

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201194

SUPPL #

HFD # 170

Trade Name Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL

Generic Name oxycodone hydrochloride

Applicant Name VistaPharm, Inc.

Approval Date, If Known January 12, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒

NO ☐

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

505(b)(2)

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

YES ☐

NO ☒

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

The Sponsor did not submit any efficacy studies, as these were not needed for approval of this NDA. The submitted clinical studies compared the BA of this oral solution formulation of oxycodone hydrochloride to the BA of the reference product, Roxicodone (oxycodone hydrochloride).

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?

Three 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#	020553	Oxycontin (oxycodone hydrochloride)CR Tablets
NDA#	021011	Roxicodone (oxycodone hydrochloride) oral tablets
NDA#	200534	Oxycodone Hydrochloride oral capsules
NDA#	200535	Oxycodone Hydrochloride oral solution
NDA#	022272	Oxycontin XR (oxycodone hydrochloride) oral tablets
NDA#	202080	Oxecta (oxycodone hydrochloride) oral tablets

And other ANDAs listed in the Orange Book

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

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

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

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

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

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"):

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 # 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?

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, Division of Anesthesia, Analgesia, and Addiction Products
Date: January 12, 2012

Name of Office/Division Director signing form: Sharon Hertz, M.D.
Title: Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products

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

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
01/12/2012

SHARON H HERTZ
01/12/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 201194	NDA Supplement # Not applicable (n/a)	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Oxycodone Hydrochloride Oral Solution, USP Established/Proper Name: oxycodone hydrochloride Dosage Form: oral solution, 5 mg/5 mL		Applicant: VistaPharm Inc. Agent for Applicant (if applicable): n/a
RPM: Dominic Chiapperino, Ph.D.		Division: Division of Anesthesia, Analgesia, and Addiction Products
<u>NDA:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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.) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 021011, Roxicodone (oxycodone hydrochloride) oral tablets Provide a brief explanation of how this product is different from the listed drug. This product is a different dosage form, an oral solution, versus the reference product, Roxicodone, an immediate-release oral tablet. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: January 11, 2012 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.		
❖ Actions		
- Proposed action - User Fee Goal Date is <u>January 14, 2012</u>		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		CR, on March 3, 2011

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.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	n/a
❖ Application Characteristics²	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 7 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	n/a
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	n/a
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(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>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
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) ☒ Verified (No patents listed) 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[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).	☒ No paragraph III certification Date patent will expire _____
[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 any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

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

n/a

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?

(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)?

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?

(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)?

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

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

(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? (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). <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> <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>	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	1/17/12
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>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP, 1/12/12; CR, 3/3/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Submitted 1/3/12
Original applicant-proposed labeling	Submitted 1 st PLR, 5/21/10 Orig. Submitted, 5/4/10
Example of class labeling, if applicable	n/a

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Submitted 1/3/12
Original applicant-proposed labeling	Submitted 5/4/10
Example of class labeling, if applicable	n/a
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	Submitted 1/3/12
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</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.	Sponsor did not seek a proprietary name. They will use the established name for marketing, "Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL"
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM n/a ☒ DMEPA 2 nd cycle rev, 12/8/11; Consult request, 7/21/11; 1 st cycle rev, 2/3/11; Consult request, 6/21/10 ☒ DRISK 1 st cycle rev, 2/10/11 ☒ DDMAC 2 nd cycle rev, 10/28/11; 10/13/11; 10/12/11; Consult request, 9/29/11; 1 st cycle rev, 2/10/11; 2/9/11; Consult request, 1/4/11 ☐ SEALD n/a ☐ CSS n/a ☒ Other reviews: See CMC review, 1/21/11, pp. 31-32; See ClinPharm reviews, 12/13/10, pp. 11-15, and 9/26/11, p. 5; See Pharm/Tox review, 1/14/11, pp. 6-7
Administrative / Regulatory Documents	

❖ Administrative Reviews (e.g., RPM Filing Review⁴/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)	RPM filing review/Memo of filing meeting, 1/14/11; no clinical filing review necessary; ClinPharm filing, 1/19/11; CMC filing, 7/8/10; PharmTox filing, 6/30/10 Cmte cleared on 2/28/11 for CR on 3/3/11; Cmte cleared on 12/5/11 for AP on 1/12/12 505(b)(2) Assessment, 1/12/12
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included 1/12/12
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication)	☐ Yes ☒ No
❖ Pediatrics (approvals only) • Date reviewed by PeRC 2/16/11 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized)	PeRC email, 2/17/11 ☒ Included
❖ 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)	☒ Verified, statement is acceptable
❖ Outgoing communications (letters (except action letters), emails, faxes, telecons)	Memo of email communications archived in DARRTS, 1/13/12; Email, 1/12/12; DR, 12/13/11; IR, 9/7/11; Class 2 resub ackn, 7/29/11; 1 st cycle, DR, 2/28/11; DR, 1/19/11; NDA filing, 7/20/10; NDA ackn, 5/13/10
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
• Regulatory Briefing (indicate date of mtg)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (indicate date of mtg)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (indicate date of mtg)	☒ No mtg
• EOP2 meeting (indicate date of mtg)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)	Pre-IND advice for NDA requirements, 8/27/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	n/a
• 48-hour alert or minutes, if available (do not include transcript)	n/a

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	2 nd cycle, 1/12/12; 1 st cycle, 3/3/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ None
PMR/PMC Development Templates (<i>indicate total number</i>)	(three total) PMR 1863-1 (PREA), 1/11/12; PMR 1863-2 (PREA), 1/11/12; PMC 1863-3 (CMC study), 1/11/12
Clinical Information ⁵	
❖ Clinical Reviews	
Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	No new efficacy or safety studies submitted or needed; only a relative BA study; see Summary Memos and Clinical Pharmacology reviews
Clinical review(s) (<i>indicate date for each review</i>)	No new efficacy or safety studies submitted or needed; only a relative BA study; see Summary Memos and Clinical Pharmacology reviews
Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None n/a
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	An acceptable Form 3454 was submitted. No efficacy studies were required or submitted for this NDA, and, therefore, a detailed review of financial disclosure was not needed.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	2 nd cycle rev, 12/5/11; Consult request, 7/21/11; 1 st cycle rev, 3/2/11; Consult request, 6/21/10
❖ Risk Management - REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - 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>)	1 st cycle rev, 1/26/11; (Note: It was later determined that a REMS was not needed for this application; no comments were communicated to sponsor, and the CR letter on 3/3/11 communicated that a REMS was not needed.); Original proposed REMS, 5/4/10
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested (See BE study audit request and audits)

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ None	
Clinical Microbiology Review(s) (indicate date for each review)	☒ None	
Biostatistics		☒ None
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None (No efficacy studies)	
Statistical Team Leader Review(s) (indicate date for each review)	☒ None (No efficacy studies)	
Statistical Review(s) (indicate date for each review)	☒ None (No efficacy studies)	
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None	
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None (co-signed primary review)	
Clinical Pharmacology review(s) (indicate date for each review)	2 nd cycle rev, 9/26/11; Addendum, 9/29/11; 1 st cycle rev, 12/13/10; Addendum, 2/8/11	
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	2 nd cycle audit result, 9/27/11; Audit request, 8/12/11; Post-1 st cycle audit comments, 3/16/11; 1 st cycle audit results (includes documentation of communications), 2/3/11; audit request, 9/20/10	
Nonclinical		☐ None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)	☒ None	
• Supervisory Review(s) (indicate date for each review)	☒ None (co-signed primary review)	
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1 st cycle rev, 1/14/11; Addendum, 2/14/11	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc	
❖ ECAC/CAC report/memo of meeting	☒ None	
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested	

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ None (co-signed primary review)
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	2 nd cycle rev, 12/23/11; 1 st cycle rev, 1/21/11
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed (advised for product quality review)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	(See product quality review, 1/21/11, p. 32)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) <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 sites⁶)</i>	Date completed: 6/8/10 (See EER printout included as p. 30, Product quality review dated 1/21/11) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ 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: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☒ Completed (Product quality review, 1/21/11, references on page 13 the acceptable analytical procedures as documented for reviewed DMFs (b) (4)) ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁶ 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.

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
01/17/2012

MEMORANDUM

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

DATE: Jan. 13, 2012

TO: File

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

SUBJECT: Archiving email communications to sponsor during NDA 201194 review cycles

APPLICATION/DRUG: NDA 201194, Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL

The emails that follow were correspondences sent during the NDA review cycle. These select emails contain content worthy of archiving in DARRTS and including in the Action Package as "Outgoing Correspondences," but have not previously been archived in DARRTS. This memo serves to archive these email communications in DARRTS.

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, December 14, 2011 3:49 PM
To: 'John Lay'
Subject: NDA 201194, CMC issue

Hi John,

Will you be available tomorrow to discuss a CMC concern with us? I have 11:00 to 11:30 AM in mind, and can provide a call-in number:

(b) (4)
Passcode: (b) (4)

To give you some idea of the topic, we are looking to discuss getting a commitment from VistaPharm to submit the method (or methods) that will be used for the demonstration of the absence of *Burkholderia cepacia* in Oxycodone Hydrochloride Oral Solution drug product. Other details can be discussed tomorrow when chemistry review team is present.

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

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, November 07, 2011 12:25 PM
To: 'John Lay'
Subject: NDA 201194, FDA-revised labeling

Attachments: NDA 201194 USPI-MedGuide FDA-revised redline 11-7-11.pdf; NDA 201194 USPI-MedGuide FDA-revised clean 11-7-11.doc

Hi John,

We have made some further revisions to the labeling for Oxycodone Hydrochloride Oral Solution, and I am providing a pdf file showing added/deleted text, as well as a Word file that is "clean" and includes these most up-to-date labeling revisions.



NDA 201194 NDA 201194
SPI-MedGuide FDA-r SPI-MedGuide FDA-r

Please review and respond when you can by submitting updated labeling files to the NDA as clean Word file, and also a track-change/redline version if you are making any further changes from the clean version we are sending you.

Thanks so much, and contact me if you have any questions or wish to discuss any of the new revisions.

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
10903 New Hampshire Avenue
Building 22, Room 3134
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Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, February 23, 2011 3:07 PM
To: 'John Lay'
Subject: Labeling for oxycodone oral solution, NDA 201194

Attachments: Package-Insert-NDA-201194-with-FDA-revisions-CLEAN.doc; Package-Insert-NDA-201194-with-FDA-revisions.pdf; ProposedMedicationGuide-with-FDA-revisions-CLEAN.doc; ProposedMedicationGuide-with-FDA-revisions.pdf

Hi John,

The Division has completed significant revisions to the product's package insert and Medication Guide. There may be additional labeling revisions and recommendations as we proceed with reviews in the next cycle, but the attached labeling will be a good starting point for future discussions of product labeling.

I am including clean final-version Word files as well as pdf files showing added and deleted text, based on your originally proposed labeling for the package insert and the Medication Guide.



Package-Insert-ND Package-Insert-ND
A-201194-with... A-201194-with...



ProposedMedicationProposedMedication
Guide-with-F... Guide-with-F...

Any future submissions of product labeling should be based on these clean Word files as starting point, and with "track-changes" showing any revisions made to these Word files.

Thank you, and feel free to contact me if there are any questions about labeling.

Sincerely,

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

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, February 04, 2011 10:44 AM
To: 'John Lay'
Subject: RE: NDA 20-1194 Oxycodone

Hi John,

Thank you for these files that were sent.

Some comments about the content:

We note your comment that not all parts of the electronic submission were included in your emailed files. Specifically, we see that you did not include the calibration data for the dosing cup, but hopefully that will be with the electronic submission. Also, we would like to request physical samples of the dosing cup, as the two-dimensional images are not sufficient for our review. You may FedEx these samples to my office address, just as you did earlier for a previous sample.

We note the inclusion of a medication guide as Appendix A in the January 11th REMS-related amendment. The medication guide is, as a concept/element, a part of the REMS, but as far as its specific content, it is part of product labeling. It should be included in eCTD Section 1.14 as a separate labeling file, or can be an appended section in the same Word file as the package insert content. So far, it does not appear to be in Section 1.14 at all, and does not appear to be among the files in your planned submission.

Is the electronic submission scheduled to arrive today? Monday?

Thank you for any updates you can provide on progress, as we are now 4 weeks away from our PDUFA action day.

Best regards,
Dominic

Dominic Chiapperino, Ph.D.
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Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

From: John Lay [mailto:jlay@vistapharm.com]
Sent: Wednesday, February 02, 2011 3:48 PM
To: Chiapperino, Dominic
Subject: NDA 20-1194 Oxycodone

Dr. Chiapperino,

As requested here is the advanced copy of the upcoming submission. I have included what I consider to be the major documents. Granted as an example I have not included the specification for the measuring device, but it will be part of the submission.

Thank you

John

John G. Lay
Director, RA/QA
VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771
(727) 530-1633 x226

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, December 10, 2010 12:02 PM
To: 'John Lay'
Subject: RE: NDA 201194

Hi John,

The review team has reviewed your proposal and determined that VistaPharm should not at this time pursue a

(b) (4)

(b) (4)

Thank you and please contact me for any further clarification you might want.

Best regards,
Dominic

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

From: John Lay [mailto:jl原因@vistapharm.com]
Sent: Thursday, December 02, 2010 7:52 AM
To: Chiapperino, Dominic
Subject: RE: NDA 201194

Good Morning Dominic,

(b) (4)

VistaPharm will conduct a suitability study for the (b) (4) as well as the drug product. We will also provide internal specification as well as a DMF reference letter.

Is this acceptable to FDA?

Thank you

John

John G. Lay

Director, RA/QA

VistaPharm Inc.

7265 Ulmerton Road

Largo, FL 33771

(727) 530-1633 x226

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

Sent: Monday, November 22, 2010 9:16 AM

To: 'John Lay'

Subject: RE: NDA 201194

John,

The telecon tomorrow would be to hear from VistaPharm their thinking on why a

(b) (4)

(b) (4)

If you would like to proceed today with whatever you need to do to the MedGuide and to CMC sections describing packaging presentation changes, etc... that would be fine.

Also, I am working from home today, but happy to discuss by phone this morning... Just call at

(b) (6)

Thanks,

Dominic

From: John Lay [mailto:jlav@vistapharm.com]

Sent: Monday, November 22, 2010 7:52 AM

To: Chiapperino, Dominic

Subject: RE: NDA 201194

Dominic,

Is it possible to discuss this issue this morning? I have the REMS document ready to submit and if FDA requires a dropper I will need to change the Med Guide.

Thank you

John

John G. Lay

Director, RA/QA

VistaPharm Inc.

7265 Ulmerton Road

Largo, FL 33771

(727) 530-1633 x226

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

Sent: Friday, November 19, 2010 5:01 PM

To: 'John Lay'

Subject: NDA 201194

Hi John,

I left a voice message for you just now...

We would like to have a brief telecon with Vistapharm about the packaging presentations for this product. I would propose 3:30 pm this coming Tuesday, Nov. 23rd?

Please let's talk and confirm plans as soon as Monday rolls around.

Thanks,

Dominic

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, December 10, 2010 2:19 PM
To: 'John Lay'
Subject: Information Request, NDA 201194, (b) (4) impurity

Dear John,

Referring to VistaPharm's NDA for Oxycodone Oral Solution, NDA 201194, we have the following request for information as we progress with our review of the application.

1. Provide an updated drug product specification table to reflect the NMT (b) (4).
2. It appears that (b) (4) is a process impurity in the drug substance. Provide any data that it is also a degradant in the drug product.

Please contact me if you have questions about this request.

Thank you, and best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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Division of Anesthesia and Analgesia Products
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Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Monday, September 27, 2010 3:38 PM
To: 'John Lay'
Subject: NDA 201194, (b) (4)

Hi John,

(b) (4)

Please contact me if there are any questions about the above request.

Thank you, sincerely,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
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Building 22, Room 3134
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Dominic.Chiapperino@fda.hhs.gov

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, May 27, 2010 11:10 AM
To: 'John Lay'
Subject: Two issues, NDA 201194

Hi John,

Referring to VistaPharm's NDA 201194 for Oxycodone Oral Solution, there are two things I'd like to note.

1. Our CMC reviewer has noted that an environmental assessment was not submitted with the NDA, nor was a request for categorical exclusion for the EA. One of these needs to be submitted as soon as you are able to do so.
2. Your recent submission of new labeling files was received, but some errors were made in processing the incoming documents, most likely because the cover letter had a heading that indicated the submission as a "Labeling Supplement." Please note that all submissions to a new, pending NDA are "amendments" to the original application. A "supplement" to an NDA is an original application of its own, and only appropriate for making changes to an approved product. I will let you know if any further action by VistaPharm is needed to correct the submission record for NDA 201194, but so far I believe it is something our technical staff will be able to re-process and fix easily enough.

Please let me know when our CMC reviewer might receive the amendment addressing the EA.

Thank you, and sincerely,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
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Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, May 12, 2010 1:03 PM
To: 'jlay@vistapharm.com'
Subject: NDA 201194, oxycodone oral solution

Hi Mr. Lay,

I just left a voice message for you. I am the assigned project manager for VistaPharm's NDA 201194, for Oxycodone Oral Solution.

The original submission that we received contains product labeling that seems closely based on Roxicodone labeling; however, VistaPharm did not submit its product's labeling in PLR format, with SPL included. Let's discuss this at your earliest convenience.

Thank you, and best regards,

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
10903 New Hampshire Avenue
Building 22, Room 3134
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/s/

DOMINIC CHIAPPERINO
01/13/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, January 12, 2012 10:23 AM
To: 'John Lay'
Subject: RE: NDA 201194, revised Highlights page of physicians insert

Hi John,

Thank you for your fast response and agreement on labeling. I will be in touch again if anything further to discuss.

Best regards,
Dominic

From: John Lay [mailto:jlay@vistapharm.com]
Sent: Thursday, January 12, 2012 8:17 AM
To: Chiapperino, Dominic
Subject: RE: NDA 201194, revised Highlights page of physicians insert

Good Morning Dominic,

VistaPharm agrees with all FDA recommended changes, these changes will be incorporated.

Regards

John

John G. Lay
Director, RA/QA
VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771
(727) 530-1633 x226

From: Chiapperino, Dominic [mailto:Dominic.Chiapperino@fda.hhs.gov]
Sent: Wednesday, January 11, 2012 6:12 PM
To: 'John Lay'
Subject: NDA 201194, revised Highlights page of physicians insert

Hi John,

You may recall that during previous cycles of labeling review and exchange of comments, we asked that VistaPharm make the Highlights section of the PI more aligned with the Full Prescribing Information.

We have determined that further revision of the Highlights section is recommended and we would like your agreement with the attached revised version. Your agreement via email reply is sufficient and you do not need to make a new formal submission of labeling. Or please also call me to discuss further, but response is requested at your very earliest convenience, preferably tomorrow morning.

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
01/12/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #/Product Name:	NDA 201194/Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL	
PMC Description:	To assess the method (or methods) that will be used for the demonstration of the absence of <i>Burkholderia cepacia</i> in Oxycodone Hydrochloride Oral Solution drug products. Sponsor will provide sufficient data to validate the ability of the assay to detect <i>Burkholderia cepacia</i> if present, as well as document the limit(s) of detection.	
PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	3/1/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this drug quality-related study report because the drug product is ready for approval and can be approved prior to review of the PMC final study report.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC study is to confirm that drug product test methods for detecting *Burkholderia cepacia* in Oxycodone Hydrochloride Oral Solution drug products and release and stability specifications are appropriate for control of the drug product quality.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor has committed to do a study to assess the ability of proposed test methods to demonstrate the absence of *Burkholderia cepacia* in Oxycodone Hydrochloride Oral Solution drug products. The Sponsor will need to provide sufficient data to validate the ability of the assay to detect *Burkholderia cepacia* if present, as well as document the limit(s) of detection.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DOMINIC CHIAPPERINO
01/11/2012

JUDITH A RACOOSIN
01/11/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 201194/Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL

PMR Description: Deferred pediatric study under PREA: evaluate the pharmacokinetics, safety, and efficacy of immediate-release oxycodone in ages 0 to 2 years.

PMR Schedule Milestones:	Final Protocol Submission:	<u>06/30/2012</u>
	Study/Trial Completion:	<u>5/31/2014</u>
	Final Report Submission:	<u>1/31/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study to evaluate the pharmacokinetics, safety, and efficacy of immediate-release oxycodone in ages 0 to 2 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To obtain adequate data from the use of oxycodone hydrochloride in the pediatric population ages 0 to 2 years to inform dosing, safety, and efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics, safety, and efficacy of immediate-release oxycodone in ages 0 to 2 years.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Pharmacokinetic, safety, and efficacy studies or clinical trials
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DOMINIC CHIAPPERINO
01/11/2012

JUDITH A RACOOSIN
01/11/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 201194/Oxycodone Hydrochloride Oral Solution, USP, 5 mg/5 mL

PMR Description: Deferred pediatric study under PREA: evaluate the pharmacokinetics and safety of immediate-release oxycodone in ages >2 to <17 years.

PMR Schedule Milestones:	Final Protocol Submission:	06/30/2012
	Study/Trial Completion:	5/31/2014
	Final Report Submission:	01/31/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics and safety of immediate-release oxycodone in ages >2 to <17 years) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To obtain adequate data to describe the dosing and safety of Oxycodone Hydrochloride Oral Solution in the pediatric population ages >2 to <17 to inform dosing and safety.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics and safety of immediate-release oxycodone in ages >2 to less than 17 years.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Pharmacokinetic and safety studies or clinical trials
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
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 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DOMINIC CHIAPPERINO
01/11/2012

JUDITH A RACOOSIN
01/11/2012



NDA 201194

DISCIPLINE REVIEW LETTER

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

Please refer to your May 4, 2010, New Drug Application (NDA), received May 5, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride Oral Solution USP, 5 mg/5 mL.

We also refer to your submission dated July 14, 2011, which was a complete response to our March 3, 2011, action letter.

The Division of Medication Error Prevention and Analysis in the Office of Surveillance and Epidemiology has completed its review of the product labeling sections of your submission, including the carton and container, package insert, and medication guide, and has identified the following deficiencies:

1. Regarding the Carton Labeling:
 - a. Increase the prominence of the strength statement, as the net quantity statement is currently of equal prominence on the principal display panel.
 - b. Add the concentration of the solution in close proximity to the strength statement on the principal display panel, in lesser prominence than the strength statement. The strength and concentration should be presented as follows:

5 mg per 5 mL
(1 mg/mL)
 - c. Decrease the prominence of the net quantity statement, as it is currently more prominent than the strength statement.
 - d. Increase the prominence of the medication guide statement by bolding the complete sentence.

- e. Relocate the storage statements to the side panel, to reduce clutter and increase readability of the remaining statements on the principal display panel.

f. (b) (4)

- g. Increase the statement for the pharmacist to dispense with the calibrated measuring cup.

- h. Remove the (b) (4) from the lower portion of the principal display panel and back panel, as it decreases the readability of the information, and places undue prominence on this area of the carton labeling.

2. Regarding the Container Labeling:

- a. Increase the prominence of the strength statement, as the net quantity statement is currently of equal prominence on the principal display panel.
- b. Add the concentration of the solution in close proximity to the strength statement on the principal display panel, in lesser prominence than the strength statement. The strength and concentration should be presented as follows:

5 mg per 5 mL
(1 mg/mL)

- c. Increase the prominence of the medication guide statement by bolding the complete sentence.
- d. Remove the (b) (4) on the lower portion of the principal display panel, as it decreases the readability of the information, and provides undue prominence to this section of the container label.

3. Regarding the Package Insert Labeling, revise the fifth bullet point in Section 17 (Patient Counseling Information) to refer to the calibrated measuring cup, as it currently refers to an (b) (4) for administration of the drug.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
12/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-DDMAC-RPM ATTN: Michael Wade, Mathilda Fienkeng, LaToya (Sheneé) Toombs		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Anesthesia, Analgesia, and Addiction Products - Dr. Bob Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183				
REQUEST DATE Sep. 29, 2011	IND NO.	NDA/BLA NO. NDA 201194	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG Oxycodone HCl Oral Solution	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 7	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Oct. 13, 2011			
NAME OF FIRM: VistaPharm Inc.		PDUFA Date: March 5, 2011				
TYPE OF LABEL TO REVIEW						
<table border="0"> <tr> <td> TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE (IFU) </td> <td> TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION </td> <td> REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION
TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION				
EDR link to submission: \\CDSESUB1\EVSPROD\NDA201194\201194.enx						
Labeling is now substantially complete.						
<u>COMMENTS/SPECIAL INSTRUCTIONS:</u> The package insert for NDA 201194 was substantially revised by the review team, including DDMAC reviewers, during the 1st review cycle and sent to the sponsor at that time. The sponsor has accepted all changes and resubmitted the labeling for this 2nd cycle pending NDA review. We are having one more labeling meeting to discuss this substantially complete USPI and MedGuide, and we would like DDMAC to also review the labeling in time to discuss any new needed revisions at the Oct. 13, 2011 combined labeling and Mid-cycle meeting. A link to copy/file of product labeling (FDA-revised) will be sent by separate email to the entire review team, but here is that link again: \\fdafs01\ode2\DAAP\NDA and sNDA\NDA 201194 (Oxycodone Oral Solution VistaPharm)\Labeling\NDA 201194 USPI-MedGuide submitted 9-7-11.doc Please note, the PDUFA date for this resubmission is January 14, 2012, but DAAAP is interested in taking an early action in 1st week of November, 2011.						
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)						
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND				

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/s/

DOMINIC CHIAPPERINO
09/29/2011



NDA 201194

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

We acknowledge receipt on July 14, 2011, of your July 7, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride Oral Solution USP, 5 mg/5 mL.

We consider this a complete, class 2 response to our March 3, 2011, action letter. Therefore, the user fee goal date is January 14, 2012.

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
07/29/2011

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: Danyal Chaudhry		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 July 21, 2011	IND NO.	NDA NO. 201194	TYPE OF DOCUMENT Class 2 resubmission	DATE OF DOCUMENT Recvd. July 14, 2011
NAME OF DRUG Oxycodone HCl, Oral Solution		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 7	DESIRED COMPLETION DATE December 13, 2011
NAME OF FIRM: VistaPharm, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: OSE reviewed this NDA in its 1 st cycle. DAAAP took CR action on Mar. 3, 2011. Please review this resubmitted NDA (#201194, with PDUFA date, January 14, 2011) from a drug safety and risk management perspective. - Package Insert labeling - Medication Guide labeling - Carton and Container labeling This drug product is an opioid schedule II compound (oxycodone). This is a (b)(2) application based on referenced drug Roxycodone Tablets (NDA 21-011). NDA 201194 is fully electronic (eCTD format) and all files can be found in EDR, direct link: \CDSESUB1\EVSPROD\NDA201194\201194.ENX All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Project Manager.				
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)		METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

DOMINIC CHIAPPERINO
07/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			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; Director-- Bob A. Rappaport, M.D. Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Project Manager, 301-796-1183	
DATE July 21, 2011	IND NO.	NDA NO. 201194	TYPE OF DOCUMENT Class 2 Resubmission	DATE OF DOCUMENT recvd: July 14, 2011
NAME OF DRUG Oxycodone HCl, Oral Solution, USP, 5mg/mL		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 7	DESIRED COMPLETION DATE December 13, 2011
NAME OF FIRM: VistaPharm, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PRE-NDA MEETING ☐ RESPONSE TO DEFICIENCY LETTER ☐ PROGRESS REPORT ☐ END-OF-PHASE 2a MEETING ☐ FINAL PRINTED LABELING ☐ NEW CORRESPONDENCE ☐ END-OF-PHASE 2 MEETING ☐ LABELING REVISION ☐ DRUG ADVERTISING ☐ RESUBMISSION ☐ ORIGINAL NEW CORRESPONDENCE ☐ ADVERSE REACTION REPORT ☐ SAFETY / EFFICACY ☐ FORMULATIVE REVIEW ☐ MANUFACTURING CHANGE / ADDITION ☐ PAPER NDA ☒ OTHER (SPECIFY BELOW): ☐ MEETING PLANNED BY ☐ CONTROL SUPPLEMENT				
II. BIOMETRICS				
☐ PRIORITY P NDA REVIEW ☐ CHEMISTRY REVIEW ☐ END-OF-PHASE 2 MEETING ☐ PHARMACOLOGY ☐ CONTROLLED STUDIES ☐ BIOPHARMACEUTICS ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): ☐ OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ DEFICIENCY LETTER RESPONSE ☐ BIOAVAILABILITY STUDIES ☐ PROTOCOL - BIOPHARMACEUTICS ☐ PHASE 4 STUDIES ☐ IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ POISON RISK ANALYSIS ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL ☐ NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: CSS was consulted to review the original NDA, which received a CR action on March 3, 2011. The Division requests that you renew your review of this resubmitted NDA from a controlled substance/abuse potential perspective and provide written feedback by December 13, 2011. Please contact Dominic Chiapperino, RPM, DAAAP (HFD-170), at 301-796-1183 with any questions. Please provide any feedback or deficiencies you wish shared with the sponsor in "letter-ready" format. This is a fully electronic NDA, available here: \\CDSESUB1\EVSPROD\NDA201194\201194.ENX				
SIGNATURE OF REQUESTOR			METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND	

Dominic Chiapperino (electronically signed)	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

DOMINIC CHIAPPERINO
07/21/2011



NDA 201194

DISCIPLINE REVIEW LETTER

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

Please refer to your New Drug Application (NDA) submitted March 4, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Oral Solution, USP, 5mg/5mL.

A review of the carton and container labeling section of your submission by the Division of Medication Error Prevention and Analysis (DMEPA) is complete, and the following deficiencies have been identified:

Regarding all container labels, i.e., for the 500 mL bottle and for the 5 mL unit dose cups:

1. A placeholder for the lot number and expiration date are not indicated on the labels. Include the lot number and expiration date on the labels.
2. Relocate the company name 'VistaPharm' from the (b) (4) of the principal display panel. Minimize the font to ensure that the company name does not compete with the prominence of the established name and the strength presentation.

Regarding the container labels for 500 mL bottle:

3. Due to the recommended dosage and administration of oxycodone, it is feasible that the bottle may be dispensed as a unit-of-use container. This is concerning because children may inadvertently access these bottles. Ensure the bottle utilizes a child-resistant closure to prevent accidental exposure.
4. We note that although the 500 mL bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure that a sufficient number of medication guides are provided with each bottle.
5. The active ingredient is 'Oxycodone Hydrochloride'. As currently presented 'Oxycodone' has a greater prominence due to the font size and the use of uppercase.

Modify the presentation of the active ingredient so that “Oxycodone” and “hydrochloride” have equal prominence. Additionally, consider revising the active ingredient to appear in title case (i.e. Oxycodone Hydrochloride). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-upper case.

6. Include a medication guide statement to remind pharmacist to dispense a medication guide to each patient. In addition, the statement should include how the medication guide is provided. For example, the statement could read, “Pharmacist: Dispense with attached Medication Guide to each patient.”
7. The black text color over the green shaded background is difficult to read. Change the color hue of the shaded background to increase the contrast with the black text.
8. Delete the negative statement, (b) (4) Negative statements can be misinterpreted as the opposite intended meaning.
9. Revise the statement, “Each 5 mL contains: Oxycodone-----5 mg” to read, “Each 5 mL Contains: Oxycodone Hydrochloride _____ 5 mg”
10. Decrease the prominence of the Manufacture’s statement, “VistaPharm, Inc., Largo....” As currently presented, it is more prominent than more important information presented above.

Regarding the container labels for 5 mL unit dose cups:

11. Remove the established name and dosage form (Oxycodone Hydrochloride Oral Solution) out of the (b) (4). Use the (b) (4) the strength statement (5 mg per 5 mL) only.
12. As currently displayed the barcode is prominently located, relocate the barcode to the bottom of the label, away from the more pertinent information on the label.
13. Modify the statement, (b) (4) to read “5 mL”. As currently presented the use of the word (b) (4) is supplied in the unit dose cup.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
02/28/2011



NDA 201194

DISCIPLINE REVIEW LETTER

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

Please refer to your New Drug Application (NDA) submitted March 4, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Oral Solution, USP, 5mg/5mL.

We also refer to your submission dated September 7, 2010.

Our review of the Chemistry, Manufacturing, and Controls (CMC), section of your submission is complete, and we have identified the following deficiencies:

1. The drug substance acceptance specification for (b) (4) must be reduced to NMT (b) (4).
2. You must provide testing and a release specification for (b) (4) in the drug substance.
3. The drug product release and stability specification for (b) (4) should be removed if this impurity is a process impurity and not a drug product degradant. If it is a degradant, the specification must be reduced to NMT (b) (4).
4. The product container for the 500 mL packaging configuration does not have a child resistant closure system. You must select a child resistant closure cap for the 500 mL container.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
01/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-DDMAC-RPM ATTN: Michael Wade, Mathilda Fienkeng, Twyla Thompson		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Anesthesia and Analgesia Products - Dr. Bob Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183				
REQUEST DATE Jan. 3, 2011	IND NO.	NDA/BLA NO. NDA 201194	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG Oxycodone HCl Oral Solution	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 7	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Feb. 5, 2011			
NAME OF FIRM: VistaPharm Inc.		PDUFA Date: March 5, 2011				
TYPE OF LABEL TO REVIEW						
<table border="0"> <tr> <td> TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU) </td> <td> TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION </td> <td> REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION
TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☐ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☒ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION				
EDR link to submission: \\CDSESUB1\EVSPROD\NDA201194\201194.enx						
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.						
COMMENTS/SPECIAL INSTRUCTIONS: The package Insert for NDA 201194 has now been revised by the review team and is considered substantially complete (not yet communicated to sponsor) and modeled on the recently approved PI for Lehigh Valley's NDA 200535 (also an oxycodone oral solution), recently approved. A copy/file of product labeling (FDA-revised) will be sent by separate email to DDMAC. Labeling Meetings: Jan. 11, Jan. 27, Feb. 2, and Feb. 10, 2011 Wrap-Up Meeting: Jan. 6, 2011						
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)						
SIGNATURE OF RECEIVER Reference ID: 2886593		METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND				

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/s/

DOMINIC CHIAPPERINO
01/04/2011



NDA 201194

FILING COMMUNICATION

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

Please refer to your new drug application (NDA) dated May 4, 2010, received May 5, 2010, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone HCl oral solution, 5mg/5mL.

We also refer to your submissions dated May 24 and 28, and June 29, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is March 5, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 5, 2011.

At this time, we are notifying you that we have identified the following review issues and the need for submission of additional information:

Chemistry, Manufacturing, and Controls

1. Provide results of photostability testing for the drug product, as per ICH Q1B.
2. Provide the name and address of the packaging and release facility for the drug product.

3. Provide a retest period for the drug substance used in the manufacture of the drug product.
4. Provide a Letter of Authorization for access to the DMF for raspberry flavor.
5. Provide samples of the unit dose cup and HDPE bottles.

Nonclinical

6. The development of tolerance to the effects of opioids results in reduced effectiveness and necessitates increased dosing in order to maintain the desired therapeutic effect. Therefore, no maximum daily dose exists for opioids. The maximum theoretical daily dose (MTDD) of oxycodone in your formulation must be considered to determine the ICH guideline qualification thresholds for impurity and degradant levels as well as the acceptable levels of total amounts of excipients. Provide clinical use data to establish the MTDD of oxycodone for your product.
7. Your NDA does not contain adequate information to justify the safety of the drug product formulation. Specifically, your NDA must include justification for the safety of the levels of each excipient when used at the MTDD of oxycodone for your product (see previous comment). Please refer to the FDA Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005), which is available on the NDA 201517 CDER web page at the following:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
8. Your proposed drug substance and drug product specifications of NMT (b) (4) for (b) (4) (b) (4), an impurity that contains an (b) (4) structural alert for genotoxicity, is not adequately justified for safety. As noted in the pre-NDA meeting minutes, impurities with structural alerts for genotoxicity must be reduced to NMT (b) (4) or adequate safety qualification must be provided. Adequate safety qualification for this impurity 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.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Anesthesia and Analgesia Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your requests for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201194	ORIG-1	VISTAPHARM INC	OXYCODONE HCL SOLUTION

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/s/

BOB A RAPPAPORT
07/20/2010

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: Abolade Adeolu, Chris Wheeler, Mary Dempsey		FROM: Division of Anesthesia and Analgesia Products – Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183		
DATE June 21, 2010	IND NO.	NDA NO. 201194	TYPE OF DOCUMENT Original submission	DATE OF DOCUMENT Recvd. May 5, 2010
NAME OF DRUG Oxycodone HCl, Oral Solution		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 7	DESIRED COMPLETION DATE January 5, 2011
NAME OF FIRM: VistaPharm, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE--NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review these various sections of this new NDA (#201194, with PDUFA date, Mar. 5, 2011) from a drug safety and risk management perspective. - Package Insert labeling - Medication Guide labeling - Carton and Container labeling - Proposed REMS as part of risk management plan (includes Medication Guide and Communication Plan) This drug product is an opioid schedule II compound (oxycodone). This is a (b)(2) application based on referenced drug Roxycodone Tablets (NDA 21-011). NDA 201194 is fully electronic (eCTD format) and all files can be found in EDR, direct link: \CDSESUB1\EVSPROD\NDA201194\201194.ENX All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Project Manager. FYI, for clinical, the NDA will be reviewed by Rob Shibuya.				
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)		METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201194	ORIG-1	VISTAPHARM INC	OXYCODONE HCL SOLUTION

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/s/

DOMINIC CHIAPPERINO
06/21/2010



NDA 201194

NDA ACKNOWLEDGMENT

VistaPharm Inc.
7265 Ulmerton Road
Largo, FL 33771

Attention: John G. Lay
Director, Regulatory Affairs and Quality Assurance

Dear Mr. Lay:

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: Oxycodone HCl, Oral Solution, USP, 5mg/5mL

Date of Application: May 4, 2010

Date of Receipt: May 5, 2010

Our Reference Number: NDA 201194

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 July 5, 2010, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201194	ORIG-1	VISTAPHARM INC	Oxycodone Hcl Oral Solution, 5 mg/ml

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/s/

DOMINIC CHIAPPERINO
05/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Controlled Substance Staff (CSS, HFD-009) ATTN: Corinne Moody		FROM (Name, Office/Division, and Phone Number of Requestor): Division of Anesthesia and Analgesia Products Director-- Bob A. Rappaport, M.D. Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Project Manager, 301-796-1183		
DATE May 12, 2010	IND NO.	NDA NO. 201194	TYPE OF DOCUMENT Original Submission NDA	DATE OF DOCUMENT recvd: May 4, 2010
NAME OF DRUG Oxycodone HCl, Oral Solution, USP, 5mg/mL		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 7	DESIRED COMPLETION DATE January 4, 2011
NAME OF FIRM: VistaPharm, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☐ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES ☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS				
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL ☐ NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: The Division requests that you please review this new NDA from a (b) (4) perspective and provide written feedback by January 4, 2011. Please contact Dominic Chiapperino, RPM, DAAP (HFD-170), at 301-796-1183 with any questions. Please provide any feedback or deficiencies you wish shared with the sponsor in "letter-ready" format. This is a fully electronic NDA, available here: \\CDSESUB1\EVSPROD\NDA201194\201194.ENX				
SIGNATURE OF REQUESTOR Dominic Chiapperino (electronically signed)			METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND	

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201194	ORIG-1	VISTAPHARM INC	OXYCODONE HCL SOLUTION

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/s/

DOMINIC CHIAPPERINO
06/21/2010