Dorantes, 6/17/12</p>
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included 10/25/13
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (approvals only) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>1/30/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized) 	<input checked="" type="checkbox"/> Included, 10/25/13
<ul style="list-style-type: none"> ❖ 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 (include certification) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons) 	<p>In reverse chronology, all information request (IR) emails, IR letters, NDA Filing/74-day letter (7/13/12), and NDA Acknowledgement letter (5/11/12)</p>
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	<p>none</p>
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • Regulatory Briefing (indicate date of mtg) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (indicate date of mtg) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • PeRC meeting 	<p>1/30/13</p>
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (indicate date of mtg) 	<p>Pre-NDA, 12/16/11 CMC Pre-NDA 1/4/12</p>
<ul style="list-style-type: none"> • EOP2 meeting (indicate date of mtg) 	<p>6/26/08</p>
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs) 	<p>none</p>

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	12/7/12
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Only transcript available (not included)
❖ Other records of contact with sponsor	Memos to file, 3/29/13, 1/14/13, 12/20/12, 9/11/12
Decisional and Summary Memos	
❖ 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>)	B. Rappaport, 10/25/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	E. Fields, CDTL addendum memo, 9/19/13; E. Fields, CDTL memo, 1/31/13
PMR/PMC Development Templates (<i>indicate total number</i>)	10 PMRs in total included as two aggregated files, signed 10/25/13
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	E. Fields co-signed clinical review
• Clinical review(s) (<i>indicate date for each review</i>)	R.A. Levin; E. Fields, Review, 1/16/13
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ 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>)	Addressed on page 17 of Levin and Fields' clinical review, 1/16/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	L. Love; S. Calderon; M. Klein, Review, 2/5/13
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	Submitted REMS and REMS materials (approved version), 7/30/13
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	Submitted REMS Supporting Document, 7/30/13
• 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>)	D. Smith; C. Manzo, Review#2, 9/23/13 J. Racoosin, REMS Memo, 9/21/13 S. Secora; C. Kornegay; J. Staffa, Epidemiology Review of informal (emailed proposal) epi study, 8/16/13 D. Smith; K. Lehrfeld, Review, 7/25/13 D. Chiapperino, Consult Request form, 5/18/12

⁶ Filing reviews should be filed with the discipline reviews.

❖ Consult Review from CDRH, audiology assessments	J. Kane; S. Nandkumar, Review, 11/15/12
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	S. Kleppinger; J. Pohlman; S. Thompson, Inspection Summary, 1/16/13 D. Chiapperino; R. Levin; F. Pucino, OSI Audit Request form, 8/8/12
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None D. Price co-signed primary review
Statistical Review(s) (indicate date for each review)	K. Meaker; D. Price, 1/25/13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None Y. Xu co-signed primary review
Clinical Pharmacology review(s) (indicate date for each review)	D.J. Lee; J.Y. Lee; V. Bhattaram; Y. Xu, Review, 1/15/13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None D. Mellon co-signed primary review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	E. Bolan; D. Mellon, Review, 1/15/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <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 checked="" type="checkbox"/> None P. Peri co-signed primary reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Y. Hu; P. Peri, Review #3, 9/24/13 Y. Hu; P. Peri, Review #2, 2/6/13 Y. Hu; P. Peri, Review #1, 1/15/13
❖ 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 (OMPQ/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)(all original applications and all efficacy supplements that could increase the patient population)</i>	Refer to Page 24 of Hu and Peri's Product Quality Review #1, 1/15/13
<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 checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 1/8/13 (refer to Pages 28-30 of Hu and Peri's Product Quality Review #1, 1/15/13) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</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 checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/

DOMINIC CHIAPPERINO
10/28/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, July 26, 2013 9:45 AM
To: Edward Smith <esmith@zogenix.com> (esmith@zogenix.com)
Subject: RE: NDA 202880, REMS edits
Attachments: rems-support-doc-clean.doc; rems-support-doc-clean.pdf; rems-and-materials-clean7 26 2013.pdf; rems-and-materials-clean 7 26 2013.doc; blueprint tracked 7 26 2013.doc; blueprint clean 7 26 2013.doc; rems-doc-clean.doc; blueprint tracked 7 26 2013.pdf

Hi Edward,

Regarding your proposed REMS for Zohydro ER, we have now concluded our consideration of the additional revisions needed to the REMS, as follows.

COMMENTS

1. FDA BLUEPRINT

On July 25, 2013, Butrans, a member of the ER/LA Opioid Analgesics REMS, had a supplemental NDA approved with a modified "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (Blueprint). Resubmit a proposed modified REMS for your product that adds the 15 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal System to the FDA Blueprint.

See the attached FDA Blueprint for recommended track changes [file named "blueprint tracked 7 26 2103.pdf"].

2. RESUBMISSION INSTRUCTIONS

Submit the following materials through the Gateway:

- **1 MS Word file of REMS Document (clean)** [See attached file named "rems-doc-clean.doc"]
- **1 MS Word file of revised FDA Blueprint (clean)** [See attached file named "blueprint clean 7 26 2013.doc"]
- **1 MS Word file of revised FDA Blueprint (tracked)** [See attached file named "blueprint tracked 7 26 2013.doc"]
- **1 MS Word file that includes the REMS document + all appended materials* (clean)** [See attached file named "rems-and-materials-clean 7 26 2013.doc"]
- **1 PDF file that includes the REMS document + all appended materials* (clean)** [See attached file named "rems-and-materials-clean7 26 2013.pdf"]

*The materials below should be appended to the REMS document (in the following order):

- Patient Counseling Document (PCD) on Extended-Release/Long- Acting Opioid Analgesics
- Revised FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Prescriber Letter 1

- Prescriber Letter 2
 - Prescriber Letter 3
 - Professional Organization/Licensing Board Letter 1
 - Professional Organization/Licensing Board Letter 2
 - ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com)
- **1 PDF file of the REMS Supporting Document (clean)** [See attached file named "rems-support-doc-clean.pdf"]
 - **1 MS Word file of the REMS Supporting Document (clean)** [See attached file named "rems-support-doc-clean.doc"]

These files should be reflective also of the revisions required in my July 23, 2013 email.

Please call me if you have any questions.

Kind regards,
Dominic

From: Chiapperino, Dominic
Sent: Wednesday, July 24, 2013 4:03 PM
To: 'Edward Smith'
Subject: RE: NDA 202880, REMS edits

Hi Edward,

Contrary to my voice message earlier today, directing you to send the REMS package as amendment with agreed-upon changes, I need to put a hold on this request and advise you to wait until Monday to hear further from us. We have discovered something else in the Blueprint that may need modification... we will clarify this to you probably by Monday.

I also listened to your recent voice message. I am listening in on a meeting until 4:30... Will touch base again after it ends.

Regards,
Dominic

From: Chiapperino, Dominic
Sent: Tuesday, July 23, 2013 5:30 PM
To: 'Edward Smith'
Subject: NDA 202880, REMS edits

Hi Edward,

Referring to your ND 202880 for Zohdyro ER, and your most recently submitted REMS-related Amendment from May 2013, our review of the REMS is completed and we have the following comments:

1.1 REMS DOCUMENT

Revise the header of the document as shown below:

1.2 ELEMENT TO ASSURE SAFE USE

1.2.1 FDA Blueprint

Currently, there is hidden text in the following sections which should be visible when viewing the table:

- Key Instructions
- Specific Drug Interactions

Revise the table as shown below:

Zohydro ER	<ul style="list-style-type: none">▪ Hydrocodone Bitartrate▪ Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none">▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none">▪ Initial dose in opioid non-tolerant patient is 10 mg.▪ Titrate using a minimum of 3-day intervals.▪ <u>Swallow capsules whole (do not chew, crush, or dissolve).</u>
Specific Drug Interactions	<ul style="list-style-type: none">▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone.▪ <u>CYP3A4 inhibitors may increase hydrocodone exposure.</u>▪ <u>CYP3A4 inducers may decrease hydrocodone exposure.</u>
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none">▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.

Tomorrow, please let me know (via email) if you agree to the Agency's suggested revisions and propose no further edits. When I hear from you, I will provide you with submission instructions for a REMS amendment.

The documents I've attached have the changes listed above. The pdf shows the edits, and the Word document should be "clean," with these changes accepted.

Thanks, and best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993

Office phone: (301) 796-1183

Facsimile: (301) 796-9723

Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
07/26/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, June 18, 2013 3:10 PM
To: 'Edward Smith'
Subject: RE: NDA 202880: RE: FDA response to your question, nonclinical carc protocol

Hi Edward,

Our nonclinical team has the following clarification for you concerning our request to further assess [REDACTED] (b) (4) in your mouse carcinogenicity study:

[REDACTED] (b) (4)

Please contact us again if you have further questions.

Best regards,
Dominic

Dominic Chiapperino, Ph.D.
*Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov*

From: Edward Smith [mailto:esmith@zogenix.com]
Sent: Tuesday, June 04, 2013 4:42 PM
To: Chiapperino, Dominic
Subject: NDA 202880: RE: FDA response to your question, nonclinical carc protocol

Hi Dominic,

Thank you very much for the response to our question about the [REDACTED] (b) (4) of the mouse carcinogenicity study. We will [REDACTED] (b) (4)

We had a follow-up question for the FDA nonclinical review team: It would be helpful to gain

additional insight into

(b) (4)

In the final study report we will provide the following information

(b) (4) :

(b) (4)

(b) (4)

Best regards,

Edward F Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs & Product Quality/Safety
Zogenix, Inc.

510 - 550 - 8325 Direct

949 - 201 - 8042 Cell

510 - 550 - 8340 Fax

esmith@zogenix.com

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5858 Horton Street, Suite 455, Emeryville, CA 94608

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From: Chiapperino, Dominic [mailto:Domnic.Chiapperino@fda.hhs.gov]

Sent: Tuesday, May 28, 2013 11:23 AM
To: Edward Smith
Subject: FDA response to your question, nonclinical carc protocol

Dear Edward,

Referring to your IND 065111, and the nonclinical carcinogenicity study in progress, "Carcinogenicity Study Protocol 8237254-Mouse," in support of NDA 202880 for Zohydro ER, we have a response to your question sent in your email dated April 30, 2013, which include [REDACTED] (b) (4)

Your Question: Zogenix [REDACTED] (b) (4) ?

FDA Response: [REDACTED] (b) (4)
[REDACTED] criteria are as follows:
[REDACTED] (b) (4)

[REDACTED] (b) (4)

Please contact me if you have any further questions concerning the [REDACTED] (b) (4) or FDA's response.

Thank you, and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

From: Edward Smith [<mailto:esmith@zogenix.com>]
Sent: Tuesday, April 30, 2013 3:59 PM
To: Chiapperino, Dominic
Subject: NDA 202-880

Hi Dominic,

I hope this note finds you well.

Zogenix (b) (4) with our ongoing carcinogenicity study, and we wish to (b) (4)
We thought the expedient approach would be to (b) (4)

Does this approach sound reasonable to the review division and review team?

On a separate note, I have some traveling coming up over the next 10 days. The best way to reach me would be directly by email. If you prefer a telephone call, send me an email first, and I can return the call when I return to cell phone range.

Best regards,

Edward F Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs & Product Quality/Safety
Zogenix, Inc.

510 - 550 - 8325 Direct
949 - 201 - 8042 Cell
510 - 550 - 8340 Fax
esmith@zogenix.com www.zogenix.com
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DOMINIC CHIAPPERINO
06/18/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, May 28, 2013 2:23 PM
To: 'Edward Smith'
Subject: FDA response to your question, nonclinical carc protocol

Dear Edward,

Referring to your IND 065111, and the nonclinical carcinogenicity study in progress, "Carcinogenicity Study Protocol 8237254-Mouse," in support of NDA 202880 for Zohydro ER, we have a response to your question sent in your email dated April 30, 2013, which included [REDACTED] (b) (4)

Your Question: Zogenix [REDACTED] (b) (4) ?

FDA Response: [REDACTED] (b) (4)
[REDACTED] criteria are as follows:

[REDACTED] (b) (4)

Please contact me if you have any further questions concerning the [REDACTED] (b) (4) or FDA's response.

Thank you, and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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FDA, Center for Drug Evaluation and Research
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Building 22, Room 3134
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Office phone: (301) 796-1183
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Dominic.Chiapperino@fda.hhs.gov

From: Edward Smith [mailto:esmith@zogenix.com]
Sent: Tuesday, April 30, 2013 3:59 PM
To: Chiapperino, Dominic
Subject: NDA 202-880

Hi Dominic,

I hope this note finds you well.

Zogenix (b) (4) **our ongoing carcinogenicity study, and we wish to** (b) (4)
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On a separate note, I have some traveling coming up over the next 10 days. The best way to reach me would be directly by email. If you prefer a telephone call, send me an email first, and I can return the call when I return to cell phone range.

Best regards,

Edward F Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs & Product Quality/Safety
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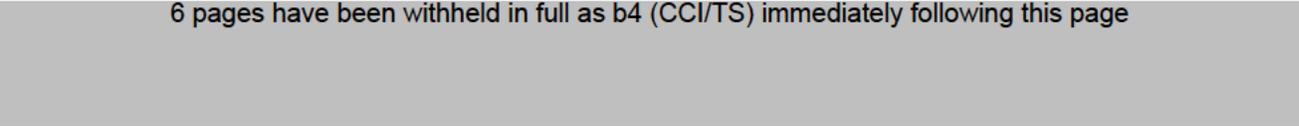
[Proposal from Zogenix, via email on April 30, 2013]

Zohydro Mouse Carcinogenicity Study Progress

(b) (4)



6 pages have been withheld in full as b4 (CCI/TS) immediately following this page



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/s/

DOMINIC CHIAPPERINO
05/28/2013

MEMORANDUM

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

DATE: March 29, 2013

TO: File

THROUGH: Bob A. Rappaport, MD, Director, Division of Anesthesia, Analgesia, and
Addiction products (DAAAP)

FROM: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP

SUBJECT: Record of Contact - Teleconference with Zogenix Inc.

APPLICATION/DRUG: NDA 202880, for Zohydro ER (hydrocodone bitartrate) extended-
release capsules, submitted by Zogenix Inc.

A teleconference was held today, 3:30 PM (EST), with the following participants:

Stephen Farr, PhD, President and Chief Operating Officer, Zogenix Inc.
Edward F. Smith III, PhD, MBA, RAC, Vice President, Regulatory Affairs &
Product Quality/Safety, Zogenix Inc.

and

Bob A. Rappaport, MD, Director, DAAAP
Sharon Hertz, MD, Deputy Director, DAAAP
Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP

Summary of discussion:

The questions from Drs. Farr and Smith during the discussion related to the revised expected timing for the action on their submitted NDA for Zohydro ER and the nature of the issues that have delayed the action on their NDA beyond the March 1, 2013 PDUFA date.

Dr. Rappaport explained that the initial estimate of a delay of weeks reflected the circumstances and discussions in mid-February at about the time of our last teleconference to update Zogenix. The current circumstances suggest that, based on ongoing discussions with upper management, including the Office of the Center Director, the delay may now be more likely several months away. The complex issues at the center of the delayed action are actively under consideration at

all levels of management in CDER. More specific information about the underlying issues to be resolved could not be shared at this time.

Dr. Farr expressed his understanding of these circumstances and his concerns with the potential impact to Zogenix in not being able to predict the timing and the outcome of FDA's decision on their application. He indicated that Zogenix would further consider their next steps and possibly request further feedback from CDER management.

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DOMINIC CHIAPPERINO
03/29/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, February 20, 2013 4:53 PM
To: 'Edward Smith'
Subject: NDA 202880, Requested REMS modifications

Dear Edward,

Regarding your NDA 202880 for Zohydro ER, we have the following comments and request for revised REMS-related documents as follows:

1. REMS Document

Revise the header of the document to read as:

Initial REMS Approval: 07/2012
Most Recent Modification: XX/2013

2. Elements to Assure Safe Use

2.1 FDA Blueprint

A. On August 28, 2012, the Agency approved the following modifications to the FDA Blueprint:

1. Section entitled "Dolophine: Specific Drug Interactions" (page 10) incorrectly stated that:
 - CYP 450 inducers may increase methadone levels
 - CYP 450 inhibitors may decrease methadone levels

The statements were revised to state the following:

- CYP 450 inducers may decrease methadone levels
- CYP 450 inhibitors may increase methadone levels

2. Addition of the intermediate dosage strengths 40 mg, 70 mg, 130 mg, and 150 mg of Kadian (morphine sulfate extended release) capsules that FDA approved on July 9, 2012 to Section entitled "Kadian" (page 11).

3. Sections entitled "Exalgo: Key Instructions" and "Exalgo: Drug Specific Adverse Reactions" (page 11), which, as approved on July 9, 2012, incorrectly stated:

- Do not use in patients with sulfa allergy—contains sodium metabisulfite.
- Allergic manifestations to sulfa component

The statements were revised to state the following:

- Do not use in patients with sulfite allergy—contains sodium metabisulfite.

- Allergic manifestations to sulfite component

4. Addition of the newly approved 32 mg dosage strength for Exalgo (Hydromorphone Hydrochloride Extended-Release) tablets that was approved on August 28, 2012 to the section entitled "Exalgo" (page 11).

B. Additionally, the following modification should be made to the subsection entitled Use in Opioid-Tolerant Patients under the drug product Kadian:

Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant patients only

This statement is revised to allow for greater consistency with the approved labeling.

C. See the attached FDA Blueprint for recommended track changes.

2.2 Prescriber Letters

Correct formatting errors in all letters (e.g. a question mark (?) appears in all places where a dash (-) should be placed).

2.3 Professional Organization Letters

Correct formatting errors in all letters (e.g. a question mark (?) appears in all places where a dash (-) should be placed).

2.4 ER/LA Opioid Analgesics REMS Website

Hydrocodone should be added to the bulleted list on the Important Safety Information page of REMS website and in the first line of fourth paragraph (pg. 9 of 11).

3. REMS Supporting Document

The Company name should be added to page 1 of REMS Supporting Document.

4. General Comments

Resubmission Requirements and Instructions: Submit the revised proposed REMS modification for the ER/LA opioid analgesics with attached materials. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document.

Please contact me if you have any questions about these requested REMS modifications.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
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Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO

02/22/2013

Archiving 2/20/13 email

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, February 12, 2013 5:59 PM
To: 'Edward Smith'
Subject: NDA 202880, request for agreement on potential PMR studies

Dear Edward,

Regarding your NDA 202880 for Zohydro ER, the Division would like to now convey what we believe would be your postmarketing required (PMR) studies in the event of approval of Zohydro ER. They are as follows:

Deferred studies required under PREA

As provided for in your Pediatric Study Plan submitted on January 18, 2013, Zogenix will commit to conducting two studies, as follows:

#1) Conduct a PK and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 12 to less than 17 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Protocol Submission: Mar. 1, 2014
Study Completion: Sep. 1, 2018
Study Submission: Mar. 1, 2019

#2) PK and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 7 to less than 12 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Protocol Submission: Mar. 1, 2017
Study Completion: Mar. 1, 2021
Study Submission: Sep. 1, 2021

Nonclinical required studies

As discussed in previous emails or noted in your NDA submission, Zogenix commits to completing the following nonclinical PMR studies:

#3) Conduct an in vivo comet assay in liver to evaluate the potential genetic toxicology of hydrocodone.

#4) Conduct a 2-year bioassay in the rat model to evaluate the carcinogenic potential of hydrocodone.

#5) Conduct a 2-year bioassay in the mouse model to evaluate the carcinogenic potential of hydrocodone.

For each of the above nonclinical PMRs, please provide at your earliest opportunity your proposed milestone dates associated with these studies. These would include actual dates for: Final Protocol Submission, Study/Trial Completion; and Final Report Submission, as shown above for the PREA studies.

When you submit your amendment to provide the requested milestone dates for the nonclinical studies, please also provide a general statement of agreement of the five PMR studies to ensure that Zogenix and FDA have the same understanding of these commitments.

Thank you, and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
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/s/

DOMINIC CHIAPPERINO
02/12/2013

PeRC PREA Subcommittee Meeting Minutes
January 30, 2013

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Rosemary Addy
Karen Davis-Bruno
Patricia Dinndorf
Tom Smith
Shrikant Pagay
William Rodriguez
Lily Mulugeta
Daiva Shetty
Andrew Mosholder
Colleen LoCicero
Martha Nguyen
Gregory Reaman
Courtney Suggs
Kevin Krudys
Dianne Murphy
Sonal Vaid

Guests Attending:

Melissa Tassinari (PMHS)	Dionna Green (OPT)
Allen Rudman (OCP)	Donna Snyder (PMHS)
Lori Gorski (PMHS)	Amy Taylor (PMHS)
Jeanine Best (PMHS)	Erica Radden (PMHS)
Mitchell Berger (CBER)	Millie Wright (PMHS)
Renan Bonnel (OPT)	Matt Bacho (PMHS)
Michelle Roth-Cline (OPT)	David Lee (OCP)
Jeremiah Momper (OCP)	Vicki Moyer (PMHS)
Ellen Fields (DAAAP)	Dominic Chiapperino (DAAAP)
Cathryn Lee (OND)	Alvina Mushtaq (OCP)
Rupal Shah (OCP)	Ruyi He (DGIEP)
John Trotani (DGIEP)	Stacey Barley (DGIEP)
Anissa Davis (DGIEP)	Jingyu Yu (OCP)
Robert Levin (DPP)	Sonny Sani (DPP)
Nitin Mehrotra (OCP)	

Agenda

NDA 202880	Zohydro (hydrocodone bitartate ER oral capsule) Partial Waiver/Deferral/Plan
NDA 204736	Aciphex (rabeprazole sodium) Partial Waiver/Assessment
(b) (4)	(b) (4)
NDA 204623	Pennsaid (b) (4) (diclofenac sodium topical solution) Full Waiver

Zohydro (hydrocodone bitartate ER oral capsule) Partial Waiver/Deferral/Plan

- NDA 202880, Zohydro (hydrocodone bitartate ER oral capsule), was studied for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.
- The application was submitted on May 1, 2012 and has a PDUFA date of March 1, 2013.
- This application triggers PREA as a new dosage form.
- The Division is requesting a partial waiver in pediatric patients from birth to less than seven years of age because studies are impossible or highly impracticable.
 - While pediatric acute pain continues to be an unmet need, chronic pain is much less common in very young pediatric patients than in adult patients and is typically associated with a co-morbid condition (e.g. cancer, cystic fibrosis, sickle-cell anemia). These subjects and their families are more likely to seek out and participate in clinical trials for medications aimed at addressing their underlying disease state, making them ineligible for a trial evaluating opioid analgesia. Combined with the very small patient population of pediatric subjects suffering from chronic pain, this has posed an extreme obstacle to product sponsors wishing to study opioid analgesics in children under seven years of age.
- The Division is requesting a partial deferral in pediatric patients seven to less than 17 years of age because the product is ready for approval in adults.

PeRC Recommendation

- The PeRC agreed to the partial waiver in pediatric patients ages birth to less than seven years of age because studies would be impossible or highly impracticable. This plan for partial waiver is consistent with previously agreed upon based on a Pediatric Analgesic Clinical Trials Workshop held in 2009. The PeRC also agreed to the deferral and pediatric plan for patients ages seven to less than 17 years of age because the product is ready for approval in adults. Furthermore, the PeRC agreed with the design of the deferred studies and that extrapolation from adults for the proposed indication was acceptable.

Additional PeRC Recommendations:

- The division should remind the sponsor that the formulation to be used in phase 3 clinical trials should ideally be the to-be-marketed formulation.

Aciphex (rabeprazole) Assessment/Partial Waiver

- NDA 204736, Aciphex (rabeprazole), was studied for healing of endoscopically proven GERD in children one through 11 years of age and maintenance of healing of endoscopically proven GERD in children one through 11 years of age.
- The application was submitted on September 27, 2012 and has a PDUFA date of March 27, 2013.
- This application triggers PREA as a new indication and dosage form.
- The division is requesting a partial waiver in pediatric patients 12 to 17 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients.

- The tablet will most likely be used in pediatric patients 12 to 17 years of age and not the sprinkle capsule.
- Studies were conducted using the sprinkle capsule in pediatric patients 1 to 11 years of age.
- The PeRC agrees with the partial waiver and assessment.
- PeRC Recommendations:
 - The PeRC recommends consulting PMHS when the division begins labeling negotiations for assistance with making the label consistent with other PPI labels.
 - The PeRC strongly recommends that specific labeling that warns that PPI's should not be used in patients birth to less than one year of age for GERD based on advice from the Pediatric Advisory Committee convened on November 5, 2010.
 - The PeRC recommends labeling the product for use in pediatric patients 12 to 17 years of age if there are adequate PK data to establish a dose for this age group. If dosing in this age group can be established then the waiver for the product for patients 12-17 years of age will not be needed.
 - The PeRC notes, it appears in this case, that (b) (4)

[Redacted text block]

[Large redacted text block]

Pennsaid (b) (4) (diclofenac sodium 2% topical solution) Full Waiver

- NDA 204-623, diclofenac sodium 2% topical solution, was studied for the treatment of signs and symptoms of osteoarthritis of the knee.

- The application was submitted on May 4, 2012 and has a PDUFA date of March 4, 2013.
- This application triggers PREA as a new dosage form.
- The Division is requesting a full waiver.
 - Osteoarthritis is on the list of automatic full waivers.
- The PeRC agrees with the full waiver.

Rivera, Luz E (CDER)

From: Edward Smith <esmith@zogenix.com>
Sent: Friday, January 18, 2013 2:51 PM
To: Rivera, Luz E (CDER)
Subject: NDA 202880 - FDA request
Attachments: NDA 202880 Jan15.pdf.pdf.pdf

Dear Dr Rivera

Zogenix is responding to the 15 January 2013 communication received from FDA, requesting Zogenix provide a statement to withdraw (b) (4) as the API supplier for hydrocodone bitartrate. Zogenix has several questions for FDA. Per your suggestion on our telecom today, we have forwarded our questions in the email message below, so that you may forward and discuss with your team.

Question 1.

Zogenix proposes to include the following statement in an amendment to our NDA 202880, and to update FDA Form 356h (establishment information – deleting (b) (4)

Per FDA request (dated 15 January 2013), Zogenix has withdrawn (b) (4) (b) (4) as the API manufacturer for the drug substance (Hydrocodone Bitartrate USP as described in (b) (4) DMF (b) (4) in the manufacture of Zohydro™ ER drug product as described in Zogenix NDA 202880. Any references to (b) (4) in this NDA are for historical support of the Zohydro™ ER (hydrocodone bitartrate) Extended-Release Capsules drug product approval.

Additionally, Zogenix proposes to include the above statement in the manufacturing section of the NDA, but not otherwise delete those sections containing (b) (4) information, as Zogenix intends to use drug product manufactured with (b) (4) API as supporting information for drug product stability and expiry determination (see next question).

Question 1: Is this approach acceptable to FDA?

Question 2.

Zogenix wants to confirm with FDA that the drug product stability information for product manufactured with (b) (4) API would still provide supportive stability information to the drug product manufactured with (b) (4) API in determination of the drug product expiry.

Question 2: Would stability information from drug product manufactured with (b) (4) API still support the expiry determination of drug product manufactured with (b) (4) API after withdrawal of (b) (4) as an API supplier?

Question 3.

Alkermes has just informed us that the 18 month stability information for drug product lots manufactured with (b) (4) API would be available for submission to FDA by 07 February 2013. Zogenix does not want to jeopardize the current review cycle for NDA 202880 by submitting

information late in the review cycle. However, if FDA would want to review this additional information without extending the review cycle, Zogenix would cooperate and provide the stability information.

Question 3: Would FDA want Zogenix / Alkermes to submit 18 month stability information for drug product manufactured with (b) (4) API, without changing the current review cycle for NDA 202880?

Best regards,

Edward F Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs & Product Quality/Safety
Zogenix, Inc.

510 - 550 - 8325 Direct
949 - 201 - 8042 Cell
510 - 550 - 8340 Fax
esmith@zogenix.com www.zogenix.com
5858 Horton Street, Suite 455, Emeryville, CA 94608

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/s/

LUZ E RIVERA
01/22/2013



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Zogenix, Inc.
Application Number:	NDA 202880
Product Name:	Hydrocodone Bitartrate Extended Release (HC-ER) Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg

Background

Zogenix is responding to the 15 January 2013 communication received from FDA, requesting Zogenix provide a statement to withdraw (b) (4) as the API supplier for hydrocodone bitartrate. Zogenix has several questions for FDA. Zogenix has several questions before responding to the FDA request.

1.0 Questions

Question 1

Zogenix proposes to include the following statement in an amendment to our NDA 202880, and to update FDA Form 356h (establishment information – deleting (b) (4)

Per FDA request (dated 15 January 2013), Zogenix has withdrawn (b) (4) as the API manufacturer for the drug substance (Hydrocodone Bitartrate USP as described in (b) (4) DMF (b) (4) in the manufacture of Hydro™ ER drug product as described in Zogenix NDA 202880. Any references to (b) (4) in this NDA are for historical support of the Hydro™ ER (hydrocodone bitartrate) Extended-Release Capsules drug product approval.

Additionally, Zogenix proposes to include the above statement in the manufacturing section of the NDA, but not otherwise delete those sections containing (b) (4) information, as Zogenix intends to use drug product manufactured with (b) (4) API as supporting information for drug product stability and expiry determination (see next question).

- 1) *Question 1#-* Is this approach acceptable to FDA?

FDA Responses: Yes, your proposal is acceptable

Question 2

Zogenix wants to confirm with FDA that the drug product stability information for product manufactured with (b) (4) API would still provide supportive stability information to the drug product manufactured with (b) (4) API in determination of the drug product expiry.

- 2) *Question #2-* Would stability information from drug product manufactured with (b) (4) API still support the expiry determination of drug product manufactured with (b) (4) API after withdrawal of (b) (4) as an API supplier?

FDA Response: Yes, your proposal is acceptable.

Question 3

Alkermes has just informed us that the 18 month stability information for drug product lots manufactured with (b) (4) API would be available for submission to FDA by 07 February 2013. Zogenix does not want to jeopardize the current review cycle for NDA 202880 by submitting information late in the review cycle. However, if FDA would want to review this additional information without extending the review cycle, Zogenix would cooperate and provide the stability information.

- 3) *Question # 3-* Would FDA want Zogenix / Alkermes to submit 18 month stability information for drug product manufactured with (b) (4) API, without changing the current review cycle for NDA 202880?

FDA Response: You do not need to submit the additional stability data at the present time

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/s/

LUZ E RIVERA
01/22/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, January 22, 2013 9:29 AM
To: 'Edward Smith'
Subject: NDA 202880, Information Request, case reports

Dear Edward,

Regarding your NDA 202880 for Zohydro ER, we request additional information to address some questions we have about Studies 801 and 802. The table below summarizes discrepancies we've noted associated with the information on record in the clinical study reports and in the adverse event forms for these studies. Provide additional information or explanation to address the discrepancies noted in the table.

Study	Subject ID	Differences between information provided in the Clinical Study Report (CSR) and in the Adverse Events Forms (AER)
801	131-02 131-03	Subjects not listed in the CSR, but AER forms list them as cases of non-compliance, drug missing
801	152-06	Difference in study phase recorded
802	106-14, 122-14 137-02, 208-15 211-29, 215-21 217-04, 224-04 225-21, 227-30 230-02, 236-10 241-05, 241-12 241-32	Amount of missing drug reported
802	236-10	Dates when study drug was missing or lost
802	102-16	Unexplained discharge for non-compliance not matching information in AER
	211-15	

802	211-23 224-04 209-23	Inconsistent identification, reporting and response to missing drug by study sites
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We look forward to your response at your earliest opportunity so that we may conclude our review of your application.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
01/22/2013



NDA 202880

INFORMATION REQUEST

Zogenix, Inc.
Attention: Nancy Yee
Director, Regulatory Affairs
5858 Horton Street, Suite 455
Emeryville, CA 94608

Dear Ms. Yee:

Please refer to your new drug application submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone bitartrate extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests.

1. [REDACTED] (b) (4) is a subsidiary of [REDACTED] (b) (4) as indicated on 3.2.S.2.1), FEI: [REDACTED] (b) (4), address [REDACTED] (b) (4) [REDACTED] (b) (4), is identified as responsible for the manufacture, test and stability for Hydrocodone bitartrate USP, from the NDA. Since the DMF was found to inadequate to support your NDA, provide a statement that you withdraw the DMF [REDACTED] (b) (4) from the application. Update Form 356h (establishment information) and the appropriate manufacturing sections of the NDA to indicate the changes.

If you have questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
01/15/2013

MEMORANDUM

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

DATE: January 14, 2013

TO: File

FROM: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

SUBJECT: Record of Contact, archival of Zogenix letter received January 7, 2013, by email

APPLICATION/DRUG: NDA 202880/Zohydro ER (hydrocodone bitartrate) extended-release capsules

Zogenix Inc., the sponsor of NDA 202880, and specifically, Edward F. Smith III, PhD, MBA, RAC, Vice President, Regulatory Affairs & Product Quality/Safety, sent an email to DAAAP to provide a scanned (pdf) copy of a signed letter from Stephen Farr, PhD, President and COO of Zogenix, addressed to Bob A. Rappaport, MD, Director, DAAAP.

This memorandum serves to archive the letter from Dr. Farr within the NDA file.

Chiapperino, Dominic

From: Edward Smith [esmith@zogenix.com]
Sent: Monday, January 07, 2013 4:09 PM
To: Chiapperino, Dominic
Subject: Correspondence for Dr Rappaport
Attachments: Rappaport Letter Jan 2013.pdf.pdf

Hi Dominic,

Here is a letter from Stephen Farr, President, Zogenix for you to forward to Dr Rappaport.

Please feel free to contact Stephen Farr or me if you or Dr Rappaport have any questions.

Best regards,

Edward F Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs & Product Quality/Safety
Zogenix, Inc.

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07 January 2013

Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Attn: Dominic Chiapperino, PhD, Sr Regulatory Health Project Manager

**Re: Zohydro ER (Hydrocodone Bitartrate Extended-Release Capsules)
NDA 202880¹**

Dear Dr. Rappaport,

In follow-up to our December 20, 2012 discussion, I am writing on behalf of Zogenix, Inc. (Zogenix) to address several policy issues that may impact the review of our pending new drug application (NDA) for Zohydro ER (Hydrocodone Bitartrate Extended-Release Capsules).

As discussed below, it is imperative that the review of the Zohydro ER NDA remain within the existing regulatory framework for the review of extended-release/long-acting (ER/LA) Schedule II opioid drugs. The framework includes a carefully constructed risk evaluation and mitigation strategy (REMS) tailored specifically to ER/LA opioid drugs. It also includes the option to formulate products without features that purport to deter opioid abuse. Under this framework, we believe Zohydro ER meets the agency's core standards of safety, efficacy, and product quality.

Zohydro ER, if approved, would be the first single-entity hydrocodone product; the first extended-release hydrocodone product; the first REMS-managed hydrocodone product; and the first Schedule II controlled hydrocodone product. It will provide an important option for patients, while also being the most comprehensively regulated hydrocodone product on the market.

As you know, the agency recently asked its Anesthetic and Analgesic Drug Products Advisory Committee to provide advice on the Zohydro ER NDA. Despite your best efforts, the Committee focused primarily on concerns about the overall class of Schedule II opioids

¹ This document contains confidential commercial and trade secret information and is subject to the pre-disclosure notification rights under 21 CFR part 20 and related provisions of law.



and the class-wide ER/LA REMS, and less so on the data in support of Zohydro ER. The discussion highlighted important concerns that experts in the field have about this class of drugs. Unfortunately, the discussion and voting strayed from the task of rigorously analyzing the risk-benefit profile of Zohydro ER under the agency's current regulatory standards.

For this reason, Zogenix is writing to provide our understanding of the regulatory framework that governs the review of Zohydro ER. We appreciate the attention being given in the media, by other sponsors, and even by members of Congress, on the risks posed by ER/LA opioid products. We recognize that the Food and Drug Administration (FDA) must make difficult decisions that balance the need for patient access with the risks of misuse, abuse, and diversion. It is also important to recognize that Zohydro ER will provide a unique treatment option to patients and its risk-benefit profile is well within the range of the other marketed products in this class. Within that context, we believe strongly that, if held to the same standards as similarly situated products in the class, the data demonstrate that the NDA for Zohydro ER should be approved.

Background

Zogenix was founded in 2006 to develop and commercialize medicines for the treatment of central nervous system disorders and pain. Since 2007, we have conducted the clinical development program for Zohydro ER in close communication with the Division. On May 1, 2012, Zogenix submitted an NDA under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA), based on the agency's prior approval of Vicoprofen® (Hydrocodone Bitartrate and Ibuprofen tablets), and a thorough clinical data set, including a pivotal placebo-controlled trial in patients with lower back pain.

Zogenix developed Zohydro ER to fulfill three critical medical needs in the chronic pain area:

- Hydrocodone is not currently available as a single-entity product. Hydrocodone/acetaminophen combination analgesics are widely used to treat pain, but are the leading cause of hepatotoxicity and liver failure due to unintentional acetaminophen overdose. A single-entity hydrocodone product will provide an important treatment option for patients with chronic pain and hepatic compromise or acetaminophen sensitivity, and will also reduce the risk of acetaminophen overdose in patients requiring higher doses of hydrocodone.
- Hydrocodone is not currently available in an extended-release dosage form. Zohydro ER will be an important therapeutic option for those patients on immediate release hydrocodone/acetaminophen whose chronic pain can be successfully managed with hydrocodone, but who will benefit from an extended-release product.
- Zohydro ER will also provide another option for patients who are already on an extended release opioid but who would benefit from the availability of a different and proven opioid when they require opioid rotation.



The Zohydro ER formulation is based on coated carrier beads in a hard gelatin capsule. The technology is very familiar to the agency as six other marketed products, including three that contain Schedule II controlled substances, use the same basic formulation. Zohydro ER has been subject to alcohol challenge studies and will include labeling describing the results of those studies, which are favorable and consistent with others in the class.

Regulatory Framework for Zohydro ER

Under section 505 of the FDCA, Zogenix is required to demonstrate that Zohydro ER is safe for the general patient population and, based on substantial evidence, is effective for its proposed use. We believe Zohydro ER clearly meets this standard.

Zogenix has submitted substantial evidence demonstrating that Zohydro ER is effective for the management of moderate-to-severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. The Advisory Committee agreed, voting 8-5, with one abstention, that Zohydro ER is effective for its intended use.²

Zohydro ER was also shown in the clinical development program to have a safety profile consistent with that of other extended-release opioids. It is our understanding, based on the Division's presentation to the Advisory Committee, that the agency has not identified any unexpected safety issues inherent in the product, or any side effects or adverse events that would outweigh the demonstrated efficacy of the product. The Advisory Committee voted 9-5 that Zogenix had not demonstrated that Zohydro ER was safe in the intended population. However, close examination of the discussion and voting shows that many committee members were expressing concern about the safety of the product outside of the intended population, and the potential for abuse and misuse of the product. These issues are appropriately addressed through implementation of the class-wide ER/LA opioid REMS; they do not support a finding that the drug is unsafe for its intended use.

Because Zohydro ER has a potential for abuse and misuse consistent with other Schedule II opioids, we are fully committed to implementation of the ER/LA opioid REMS as a requirement for Zohydro ER approval. The Advisory Committee, even when pressed by the agency, did not identify any risks for Zohydro ER that are categorically different from other opioid analgesics in the class, including other marketed opioid analgesics that – like Zohydro ER – do not purport to contain abuse-deterrent features. To our knowledge, the Division also has not identified any risks based on the clinical data that would justify or support requiring additional REMS measures. Thus, the risks associated with Zohydro ER – including non-medical use and abuse of the drug – can be managed through the class-wide ER/LA opioid REMS designed by the agency for that purpose. That said, as discussed below, Zogenix intends to implement additional controls on a voluntary basis.

Finally, the committee voted 11-2, with one abstention, to not support the approval of the drug. The majority of committee members clearly acknowledged that Zohydro ER met the governing regulatory requirements for approval. However, the members candidly noted their

² After the vote, the abstaining vote explained that she meant to vote yes.

concerns about the dangers inherent in the class and their uncertainty about the ability of the class-wide REMS to protect the public against non-medical use and abuse of ER/LA opioids in general. Most members agreed that Zohydro ER was not likely to be abused to a greater degree than other single-entity ER/LA opioids.

Accordingly, we believe the advice provided by the Advisory Committee must be put into the proper context. This was the first such meeting in which the members had an opportunity to consider the ER/LA opioid REMS in the context of a new approval. Clearly, the members harbor concerns about all drugs in this class. However, to the extent they specifically considered the data developed for Zohydro ER, the committee raised few if any serious questions about the strength of the data under the relevant legal and regulatory standards for approval.

In short, Zohydro ER has been shown to be effective in patients suffering from moderate to severe chronic pain. The safety profile of the product, including risks related to abuse and misuse, is fully consistent with that of other marketed products in the class. As a single-entity hydrocodone product, Zohydro ER represents a significant advance over other available hydrocodone products, particularly for those at risk of hepatotoxicity. In addition, if approved, Zohydro ER will be the only hydrocodone product subject to a REMS and to Schedule II controls under the Controlled Substances Act, regulatory controls designed to mitigate the abuse, misuse, and diversion of the product.

FDA Policy Does Not Require the Use of Abuse-Deterrent Formulations

Zogenix has been transparent throughout the clinical development process that Zohydro ER is not designed to contain abuse-deterrent features. As with most other marketed drug products in the ER/LA opioid class, we do not claim that Zohydro ER is able to defeat intentional tampering or resist prevalent forms of abuse, such as oral abuse. Instead, like other opioid analgesics, the risk of abuse and misuse of Zohydro ER can be adequately addressed and mitigated by the class-wide REMS and through DEA and state regulation of controlled substances.

We believe we are in agreement with the agency on this point. In discussions during our November 17, 2011 pre-NDA meeting, the Division stated “there has been no fundamental change in thinking about the present formulation” and reiterated that the lack of abuse-deterrent properties would not preclude approval of Zohydro ER.³ Furthermore, the Division made clear that Zohydro ER “will not be held to a different or higher standard than other ER/LA opioid products that the Division has approved or will consider for approval.”⁴ We understood this to mean that, consistent with agency policy, the use of abuse-deterrent features is not a required condition of approval.

³ Minutes from November 17, 2011 Pre-NDA meeting (dated December 16, 2011) (Pre-NDA meeting minutes) at pages 20 -21.

⁴ Pre-NDA meeting minutes at page 22.



To our knowledge, FDA has consistently resisted the idea of adopting a policy that would require all ER/LA opioid products to include abuse-deterrent formulations. In fact, we are not aware that any of the marketed ER/LA morphine, hydromorphone, fentanyl, buprenorphine and methadone products purport to be formulated with abuse-deterrent features.⁵ Furthermore, FDA has been reluctant to recognize abuse-deterrent labeling claims and has maintained a clear and consistent policy that any claims related to abuse deterrence must be based on long-term *post-market* data. Thus, abuse-deterrent formulations have, as a matter of policy, not been a pre-market approval requirement for this class.

We firmly believe the agency cannot simply change its position on this policy on the eve of taking final action on our pending NDA. If the agency intends to change its longstanding and consistent approach to non-abuse-deterrent ER/LA opioids, it must do so publicly on a class-wide basis and with adequate notice and an opportunity for us and others to be heard. The Division appears to share this view. As stated at the Advisory Committee meeting, “if the new drug has a signal for a problem that exists throughout the class, and if that problem appears to be occurring at a similar frequency and with a similar level of clinical significance, any regulatory action would have to be imposed on the entire class.”⁶

Zogenix has relied on the statements by the agency during our development program, during several other advisory committee meetings on ER/LA opioid drug products, and on prior agency determinations on similar drugs. We and our business partners have made a significant investment of time and resources to develop Zohydro ER under the current policy. Thus, we believe any decision regarding the safety, effectiveness, and quality of Zohydro ER must be made under the existing framework, with Zohydro ER held to the same standards as others in the class.

Additional Safe-use Measures

In addition to complying with the FDA requirements including the ER/LA opioid class REMS and Schedule II DEA controls, Zogenix is committed to implementing additional measures to reinforce the safe-use of Zohydro ER and gather additional information on the risk profile of the product in an actual-use setting.

The Zohydro ER Safe Use Initiative includes additional training for prescribers and pharmacists; training and patient assistance with safe storage of the drug to reduce diversion; and a program for field representatives that rewards success in education rather than sales. The Safe Use Initiative also includes a surveillance program to actively monitor information from the healthcare system, distribution channels, and end users, and an independent Safe Use Board composed of opioid safe use and epidemiology experts. The Board will be empowered to communicate directly to FDA any safety issue uncovered through the surveillance program, and Zogenix is committed to taking immediate and meaningful action

⁵ It is our understanding that even those products designed to include purported abuse-deterrent features have not been shown through substantial evidence to be effective in the actual deterrence of abuse.

⁶ December 7, 2012, meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, Transcript at page 5.



when faced with misuse, including ceasing product distribution to suspected diversion sources, and reporting diversion to the appropriate authorities. The Zohydro ER Safe Use Initiative can be expected to provide valuable information to FDA as it monitors and considers modifications to the ER/LA opioid REMS.

In addition, Zogenix is committed to developing a next generation formulation of Zohydro ER that incorporates abuse-deterrent technology. Zogenix (b) (4)

New and enhanced abuse-deterrent technologies will only come from advances in research and development. There are a very limited number of approaches that have made it to market, and the efficacy of these measures remains unproven. Finally, the design of an abuse-deterrent product is dependent on a complex intellectual property landscape, with significant challenges to our freedom to operate in this field. Thus, there are many factors that must be considered before the agency mandates that a product such a Zohydro ER only be offered in an abuse-deterrent format.

* * *

In summary, Zogenix has submitted information that demonstrates the safety and efficacy of Zohydro ER, a product expected to provide an important option for the treatment of chronic pain. FDA asked the Advisory Committee to identify any risks that distinguished Zohydro ER from other opioid analgesics in the class. The Committee members did not identify any information to suggest that Zohydro ER would have a different risk/benefit profile than other products in the class. Like the other products in the class, the risks of Zohydro ER will be appropriately managed through the ER/LA opioid REMs and the Schedule II controls under the CSA. Based on the advice, input and statements made by the Division to date, we believe the Division is in full agreement with our assessment of the regulatory framework governing the review and approval of Zohydro ER.

Thank you for your time and attention to this important matter. We look forward to working with the Division to resolve any remaining issues under the pending NDA for Zohydro ER during the remainder of the current review cycle.

Sincerely,

Stephen Farr, Ph.D.
President and Chief Operating Officer

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/s/

DOMINIC CHIAPPERINO
01/14/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, December 13, 2012 2:00 PM
To: 'Edward Smith'
Subject: NDA 202880, Nonclinical comment

Hi Ed,

I wanted to provide you with an informal notification of a possible postmarketing requirement identified by our nonclinical team. This would more appropriately be described in a Discipline Review letter and/or during discussions of postmarketing commitments/requirements, when the nonclinical review is complete. However, we thought there might be value to you if you were aware of it now, in case you would want to begin working on this right away:

We have completed review of the genetic toxicology studies with hydrocodone that you submitted to your NDA. We note that hydrocodone tested positive in the in vitro chromosome aberration assay in the presence of S9. Consistent with ICH S2(R1), you should conduct a fourth assay in order to construct a weight-of-evidence approach. Since the positive result was seen in the presence of metabolic activation, we recommend conducting an in vivo Comet assay with liver.

We can certainly discuss this more at any time.

I am also compiling a set of carton/container labeling-related comments for you and will provide that as soon as I can.

Best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
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/s/

DOMINIC CHIAPPERINO

01/14/2013

Archiving email communication from Dec. 13, 2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, January 09, 2013 8:44 AM
To: 'Nancy Yee'
Cc: 'Edward Smith'
Subject: RE: NDA 202880, Information requests, CMC and container labeling

Hi Nancy,

We have reviewed the draft revised container labels you sent to us Dec. 21st. We have the following comments:

- 1) The color scheme utilized for the presentation of the 15 mg and 50 mg strengths is similar. To avoid selection errors, revise the color scheme by choosing a unique color for each strength so that they are adequately differentiated from each other. Additionally, ensure that the colors do not overlap with other strengths within the product line.
- 2) Relocate the net quantity and Rx only statements away from the statement of strength to avoid confusion between the net quantity and strength.
- 3) Relocate the statement "Swallow capsule whole. Do not . . ." to the bottom of the principal display panel so that it does not have more prominence than drug identifying information (e.g., proprietary and established names).

Thank you, and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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Dominic.Chiapperino@fda.hhs.gov

From: Nancy Yee [mailto:nyee@zogenix.com]
Sent: Friday, December 21, 2012 6:30 PM
To: Chiapperino, Dominic
Subject: FW: NDA 202880, Information requests, CMC and container labeling

Hi Dominic,

Attached please find the labels we have revised in response to the Agency's below comments. Would you please confirm they are acceptable? If so, we will formally submit them to the NDA.

Thank you and happy holidays,
Nancy

From: Chiapperino, Dominic [<mailto:Dominic.Chiapperino@fda.hhs.gov>]
Sent: Tuesday, December 18, 2012 1:48 PM
To: Edward Smith
Subject: NDA 202880, Information requests, CMC and container labeling

Dear Edward,

Referring to your NDA 202880 for Zohydro ER, we have the following requests and comments at this time.

Regarding the CMC sections of your NDA:

1. We note that (b) (4) drug substance DMF (b) (4) is deficient. Therefore, (b) (4) is not an acceptable supplier of the drug substance, hydrocodone bitartrate, for the manufacture of your drug product.
2. (b) (4) the specification limit for Total Impurities in (b) (4) sourced drug substance so that it is in line with the recently proposed limit for Total Impurities in the DMF (b) (4) specification.
3. We recently requested that Alkermes revise and/or justify their drug product specification for "Microbial Limits", "Sum of All Reportable Impurities" and "Attribute Testing". Submit a revised drug product specification to the NDA accordingly.

Regarding your proposed container labels, as revised in your amendment dated November 14, 2012:

1. The color scheme utilized for the strength presentation of the 15 mg and 20 mg strengths (b) (4) is similar. In addition, the color scheme for the strength presentation of the 40 mg and 50 mg strengths is similar. To avoid selection errors, revise the color scheme by choosing a unique color for each strength so that they are adequately differentiated from each other. Consider utilizing the same color to box each strength to increase the differentiation between the strengths. Additionally, ensure that the colors do not overlap with other strengths within the product line.
2. Relocate the statement "Swallow capsule whole. Do not . . ." to the principal display panel and increase its prominence by bolding.
3. Delete the box surrounding the Medication Guide statement as this clutters the label and elevates its prominence above information used to identify the drug product.
4. Relocate the controlled substance symbol to appear in the right hand corner of the principal display panel (where the net quantity and "Rx only" statements are located currently; see item 5).
5. Relocate the net quantity and Rx only statements to appear at the bottom of the principal display panel.

Please contact me if you have any questions about these requests.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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/s/

DOMINIC CHIAPPERINO
01/09/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, January 04, 2013 12:51 PM
To: 'Edward Smith'
Subject: NDA 202880, Information request, revised peds plan

Dear Edward,

Referring to your NDA 202880 fro Zohydro ER, we have the following comments and requests related to your submitted pediatric plan to address PREA requirements:

We have reviewed your pediatric plan for Zohydro ER and have found it to be inadequate. You are requesting a waiver for studies in pediatric patients under the age of 7 years, and deferral of a pharmacokinetic and safety study in pediatric patients ages 7 to 12 years, both of which are acceptable. However, you are also proposing to

(b) (4)

has been reviewed by the clinical pharmacology team and has been found unacceptable. Therefore, submit a revised pediatric plan as follows:

1. Waiver request for pediatric studies for patients less than 7 years of age
2. Deferral request for pediatric studies ages 7 to less than 12 years and 12 to less than 17 years
3. Studies for the deferred age groups must include safety and pharmacokinetic assessments
4. Studies may be done sequentially; oldest age group first followed by younger age group
5. The revised pediatric plan must include the following milestone dates for each study:
 - a. Final protocol submission
 - b. Study start
 - c. Study stop
 - d. Final study report submission to Agency

Please contact me if you have any questions. A response to these comments within a two-week timeframe is requested.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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Dominic.Chiapperino@fda.hhs.gov

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, January 04, 2013 1:01 PM
To: 'Edward Smith'
Subject: RE: NDA 202880, Information request, revised peds plan

Hi Edward,

One quick clarification regarding the [REDACTED] (b) (4)
[REDACTED] You may use [REDACTED] (b) (4). However, you will still
need to obtain adequate PK data in this age group to confirm it.

Thanks, and kind regards,

Dominic

From: Chiapperino, Dominic
Sent: Friday, January 04, 2013 12:51 PM
To: 'Edward Smith'
Subject: NDA 202880, Information request, revised peds plan

Dear Edward,

Referring to your NDA 202880 fro Zohydro ER, we have the following comments and requests related to your submitted pediatric plan to address PREA requirements:

We have reviewed your pediatric plan for Zohydro ER and have found it to be inadequate. You are requesting a waiver for studies in pediatric patients under the age of 7 years, and deferral of a pharmacokinetic and safety study in pediatric patients ages 7 to 12 years, both of which are acceptable. However, you are also proposing to [REDACTED] (b) (4)

[REDACTED] has been reviewed by the clinical pharmacology team and has been found unacceptable. Therefore, submit a revised pediatric plan as follows:

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 - c. Study stop
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Please contact me if you have any questions. A response to these comments within a two-week timeframe is requested.

Kind regards,
Dominic

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DOMINIC CHIAPPERINO
01/04/2013

MEMORANDUM

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

DATE: December 20, 2012

TO: File

THROUGH: Bob A. Rappaport, MD, Director, Division of Anesthesia, Analgesia, and
Addiction products (DAAAP)

FROM: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP

SUBJECT: Record of Contact - Teleconference with Stephen Farr, MD, Zogenix Inc.

APPLICATION/DRUG: NDA 202880, for Zohydro ER (hydrocodone bitartrate) extended-
release capsules, submitted by Zogenix Inc.

A teleconference was held today, 2:00 PM (EST), with the following participants:

Stephen Farr, MD, President and Chief Operating Officer, Zogenix Inc
and

Bob A. Rappaport, MD, Director, DAAAP
Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, DAAAP

Summary of discussion:

Dr. Farr stated that the Advisory Committee meeting [held Dec. 7, 2012] and the discussion among the Committee members concerning the proposed product, Zohydro ER, were more severe than anticipated. The conversation today was requested so that Zogenix could present their perspective on these events and seek the Division's advice for next steps.

Dr. Farr outlined the following:

- Zogenix intends to have rigorous [distribution/prescribing] controls in place in bringing this first hydrocodone ER product to market
- Zogenix and FDA have maintained a good and transparent relationship during development of Zohydro ER
- Zogenix demonstrated safety and efficacy of Zohydro ER
- The profile of Zohydro ER is the same as all other ER/LA opioid analgesics

- Zogenix presented at the AC details about their planned Safety Initiative to accompany product launch, although the AC members did not appear to engage very extensively to discuss the program's specifics
- The important broad issue in these discussions is the abusability or lack of abuse-deterrent (AD) features with Zohydro ER, Zogenix' first-generation formulation of hydrocodone ER. (b) (4)

Dr. Farr asked what Zogenix could or should be doing at this time to support the approvability of Zohydro ER, and asked also if his summary of the AC meeting demonstrates that they are viewing the current situation correctly.

Dr. Rappaport indicated that FDA's take-away messages from the AC meeting discussion were much as expressed by Dr. Farr, so it appears both Zogenix and FDA heard the same messages at the AC meeting. The planned high-level internal discussion within FDA, about which Zogenix was already informed, is expected to occur soon in January. The outcome of that discussion has the potential to affect other products, not just Zohydro ER. At this time, it is simply not known as to where the discussion will lead for future FDA action on Zohydro ER and perhaps other impacted products.

Dr. Farr asked if Zogenix can contribute, ahead of the FDA internal discussions, any written comments about their assessment of the AC meeting or about their planned Safety Initiative for Zohydro ER.

Dr. Rappaport stated that Zogenix can do this if they wish but emphasized that the discussions are not expected to be specific to Zohydro ER, but more in the vein of policy discussion, potentially impacting Zohydro ER along with other similar products.

Dr. Farr asked if it would be helpful for Zogenix to offer any particular Phase 4 commitments at this time.

Dr. Rappaport stated that this was not an issue in the current deliberations. If Zohydro ER were to be approved, there would be Phase 4 commitments as with other products of this type.

Dr. Farr asked if there was any other information they might receive before the March 1, 2013 PDUFA date for the Zohydro ER application, and also mentioned the upcoming Part 15 hearing in February 2013 to discuss opioid analgesics and their degree of efficacy in treating chronic pain, asking if this meeting might be relevant for Zohydro ER.

Dr. Rappaport stated that we will be as transparent and forthcoming as we can possibly be, but it

is unclear at this time where the internal discussions will lead and what communication to Zogenix or the public will be appropriate for the positions FDA will take. The Part 15 hearing may have relevance for Zohydro ER. It is likely that there will be much public commenting in the aftermath of that hearing and there will also likely be extensive docket comments to review, so the FDA action on Zohydro ER is likely to occur prior to any eventual outcome of the Part 15 public meeting. However, it is possible that what we hear at that time might have some influence on our thinking and impact the action on the Zohydro ER application.

Dr. Farr thanked us for having the discussion today and offered that we should contact Edward Smith [Zogenix] directly with any follow-up or requests related to the Zohydro ER application.

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/s/

DOMINIC CHIAPPERINO
12/20/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, December 18, 2012 4:48 PM
To: 'Edward Smith'
Subject: NDA 202880, Information requests, CMC and container labeling

Dear Edward,

Referring to your NDA 202880 for Zohydro ER, we have the following requests and comments at this time.

Regarding the CMC sections of your NDA:

1. We note that (b) (4) drug substance DMF (b) (4) is deficient. Therefore, (b) (4) is not an acceptable supplier of the drug substance, hydrocodone bitartrate, for the manufacture of your drug product.
2. (b) (4) the specification limit for Total Impurities in (b) (4) sourced drug substance so that it is in line with the recently proposed limit for Total Impurities in the DMF (b) (4) specification.
3. We recently requested that Alkermes revise and/or justify their drug product specification for "Microbial Limits", "Sum of All Reportable Impurities" and "Attribute Testing". Submit a revised drug product specification to the NDA accordingly.

Regarding your proposed container labels, as revised in your amendment dated November 14, 2012:

1. The color scheme utilized for the strength presentation of the 15 mg and 20 mg strengths ((b) (4) is similar. In addition, the color scheme for the strength presentation of the 40 mg and 50 mg strengths is similar. To avoid selection errors, revise the color scheme by choosing a unique color for each strength so that they are adequately differentiated from each other. Consider utilizing the same color to box each strength to increase the differentiation between the strengths. Additionally, ensure that the colors do not overlap with other strengths within the product line.
2. Relocate the statement "Swallow capsule whole. Do not . . ." to the principal display panel and increase its prominence by bolding.
3. Delete the box surrounding the Medication Guide statement as this clutters the label and elevates its prominence above information used to identify the drug product.
4. Relocate the controlled substance symbol to appear in the right hand corner of the principal display panel (where the net quantity and "Rx only" statements are located currently; see item 5).
5. Relocate the net quantity and Rx only statements to appear at the bottom of the principal display panel.

Please contact me if you have any questions about these requests.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
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/s/

DOMINIC CHIAPPERINO
12/18/2012

Chiapperino, Dominic

From Chiapperino, Dominic
Sent Tuesday, December 18, 2012 5:25 PM
To 'Edward Smith'
Subject RE: NDA 202880, Information Request, REMS
Attachments rems-and-materials pdf; fda-blueprint 082012.doc

Hi Ed,

I have received further guidance/comment from DRISK related to your questions about the REMS.

Please find attachments: 1) a pdf of the REMS and related documents, as found in our approval letter for Nucynta ER (NDA 200533, new DPN indication) on August 28, 2012; and 2) a Word format file of the FDA Blueprint that should be identical to the FDA Blueprint pages of the REMS pdf from item#1.

You may wish to utilize these files to create and submit the files needed for your REMS amendment. The FDA Blueprint document as well as the web screen shots should include Zohydro ER, so I suppose you will need to work with RPC to generate those revised screen shots. You will also need to request from RPC the REMS Supporting Document to include with your amendment. This would be the version from July 9, 2012, as there were no changes to this document for the August 28, 2012 REMS modification.

Just to clarify, it is true that RPC was not directly involved and did not submit the documents for the August 28, 2012 REMS modification. That revised REMS on August 28th was submitted only by Janssen for their pending efficacy supplement (I believe they had worked with RPC just as you are doing now for Zohydro ER to obtain some source files). The RPC member companies never had to submit revised REMS for their products to "catch up" to Janssen's modified REMS approved for Nucynta ER because it was recognized soon after the August 28th FDA action that additional changes were needed to the ER/LA REMS. Therefore, all companies, including Janssen, have the further-revised REMS submitted for their NDAs as of October 2012. However, as I indicated in earlier email, the action on your NDA for Zohydro ER may occur earlier than the action of the revised REMS pending for all other ER/LA opioid products, and so your submitted REMS must match the August 28, 2012 version (but including all changes needed for Zohydro ER as new member product), at least for now.

Please contact me if you have any remaining questions.

Thanks, and kind regards,
 Dominic

Dominic Chiapperino, Ph D
 Senior Regulatory Health Project Manager
 FDA, Center for Drug Evaluation and Research
 Office of Drug Evaluation II
 Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Avenue
 Building 22, Room 3134
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 Office phone: (301) 796-1183
 Facsimile: (301) 796-9723
 Dominic.Chiapperino@fda.hhs.gov

From: Edward Smith [mailto:esmith@zogenix.com]
Sent: Friday, December 14, 2012 5:41 PM
To: Chiapperino, Dominic
Subject: RE: NDA 202880, Information Request, REMS

Hi Dominic,

Thanks again for taking time to work through our questions and comments this afternoon. The comments are helpful to us.

I am back on the REMS topic. What I am understanding from the RPC subteams is that there was no Aug 28th submission. It seems the only submissions have been the original in July (which may have a different date on it!), which has been approved, and the second submission in Oct 2012, which is still under FDA review. Below comments are from the RPC.

I have reached out to the FDA Subteam (cc'd on this E-mail), and they have notified me that there is no Aug 28th Submission
 The only approved REMS Submissions are from July The Submission from last October (target date: 10/19), has not officially been approved

So, I think the intent is that Zogenix submit the last REMS submission that has been approved by FDA, which in this case is still the first REMS submission that the RPC provided in July 2012. Am I understanding your request correctly?

I would also point out that the ER/LA-opioidREMS website screenshot and the Section on Selected Important Safety Information sections list the other opioid analgesics covered by the class, but these two sections do not include Zohydro ER or hydrocodone in the listings, yet (see screen shots below). For our REMS update submission at this time, shall we submit the REMS version that does not include Zohydro ER or hydrocodone in the class-wide REMS descriptions? And that we would include those changes in a new submission following Zohydro ER approval? If we can submit without including Zohydro ER or hydrocodone in the REMS document, we can submit this rather quickly. If we have to include the brand and generic names in this document (including the website screen shot), that will require more time as we will need to work with the RPC to create new documents.

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Bookmarks

- EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID ANALGESICS RISK EVALUATION
- GOAL
- I. REMS ELEMENTS
- II. Implementation System
- III. Timetable for Submission of Assessments
- Patient Counseling Document (PCD)
- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting
- Prescriber Letter #1 FDA-Required

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics 7/1/2012

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) Dolophine (methadone HCl tablets) Embeda (morphine sulfate ER-naltrexone capsules) Kadian (morphine sulfate ER capsules) Nucynta ER (tapentadol HCl ER tablets) OxyContin (oxycodone HCl CR tablets)	Butrans (buprenorphine transdermal system) Duragesic (fentanyl transdermal system) Exalgo (hydromorphone HCl ER tablets) MS Contin (morphine sulfate CR tablets) Opana ER (oxymorphone HCl ER tablets)
Dosing Interval	Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. If pain increases, attempt to identify the source, while adjusting the dose. When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the

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Bookmarks

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- Prescriber Letter #1 FDA-Required
- Prescriber Letter #2 FDA-Required
- Prescriber Letter #3 FDA-Required
- Professional Organization/Licens

Brand Name Products

Trade Name	Generic Name	Company	Contact	Links
Avinza®	Morphine sulfate extended-release capsules	Pfizer Inc.	1-800-438-1985	• U.S. Prescribing Information • Medication Guide
Butrans®	Buprenorphine transdermal system	Purdue Pharma L.P.	1-888-726-7535	• U.S. Prescribing Information • Medication Guide
Dolophine®	Methadone hydrochloride tablets	Roxane Laboratories, Inc.	1-800-962-8384	• U.S. Prescribing Information • Medication Guide
Duragesic®	Fentanyl transdermal system	Janssen Pharmaceuticals, Inc.	1-800-526-7736	• U.S. Prescribing Information • Medication Guide
***Embeda®	Morphine sulfate and naltrexone extended-release capsules	Pfizer Inc.	1-800-438-1985	• U.S. Prescribing Information • Medication Guide
EXALGO®	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt	1-800-778-7998	• U.S. Prescribing Information • Medication Guide
Kadian®	Morphine sulfate extended-release capsules	Actavis	1-888-496-3082	• U.S. Prescribing Information • Medication Guide
MS Contin®	Morphine sulfate controlled-release tablets	Purdue Pharma L.P.	1-888-726-7535	• U.S. Prescribing Information • Medication Guide
Nucynta® ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals, Inc.	1-800-526-7736	• U.S. Prescribing Information • Medication Guide
Opana® ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals Inc.	1-800-462-3636	• U.S. Prescribing Information • Medication Guide
OxyContin®	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma L.P.	1-888-726-7535	• U.S. Prescribing Information • Medication Guide
*Palladone®	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma L.P.	1-888-726-7535	• U.S. Prescribing Information • Medication Guide

*No longer being marketed, but is still approved.
 ***Not currently available or marketed due to a voluntary recall, but is still approved.

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Bookmarks

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 - Prescriber Letter #1 FDA- Required REMS Program for Serious Drug Risks
 - Prescriber Letter #2 FDA- Required REMS Program for Serious Drug Risks
 - Prescriber Letter

Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
 - hydromorphone,
 - morphine,
 - oxycodone,
 - oxymorphone, or
 - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

Have a great weekend!

Best regards,

Edward F Smith III, PhD, MBA, RAC

Vice President, Regulatory Affairs & Product Quality/Safety

Zogenix, Inc.

510 - 550 - 8325 Direct

949 - 201 - 8042 Cell

510 - 550 - 8340 Fax

esmith@zogenix.com

www.zogenix.com

5858 Horton Street, Suite 455, Emeryville, CA 94608

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From: Chiapperino, Dominic [mailto: Dominic.Chiapperino@fda.hhs.gov]

Sent: Thursday, December 13, 2012 4:52 PM

To: Edward Smith

Subject: RE: NDA 202880, Information Request, REMS

Hi Ed,

We need to have the Aug. 28, 2012 version submitted, at least for now. If FDA takes an approval action on any other revised REMS for other ER/LA REMS products, we would then ask Zogenix to update again with that newer version. However, we have to be prepared to take an action on the Zohydro ER NDA by Mar. 1, 2013, and it is not clear if we will already have taken action on other ER/LA REMS (Oct. 2012 version) before Mar. 1, 2013.

I am available tomorrow to chat about REMS, labeling, and nonclinical concerns. If there is a specific time that is good for you just let me know when... My own schedule is pretty open tomorrow.

Nice to see you as well last Friday.

Thanks, and kind regards,
Dominic

From: Edward Smith [mailto:esmith@zogenix.com]

Sent: Thursday, December 13, 2012 7:39 PM

To: Edward Smith; Chiapperino, Dominic

Subject: RE: NDA 202880, Information Request, REMS

Hi Dominic,

According to the RPC, the latest version of the REMS was submitted in Oct 2012. I am confirming that submission date with the RPC. Should I submit that latest version, or does the division prefer we submit the 28 August 2012 version instead?

We can chat about these specifics tomorrow if you have time for a quick call.

Best regards,

Edward F Smith III, PhD, MBA, RAC
 Vice President, Regulatory Affairs & Product Quality/Safety
 Zogenix, Inc.

510 - 550 - 8325 Direct
 949 - 201 - 8042 Cell
 510 - 550 - 8340 Fax
esmith@zogenix.com www.zogenix.com
 5858 Horton Street, Suite 455, Emeryville, CA 94608

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From: Edward Smith
Sent: Thursday, December 13, 2012 3:40 PM
To: 'Chiapperino, Dominic'
Subject: RE: NDA 202880, Information Request, REMS

Hi Dominic,

Nice to see you, albeit briefly last week.

Just a quick note to confirm receipt of your two messages today. First, in regards to the REMS request, that is very straightforward. I can get you a timeline for this by early next week.

Second, regarding your nonclinical DR letter email, it is mostly straightforward, but I have a couple of follow-up questions / comments for you. Would you have time tomorrow for a quick call?

Best regards,

Edward F Smith III, PhD, MBA, RAC
 Vice President, Regulatory Affairs & Product Quality/Safety
 Zogenix, Inc.

510 - 550 - 8325 Direct
 949 - 201 - 8042 Cell
 510 - 550 - 8340 Fax
esmith@zogenix.com www.zogenix.com
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From: Chiapperino, Dominic [<mailto: Dominic.Chiapperino@fda.hhs.gov>]
Sent: Thursday, December 13, 2012 2:05 PM
To: Edward Smith
Subject: NDA 202880, Information Request, REMS

Dear Edward,

Referring to your NDA 202880 for Zohydro ER, we have the following comments related to the REMS submitted with your NDA.

As you know, Zohydro ER would be required to have the extended-release and long-acting (ER/LA) opioid analgesics class REMS. The proposed ER/LA REMS we received with your NDA on May 1, 2012, has not yet been updated via amendment to reflect the first FDA approval of the ER/LA class REMS on July 9, 2012, or updated to reflect the modifications made to the ER/LA REMS on August 28, 2012.

We request that you submit at your earliest opportunity a revised REMS that is in accordance with the most updated version (as of August 28, 2012) of the ER/LA REMS and that includes all necessary drug-specific information for Zohydro ER, e.g., for the FDA Blueprint document. We trust that Zogenix is in contact as necessary with the ER/LA REMS RPC (REMS Program Companies, contact person, Lisa Malandro, MBA, with Pfizer Inc.), which may be a source of assistance in obtaining source files/content not in pdf file format. However, the currently approved ER/LA REMS is publically available at the following link (from FDA's approval action of Nucynta ER efficacy supplement for new DPN indication): <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>

Please contact me if you have any questions about our request for an amendment containing a revised proposed REMS.

Kind regards,
 Dominic

Dominic Chiapperino, Ph D
 Senior Regulatory Health Project Manager
 FDA, Center for Drug Evaluation and Research

Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
12/18/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, December 13, 2012 5:05 PM
To: 'Edward Smith'
Subject: NDA 202880, Information Request, REMS

Dear Edward,

Referring to your NDA 202880 for Zohydro ER, we have the following comments related to the REMS submitted with your NDA.

As you know, Zohydro ER would be required to have the extended-release and long-acting (ER/LA) opioid analgesics class REMS. The proposed ER/LA REMS we received with your NDA on May 1, 2012, has not yet been updated via amendment to reflect the first FDA approval of the ER/LA class REMS on July 9, 2012, or updated to reflect the modifications made to the ER/LA REMS on August 28, 2012.

We request that you submit at your earliest opportunity a revised REMS that is in accordance with the most updated version (as of August 28, 2012) of the ER/LA REMS and that includes all necessary drug-specific information for Zohydro ER, e.g., for the FDA Blueprint document. We trust that Zogenix is in contact as necessary with the ER/LA REMS RPC (REMS Program Companies, contact person, Lisa Malandro, MBA, with Pfizer Inc.), which may be a source of assistance in obtaining source files/content not in pdf file format. However, the currently approved ER/LA REMS is publically available at the following link (from FDA's approval action of Nucynta ER efficacy supplement for new DPN indication):
<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM3>

Please contact me if you have any questions about our request for an amendment containing a revised proposed REMS.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
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Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
12/13/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, October 04, 2012 10:14 AM
To: 'Edward Smith'
Cc: 'Nancy Yee'
Subject: NDA 202880, Information Request, PK studies

Dear Edward,

Referring to your NDA 202880 for Zohydro ER, we have the following request for additional information based on our review thus far:

In order to supplement the analytical information submitted under *2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods*, submit the individual PK study analytical information (e.g., information from actual sample run day - standard curve range; QC samples sensitivity, linearity, specificity, recovery, intra-assay variability, etc.) from all PK studies (ELN-0302002, ZX002-0901, -1001, -1002, -1102, ELN154088-201, and -203).

Also, we remind you of our request for submission of a revised Medication Guide (in accordance with one-page-format Medication Guide for extended-release/long-acting opioid products), as previously discussed via phone call two weeks ago.

Please provide the information via an amendment(s) to the pending NDA at your earliest opportunity, or please contact me if you have any questions.

Thank you, and kind regards,

Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
10/04/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division: Division of Ophthalmic and Ear, Nose, and Throat

Mail Code: HF

Consulting Reviewer Name: Srinivas Nandkumar

Building/Room #: WO66/2436

Phone #: 301-796-6480

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Anesthesia, Analgesia, and Addiction Products

Mail Code: HFD-170

Requesting Reviewer Name: Robert A. Levin, MD

Building/Room #: WO 22/3206

Phone #: 301-796-1963

Fax #:

Email Address: robert.a.levin@fda.hhs.gov

RPM/CSO Name and Mail Code: Dominic Chiapperino, Ph D, HFD-170

Requesting Reviewer's Concurring

Supervisor's Name: Ellen Fields, M.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: Sep. 28, 2012

Requested Completion Date: Dec. 5, 2012

Submission/Application Number: NDA 202880
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: May 1, 2012

Official Submission Due Date: Mar. 1, 2013 (PDUFA date)

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

DAAAP has received an NDA submission for Zohydro, hydrocodone extended release tablets. A single Phase 3 study was conducted to assess the efficacy and safety of the product. Since hearing loss has been associated with the use of hydrocodone, audiologic assessments were included in the protocol. We would greatly appreciate your review of the Sponsor's audiologic assessments in study ZX002-0801, and also the treatment emergent adverse events that were reported during the study that relate to hearing. Audiologic assessments are discussed by the sponsor in Section 12.5.3 of the Study report. There will be an Advisory Committee meeting on Dec. 7, 2012, for discussing risk/benefit profile of Zohydro ER. Your feedback before the AC meeting date would be very appreciated. Dr. James K. Kane has provided previous CDRH consult advice at EOP2 and pre-NDA stage for IND 065111 (associated IND for this pending NDA).

Reference ID: 3197017

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/s/

DOMINIC CHIAPPERINO
09/28/2012



NDA 202880

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Zogenix, Inc
5858 Horton Street
Suite 455
Emeryville, CA 94608

ATTENTION: Edward F. Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs and Product Quality/Safety

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated and received May 1, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate Extended-release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

We also refer to your correspondence dated and received June 14, 2012, requesting review of your proposed proprietary name, Zohydro ER. We have completed our review of the proposed proprietary name, Zohydro ER and have concluded that it is acceptable.

The proposed proprietary name, Zohydro ER, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If **any** of the proposed product characteristics as stated in your May 1, 2012, 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 Mark Liberatore, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2221. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dominic Chiapperino at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
09/12/2012

MEMORANDUM

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

DATE: September 11, 2012

TO: File

FROM: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products

SUBJECT: Record of Contact (verbal), requesting revised labeling

APPLICATION/DRUG: NDA 202880

The sponsor, Zogenix Inc., specifically, Edward F. Smith III, PhD, MBA, RAC Vice President, Regulatory Affairs & Product Quality/Safety, was contact by phone on September 10, 2012.

Zogenix was informed that their submitted proposed Medication Guide for Zohydro ER did not align well with the one-page format Medication Guide currently approved for other extended-release/long-acting (ER/LA) opioid formulations. It was agreed that Zogenix would submit at the earliest opportunity a revised Medication Guide in the one-page format for Zohydro ER.

It was also discussed that the NDA submission did not contain proposed carton labeling. Zogenix confirmed that their plan is to package the (b) (4) and 100 count bottles (for all strengths) in (b) (4), and not have (b) (4) as part of packaging/labeling.

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/s/

DOMINIC CHIAPPERINO
09/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam ATTN: Chris Wheeler, Carol A. McAlman		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183	
REQUEST DATE: August 2, 2012	NDA/BLA NO.: NDA 202880	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW) Original NDA	
NAME OF DRUG: Zohydro ER (hydrocodone bitartrate) extended-release capsules	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) Jan. 8, 2013
SPONSOR: Zogenix, Inc.		PDUFA Date: March 1, 2013	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
EDR link to submission: \\CDSESUB1\EVSPROD\NDA202880\202880.ENX			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: Remaining team meetings: Team Meeting, Tues/Aug. 14, 2012, 11:00-12:00, Rm 3270 Label review planning, Wed/Sep. 12, 2012, 4:00-5:00, Rm 3270 Mid-Cycle, Wed/Oct. 3, 2012, 3:00-4:30, Rm 3270 Labeling, Wed/Nov. 7, 2012, 3:00-4:30, Rm 3270 Team Meeting, Thur/Nov. 8, 2012, 2:00-3:00, Rm 3270 Labeling, Mon/Nov. 19, 2012, 1:30-3:00, Rm 3270 Labeling, Thur/Dec. 13, 2012, 11:30-1:00, Rm 3270 Team Meeting/post-AC, Thur/Dec. 20, 2012, 1:30-3:00, Rm 3270 Labeling, Tues/Jan. 8, 2013, 10:00-11:00, Rm 3270 Wrap-Up, Mon/Jan. 14, 2013, 1:30-3:00, Rm 3270 Labeling, Thur/Jan. 17, 2013, 11:30-1:00, Rm 3270			
SIGNATURE OF REQUESTER Dominic Chiapperino (electronically signed)			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS	

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/s/

DOMINIC CHIAPPERINO
08/02/2012

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

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

TO: CDER-DDMAC-RPM (Mike Wade, Olga Salis, and Becki Vogt), Eunice Chung-Davies, and LaToya (Sheneé) Toombs	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Anesthesia, Analgesia, and Addiction Products Dr. Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183
---	---

REQUEST DATE Aug. 2, 2012	IND NO.	NDA/BLA NO. NDA 202880	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Original NDA, labeling
-------------------------------------	---------	----------------------------------	---

NAME OF DRUG Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10, 15, 20, 30 40, and 50 mg	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 3 (new formulation)	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Jan. 8, 2013
--	---	--	---

NAME OF FIRM: Zogenix, Inc	PDUFA Date: Mar. 1, 2013
--------------------------------------	---------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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EDR link to submission: <\\CDSESUB1\EVSPROD\NDA202880\202880.enx> (May 1, 2012 submission)

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
Note: The Medication Guide should follow the format of the ER/LA REMS opioid products' MedGuides approved July 9, 2012.

Remaining team meetings:
Team Meeting, Tues/Aug. 14, 2012, 11:00-12:00, Rm 3270
Label review planning, Wed/Sep. 12, 2012, 4:00-5:00, Rm 3270
Mid-Cycle, Wed/Oct. 3, 2012, 3:00-4:30, Rm 3270
Labeling, Wed/Nov. 7, 2012, 3:00-4:30, Rm 3270
Team Meeting, Thur/Nov. 8, 2012, 2:00-3:00, Rm 3270
Labeling, Mon/Nov. 19, 2012, 1:30-3:00, Rm 3270
Labeling, Thur/Dec. 13, 2012, 11:30-1:00, Rm 3270
Team Meeting/post-AC, Thur/Dec. 20, 2012, 1:30-3:00, Rm 3270
Labeling, Tues/Jan. 8, 2013, 10:00-11:00, Rm 3270
Wrap-Up, Mon/Jan. 14, 2013, 1:30-3:00, Rm 3270
Labeling, Thur/Jan. 17, 2013, 11:30-1:00, Rm 3270

SIGNATURE OF REQUESTER Dominic Chiapperino (electronically signed)	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/

DOMINIC CHIAPPERINO
08/02/2012



NDA 202880

FILING COMMUNICATION

Zogenix, Inc.
5858 Horton Street
Suite 455
Emeryville, CA 94608

Attention: Edward F. Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs and Product Quality/Safety

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated April 30, 2012, received May 1, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

We also refer to your amendments dated June 14 and July 5, 2012.

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 March 1, 2013.

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, midcycle, 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 February 8, 2013.

At this time, we are notifying you that we have identified the following potential review issues:

1. The specification for (b) (4) in the hydrocodone drug substance obtained from (b) (4) exceeds the ICH Q3A(R2) qualification threshold. Although adequate genetic toxicology data exist, there are no repeat-dose toxicity data to support your proposed specification. You must either (b) (4) the specification to meet the ICH Q3A(R2)

qualification threshold of NMT 0.05% or provide adequate justification for the proposed level in the form of a repeat-dose toxicology study of 90-days duration in a single species.

2. We note that the food effect study was conducted using the Athlone formulation. You have stated that the Athlone formulation and the proposed commercial formulation (Gainesville formulation) are equivalent based on the results of in vitro dissolution, Level A IVIVC, and the successful inclusion of pharmacokinetic data from the study conducted with Athlone and Gainesville formulations. The adequacy of the food effect data will be a review issue.

Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. We remind you of the need to submit the relative bioavailability study with Vicoprofen as soon as the study report is available to allow sufficient review time.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. All headings in Highlights (HL) must be presented in the center of a horizontal line, in upper-case letters, and bolded.
2. The initial U.S. approval listed in HL should reflect the year of the first approval of the active moiety, hydrocodone, which is 1943.
3. In HL section, INDICATIONS AND USAGE, since hydrocodone is in the pharmacologic class of opioid analgesics, the first bullet should be modified as follows: "Zohydro is an opioid analgesic indicated for..."
4. In HL section, ADVERSE REACTIONS, the required bolded statement should have the words "SUSPECTED ADVERSE REACTIONS" in all-caps font.
5. The section headings and subheadings in the Table of Contents (TOC) must match the headings and subheadings in the Full Prescribing Information (FPI). Note that subsection 7.5 from the FPI is missing from the TOC and subheading 17.1, shown in the TOC, is not listed as a subheading in the FPI.
6. The TOC includes only the heading "BOXED WARNING". It should include the entire boxed warning title, "BOXED WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE".

7. FDA-approved patient labeling, such as the proposed Medication Guide, must appear at the end of the package insert (PI) upon approval. We note that your proposed Medication Guide has only been provided within the Risk Management Plans tab of the eCTD submission. Include the Medication Guide in the Labeling tab, 1.12, of the eCTD application. You may replace all PI files currently submitted in tab 1.12 with files that contain the Medication Guide, separated from the end of the PI text with a page break.
8. At the beginning of FPI section 17 PATIENT COUNSELING INFORMATION, the statement “See FDA-Approved Medication Guide” should be replaced with “See FDA-approved patient labeling (Medication Guide)”.

We request that you resubmit labeling that addresses these issues by August 8, 2012. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your requests for a partial waiver of pediatric studies in subjects from 0 to less than 7 years of age and for a partial deferral of pediatric studies in subjects 7 to 17 years of age for this application. Once we have reviewed your requests, we will notify you whether the partial waiver and/or partial deferral requests are granted or denied.

If you have any questions, call Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ on behalf of BOB A RAPPAPORT
07/13/2012
Signing for Bob Rappaport, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Office of Surveillance and Epidemiology ATTN: Mark Liberatore, Safety Regulatory Project Manager		FROM: Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183		
DATE May 18, 2012	IND NO.	NDA NO. 202880	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT Recvd. May 1, 2012
NAME OF DRUG Hydrocodone bitartrate extended-release oral capsules		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 3	DESIRED COMPLETION DATE Dec. 28, 2012
NAME OF FIRM: Zogenix, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): REMS				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DAAAP received this new NDA (10 month PDUFA clock, due Mar. 1, 2013) for single-entity hydrocodone, Schedule II, with proposed indication, "for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." We are requesting consult review by OSE to include the following: <ul style="list-style-type: none"> • DRISK review of REMS (to be in accordance with the ER/LA opioid class REMS) • DMEPA review of all proposed labeling 				
NDA 202880 is fully electronic (eCTD format) and all files can be found in EDR, direct link: \\CDSESUB1\EVSPROD\NDA202880\202880.ENX All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Health Project Manager. The assigned clinical reviewer is Robert A. Levin.				
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

DOMINIC CHIAPPERINO
05/18/2012

REQUEST FOR CONSULTATION

TO (Office/Division):
Controlled Substance Staff (CSS, HFD-009)
ATTN: Corinne Moody, Sandra Saltz

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Anesthesia, Analgesia, and Addiction Products;
Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D., Senior
Regulatory Health Project Manager, 301-796-1183

DATE
May 15, 2012

IND NO.

NDA NO.
NDA 202880

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
recvd: May 1, 2012

NAME OF DRUG
Hydrocodone bitartrate
extended-release oral tablets

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
3

DESIRED COMPLETION DATE
Dec. 31, 2012

NAME OF FIRM: Zogenix, Inc.

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 checked="" 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:

DAAAP received this NDA (10 month PDUFA clock) for single-entity hydrocodone, for the indication, "Management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time."

NDA 202880 is fully electronic (eCTD format) and all files can be found in EDR, direct link:

\\CDSESUB1\EVSPROD\NDA202880\202880.ENX

All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Health Project Manager. The assigned Medical Officer in DAAAP is Robert A. Levin, MD.

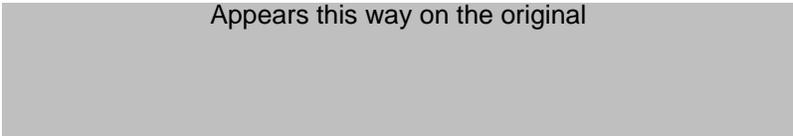
SIGNATURE OF REQUESTOR
Dominic Chiapperino (electronically signed)

METHOD OF DELIVERY (Check one)
 DARTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

DOMINIC CHIAPPERINO
05/15/2012



NDA 202880

NDA ACKNOWLEDGMENT

Zogenix, Inc.
5858 Horton Street
Suite 455
Emeryville, CA 94608

Attention: Nancy Yee
Director, Regulatory Affairs

Dear Ms. Yee:

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: Hydrocodone bitartrate extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg

Date of Application: May 1, 2012

Date of Receipt: May 1, 2012

Our Reference Number: NDA 202880

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 June 30, 2012, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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 Anesthesia, Analgesia, and Addiction 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>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DOMINIC CHIAPPERINO
05/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 065111

MEETING MINUTES

Zogenix, Inc.
Attention: Nancy Yee
Director, Regulatory Affairs
5858 Horton Street, Suite 455
Emeryville, CA 94608

Dear Ms. Yee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HC-ER (hydrocodone bitartrate extended release capsules).

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2011. The purpose of the meeting was to discuss Hydrocodone-extended release development and plans for submission of an NDA in early 2012.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri
Branch Chief, Br. VIII
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA CMC

Meeting Date and Time: November 18, 2011, 1:30 to 2:30 pm
Meeting Location: WO, Bld.21, Rm.1315

Application Number: IND 65111
Product Name: HC-ER (hydrocodone bitartrate extended release capsules)
Indication: management of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid analgesic for extended period of time
Sponsor/Applicant Name: Zogenix, Inc.

Meeting Chair: Prasad Peri
Meeting Recorder: Swati Patwardhan

FDA ATTENDEES

Office of New Drug Quality Assessment:

- Prasad Peri, Ph.D., Branch Chief, Branch VIII
- Danae Christodoulou, Ph.D., CMC Lead, Branch VIII
- Yong Hu, Ph.D., CMC Reviewer, Branch VIII
- Akm Khairuzzaman, Ph.D., Biopharmaceutics Reviewer, ONDQA
- Swati Patwardhan, Regulatory Project Manager, Branch VIII

Controlled Substance Staff

- Silvia Calderon, Ph. D., Team Leader Pharmacologist
- James Tolliver, Ph.D., Pharmacologist

SPONSOR ATTENDEES

- Stephen Farr, PhD, President and Chief Operating Officer
- Cynthia Robinson, PhD, Chief Development Officer
- Edward F. Smith III, PhD., Vice President, Regulatory Affairs and Product Quality/Safety
- Brooks Boyd, PhD, Senior Director, Product Development
- Andrew Hartman, Senior Director, Project Management

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

- Nancy Yee, Director, Regulatory Affairs
- Sharon Hamm, PharmD, RPh, Consultant, Alkermes (formerly Elan Drug Technologies)
- Wayne Wiley, R.Ph., Sr. Director, Regulatory Affairs, Alkermes

1.0 BACKGROUND

Zogenix is developing HC-ER (hydrocodone bitartrate extended release capsules) for management of moderate to severe pain in patients requiring continuous around the clock opioid analgesics for extended period of time. Zogenix has completed Phase 3 clinical study, a single well controlled efficacy protocol, that will support 505(b)(2) submission. Zogenix submitted Pre-NDA CMC only meeting request on September 2, 2011, to discuss Hydrocodone-extended release development and plans for submission of an NDA in early 2012. A briefing package was received on October 11, 2011.

2.0 DISCUSSION

After initial introductions and introductory remarks Zogenix presented slides to facilitate the discussion. Please refer to Attachment I to review the slides.

Question 1: *Does the Agency agree that there is sufficient stability information planned for submission under the (b) (4) and bracketed registration stability protocols to support approvability of 10, 15, 20, 30, 40, and 50 mg dosage strengths of HC-ER provided in (b) (4) count and 100 count bottles, and manufactured with drug substance supplied by either (b) (4) or (b) (4)*

FDA Response: We can not agree on the stability program design at this time. Justify the bracketing design by demonstrating that the factor combinations (such as strength, container size, and fill count) are extremes. We strongly recommend that a (b) (4) is not used so that adequate stability data are generated for this extended-release, high risk product, given that a bracketing strategy is to be pursued. Note that sufficient dissolution data are needed for assessment of drug product performance and expiration dating.

Discussion:

Zogenix presented background information and their revised proposal for the stability program (see attached slides). Zogenix clarified that the only proposed commercial packaging configuration will be 100-count bottle for all strengths ((b) (4) count bottle will not be used for their commercial product). It is also understood that (b) (4), (b) (4), and (b) (4) bottles will be used depending on the strength of the product. The Agency stated that the bracketing design presented on Slide 6 seemed reasonable. Zogenix was requested to provide oxygen and water vapor transmission data for the bottles to further justify the bracketing approach with 10 and 50 mg. However, the Agency reiterated that they have reservation with the (b) (4) approach as presented on Slide 4. Given that Zogenix will provide 12 months stability data for the drug product manufactured with (b) (4) drug substance and packaged in 100-count bottles (Slide 4), the Agency was concerned about missing testing points of 3 and 9 months. The Agency indicated that it is Zogenix's responsibility to justify in the NDA how the overall stability data collected would support the expiration dating period of the product with the various strengths, bottle sizes, and API sources. The adequacy of the stability data will be an NDA review issue.

Zogenix was requested to submit in their NDA, the data set, dissolution trend, and the complete dissolution method development report. The Agency stated that the extended release claim for their product needed to be supported and noted that Zogenix had not conducted a steady state study comparing their ER product with an IR product. Zogenix was asked to provide the comparative drug plasma fluctuation index (*C_{max} to C_{min} ratio*) for their HC-ER product compared to that of the IR hydrocodone product (*currently available in the market as a combination product*), as per the requirement described under 21 CFR 320.25 (f) (iii). The Agency recommended that this information be provided for review, prior to NDA submission. Zogenix pointed out that there is no IR product currently available in the market (*the RLD is a fixed dose combination product*). The Agency stated that for this analysis, the data could be pulled from their two different clinical studies. Zogenix agreed to provide the in-vivo fluctuation index data for these two studies.

Post-Meeting Comments:

The Agency acknowledges Zogenix amendment dated December 7, 2011, which also includes the in-vivo fluctuation information that was requested during the November 18, 2011 meeting. Based on the evaluation of the provided in-vivo PK and clinical data and justification supporting the “extended release claim” for the proposed HC-ER product, the Agency agrees that an in-vivo steady-state pharmacokinetic study evaluating the fluctuation index of the proposed HC-ER product vs. a reference IR hydrocodone product is not needed.

Additionally, in the amendment dated December 7, 2011, Zogenix included the following question;

Would it be possible to have the Agency’s written concurrence that a specific study to evaluate a steady-state pharmacokinetic comparison of HC-ER with an immediate release product of hydrocodone in order to justify the “extended release claim” for HC-ER is not required for the HC-ER NDA filing?

FDA Response:

The Agency concurs that a specific steady state PK study comparing your proposed HC-ER product to an IR hydrocodone product is not needed to support the "extended release claim" and therefore, this study is not required for the filing of your NDA. However, you still are requested to include in your NDA submission details on the in vivo PK and clinical information justifying/supporting the "extended release claim" for your product.

Question 2: *Does the Agency agree that stability information can be provided to the NDA at time of the 120 day safety/stability update in support of the additional dosage strength and API source?*

FDA Response: No, we do not agree. The stability information should be provided at the time of the NDA submission. Include batch release data for the additional strength of 15 mg in the NDA. Alternatively, you may submit the information in a post approval supplement to support the additional dosage strength and/or API source.

Discussion: In addition to batch release data for all other strengths, Zogenix was requested to provide release data for the 15 mg strength. Zogenix agreed to provide the release data for 15

mg in the NDA submission. Zogenix also plans to submit a Biowaiver request (for the 15 mg strength) when submitting a New Drug Application.

Question 3: *The CMC information for HC-ER drug product is described in Alkermes' Type II drug master file (DMF (b) (4)). In addition, both suppliers of the drug substance (i.e. (b) (4), or (b) (4), have filed DMFs (b) (4).*

(i.e., Section 2.3 Quality Overall Summary and Section 3.2.P in its entirety). No other information will be included by Zogenix in Module 3 or Section 2.3 of the NDA. Does the Agency agree with this approach?

FDA Response: No, we do not agree. You should provide the following information in the NDA:

Information on Drug Substance

1. Nomenclature
2. Description
3. Molecular Structure, Molecular Weight and Molecular Formula
4. Physicochemical Properties
5. Manufacturer(s)
6. Specifications (Release and Stability, if different)
7. Stability Protocol and Stability Commitment
8. Stability Data

Information on Drug Product

1. Description
2. Drug Components and Composition
3. Manufacturer(s)
4. Specifications (Release and Stability, if different)
5. Stability Protocol and Stability Commitment
6. Stability Data
7. Container Closure
8. Container and Carton Labels
9. Environmental Assessment

Discussion:

Zogenix asked whether it was acceptable to just refer to the DMFs for the specifications, stability protocols and data and not provide the information in the NDA. The Agency stated that Zogenix should include specifications in the NDA as "acceptance specifications" by the applicant, i.e., Zogenix. Zogenix would need to verify the information on the certificates of analysis provided by the suppliers, based on their acceptance specifications. In addition, acceptance specifications would be used if Zogenix needs to qualify a new supplier in the future. In terms of stability data, the Agency stated that Zogenix can include a summary of stability data in the NDA while referring to the DMFs for detailed information. Zogenix agreed that all information requested

above will be submitted in the NDA except that the stability data section would contain summaries.

Question 4: *A letter of authorization to Zogenix from Alkermes to reference Alkermes' DMF will be included in the Zogenix NDA submission. Additionally,* (b) (4)

Does the Agency agree with this approach?

FDA Response: No, we do not agree. Provide letters of authorization from both drug substance suppliers addressed to Zogenix in the NDA.

Discussion: Sponsor was satisfied with the preliminary responses and no discussion occurred.

Question 5: *An outline of the planned studies for the conduct of the abuse liability assessment for the HC-ER drug product per the Agency's draft guidance document "Assessment of Abuse Potential of Drugs", is provided in Table 4-2. Will the Agency confirm that this plan is adequate to address abuse liability assessment for this Schedule II product submitted as a 505(b)(2) NDA with* (b) (4) *as the reference product, and that no additional studies or requirements are necessary for NDA filing and review?*

FDA Response: There is no "Table 4.2" provided in the pre-NDA CMC meeting briefing document. It is assumed that the question pertains to Table 4.1 found on page 21 of the briefing document, and is a tabular summary, and not a complete protocol, of the in vitro studies completed.

Although additional studies assessing the potential to misuse and abuse the to-be-marketed HC-ER capsules are not necessary for purposes of determining the appropriate schedule for placement of HC-ER under the Controlled Substances Act (CSA), there are insufficient scientific data and other information to complete such an assessment with your to-be-marketed product. Such a complete assessment would be helpful in evaluating REMS for HC-ER capsules.

Considering the high doses of hydrocodone along with the lack of any abuse deterrent properties, it is recommended that you examine in detail the vulnerability of the to-be-marketed HC-ER product formulation for susceptibility to physical manipulation and chemical extraction of hydrocodone. As such, the in vitro abuse liability assessment described in Table 4.1 should be expanded. Instead it is recommended that the in vitro abuse potential assessment of the to-be-marketed HC-ER formulation include the following components:

- Assess the ease of physical manipulation of HC-ER capsules and beads using selected tools such as a pill crusher and mortar and pestle. Established procedures should be utilized to measure particle size.
- Assess the ease of hydrocodone extraction from intact capsules and manipulated capsules and beads using solvents of different polarity and pH, including but not limited to: water, alcohol, basic solutions, acidic solutions, acetone, isopropyl alcohol, methanol, methylene chloride, toluene, and ethyl acetate. Chemical extraction should be done

under rigorous agitation and assessed at multiple time points out to 12 hours or until most of the hydrocodone has been extracted.

- Evaluate the effect of elevated solvent temperature on extraction of hydrocodone from intact capsules and manipulated capsules and beads.
- Assess ways to tamper with the to-be-marketed product formulation in order to obtain a hydrocodone preparation suitable for intranasal and intravenous abuse.

As part of the overall assessment of the potential to misuse and abuse HC-ER, as well as possible safety issues resulting from such misuse or abuse, it is recommended that you conduct a human abuse potential study in nondependent, experienced opioid abusers using the oral route for intact, crushed, and chewed HC-ER capsules. This study should be scientifically rigorous, well controlled, use appropriate drug comparators [such as immediate release oxycodone], and employ appropriate outcome measures, including pharmacokinetic and pharmacodynamic (subjective effects) measures. CSS is willing to review and provide comments on complete protocol for the study prior to initiation of the study.

Discussion:

CSS stated that, in light of the summary data submitted by the Sponsor on November 17, 2011, no additional *in vitro* studies were requested. Prior to the meeting the Sponsor provided a summary slide addressing the dissolution profile of the formulation, basic extraction study results using intact and manipulated formulation and five solvents, isolation of hydrocodone from the manipulated formulation with the purpose of preparing an injectable solution, and manipulation of the formulation to produce a powder suitable for nasal insufflation. The data summarized by the Sponsor confirms that 95 % of the hydrocodone present in the formulation can be easily extracted in water, when ground beads are taken in 20 ml of water and with vigorous shaking.

Regarding the request for the measurement of particle size, the Sponsor agreed to measure particle size of crushed material.

Question 6: *Does the Agency agree with placement of the above-mentioned in vitro abuse assessment information in Sections 2.5 (Clinical Overview-Benefits and Risks Conclusions) of the NDA and Section 3.2.P.2 (Pharmaceutical Development) of Alkermes' DMF?*

FDA Response: No. The *in vitro* abuse assessment information should be sent as part of the NDA, and is critical in the assessment of risks associated with the misuse and abuse of your product. The FDA draft guidance document entitled "Guidance of Industry: Assessment of Abuse Potential for Drugs" provides guidance on the proper location to place abuse potential data and information when submitting an NDA in electronic format. Chemistry related data and studies pertaining to abuse potential should be placed in Module 3. As such it is appropriate to place the *in vitro* abuse assessment information in Section 3.2.P.2 (Pharmaceutical Development). According to the guidance document, Module 3 can contain links to the summary of abuse data including chemistry data found in Module 2.

Discussion: Sponsor was satisfied with the preliminary responses and no discussion occurred.

Question 7: *Does the Agency agree that the in vitro alcohol dissolution work is adequate for labeling and that no further in vitro work to characterize this attribute is required?*

FDA Response: Your in vitro testing design for alcohol induced dose dumping study appears to be reasonable. However, the data show a trend of dose dumping starting from 10% alcohol. Since you have conducted an in vivo alcohol induced dose dumping study, the evaluation of the results from this study will be performed by the Office of Clinical Pharmacology.

Discussion: Sponsor was satisfied with the preliminary responses and no discussion occurred.

Question 8: *Does the Agency further agree that the in vitro alcohol assessment should also be included in Section 3.2.P.2 of Alkermes' DMF, and summarized in the summary biopharmaceutical assessment in Section 2.7.1 of the HC-ER NDA?*

FDA Response: We recommend that you submit *in vitro* alcohol assessment report in the NDA for the ease of review.

Discussion: Sponsor was satisfied with the preliminary responses and no discussion occurred.

Question 9: *Will the Agency expect a methods validation package to be submitted as part of the NDA submission (in addition to inclusion in Alkermes DMF), or should it just be held available for submission upon request from the Agency?*

FDA Response: For the ease of review, we encourage you to submit a methods validation package in the NDA (in addition to inclusion in Alkermes DMF).

Discussion: Sponsor was satisfied with the preliminary responses and no discussion occurred.

Additional Pre-NDA meeting Comments:

1. Provide batch analysis data for the 15 mg capsule strength in the NDA.
2. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
3. Refer to ICH Q3A and Q3B for reporting, identifying, and qualifying impurities in the drug substances and drug product. To support up to 3 g/day drug intake, the impurities in the drug substance should be identified and qualified at 0.05% threshold and the impurities in the drug product should be identified and qualified at 0.10% and 0.15% thresholds, respectively.
4. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
5. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number, email address and facsimile number at the site.

6. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester, etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
7. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.
8. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis); and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

Discussion:

Zogenix requested clarification related to the above comment. The Agency stated that the presentation of stability data as discussed above facilitates review of the stability data and trending parameters. It is preferred that graphs with independent data points with each parameter and with separate condition be submitted.

9. Provide an updated DMF (b) (4) in CTD format to support your NDA. For the ease of NDA review, we encourage you to also include appropriate information from the DMF in the NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ATTACHMENTS AND HANDOUTS

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/s/

PRASAD PERI
01/04/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 065111

MEETING MINUTES

Zogenix, Inc.
5858 Horton Street, Suite 455
Emeryville, CA 94608

Attention: Edward F. Smith, III, Ph.D., RAC
Senior Director, Clinical Operations

Dear Dr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HC-ER (hydrocodone bitartrate extended-release capsules).

We also refer to the meeting between representatives of Zogenix and the FDA on November 17, 2011. The purpose of the meeting was to discuss your HC-ER clinical development program and planned 505(b)(2) NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Memorandum of Meeting Minutes
Attachment 1: General Advice Offered at Pre-NDA Stage of Development
Attachment 2: Opioid Medication Guide Template
Attachment 3: Abuse Assessment Summary

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 17, 2011
TIME: 3:00 to 4:00 PM
LOCATION: Building 22, Room 1315
FDA White Oak Campus
Silver Spring, MD 20903
APPLICATION: IND 065111
PRODUCT: HC-ER (hydrocodone bitartrate extended-release capsules)
SPONSOR: Zogenix, Inc.
TYPE OF MEETING: Type B, Pre-NDA
MEETING CHAIR: Ellen Fields, M.D., Clinical Team Leader, Division of Anesthesia,
Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project
Manager, DAAAP

ATTENDEES:

FDA Attendees

Bob A. Rappaport, M.D., Director, DAAAP
Sharon Hertz, M.D., Deputy Director, DAAAP
Ellen Fields, M.D., Clinical Team Leader, DAAAP
Elizabeth Kilgore, M.D., Medical Officer, DAAAP
Dan Mellon, Ph.D., Pharmacology Toxicology Supervisor, DAAAP
Elizabeth Bolan, Ph.D., Pharmacology Toxicology Reviewer, DAAAP
Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP
Yun Xu, PhD, Clinical Pharmacology Team Leader, Division of Clinical
Pharmacology II (DCP2)
David J. Lee, Ph.D., DCP2
Dionne Price, Ph.D., Biostatistics Team Leader, Division of Biometrics II (DB2)
Jonathan Norton, Ph.D., Biostatistics Reviewer, DB2
Silvia Calderon, Ph.D., Team Leader, Controlled Substance Staff (CSS)
Lori A. Love, M.D., Lead Medical Officer, CSS
James M. Tolliver, Ph.D., Pharmacologist, CSS
Danae Christodoulou, Ph.D., Chemistry, Manufacturing, and Controls (CMC) Lead, Office of
New Drug Quality Assessment (ONDQA)
Anne C. Tobenkin, Pharm.D., Safety Evaluator, Division of Medication Error Prevention and
Analysis (DMEPA)

Zogenix Attendees

Stephen Farr, Ph.D., President and Chief Operating Officer
Cynthia Robinson, Ph.D., Chief Development Officer
Edward F. Smith III, Ph.D., Vice President, Regulatory Affairs and Product Quality/Safety
Brooks Boyd, Ph.D., Senior Director, Product Development

Andrew Hartman, Senior Director, Project Management
John Ning, M.D., Ph.D., Medical Director, Drug Safety and Clinical Affairs
Nancy Yee, Director, Regulatory Affairs
Chris Rubino, Pharm.D., Clinical Pharmacology Consultant
Sharon Hamm, Pharm.D., R.Ph., Consultant, representing Alkermes (formerly Elan Drug Technologies)
[REDACTED] (b) (4) Ph.D., Statistical Consultant
[REDACTED] (b) (4) M.D., Audiology Consultant

BACKGROUND

Zogenix requested a meeting with the Division to discuss the nonclinical and clinical development of HC-ER and the submission requirements for a 505(b)(2) New Drug Application (NDA).

Below are the Division's responses to the questions from Zogenix's October 10, 2011, meeting package, which were sent to Zogenix as "Preliminary Comments" on November 14, 2011, ahead of the November 17, 2011, meeting. Zogenix specified (via Nov. 16, 2011 email) the following questions/topics, in order of priority, that they wished to discuss during the meeting:

- CSS additional comments: the need to additionally assess the potential for misuse and abuse of the product
- Clinical Question 4-1 and Administrative Question 6-4 comments regarding an appropriate 505(b)(2) reference product
- Clinical Question 4-8 comments regarding audiology assessments
- Additional comments regarding statistical analysis.

DISCUSSION

All questions and responses are presented below in their original order, with Zogenix' questions in italics and the Division's responses in bolded text, identical to responses sent as Preliminary Comments, November 14, 2011. Discussion of Zogenix' specified topics is captured in normal font, directly following the relevant responses or comments. Final understandings from these discussions during the meeting are summarized after the Discussion section. Attachments 1 and 2 from the November 14, 2011, Preliminary Comments are again attached for completeness.

Nonclinical Questions

Question 3-1. Does the Agency agree that the Fertility and General Reproductive Toxicity (Segment I) study in rats was adequate and acceptable, and that no further Segment I studies are required?

FDA Response:

Based on the information submitted, your nonclinical development plan appears to be adequate to support filing of your NDA. However, final determination of the adequacy of the data to support approval of your NDA cannot be determined until formal review of the NDA.

Discussion:

No discussion was necessary for this question.

Question 3-2. Does the Agency agree that the Developmental Toxicity (Segment II) study in rats, and the Developmental and Perinatal/Postnatal Reproduction Toxicity (Segment III) study in rats were acceptable, and that no further Segment II or Segment III studies in rats are required?

FDA Response:

See our response to Question 3-1.

Discussion:

No discussion was necessary for this question.

Question 3-3. Does the Agency agree that the Development Toxicity (Segment II) study in rabbits was acceptable, and that no further Segment II studies in rabbits are required?

FDA Response:

See our response to Question 3-1.

Discussion:

No discussion was necessary for this question.

Question 3-4. Does the Agency agree that appropriate evaluations have been undertaken by (b) (4) and (b) (4), and provided that there are no additional (b) (4) above the (b) (4) mcg per day limit, that no further qualification is required by Zogenix?

FDA Response:

Provide the impurity qualification information in the NDA or DMFs, preferably in the NDA. We will evaluate the information as part of the NDA review. Impurity limits must comply with ICH Q3A, Q3B and structural alerts should be no more than (b) (4) mcg total daily exposure.

Discussion:

No discussion was necessary for this question.

Question 3-5. Does the Agency agree that the qualification of (b) (4) as a degradation product in the HC-ER drug product is adequate and that no further qualification is required by Zogenix?

FDA Response:

See our response to Question 3-1.

Discussion:

No discussion was necessary for this question.

Question 3-6. Does the Agency agree that the information provided demonstrate the acceptability of the excipients in the HC-ER drug product up to the maximum theoretical daily dose of 3 g hydrocodone bitartrate?

FDA Response:

See our response to Question 3-1.

Discussion:

No discussion was necessary for this question.

Question 3-7. Does the Agency agree that the proposed evaluations of impurities / degradation products, (b) (4) control and container closure materials for the HC-ER drug product at hydrocodone bitartrate doses of up to 3 g/day are acceptable and that no further material qualification studies are required?

FDA Response:

See our response to Question 3-1.

Additionally, note that the impurity identification threshold is 0.10% and the qualification threshold is 0.15% for the drug product in order to support up to 3 gm as the total daily dose in accordance with ICH Q3B.

With respect to container/closure materials, note that the primary stability batches' packaging must be representative of the proposed commercial packaging.

Discussion:

No discussion was necessary for this question.

Question 3-8. An overview of nonclinical studies to support the NDA and as post-approval commitments is provided in Table 3-1 and Table 3-2. Does the Agency agree that the nonclinical plan to support a 505(b)(2) NDA approval is acceptable and no additional nonclinical studies are required?

FDA Response:

See our response to Question 3-1.

Discussion:

No discussion was necessary for this question.

Clinical Questions

Question 4-1. The following five clinical pharmacology studies have been completed: ELN-0901001, ELN-0302002, ZX002-0901, ZX002-1001, and ZX002-1002. Does the Agency agree that these studies adequately support the approvability of HC-ER in the 10, 15, 20, 30, 40 and 50 mg dosage strengths?

FDA Response:

We note that you wish to file a 505(b)(2) application with (b) (4) as the reference product. A 505(b)(2) application may only rely upon the Agency's previous finding of safety and effectiveness of a drug approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (i.e., NDAs). As the (b) (4) ANDA was approved under section 505(j) (i.e., ANDAs, generics) there is no Agency previous finding of safety and effectiveness to rely upon.

You must select an approved NDA product listed in the Orange Book as your 505(b)(2) reference and conduct a relative bioavailability study with this product as a scientific bridge to the Agency's prior findings of safety and efficacy for that product. Otherwise, the information about the proposed studies appears to be adequate to support the filing of your NDA. The approvability of the NDA is a review issue.

If the formulation used in these studies is different from your final to-be-marketed formulation, you must provide bridging information or an adequate rationale to justify why the study results can be used to support your application.

Discussion:

The Division acknowledged that our advice regarding 505(b)(2) reference products has been refined over time, as the legal guidance we have received has evolved. The Division stated that 505(b)(2) submissions must reference an NDA, not an ANDA product, as a 505(b)(2) NDA relies on prior Agency findings of safety and effectiveness, and ANDA approvals are not supported by such findings, but also rely on previous Agency findings of safety and effectiveness.

The Division stated that an in vivo pharmacokinetic (PK)/relative bioavailability (BA) study using the referenced NDA product must be conducted to confirm an appropriate bridge. The relative BA study should utilize a single extended-release dose of a comparable mass dose when feasible, e.g., one dose of 12-hour extended-release product versus two sequential doses of 6-hour immediate release product over the 12-hour period. In lieu of comparable doses, the Agency agreed that the use of dose-normalized concentrations and exposure estimates would be acceptable. The Division stated that it is not expected that HC-ER would be bioequivalent to the reference product due to the inherent differences in IR and ER dosage forms. However, the Division encouraged Zogenix to set typical BE criteria for analysis and provide the comparative profiles so comparability can be assessed.

It was also agreed that the additional relative BA study data should be included in the NDA's integrated summary of safety, though the data do not need to be integrated into the pooled dataset. The Division clarified that safety data from studies where subjects received naltrexone blocks should not be pooled with data from non-blocked subjects or patients.

Question 4-2. Does the Agency agree that all dose proportionality study needs have been met for the approvability of the 10, 15, 20, 30, 40 and 50 mg dosage strengths of HC-ER?

FDA Response:

You used study results from Study ELN154088-201, Study ELN154088-203, and a population PK analysis to support the dose proportionality up to 50 mg of your product. These studies are adequate to support the NDA filing of your product. However, whether your product is dose proportional and the approvability of the NDA will be review issues.

It appears you do not have any PK information for the 15 mg dosage strength and that you are seeking a biowaiver for this strength. You will need to provide an appropriate justification to support the biowaiver.

Discussion:

No discussion was necessary for this question.

Question 4-3. Will the Agency confirm that the design of the alcohol interaction study ZX002-0901 is sufficient to support product labeling, which warns against the consumption of alcohol or prescription or non-prescription products containing alcohol while on HC-ER therapy?

FDA Response:

The design of the alcohol interaction study, Study ZX002-0901, appears to be sufficient to support the filing of your NDA. The adequacy of the study and whether the information will be in the product labeling are review issues.

Discussion:

No discussion was necessary for this question.

Question 4-4. As described in Section 4.3, the ISS will include integrated safety data for all nine clinical studies. In addition to the All Treated population, the safety data will be summarized for Controlled Acute Population (ELN-154088-201 only), Chronic Population (Phase 3 studies ZX002-0801 and ZX002-0802 only), Impaired Volunteers Population (subjects with renal and hepatic impairment from studies ZX002-1001 and ZX002-1002), and the Healthy Volunteers population. In the NDA filing the ISS will include the interim safety data analysis for Study ZX002-0802 and will be updated with final data from this study for the 120-day safety update. Does the Agency agree with Zogenix's approach to the presentation of the integrated safety data?

FDA Response:

Yes, your approach for integrated safety data in the ISS appears acceptable. In order for FDA staff to comply with Good Review Management Practices (GRMP) Timelines, you must submit all data necessary for review in the original NDA submission. The 120-day safety update is only intended to contain additional data that become available after the data required to support filing.

In addition to the pooled safety data, we will also review controlled and uncontrolled data separately.

Discussion:

No discussion was necessary for this question.

Question 4-5. Does the Agency agree that the Chronic Population analysis from the ISS (Studies ZX002-0801 and ZX002-0802) will be most relevant source for labeling for an indication for chronic use?

FDA Response:

Yes, we agree that the chronic pain population safety analysis is the most relevant for labeling for an indication for the management of chronic pain; however, all safety data will be reviewed. The exact language included in the product labeling will be a review issue.

Discussion:

No discussion was necessary for this question.

Question 4-6. Zogenix plans to file an NDA with an interim analysis of the ZX002-0802 Phase 3 safety study that provides the agreed-to safety database of six months of exposure data for > 300 subjects and 12 months of exposure data for > 100 subjects. The study will be carried to completion and all remaining data submitted in the 120-day safety update. Does the Agency agree with this plan?

FDA Response:

Yes. See our response to Question 4-4.

Discussion:

No discussion was necessary for this question.

Question 4-7. In addition to submitting completed case report forms (CRFs) for deaths, other serious adverse events, and withdrawals due to adverse events, Zogenix is planning on submitting completed CRFs for all subjects who withdrew consent from our Phase 3 efficacy study ZX002-0801. Is the Agency in agreement with this plan?

FDA Response:

Yes. The NDA submission must contain complete information, including case report forms and final outcomes for all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study. See additional CSS comments at the end of the document.

Discussion:

No discussion was necessary for this question.

Question 4-8. Does the Agency agree that the audiology assessments performed in Study ZX002-0801 are adequate to address the Agency's request for an audiology assessment of HC-ER?

FDA Response:

DAAAP has consulted the Center for Devices and Radiological Health (CDRH) and will provide a response to this question as a post-meeting note with the official meeting minutes.

Discussion:

Zogenix introduced Dr. (b) (4). Dr.

(b) (4) presented his expert opinions and clinical findings of profound hearing loss associated with hydrocodone/acetaminophen abuse (Friedman et al., 2000-Attachment 3 of Appendix 10, Meeting Briefing Package). Dr. (b) (4) also discussed his colleague's findings in an in vitro cell-based study indicating that acetaminophen is likely responsible for combination product ototoxicity resulting from hydrocodone/acetaminophen abuse (Yorgason et al., 2010-Attachment 4 of Appendix 10, Meeting Briefing Package). The Division stated that we are not aware of any incidence of hearing loss in people taking acetaminophen alone or abusing Percocet (oxycodone/acetaminophen), indicating that there appears to be an association of this ototoxicity specific to hydrocodone products, perhaps due to an interaction between hydrocodone and acetaminophen.

Zogenix stated that audiology data from completed Clinical Study ZX002-0801 are available. Zogenix also noted that no hypoacusis has been reported as an adverse event in Clinical Study ZX002-0802. The Division stated that all of these data should be submitted with the NDA, along with Dr. (b) (4) findings. The auditory assessments and results would not be a fileability issue, but the data will be evaluated as part of the NDA review.

It was agreed that written audiology comments from the Division, following internal advisement from CDRH, would be provided to Zogenix. A follow-up teleconference would be granted for any discussion necessary among Zogenix, DAAAP, and CDRH.

Post-meeting note:

- CDRH has reviewed the additional information you provided in support of the audiology safety assessments performed in Study ZX002-0801 for monitoring the potential ototoxic effects of HC-ER and has determined that the audiological safety monitoring appears to have been adequate.

Question 4-9. At the EOP2 meeting, the Agency indicated that single, well-controlled efficacy study would be sufficient for a 505(b)(2). Zogenix has completed Study ZX002-0801 and intends that this study will serve this purpose. Does the Agency confirm the acceptability of this approach and agree that the design of ZX002-0801 is acceptable for a 505(b)(2) submission?

FDA Response:

Study ZX002-0801, a Phase 3 randomized, double-blind, placebo-controlled efficacy, tolerability and safety study, with the primary endpoint of average NRS from baseline to Day 85 of HC-ER in opioid-experienced patients for a 12-week duration, appears adequately designed to support filing of the NDA. The approvability of HC-ER will be a review issue.

Discussion:

No discussion was necessary for this question.

Question 4-10. Zogenix intends to submit an Integrated Summary of Effectiveness (ISE) as per FDA's guidance. The primary focus of this document will be to summarize efficacy data from the single pivotal Phase 3 study (ZX002-0801). Additional controlled and uncontrolled efficacy data from other studies (Phase 2 and Phase 3) will also be summarized as appropriate. However, due to the differences in population, study design, and treatment indication, these efficacy data will not be integrated across studies. Does the Agency agree with this approach?

FDA Response:

Yes, this strategy appears acceptable.

Discussion:

No discussion was necessary for this question.

Question 4-11. Does the Division agree that [REDACTED] (b)(4) [REDACTED] is appropriate? If not, would the Division agree to a waiver for studies in pediatric patients ages 0-12 and a deferral for studies in pediatric patients ages 12-17?

FDA Response:

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(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable. In addition, PREA requires that the FDA Pediatric Review Committee (PeRC) review all pediatric assessments, pediatric plans, and waiver or deferral requests prior to the Division taking an approval action.

We encourage you to submit a pediatric assessment with your NDA (a pediatric assessment is data sufficient to support dosing, safety, and efficacy in the relevant pediatric populations). However, if the pediatric assessment is not complete at the time of NDA submission, you must provide a pediatric development plan with a request for a waiver and/or deferral of studies in the appropriate pediatric populations, justification for waiving and/or deferring the assessments, and evidence that the deferred pediatric studies are being conducted or will be conducted with due diligence. In addition, provide a timeline for completion of deferred studies. At a minimum, you must provide the date the protocol will be submitted, the date the studies will be completed, and the date the studies will be submitted. We refer you to the industry guidance titled "How to Comply with the Pediatric Research Equity Act" (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>)

Under PREA, you may be required to conduct pharmacokinetic (PK), safety, and possibly efficacy studies for your proposed indication in pediatric patients < 17 years old pending FDA's decision on the need for data in this population. Please note that pediatric

participants in clinical studies must be symptomatic or at risk for the condition(s) treated by the product to be consistent with 21 CFR 50 subpart D and the related ethical framework for research in children.

The proposed indication for your product is “the management of moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic treatment is needed for an extended period of time.” As such:

- For opioid analgesics indicated for the treatment of chronic pain, the pediatric requirements include PK and safety studies in patients ages 7 to 17 years.
- Efficacy findings in adults may be extrapolated to the pediatric age group over 7 years of age, since the underlying painful conditions and mechanism of action of the opioid class of drugs are similar in adults and pediatric patients in this age group.
- Studies in pediatric patients under the age of 7 years may be waived with acceptable justification, e.g., a small population of pediatric patients in this age group with chronic pain requiring treatment with around-the-clock opioids.

According to PREA, you are required to develop an age appropriate formulation. If you cannot achieve this, submit documentation regarding your attempts at formulation development.

Keep in mind that an adequate amount of time should be included in the timeline prior to the date of final protocol submission in order to obtain comments from the Division on the proposed protocol. We encourage you to submit pediatric protocols as soon as possible and to initiate pediatric studies as soon as sufficient data in adults has been collected to ensure that it is safe to proceed in pediatric patients.

Include protocol synopses with the pediatric plan.

Discussion:

No discussion was necessary for this question.

Question 4-12. Does Study [redacted] (b) (4)

[redacted] as follows:

[redacted] (b) (4)

FDA Response:

No, Study [redacted] (b) (4). In order to obtain [redacted] (b) (4)

(b) (4)

Discussion:
No discussion was necessary for this question.

Question 4-13. If Study [redacted] (b) (4).
[redacted] *could the Agency provide guidance as to the*
requirement(s) to [redacted] (b) (4).
[redacted]

FDA Response:
See response to Question 4-12.

Discussion:
No discussion was necessary for this question.

Question 4-14. If the Agency agrees with [redacted] (b) (4)
[redacted]
[redacted] ?

FDA Response:
We do not agree that [redacted] (b) (4)
[redacted]

Discussion:
No discussion was necessary for this question.

Question 4-15. If the Agency does not agree with [REDACTED] (b) (4) [REDACTED] does the Agency agree with the following labeling indication for the management of chronic pain:

“HC-ER is an extended-release oral formulation of hydrocodone bitartrate indicated for the management of moderate-to-severe chronic pain when a continuous opioid analgesic is needed for an extended period of time.”

FDA Response:

The following indication is appropriate for an extended-release opioid such as yours:

“HC-ER is an extended-release oral formulation of hydrocodone bitartrate indicated for the management of moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.”

Additional Comments Regarding Statistical Analysis and Electronic Submission

- The primary efficacy analysis for study ZX002-0801 addressed missing data by using last observation carried forward (LOCF), baseline observation carried forward (BOCF), or screening observation carried forward, depending on why the observation is missing.

You should be aware that in July 2010, the National Academy of Sciences (NAS) released a report on missing data which was commissioned by FDA. The report recommends that, “Single imputation methods like [LOCF] and [BOCF] should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.” The report can be found online at http://www.nap.edu/catalog.php?record_id=12955.

Your proposed approach is a single imputation method, because each missing observation is filled in with a single value. We agree with the concerns that the NAS raises. However, we continue to favor methods for handling missing pain data which attribute poor outcomes to those patients who discontinue early, particularly when the reason is an adverse event. We are also concerned about the impact of opioid withdrawal on the analysis, when that is applicable (e.g., in a randomized withdrawal design).

At this time, we are recommending that all sponsors consider the NAS report when planning, conducting, and analyzing clinical trials. We understand that study ZX002-0801 is complete and has been analyzed and unblinded; therefore, the NDA may be submitted without additional analyses. We will thoroughly investigate the impact of missing data during the course of the review.

- In an e-mail of November 1, 2011, you indicated that you plan to submit the NDA as an eCTD and that you will include electronic datasets.

In regard to the eCTD format, refer to the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, which is available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

In regard to the electronic datasets, we encourage you to submit CDISC-compliant analysis and tabulation files. Our recommendations for implementation of the CDISC standards can be found in the CDER Common Data Standards Issues Document:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>

We also refer you to the following resources which are intended to assist submitters in the preparation and submission of standardized study data to CDER:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Discussion:

Zogenix asked about the additional analyses that FDA may conduct for Study ZX002-0801, as Zogenix [REDACTED] (b) (4).

The Division stated that we continue to assess the landscape of possible methodologies following the NAS 2010 report and will be interested in seeing how different analyses that address both the concerns outlined in the report and concerns unique to pain trials perform on actual data. The Division did not specify at this time any statistical methods that are planned, but stated that we would most likely contact Zogenix via an Information Request to identify particular statistical analyses of interest during the NDA review so that Zogenix [REDACTED] (b) (4).

The Division also stated that Zogenix could consider including a justification in the NDA as to the appropriateness of the single imputation method that they used.

REMS Questions

Question 5-1. The REMS and components are designed to be consistent with FDA's letter sent to opioid manufacturers outlining opioid REMS implementation on 19 April 2011 and information provided in the subsequent conference call as well as the publically available information from the May 16, 2011 meeting between the Industry Working Group (IWG) and FDA. Does the Agency agree that the components of the REMS program for HC-ER, as outlined in the materials provided, meet the Agency's requirements for a REMS for this product?

FDA Response:

A complete review of the full REMS after the NDA is submitted will be necessary to determine whether the proposed approach is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

You plan to submit a REMS with the original NDA submission. Therefore, please submit, with your NDA, all planned materials (e.g., proposed communications and education materials) identified within the plan that will be necessary to implement your proposal.

In addition, we have the following high-level comments on the proposed REMS submitted as part of this meeting package. These comments should be considered as general advice only, as we will conduct a thorough review of a proposed REMS only following NDA submission.

- Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- Product marketing materials generally are not appropriate to educate about product risks.
- As you are not currently a member of the Industry Working Group (IWG), which is developing a class-wide extended release/long acting (ER/LA) Opioid REMS, your proposed REMS does not contain a comparable level of detail as the proposed REMS for ER/LA opioid products sponsored by participating members of the IWG. Upon submission of your NDA, we encourage you to participate with the IWG to ensure that your REMS contains the appropriate information.

We remind you that a proposed REMS will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the criteria specified in Section 505-1 of the FDCA.

Discussion:

No discussion was necessary for this question.

Question 5-2. Zogenix has developed a Medication Guide based upon available FDA guidance, which has been provided in Appendix 12. Is this Medication Guide acceptable?

It is Zogenix's understanding that FDA is/has developing/ed a Medication Guide Template for long acting opioids. Will FDA be able to provide Zogenix access to the Medication Guide Template? If so, what is the anticipated timing of the availability of the template?

FDA Response:

A complete review of the REMS in conjunction with the full clinical review after the NDA is submitted will be necessary to determine whether the Medication Guide is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

We have included an opioid-specific Medication Guide Template as an "enclosure" (Attachment 2), appended to this communication.

Discussion:

No discussion was necessary for this question.

Question 5-3. Zogenix assumes that the HC-ER REMS will to be part of the class-wide long-acting opioid REMS at the time of product launch. What is the Agency's expectation regarding the timing of the integration of the HC-ER REMS into the class-wide long-acting opioid REMS?

FDA Response:

The class-wide ER/LA Opioid REMS is anticipated to be approved in early 2012. If approved, it is expected that your product, HC-ER, will be approved with the class-wide ER/LA Opioid REMS program. Once you submit your NDA, we encourage you to join the IWG to ensure appropriate integration into the single-shared system.

Discussion:

No discussion was necessary for this question.

Question 5-4. At the time HC-ER becomes part of the class-wide opioid REMS, will there be additional or specific REMS components and/or assessments that the FDA anticipates will pertain solely to HC-ER and remain outside of the class-wide program?

FDA Response:

At this time, the class-wide ER/LA Opioid REMS is not yet approved and, therefore, its specific detailed components are not yet finalized. Also, any additionally needed components of your REMS, specific to HC-ER, could only be described following our thorough clinical review of the NDA. In broad terms, we have not as of yet identified additional components and/or assessments that we anticipate would need to be incorporated into a REMS for HC-ER.

Discussion:

No discussion was necessary for this question.

Question 5-5. With regards to the requirement for Continuing Medical Education (CME), Zogenix assumes that the HC-ER REMS will be part of the "blueprint approach" for CME providers with content consistent with Appendix A of the April 19, 2011 FDA letter sent to opioid manufacturers outlining opioid REMS implementation. Therefore, Zogenix has included HC-ER-specific materials as part of the current outline and anticipates working with the IWG to coordinate immediately upon filing acceptance of the HC-ER NDA (as IWG membership and/or participation is limited to those companies with approved and/or pending marketing applications). Does the Agency concur with this approach?

FDA Response:

This approach is reasonable.

Discussion:

No discussion was necessary for this question.

Question 5-6. Zogenix understands that the HC-ER REMS assessment plan should be consistent with or part of the class-wide assessment plan. It is anticipated that Zogenix will need to coordinate with the IWG immediately upon filing acceptance of the HC-ER NDA (as IWG membership and/or participation is limited to those companies with approved and/or pending marketing applications). Therefore, Zogenix plans to provide methodology for the assessment surveys at the time of NDA submission and then coordinate methodologies for the surveillance plan, drug utilization patterns, and evaluation of changes in prescribing behavior of prescribers with the IWG after submission of the NDA. Does the Agency concur with this approach?

FDA Response:

This approach is reasonable.

Discussion:

No discussion was necessary for this question.

Administrative Questions

Question 6-1. Does the FDA have any comments on the overall format and content of the proposed draft label, given that some of the content may be revised as additional data become available?

FDA Response:

The label is in PLR format which is appropriate. The contents of the label will be a review issue.

Discussion:

No discussion was necessary for this question.

Question 6-2. Does the Agency agree with the time periods proposed in the Table 6-1?

FDA Response:

We acknowledge your interest in harmonizing reporting periods for required Periodic Safety Updates and REMS Assessments. Consideration of post-approval reporting requirements and time periods can be discussed as necessary during the NDA review cycle and would be described in a letter of approval for the NDA.

Discussion:

No discussion was necessary for this question.

Question 6-3. HC-ER is a single-entity extended release formulation of hydrocodone bitartrate, without added acetaminophen. Zogenix is considering a request for a priority review of this NDA

Does the FDA agree that the HC-ER NDA would qualify for a priority review in light of

?

FDA Response:

For a designation of a Priority review, the drug product, if approved, must have the potential to provide, in the treatment, prevention, or diagnosis of a disease one of the following:

- (1) safe and effective therapy where no satisfactory alternative therapy exists; or
- (2) a significant improvement compared to marketed products (approved, if approval is required), including *nondrug* products or therapies.

Significant improvement is illustrated by the following examples:

- (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
- (2) elimination or substantial reduction of a treatment-limiting drug reaction;
- (3) documented enhancement of patient compliance; or
- (4) evidence of safety and effectiveness in a new subpopulation; although such evidence can come from clinical trials directly comparing a marketed product with the investigational drug, a priority designation can be based on other scientifically valid information

[REDACTED] (b) (4)

Therefore, it is unlikely that this application would be granted a Priority review designation.

Discussion:

No discussion was necessary for this question.

Question 6-4. Does the FDA agree that the HC-ER NDA can be filed using [REDACTED] (b) (4) as the reference product?

FDA Response:

No. [REDACTED] (b) (4) was approved as an ANDA, and only an NDA may be relied upon for a 505(b)(2) application since only an NDA has FDA findings of efficacy and safety for the drug.

General additional comments regarding, 505(b)(2) applications:

- If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a "bridge" (e.g., via

comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

- Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Discussion:

Refer to the discussion following Question 4-1.

CSS additional comments:

1. In draft labeling and for REMS purposes you have compared your product to (b)(4)-containing products. However, as a single entity hydrocodone extended-release formulation without any abuse deterrent features, the appropriate comparator for your product is oxycodone. The original, not-reformulated, OxyContin extended-release tablets would be the appropriate comparator if it was available, but since it is not, immediate-release oxycodone should provide a reasonable comparison. A recent study has shown that when measuring subjective effects of liking in subjects with a history of abusing prescription drugs, hydrocodone bitartrate is equipotent to oxycodone hydrocodone on a mg per mg basis. Thus, it is expected that the non-abuse deterrent HC-ER capsules will have a similar abuse liability to the original OxyContin (Walsh SL et al. *The Relative Abuse Liability of Oral Oxycodone, Hydrocodone and Hydromorphone Assessed in Prescription Opioid Abusers*, Drug and Alcohol Dependence 2008, 98(3), 191-202).
2. In light of the current levels of abuse of hydrocodone combination-containing products and our past experience with the original OxyContin formulation, which also contained large amounts of opioid without tamper-resistant properties, it is expected that large amounts of hydrocodone may be released by simple manipulation of the formulation and would, therefore, be available for misuse or abuse through the oral route as well as through other routes of administration.
3. Drug accountability issues and diversion were noted during clinical development and increase our concerns about the risks of abuse and misuse with the currently proposed formulation.

4. **To provide necessary scientific information for a complete assessment of the potential for misuse and abuse of the to-be-marketed product, as well as related safety issues, you should:**
- a) **Conduct detailed in vitro physical manipulation and chemical extraction studies on the formulation to better understand the extent to which HC-ER capsules will be susceptible to tampering and subsequent misuse and abuse by multiple routes of administration. See the CSS responses posed under the CMC separate meeting request for more details on the recommended type of in vitro manipulation studies.**
 - b) **Conduct a human abuse potential study in nondependent, experienced opioid abusers using the oral route for intact and manipulated (chewed, crushed, dissolved, etc.) product. This study must be scientifically rigorous, well controlled, use appropriate drug comparators (such as immediate release oxycodone), and employ appropriate pharmacokinetic and pharmacodynamic outcome measures.**
 - c) **Pharmacokinetic studies alone or in combination with additional human abuse potential studies utilizing routes of administration other than oral, may be appropriate depending upon the results obtained from detailed in vitro physical manipulation and chemical extraction studies.**
 - d) **CSS is willing to review and provide comments on complete protocols for the above studies prior to initiation of the studies.**
5. **As recommended to other Sponsors that have developed opioid ER formulations, you are strongly encouraged to consider reformulating HC-ER to incorporate abuse deterrent properties so as to enhance the safety profile associated with the potential misuse and abuse of your product.**

Discussion:

Zogenix stated that, from previous interactions with FDA, they felt that FDA was supportive of the development of this single-entity, hydrocodone-only HC-ER formulation. Zogenix noted that they have been transparent throughout the development program that HC-ER would not be an abuse-deterrent formulation. They have always intended that the risks associated with opioid abuse would be managed via scheduling, as a Schedule II drug, and with an appropriate REMS for the product, anticipating that it would become part of the shared REMS for extended-release and long-acting (ER/LA) opioids.

Because of their perceptions of heightened potential risk-benefit concerns following the Division's preliminary responses and CSS additional comments, Zogenix questioned whether there was a fundamental change in thinking concerning the lack of abuse-deterrent properties with the HC-ER formulation and potential approvability of their NDA for this product

The Division clarified that there has been no fundamental change in thinking about the present formulation. None of the requested and strongly recommended studies of abuse potential are requirements for the filing of the NDA submission, nor does the present lack

of abuse-deterrent properties preclude a potential approval of HC-ER. There is concern regarding the risk of abuse with this hydrocodone formulation. The Division anticipates the abuse will be similar to other non-abuse-deterrent formulations. Additional information and study requests may be made that might address the safe use of the product.

The Division encouraged the Sponsor to move towards an abuse-deterrent platform. It was noted that even incremental improvements that reduce abuse liability are worthwhile and desirable. It was agreed that activities toward pursuit of a more abuse-deterrent hydrocodone formulation, and the related dialog between FDA and Zogenix, could continue in the pre- and post-approval setting with respect to the NDA for HC-ER as currently formulated. Zogenix stated that they will continue to research new formulations, but could not specify a timeframe for development of a new, more abuse-deterrent formulation.

Regarding the in vitro and human abuse potential studies of HC-ER, CSS stated that, in light of the summary data submitted by the Sponsor the day before the meeting, no additional in vitro studies will be requested. The Sponsor provided a summary slide addressing the dissolution profile of the formulation, basic extraction study results using intact and manipulated formulation and five solvents, isolation of hydrocodone from the manipulated formulation with the purpose of preparing an injectable solution, and manipulation of the formulation to produce a powder suitable for nasal insufflation (See Attachment 3). The data summarized by the Sponsor confirms that 95% of the hydrocodone present in the formulation can be easily extracted in water, when ground beads are taken in 20 ml of water and with vigorous shaking.

Regarding the prior request for human abuse potential studies comparing the effects of the intact and manipulated formulation to another formulation with recognized abuse potential, FDA stated that no additional abuse potential studies are required for filing of the NDA. However, these additional studies (both in vivo and in vitro abuse potential studies) might generate data that would help to better understand important differences among extended-release formulations.

Additional discussion at close of meeting:

Zogenix requested clarification regarding future dialog with DAAAP and CSS during the review of the NDA for HC-ER. The Division confirmed that Zogenix should always correspond directly with DAAAP, who will coordinate any communications with CSS.

The Division asked for a projected NDA submission date. Zogenix explained that the submission was originally planned for the first quarter of 2012, which will now need to be reevaluated in light of the additional BA/BE study that is required.

Zogenix asked if the Division anticipated the need for an advisory committee meeting during the review of the NDA for HC-ER, which has no inherent abuse-deterrent properties. The Division stated that they did not foresee the need for an advisory committee meeting.

Post-meeting notes:

- We note your December 7, 2011, correspondence, received Dec. 8, 2011, with proposals related to dataset submission with your NDA, based upon the general advice you received from us in our “Preliminary Comments” on November 14, 2011 (and appended as Attachment 1). Your proposals appear to be acceptable at this time.
- The Division acknowledges that the requirement for the relative BA study to be conducted using a listed product approved under an NDA, rather than the hydrocodone/acetaminophen combination products approved under ANDAs, represents new advice. As the relative BA study is not intended to demonstrate bioequivalence, but to provide the scientific bridge for the purpose of relying on the Agency’s prior findings, and as the application will have safety and efficacy data from clinical studies of this new formulation, in this particular situation, it is acceptable to submit the new relative BA study as soon as the data become available, and it is acceptable to submit the NDA for review prior to completion of that study. However, as these data would be necessary for approval of the application, we strongly recommend that you submit the study results as early as possible, leaving adequate time for review before the PDUFA action date.

FINAL UNDERSTANDINGS AND ACTION ITEMS

1. Zogenix stated its understanding that no additional in vitro or in vivo abuse potential studies are required for the filing of their NDA for HC-ER.
2. Zogenix stated that they will continue to plan for a shift to a more abuse-deterrent formulation, and that this would be the subject of future discussions with FDA.
3. Zogenix stated its understanding of the Division’s position that incremental improvements for reducing abuse liability were worthwhile and desirable.
4. It was confirmed that HC-ER will not be held to a different or higher standard than other ER/LA opioid products that the Division has approved or will consider for approval.
5. Regarding the 505(b)(2) regulatory pathway, Zogenix will need to reference a product approved under an NDA, e.g., Vicoprofen, and conduct a relative BA study comparing the profile of HC-ER to the referenced NDA product. Zogenix should use the approved dosing regimen of Vicoprofen, as indicated in its label, in the study.
6. Safety data generated from the new BE study will be captured in the Integrated Summary of Safety, but will not need to be incorporated into the pooled dataset. Study subjects who received a naltrexone block should not be pooled with subjects or patients who did not receive a block.
7. Regarding hearing assessments and ototoxicity [notwithstanding the Division’s post-meeting note, page 9], Zogenix will submit with their NDA all data from their clinical

studies, their rationales for the hearing assessment methodologies, and all supporting information, including Dr. (b) (4) opinions and study data. As stated in the post-meeting note, the Division finds the audiological monitoring and the assessment protocol adequate.

8. Zogenix stated their understanding that no particular statistical analyses are being recommended at this time, but FDA will likely conduct and request some sort of responder analysis.
9. Zogenix stated their understanding that they should always contact the Division as the primary point of contact for future discussions and follow-up, e.g., for dialogue concerning abuse liability.
10. Zogenix stated their understanding that the Division does not at this time consider an advisory committee meeting as necessary during the NDA review cycle for HC-ER.

**Attachment 1:
General Advice Offered at Pre-NDA Stage of Development
(Below advice would be superseded by FDA responses to specific
questions/subject-matter addressed above)**

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

As noted in the document cited above, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**" (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT ^{(b) (4)}mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified.

Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.” The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.
9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

See the separate CMC comments for the pre-NDA CMC meeting between FDA and Zogenix.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the non-clinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites
7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Advice to Avoid Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the

Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change.

21. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

22. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

23. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
24. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRul es/ucm084159.htm>
25. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
26. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
27. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
28. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].

29. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 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 to give it more prominence.
30. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
31. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
32. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
33. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
34. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format.
35. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Content of Labeling (April 2005): <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the **Guidance for Industry Integrated Summary of Effectiveness** located at the following web page:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to **Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document** located at the following web page:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
- b. Study/protocol number
- c. Patient's treatment assignment
- d. Demographic characteristics, including gender, chronological age (not date of birth), and race
- e. Dosing at time of adverse event
- f. Dosing prior to event (if different)
- g. Duration of event (or start and stop dates)
- h. Days on study drug at time of event
- i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)

- j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)

14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

**Attachment 2:
Opioid Medication Guide Template**

Medication Guide
TRADENAME® (phonetic)
(established name) Tablets, CII

This Medication Guide has been approved by the U.S. FDA
Issue: DATE

TRADENAME is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to relieve moderate to severe around-the-clock pain.

Important information about TRADENAME:

- Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** TRADENAME may harm your unborn baby.
- **breastfeeding.** TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over the counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:

- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take each dose every x hours at the same time every day. If you miss a dose, take TRADENAME as soon as possible and then take your next dose x hours later. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.
- Swallow TRADENAME whole. Do not break, chew, crush, dissolve, or inject TRADENAME.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TRADENAME without talking to your healthcare provider.**
- After you stop taking TRADENAME, flush any unused tablets down the toilet.

While taking TRADENAME Do Not:

- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over the counter medicines that contain alcohol.

The possible side effects of TRADENAME are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: company X

**Attachment 3:
Abuse Assessment Summary**

Abuse Assessment Summary

o Dissolution Profile

- The presence of alcohol results in no effect at 5% relative to 0%, but significant effect at 20% and 40% Ethanol
- Pounded capsule (5x in mortar and pestle) and ground beads release most (70-85%) of drug in <1 hour in phosphate buffer

o Extraction for 15 min with vigorous shaking in 20 mL water

Solvent	Intact Beads	Ground Beads
DI Water	53%	95%
0.1 N HCl	43%	93%
0.1N NaOH	39%	95%
40% EtOH	96%	94%
Acetone	44%	45%

o Isolation / Injectability

- Extraction of ground beads into 1 mL water, acid or base yields >90% (room temp. or heated)

o Nasal Insufflation

- Beads are easily ground in a mortar and pestle with 3-5 strokes
- Ground beads result in a free-flowing powder

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

/s/

DOMINIC CHIAPPERINO
12/16/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 65,111

Zogenix, Inc.
5858 Horton St., Suite 455
Emeryville, CA 94608

Attention: Edward Smith III, PhD, RAC
Senior Director, Regulatory Affairs

Dear Dr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone (hydrocodone bitartrate) Controlled-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on June 4, 2008. The purpose of the meeting was to discuss the development plans for hydrocodone.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2254.

Sincerely,

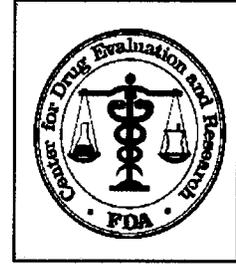
{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEETING MINUTES

Meeting Date: June 4, 2008
Location: White Oak, Building 22, Conference Room 1311
IND/ Name: 65,111/Hydrocodone (hydrocodone bitartrate)
Indication: Moderate to severe pain
Sponsor: Zogenix, Inc.
Type of Meeting: Type B
Meeting Chair: Sharon Hertz, MD
Division of Anesthesia, Analgesia and Rheumatology
Products, HFD-170
Minutes Recorder: Sharon Turner-Rinehardt, RPM



BACKGROUND: Hydrocodone is a semi-synthetic narcotic analgesic and antitussive agent. Hydrocodone Controlled Release (HC-CR) product is a 12-hour extended release formulation that utilizes Spheroidal Drug Absorption System (SODAS[®]) drug delivery technology. This IND was transferred from Elan Pharmaceuticals to Zogenix Pharmaceutical in January 2008. Zogenix intends to develop HC-CR for moderate to severe pain.

Zogenix Attendees	
Name	Title
Stephen Farr, PhD	President, Chief Operating Officer
Stephen Peroutka, MD, PhD	Chief Medical Officer
Edward Smith III, PhD	Senior Director, Regulatory Affairs
Candy Robinson, PhD	Chief Development Officer
(b) (4)	Toxicology Consultant
(b) (4)	Regulatory Consultant
(b) (4)	Statistical Consultant
(b) (4)	Risk Management Consultant
Sharon Hamm, Pharm D, RPh	Senior Vice President, R&D Technical Operations, Elan Drug Technologies
(b) (4)	Regulatory Consultant
FDA Attendees	
Name	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, MD	Deputy Director
Ellen Fields, MD	Clinical Team Leader
Elizabeth Kilgore, MD	Medical Officer
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology
Elizabeth Bolan, PhD	Pharmacology/Toxicology Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
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GENERAL DISCUSSION: Following introductions, the meeting focused on the responses to the questions included in the May 5, 2008, meeting package for IND 65,111. The responses to the questions were provided to the Sponsor on June 2, 2008. The questions are presented below in *italicized* text in the order in which they were addressed at the meeting. The Division's responses, prepared prior to the meeting and presented as handout, are **bolded**. Discussion is presented in normal text.

The Sponsor stated that they intended to pursue a 505(b)(1) pathway because they believed the 505(b)(2) pathway was not applicable to their product since other products were combination products and the proposed doses are higher than the current products. However, in light of the Division's responses, the Sponsor intends to explore the 505(b)(2) pathway.

AGENDA QUESTIONS from SPONSOR and FDA COMMENTS

Question 1: Does the Agency agree that the overall CMC information provided in the DMF is adequate to support use of the 10, 20, 30 and 40 mg HC-CR capsule formulations in the Phase 3 program?

FDA Response

The information provided in the DMF supports use of the proposed strengths for the Phase 3 trials. However, review of the DMF and communication of additional information requests and/or deficiencies will be complete as a part of the review of the NDA.

Note, that the manufacturing process used for Phase 3 clinical supplies should be representative of the commercial process. Scale up of the critical process parameters should be demonstrated and documented in a Pharmaceutical Development Report, either in the DMF or the NDA. In addition, provide sufficient documentation and supporting data for your in-process content uniformity controls.

Discussion: The Sponsor stated that they have a letter of authorization (LoA) for Elan's DMF, which references the DMF of the drug substance supplier. The Division stated that both DMF references and LoAs should be included in the NDA submission. The drug substance manufacturing facility(ies) with complete address(es) should be listed in the NDA.

Question 2: Does the Agency agree that the approach for providing CMC information to support the higher dose strengths (50, 60 and 80 mg capsules) is adequate to support use in the Phase 3 program?

FDA Response

Since the higher strength capsules are comprised of (b) (4) the approach to include manufacturing process, dissolution and stability data in the DMF is reasonable. Also, the proposed bracketing of your stability protocol is reasonable.

Provide in-vitro dissolution data in ethanolic media as follows: 0, 4, 20 and 40% EtOH/buffer and 20% EtOH in simulated gastric fluid without enzymes.

Discussion: The Sponsor asked whether a guidance regarding alcohol in vitro testing would be published. The Division stated that there have been internal discussions regarding a guidance but nothing is scheduled to be published at this time.

The Division corrected the pre-meeting responses clarifying that the percentage should be 0 and 4% and not 0.4% for the in vitro dissolution data in ethanolic media as stated in the FDA response.

The Sponsor asked what the range of the capsule strength should be and what the quantity should be for the in vitro dissolution data. The Division stated that low, middle and high strengths should be tested; the quantity of capsules may be determined by their testing method, e.g., n=6 (S1 level testing), n=12 (S2 level testing).

Question 3: Since norhydrocodone has been a major metabolite in all approved hydrocodone products and was produced following administration of 10 mg HC-CR in man at levels similar to those seen with 10 mg HC/325 mg acetaminophen in Study ELN154088-201, toxicokinetic profiling studies for norhydrocodone are not planned. Does the Division agree with this approach?

FDA Response

No. In the absence of data to show that norhydrocodone is not a human-specific metabolite, it must be qualified. If norhydrocodone is present in rat and rabbit, the studies that you have previously conducted and plan to conduct will be considered sufficient toxicological assessment. If norhydrocodone is shown to be a human-specific metabolite, inclusion of a high dose arm of the metabolite in the rat and rabbit Segment II studies can serve as appropriate qualification.

Discussion: The Sponsor stated that they have found norhydrocodone in human plasma but have not measured it in animals. The Division stated that, in order to design the reproductive toxicology studies (Segment I, II and III in rat and Segment II in rabbit) and carcinogenicity studies (rat and mouse), it would be necessary to know the levels of norhydrocodone in the species being utilized. If norhydrocodone is present in the species being utilized, the impurity can be considered qualified. If it is not present or is present at very low levels, the Sponsor may need to include a separate norhydrocodone arm in the studies.

The Sponsor asked whether it would be acceptable to perform reproductive toxicology studies in parallel with the Phase 3 studies using double forms of contraception. The Division stated that, because of the extensive clinical experience with hydrocodone, it would be acceptable for this particular drug product in this particular situation to perform the reproductive toxicology studies concurrently with the Phase 3 trials.

The Division also reminded the Sponsor to contact their DMF holder and clarify that the levels of (b) (4) in the drug substance are acceptable. The Sponsor stated that they had spoken with the DMF holder who said that there should be no problem with the levels but the Sponsor stated that they will obtain this in writing. The Division also stated that the acceptable levels of (b) (4) (< (b) (4) mcg/day) are based on the maximum daily dose of hydrocodone and that the maximum daily dose for hydrocodone could reach gram quantities.

Question 4: (b) (4) carcinogenicity studies with hydrocodone in support of an indication for the management of chronic moderate-to-severe pain. Does the Division agree with this plan?

FDA Response

No. As a single entity hydrocodone formulation, the proposed drug product will yield exposures of hydrocodone much greater than seen with previous clinical experience. Therefore, carcinogenicity studies in two species must be completed and submitted with the NDA.

Prior to initiation of carcinogenicity studies, you are encouraged to submit your study protocols to the Division and obtain concurrence from the Executive Carcinogenicity Assessment Committee (eCAC). Refer to the following guidance document: Carcinogenicity Study Protocol Submissions (May 2002), which is available on the CDER website at the following location: <http://www.fda.gov/cder/guidance/4804fnl.pdf>.

Discussion: The Sponsor asked if the carcinogenicity studies could be submitted post marketing. The Division stated that, for this product and under these circumstances, the carcinogenicity studies may be performed as a Phase 4 requirement. The Division also stated that the studies must be started by the time of NDA submission.

Question 5: Does the Division agree that the completed nonclinical studies are adequate to support the Phase 3 programs?

FDA Response

Your completed acute and repeat-dose toxicology studies, and genetic toxicology studies appear adequate to support your proposed Phase 3 clinical study. However, it is not clear from your meeting package when you plan to submit the results of the Segment I and II reproductive and developmental toxicology studies. As per ICHM3, these studies should be completed prior to Phase 3 clinical trials.

Discussion: See Discussion for Question 3.

Question 6: Except for a full reproductive toxicology panel, no additional nonclinical toxicology studies are planned for the NDA submission. Is this acceptable to the Division?

FDA Response

The acceptability of your nonclinical development program to support your NDA submission will depend upon the regulatory pathway you intend to pursue. (b) (4)

For a 505(b)(1) application the following studies must be submitted in addition to the studies described above and already completed to date:

- 1. Pharmacology studies**
- 2. Absorption, Distribution, Metabolism, Elimination (ADME) studies, including pharmacokinetic characterization in the nonclinical species tested.**
- 3. Safety Pharmacology studies**
- 4. Chronic toxicology studies (6-month rodent, 9-month nonrodent)**

However, if you intend to rely upon the FDA's findings of safety and/or effectiveness of one or more listed drugs and/or literature or other studies for which you do not have right of reference to but are necessary for approval of your product, you must file you application as a 505(b)(2) application. A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailvs/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted

that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a Sponsor relies.

The adequacy of your nonclinical development program will be determined upon review of your final study reports and your final regulatory pathway. Should you pursue a 505(b)(2) application, you are encouraged to submit your proposed annotated labeling, clearly indicating the source for all information cited and planned patent certification according to the draft guidance document referenced above.

Discussion: The Sponsor acknowledged that both the proposed 505(b)(1) and 505(b)(2) pathways require reproductive toxicology and carcinogenicity studies. If the 505(b)(1) pathway is pursued then all studies including pharmacology, safety pharmacology, ADME, and chronic toxicology (6-month rodent and 9-month nonrodent) must be performed. If the 505(b)(2) pathway is pursued, the aforementioned studies will not be necessary and only the reproductive toxicology and carcinogenicity studies will be required.

The Division stated that for a 505(b)(1) application, the Sponsor must own or have right of reference to all of the data in the application, and for a 505(b)(2) application, the Sponsor may rely on prior findings of safety and efficacy for approved drugs, which are described in the product labels and possibly published literature that meets the Agency's standards to support an application. In some circumstances, a sponsor may rely upon published information and still be considered a 505(b)(1) application, if the information is considered to be general or common knowledge. However, the term "general or common knowledge" is difficult to define and the regulations do not define this terminology. For a 505(b)(2), the Sponsor may rely upon literature reports that do not reference a particular product without having to provide patent certification; however, if a published report references a specific product, Sponsors are required to file adequate patent certification to those products as well. For 505(b)(2), the general requirements for relying on previous findings refer to the label and require adequate patent certification and relative bioavailability studies.

The Sponsor also inquired about the species selection for chronic toxicology studies; specifically that the dog may be a better model than the rat. The Division noted that for a 505(b)(1) study both a rodent and a nonrodent species would be required for chronic toxicity testing. However, the Division stated that when this program was introduced at the Pre-IND meeting, it was presented as a 505(b)(2) with a bridging program to the Agency's previous findings. The Sponsor stated that when this program was introduced as a 505(b)(2) the proposed clinical doses were lower than the current proposed doses. The Division stated that, even with the higher planned exposures, if this application were to be a 505(b)(2), the 90-day bridging study that has already been completed by the Sponsor may obviate the need for further chronic toxicology testing. The Sponsor should submit their rationale for why this 90-day bridging study in the dog provides adequate information to support the conclusion that further repeat-dose toxicology studies are not required for a 505(b)(2) program.

If during review of an NDA application, the Division determines that there is inadequate patent certification, the Sponsor may be required to withdraw the NDA and resubmit with appropriate patent certification and with a new user fee. Therefore, the Division strongly encouraged the Sponsor to draft annotated labeling for their product to clearly identify what information in the label they may be referencing for a 505(b)(2) application prior to their NDA filing to ensure that the NDA contains all necessary patent certification statements.

Question 7: Does the Division agree that the completed clinical pharmacology studies, as well as the in vitro alcohol interaction study are adequate to support NDA approval for HC-CR for the proposed chronic pain indication?

FDA Response

No, we do not agree. It is very common to conduct successful pharmacokinetic studies in healthy volunteers under a naltrexone block. As such, you must acquire additional pharmacokinetic data to reflect the current product development strategy.

You must assess dose-proportionality up to the 80-mg strength. If dose-proportionality is demonstrated at 80-mg strength, then food effect information obtained with 20-mg strength may suffice.

The extended-release characteristics of a modified-release product are commonly assessed by comparing its profile relative to the profile of an immediate-release product under steady-state conditions. You must acquire this information.

With respect to renal and hepatic impaired patients, you need to provide the hydrocodone (and its' metabolites) exposure information in renal or hepatic impaired patients. You can use a reduced-design (consult the Hepatic and Renal Guidances) with a 20-mg dose.

If the results of the in vitro alcohol interaction study are positive, then you may want to consider further evaluation of this interaction in a human pharmacokinetic study.

Discussion: The Sponsor asked whether, for a 505(b)(2) application, the single dose relative bioavailability study already performed be acceptable. The Division stated that this is acceptable. The Sponsor asked if they can use 20, 30, 40, and 80 mg strengths for the dose-proportionality study. The Division recommended that the Sponsor perform a single ,dose linear study using 50, 60, and 80 mg and include a low dose, 20 mg. This should be a crossover design study.

The Sponsor asked whether studies in renal and hepatic populations, an existing food effect study, and an in vitro alcohol study would be acceptable as Phase 1 studies, if the product is found to be dose proportional. The Division stated that this would be acceptable and no other studies would be required if linear kinetics are present.

Question 10: Zogenix proposes that [REDACTED] (b) (4) [REDACTED] for the proposed indication for treatment of chronic pain. Does the Division agree?

FDA Response

A single efficacy study is not adequate to demonstrate efficacy of HC-CR for the treatment of chronic pain. An enrichment design with a randomized withdrawal is an acceptable study design.

The opioid conversion from the patients' prior opioid to HC-CR is not adequately conservative. Conversion using the proposed ratios directly to the comparable dose of HC-CR may result in too high an initial dose of HC-CR. Once the morphine equivalents of the patient's prior opioid are calculated, the dose should be cut in half and then converted to HC-CR. Titration to an effective dose may then be carried out as tolerated.

Restricting up or down titration during the double-blind period to only one increase and/or decrease in dose is not necessary. Permitting multiple titrations for tolerability or efficacy during the double-blind period can improve patient retention in the study and reduce missing data. It is necessary to very carefully track and record the dosing throughout the trial and to rigorously collect safety data, specifically at what dose and at what date and time the adverse events occur so that dosing and adverse events can be compared.

Discussion: The Sponsor asked whether it is necessary to reduce the dose by half when converting patients from their baseline opioid to hydrocodone. The Division stated that the dose should be reduced by some percentage that would clearly provide a margin of safety, but not necessarily by half.

Question 11: Does the Division agree that the proposed primary endpoint is acceptable for a pivotal Phase 3 study for the proposed indication?

FDA Response

The proposed primary endpoint is mean change from baseline to Week 12 in Treatment Phase in the average 24-hr pain intensity rating where baseline is the average of the last 5 days on stabilized dosing prior to randomization. Week 12 is the average of the last 7 days prior to the Wk 12 visit of the Treatment Phase.

The preferred primary endpoint would be an average of the worst pain intensity in 24 hrs.

Discussion: The Division stated that, when patients recall pain, they typically recall their worst pain or recent pain. The Study Endpoint and Labeling group prefers worst pain because it is more specific. However, the Division would not require that the Sponsor use worst pain as a primary endpoint. Average pain over 24-hours, averaged over the last seven days prior to the Week 12 visit, as proposed, may be used as the primary endpoint; however, "worst" pain for the same time period should be a secondary endpoint. The Division recommended the Sponsor look

at the Patient Reported Outcome Guidance document to gain an understanding of the Agency's endpoint standards.

Question 12: Does the Division agree that the proposed treatment duration of 12 weeks is acceptable and supports the proposed indication?

FDA Response

Yes.

Discussion: No discussion required for this question.

Question 13: Does the Division agree that the proposed data analysis plan of the primary and secondary endpoints is acceptable, including the imputation method?

FDA Response

You propose to analyze the mean change in the average 24-hour pain intensity from baseline to Week 12 using an analysis of covariance model. The model will include treatment as a factor and baseline pain score, screening pain score, and stabilized dose as covariates. The analysis population will include all randomized patients receiving at least one dose of study medication. Missing data due to lack of efficacy will be imputed via a last observation carried forward strategy. Missing data due to opioid withdrawal will be imputed via the baseline observation carried forward strategy where baseline is defined as the average pain score of the last five days prior to randomization. Missing data due to adverse events will be imputed via the screening observation carried forward where the screening value is the average 24-hour pain score prior to titration. Lastly, missing data resulting from any other reason will be imputed via a last observation carried forward strategy.

The proposed primary analysis and imputation strategy is acceptable. You should additionally perform a continuous responder analysis¹ by calculating the proportion of responders for each treatment arm using multiple cutoffs to define responders. Any subjects who drop out or discontinue regardless of the reason of drop-out should be classified as non-responders (i.e. treatment failures). Also, you should explore the homogeneity of the treatment effect across centers.

You propose several secondary variables and respective analyses. The analyses appear acceptable. Describe which, if any, secondary outcomes you may wish to use for labeling or promotional purposes. These will need to be discussed with the Division, and if appropriate, a statistical approach to multiplicity will need to be addressed.

¹Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. *J Pain Symptom Manage.* 2006;31:369-77.

Discussion: No discussion required for this question.

Question 14: Does the Division agree that the proposed sample size is acceptable to demonstrate efficacy?

FDA Response

Your proposed sample size is formulated to detect a treatment difference of 1.0 assuming a standard deviation of 2.5 for the hydrocodone arm and 3.0 for the placebo arm. The sample size of approximately 170 patients per treatment arm will provide 90% power to detect a difference at the 5% significance level. Based on your assumed parameters, the sample size is acceptable.

Discussion: No discussion required for this question.

Question 15: Are the measurements of withdrawal and the method for determining if subjects are experiencing withdrawal sufficient?

FDA Response

The timing and the use of the COWS and SOWS assessments are adequate. Carefully collect COWS and SOWS scores so that the scores of individual items on the scales for every subject can be submitted with the NDA. Provide the criteria you will use for determining whether a subject discontinues treatment due to withdrawal symptoms. As part of the NDA review process, these determinations will be reviewed and may be readjudicated.

Discussion: No discussion required for this question.

Question 16: Is the plan for the blinded taper at the start of the Treatment Phase appropriate?

FDA Response

Yes.

Discussion: No discussion required for this question.

Question 17: Is the unblinding of the investigator for individual subjects immediately following subject participation in Study ZX002-0801 at the end of Week 12 in order to allow for a direct rollover into Open Label Extension Study ZX001-0803 acceptable to the Division in terms of maintaining the statistical integrity of the ZX002-0801 Study results?

FDA Response

The unblinding of the investigator following completion of the 12-Week double-blind completion phase is acceptable as long as there will be no opportunity to make alterations to the CRF for the blinded study.

Discussion: No discussion required for this question.

Question 18: Is the subject population proposed in the Clinical Development Program acceptable to gain NDA approval for the proposed chronic pain indication?

FDA Response

As stated in the response to Question 9, For a 505(b)(1) application, at least 2 adequate and well-controlled efficacy trials are required to establish the efficacy of HC-CR for the treatment of chronic pain and the populations should not be identical for the two studies.

The proposed safety database is sufficient for a 505(b)(2) application. However, as stated in the response to Question 8, for a 505(b)(1) application, the safety database must be based on ICH E1 guidelines, that is, a total exposure of at least 1500 subjects, at least 100 of whom should be treated for 12 months and 300 to 500 for 6 months.

Discussion: The Sponsor asked whether one study would be acceptable for this indication for a 505(b)(2) submission. The Division stated that, because this drug is well-known, one study would be acceptable with a single population.

Question 19: Does the Division agree that a request (b) (4) pediatric studies is appropriate?

FDA Response

Analgesia in the pediatric population continues to be an unmet need. A deferral for pediatric studies may be appropriate, however justification should be provided as to why the pediatric program cannot begin at this time.

In accordance with the requirements of Titles IV and V of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. No. 110-85, 121 Stat. 823), the Pediatric Review Committee (PeRC) must review all Pediatric Assessments, Pediatric Plans, and Waiver and Deferral requests. It is premature to agree with such request at this point.

A pediatric plan must be submitted for review. This is a statement of intent which outlines the planned pediatric studies, and should also address the development of an age appropriate formulation.

Discussion: No discussion required for this question.

Question 20: Is the proposed Risk Management Plan for the Schedule II product acceptable?

FDA Response

A complete review of the full risk evaluation and mitigation strategy or REMS (also referred to as Risk Minimization Action Plan or RiskMAP) during the NDA review cycle submitted will be necessary to determine whether the proposed program is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

Discussion: The Division stated that the Sponsor must submit a comprehensive REMS package with the NDA application. A Medication Guide will also be needed for this application. The sponsor was encouraged to include information on their proposed REMS in the Pre-NDA meeting package. A separate letter with more detailed information on the requirements for the REMS will be issued as soon as possible.

Question 21: Given the proposed development plans and additional understanding of hydrocodone, is Zogenix's plan to [REDACTED] (b) (4) [REDACTED] acceptable?

FDA Response

It is your choice whether you [REDACTED] (b) (4)

Discussion: See section under Background section of meeting minutes.

Additional Comments

- 1. Since progressive hearing loss has been associated with the abuse of hydrocodone/APAP combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, hearing must be monitored during proposed Phase 3 trials.**

Discussion: No discussion required for this question.

- 2. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:**

- a. **Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- b. **Repeat dose toxicology of appropriate duration to support the proposed indication (for a chronic indication, a 90-day repeat dose toxicology study will be required).**

Discussion: The Division stated that the Sponsor should look at the drug impurities in light of the maximum feasible dose. The Sponsor should determine the maximum dose, but gram quantities are expected for this product.

3. **Opioid drug products derived from (b) (4) may contain impurities containing an (b) (4) moiety, which is a structural alert for mutagenicity. The Division recommends that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining. If present, the specification of these impurities in the drug substance should be reduced to NMT (b) (4) µg/day or adequate safety qualification should be provided. Adequate safety qualification for any potential genotoxic impurities must be provided with the NDA submission and must include:**
 - a. **Minimal genetic toxicology screen (two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
 - b. **Repeat dose toxicology of appropriate duration to support the proposed indication (90-day repeat dose toxicology).**
 - c. **Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT (b) (4) mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.**

Discussion: No discussion required for this question.

Major Points and Action Items for IND 65, 111

1. The Sponsor will consider submitting a 505(b)(2) package (b) (4).
2. In this particular setting, where there is a long history of hydrocodone use in the population, the reproductive toxicology studies may be performed in parallel with the Phase 3 studies.

3. The Sponsor will add the norhydrocodone arm to the reproductive toxicology studies and Segment I, II and III nonclinical studies if norhydrocone is not detected in rat, rabbit, or mouse plasma.
4. The Sponsor will determine if norhydrocodone is present in rat, rabbit, and mouse in the carcinogenicity studies.
5. The Sponsor will perform a single dose crossover dose proportionality study with increasing doses as 20, 50, 60 and 80 mg, as well as renal and hepatic studies.
6. The Sponsor will perform carcinogenicity studies at the low, middle and high dose ranges.
7. The Sponsor will provide a proposal for the assessment of hearing loss in subjects receiving hydrocodone CR.

Linked Applications

Sponsor Name

Drug Name

IND 65111

ZOGENIX INC

HYDROCODONE(HYDROCODONE
BITARTRATE) ER

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

/s/

SHARON M TURNER RINEHARDT
06/26/2008