CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200535Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200535 SUPPL # HFD # 170

Trade Name N/A

Generic Name Oxycodone Hydrochloride Oral Solution, 100 mg/5mL (20 mg/mL)

Applicant Name LeHigh Valley Technologies, Inc.

Approval Date, If Known Oct. 20, 2010

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 study is a bioavailability study because all that was measured was pharmacokinetic endpoints. There is no disagreement with the applicant.

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:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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?

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# 21011 Roxicodone Tablets

(b) (4)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

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

NDA#

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:

The product is currently marketed, but not approved.

(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: Tanya D. Clayton
Title: Senior Regulatory Project Manager
Date: Oct. 14, 2010

Name of Office/Division Director signing form: ODE II/DAAP/Sharon Hertz, MD
Title: Deputy Director

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/

TANYA D CLAYTON
10/19/2010

SHARON H HERTZ
10/19/2010

LVT Lehigh Valley Technologies, Inc.

514 North 12th Street • Allentown, PA 18102
Phone: 610-782-9780 • Fax: 610-782-9781

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Lehigh Valley Technologies, Inc., hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA. This certification is based upon the list of debarred individuals available on the FDA website (http://www.fda.gov/ora/compliance_ref/debar/default.htm), last updated on 15 September 2009.

Debarment certifications from the study site are included with the individual study reports.

William Reightler
Director QA/Regulatory Affairs
Lehigh Valley Technologies, Inc.

10/1/09
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 200535 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Oxycodone Hydrochloride Dosage Form: Oral Solution, 20mg/mL		Applicant: LeHigh Valley Technology Agent for Applicant (if applicable):
RPM: Tanya Clayton		Division: 170

NDAs:
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.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Roxicodone Tablets

Provide a brief explanation of how this product is different from the listed drug.

Different Dosage form, Oral Solution, 20mg/mL

If no listed drug, explain.
- ☒ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

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.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 10/20/2010

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 Oct. 22, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ 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 _____	☐ Received

[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.

❖ Application Characteristics [2]

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

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ 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

REMS: ☒ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• 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
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ 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)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ 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)? *(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.)*	☐ 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 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ 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.

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	10/21/10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 10/20/10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Oct. 14, 2010
• Original applicant-proposed labeling	Dec. 22. 2009
• 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 *(write submission/communication date at upper right of first page of each piece)*	☒ 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.	Oct. 14, 2010
• Original applicant-proposed labeling	Dec. 22, 2009
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Dec. 22, 2009
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	None Submitted
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA Oct. 19, 2010 ☒ DRISK Oct. 13, 2010 ☒ DDMAC Oct. 13, 2010 ☒ CSS Oct. 6, 2010 ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/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)*	☐ Not a (b)(2) ☐ Not a (b)(2) Oct. 12 2010
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ 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 o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC Oct. 13, 2010 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ 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)*	Emails, faxes, filing letter

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

❖ Internal memoranda, telecons, etc.	
❖ 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 March 31, 2009
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	PIND Dec. 6, 2007
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None Pending
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A no clinical studies
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ 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 *(indicate date of review/memo)*	See Sharon Hertz's Memo, Oct. 20, 2010
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable Oct. 6, 2010
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Notification Letter May 26, 2010 Sponsor Submission June 9, 2010 May 25, 2020 ☐ None DRISK Oct 13, 2010 REMS Memo-May 25, 2010
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[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
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
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
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Oct. 12, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None Oct. 1, 2010
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
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Oct. 12, 2010
❖ 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 Included in P/T review, page
❖ 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) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None Oct. 18, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ None Aug. 19, 2010
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Sept. 22. and Oct. 14, 2010
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 57 of CMC Review, Oct. 15, 2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(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 sites[6])*	Date completed: Jan. 7, 2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ 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.

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/s/

TANYA D CLAYTON
10/21/2010

From:	Greeley, George
To:	Clayton, Tanya;
cc:	Salis, Olga;
Subject:	NDA"s 200-534 & 200-535 Oxycodone HCL
Date:	Wednesday, October 20, 2010 1:40:05 PM
Attachments:	1_Pediatric_Record_CAPSULE.pdf 1_Pediatric_Record_SOLUTION.pdf

---

Hi Tanya,

The Oxycodone deferral and plan was reviewed by the PeRC PREA Subcommittee on October 13, 2010.

The Division presented a deferral and plan for patients ages birth through sixteen years because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a deferral for this product. The pediatric record is attached reflecting the PeRC review for Oxycodone HCL.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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/s/

TANYA D CLAYTON
10/20/2010

From: Clayton, Tanya
To: "Bill Reightler";
Subject: Oxycodone Hydrochloride Oral Solution
Date: Tuesday, October 19, 2010 3:45:32 PM

Hello Bill,

For your Oxycodone Hydrochloride Oral Solution:
Your proposed oral formulation contains (b) (4)

Please let me know if you have any questions.
Kind Regards,
Tanya D.Clayton
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Anesthesia and Analgesia Products
(301) 796-0871 Phone
Tanya.Clayton@fda.hhs.gov

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/s/

TANYA D CLAYTON
10/19/2010

NDA 200535

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: Sep 23, 2010

To: Bill Reightler	**From:** Tanya Clayton, SRPM
Company: Lehigh Valley Technologies, Inc.	Division of Anesthesia and Analgesia Products
Fax number:	**Fax number:**
Phone number:	**Phone number:** 301-796-0871

Subject: Information Request

Total no. of pages including cover: 3

Comments: Please provide a complete response by Oct 4, 2010.

Document to be mailed: YES x NO

Please refer to your new drug applications (NDA) dated December 22, 2009, received December 22, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone Hydrochloride Solution, 20 mg/mL.

We also refer to the teleconference held today, Sep 23, 2010.

NDA 200-535

1. Submit revised regulatory drug substance specification sheet as discussed during teleconference, with data-based acceptance criteria for residual solvents.

2. Submit revised regulatory drug product specification sheet with method and interim acceptance criteria for microbial limits and heavy metals. Also, tighten the acceptance criteria for total impurities, and revised description for individual impurities, as discussed during teleconference.

3. Provide detailed protocol for addressing microbial controls in the drug product, which you are not able to address by Oct 4, 2010. Include the submission date for the prior approval supplement which will satisfactorily address all the outstanding issues from the following comments:

    a. In the (b) (4) summary report, the content of sodium benzoate in the tested formulations was not correlated to the summary results. Please provide a chart linking the batch codes to the content of sodium benzoate in the formulations used for the (b) (4) .

    b. No release specification for microbial limits was provided in the NDA submission. Please provide a microbial limit specification at release which includes acceptance criteria and associated test methodology (see USP<61>, <62> and <1111>). Microbial limits testing should also be conducted within the stability program. Also, as an alternative, you may propose to omit finished product microbial limits testing for batch release and substitute inprocess manufacturing controls, tests and acceptance criteria that provide assurance of the microbiological quality for each batch of your product. The product specification should state that the product will meet the requirements of USP<1111>, if tested. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:
        - Microbial limits data for critical raw materials,
        - Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and
        - In-process control parameters that may affect product quality microbiology.

    In addition, microbial limits testing should be always performed at the initial time point (at a minimum) on stability samples.

c. Provide test methods and acceptance criteria to demonstrate the product is free of *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested. The following references may be helpful in addressing the method development.

"An optimal recovery method for *Burkholderia cepacia* has yet to be determined. You may develop your own and validate it for use. You should be aware of certain limitations to commonly-used media when trying to recover *B. cepacia* (Carson *et al.*, 1973. Applied Microbiology 25(3):476-483, AND Miller *et al.*, 2002. Applied and Environmental Microbiology 68(8):3750-3758). Selective media have been described for detection of *B. cepacia* (Henry *et al.*, 1999. Journal of Clinical Microbiology 37(4):1004-1007), however those are intended for recovery from patients. An enrichment culture is recommended prior to use of selective media."

4. Submit updated stability data for the market-representative drug product batches, with actual impurity results (b) (4) If the levels are below LOQ, please report the actual LOQ numerical value for the used analytical method.

If you have any questions, please contact Tanya Clayton, Senior Regulatory Project Manager, at 301-796-0871.

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/s/

TANYA D CLAYTON
09/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: David Hussong, Ph.D. New Drug Microbiology, OPS			FROM: Eugenia Nashed, ONDQA, Div. 3, Branch 8	
DATE Sep 15, 2010	IND NO.	NDA NO. 200-535	TYPE OF DOCUMENT	DATE OF DOCUMENT 12/22/2009 – original NDA
NAME OF DRUG Oxycodone hydrochloride oral solution, (b) (4) 20 mg/mL	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG 2S	DESIRED COMPLETION DATE Sep 29, 2010
NAME OF FIRM: Lehigh Valley Technologies, 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
X 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
☐ BIOAVAILABILTY 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
☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please evaluate (b) (4) for the oral solution drug product. The NDA is electronic - Refer to section 3.2.P.2 of the original submission. The latest version of Specifications is in Amendment dated Aug 19, 2010.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X Electronic MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

EUGENIA M NASHED
09/15/2010

NDA 200535

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 22, 2010

To:	**From:** Tanya Clayton, SRPM
Company:	Division of Anesthesia and Analgesia Products
Fax number:	**Fax number:** 301-796-
Phone number:	**Phone number:** 301-796-0871

Subject: Information Request

Total no. of pages including cover: 3

Comments: Please provide a response to the request by Aug 16, 2010.

Document to be mailed: YES x NO

Please refer to your new drug application (NDA) dated December 22, 2009, received December 22, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone Hydrochloride Oral Solution USP.

We also refer to your submissions dated March 29, and Apr 5, 2010.

1. Submit revised regulatory drug substance specification sheet with data-based acceptance criteria and provide supportive batch data. The impurity profile should include a full list of individual impurities as requested in our letter dated March 5, 2010, and per your agreement in submissions dated March 29, and April 5, 2010. All unidentified (unknown) impurities at, or above (b) (4) have to be listed in the table with the corresponding RRT values, and for all identified impurities a list of full chemical names and structures need to be attached to the table, as requested. Also, include testing for heavy metals and microbial limits.

2. Submit revised regulatory drug product specification sheet with data-based acceptance criteria and provide supportive batch data with justification. Revise the tested attributes as follow.

    a. Revise the impurity profile to include a full list of individual impurities as requested in our letter dated March 5, 2010, and per your agreement in submissions dated March 29, and April 5, 2010. All unidentified (unknown) impurities at, or above (b) (4) have to be listed in the table with the corresponding RRT values, and for all identified impurities a list of full chemical names and structures need to be attached to the table, as requested.

    b. Tighten the proposed acceptance criteria for pH. The currently proposed criteria (b) (4)

    c. Include acceptance criteria for leachables from the container closure as needed based on the results of the requested study report for extractables and leachables (see comment below).

    d. Include safety information about the residual solvents into the specification table, e.g., Residual Solvents: Meets USP <467>. *Residual solvents in drug product ingredients x, y and z are controlled in the corresponding acceptance criteria by the drug product manufacturer, and no additional solvents are used in the drug product manufacturing process.

3. Provide study report on extractables/leachables from all part of container closure system that are in contact with the drug product formulation, as discussed during teleconference on July 12, 2010. Also, refer to comments #3 and 9, in our letter

dated March 5, 2010. Note, that the study report has to account for the unique extractable properties of your drug product formulation and accommodate review concerns associated with liquid-based oral drug products with chronic dosing regiments and containing potential co-solvents.

4. Submit updated release and stability data for each strength of the market-representative drug product batches, reported in the revised format as requested above.

If you have any questions, please contact Tanya Clayton, Senior Regulatory Project Manager, at 301-796-0871.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

DANAE D CHRISTODOULOU
07/23/2010
CMC IR
Signature for Jean Nashed

PRASAD PERI
07/23/2010
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Tanya Clayton, Project Manager, DAAP	
DATE July 6, 2010	IND NO.	NDA NO. 200535	TYPE OF DOCUMENT REMS Proposal	DATE OF DOCUMENT June, 2010
NAME OF DRUG Oxycodone Hydrochloride Oral Solution ((b) (4) 20mg/ml)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Pain	DESIRED COMPLETION DATE September 3, 2010

NAME OF FIRM: LeHigh Valley Technologies

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)*: REMS Proposal

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
- ☐ BIOAVAILABILTY 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:

We are requesting a review for a proposed REMS submitted June 9, 2010. We sent a REMS notification letter May 26, 2010.

Product: Oxycodone HCL Oral Solution ((b) (4) 20mg/ml).
PDUFA Date: October 22, 2010
Documents for Review: **\\CDSESUB1\EVSPROD\NDA200535; June 9, 2010**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
	☐ MAIL ☐ HAND

Tanya D. Clayton, 60871	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

TANYA D CLAYTON
07/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: CSS, Corinne Moody

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Tanya Clayton, Project Manager, DAAP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 9, 2010		200534, 200535	NDA	Dec. 22, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Oxycodone Capsules (5mg) and Oral Solution ((b) (4) 20mg/ml)	Standard	Pain	August 22, 2010

NAME OF FIRM: LeHigh Valley Technologies

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
- ☐ BIOAVAILABILTY 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:

We are requesting reviews for two NDAs, Oxycodone HCL Oral Solution ((b) (4) 20mg/ml) and HCL Capsules (5 mg). The labeling for review is fully electronic and is located in the EDR under \\CDSESUB1\EVSPROD\NDA200534 and \\CDSESUB1\EVSPROD\NDA200535.

PDUFA Date: October 22, 2010

SIGNATURE OF REQUESTOR
Tanya D. Clayton

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-200534	ORIG-1	Lehigh Valley Technologies, Inc. 514 N. 12th Street, Allentown, PA 18105	OXYCODONE HCL CAPSULES
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

TANYA D CLAYTON
06/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200535 **REMS NOTIFICATION LETTER**

Lehigh Valley Technologies, Inc.
Attention: William Reightler
Director QA, Regulatory Affairs
514 North 12th Street
Allentown, PA 18102

Dear Mr. Reightler:

Please refer to your New Drug Application (NDA) dated and received December 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL).

We also refer to the teleconference held on May 25, 2010, between the Division of Anesthesia and Analgesia Products and Leigh Valley Technologies, Inc. in which we indicated that you must submit a REMS that includes a Medication Guide and Timetable for Submission of Assessments.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Oxycodone Hydrochloride Oral Solution to ensure that the benefits of the drug outweigh the risk of medication errors, which may result in overdose.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Oxycodone Hydrochloride Oral Solution, when available in multiple formulations, including (b) (4) 20 mg/mL, poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Oxycodone Hydrochloride Oral Solution. FDA has determined that Oxycodone Hydrochloride Oral Solution is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or

continue to use Oxycodone Hydrochloride Oral Solution. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Oxycodone Hydrochloride Oral Solution.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but not limited to an evaluation of patients' understanding of the serious risks of Oxycodone Hydrochloride Oral Solution.

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 200535 PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 200535
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Tanya Clayton, Senior Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Deputy Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

Lehigh Valley Technologies, Inc. will submit REMS Assessments to the FDA at a minimum, 18 months, 3 years and in the 7th year from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Lehigh Valley Technologies, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B:
REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Medication Guide

    b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)

5. REMS Assessment Plan (for products approved under an NDA or BLA)

6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

SHARON H HERTZ
05/26/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Tanya Clayton, Project Manager, DAAP	
DATE April 6, 2010	IND NO.	NDA NO. 200534, 200535	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT Dec. 22, 2009
NAME OF DRUG Oxycodone Capsules (5mg) and Oral Solution ((b) (4) 20mg/ml)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Pain	DESIRED COMPLETION DATE September 3, 2010

NAME OF FIRM: LeHigh Valley Technologies

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)*: Labeling Review

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
- ☐ BIOAVAILABILTY 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:

We are requesting labeling reviews for two NDAs, Oxycodone HCL Oral Solution ((b) (4) 20mg/ml) and HCL Capsules (5 mg). The labeling for review is fully electronic and is located in the EDR under **\\CDSESUB1\EVSPROD\NDA200534 and \\CDSESUB1\EVSPROD\NDA200535.**

PDUFA Date: October 22, 2010
Documents for Review: Draft Package Insert and Container labeling

SIGNATURE OF REQUESTER Tanya D. Clayton, 60871	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

TANYA D CLAYTON
04/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200535

FILING COMMUNICATION

Lehigh Valley Technologies, Inc.
514 North 12th Street
Allentown, PA 18102

Dear Mr. Reightler:

Please refer to your new drug application (NDA) dated December 22, 2009, received December 22, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone Hydrochloride Oral Solution USP.

We also refer to your submissions dated January 8 and February 23, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 22, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 29, 2010.

During our filing review of your application, we identified the following potential review issues:

1. The proposed drug substance impurity specification for 6-α-oxycodol ((b) (4)) exceeds the ICHQ3A(R2) qualification threshold of NMT 0.15%. Either this specification must be tightened to NMT 0.15% or you must provide adequate safety qualification for this impurity. As noted in the preNDA meeting minutes March 31, 2009, adequate qualification of an 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.

b. Repeat dose toxicology of appropriate duration to support the proposed indication. For a chronic indication, a study of at least 90-days is appropriate.

2. The proposed drug product specification for (b) (4) (b) (4)) exceeds the ICHQ3B(R2) qualification threshold of NMT 0.2% for a drug product with a maximum daily dose of >100 mg to 2 g. Unless you can provide adequate clinical use data to document that these products will not be used at a maximum daily dose that exceeds 100 mg/day, either this specification must be tightened to NMT 0.2% or you must provide adequate safety qualification for this impurity. As noted in the preNDA meeting minutes March 31, 2009, adequate qualification of an 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.

   b. Repeat dose toxicology of appropriate duration to support the proposed indication. For a chronic indication, a study of at least 90-days is appropriate.

3. This application must contain information on potential leachables and extractables from the drug container closure system (HDPE bottle, innerseal cap and (b) (4)). Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled oral route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic dosing). This should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

4. Resubmit drug substance specifications to include reporting of each impurity occurring at, or above, (b) (4), with corresponding RRT or name if known. Tighten the proposed acceptance criteria for 6-α-oxycodol or qualify this impurity as specified in request number 2 in this letter. . Attach, to the specification sheet, a complete list of identified impurities with the chemical names and structures.

5. Provide data on compatibility studies for the proposed commercial drug product formulations. Alternatively, provide precise references to the appropriate sections of the US-approved reference drug products.

6. Submit revised drug product specifications to include controls for the content of residual solvents and improved controls for impurities. Note that each impurity occurring in the drug product at, or above (b) (4) needs to be reported with RRT value or name if known, and each impurity at, or above (b) (4) needs to be qualified. Refer to request number 2 in this letter. Attach, to the specification sheet, a complete list of identified impurities with the chemical names and structures.

7. Resubmit batch analyses data to include testing for all drug product attributes as requested in comment above, including results for individual and total impurities.

8. Provide updated stability data for the commercial drug product formulations to support the requested expiry period. Submit revised stability specifications, as requested for the drug product in request number 5 in this letter. Provide data collected according to the revised protocol for each testing interval.

9. Submit data for extractables testing performed on each part of the container closure system (bottle, cap seal and (b) (4)) and leachables data for the drug product. Include results from testing for leachables on stability. Provide references to appropriate 21 CFR food contact regulations for the container closure system.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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 Division of Anesthesia, Analgesia and Rheumatology 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 request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Tanya Clayton, Senior Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

BOB A RAPPAPORT
03/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200535 **NDA ACKNOWLEDGMENT**

Lehigh Valley Technologies, Inc.
514 North 12th Street
Allentown, PA 18102

Dear Mr. Reightler:

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 Hydrochloride Oral Solution USP, (b) (4) 20 mg/mL

Date of Application: December 22, 2009

Date of Receipt: December 22, 2009

Our Reference Number: NDA 200535

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 February 20, 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, Analgesia
and Rheumatology 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 Tanya Clayton, Senior Regulatory Health Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya D. Clayton
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

TANYA D CLAYTON
01/08/2010

SPONSOR MEETING AGENDA

MEETING DATE: March 31, 2009

TIME: 1 PM

LOCATION: FDA White Oak Campus

APPLICATION: **IND 78,623 and IND 78,624**

STATUS OF APPLICATION: **Active**

PRODUCT: Oxycodone Hydrochloride Capsules, 5mg and Oxycodone Hydrochloride Oral Solution.

INDICATION: **Moderate to severe pain**

SPONSOR: **Glenmark Generics, Inc.**

TYPE OF MEETING: B

MEETING CHAIR: Ellen Fields, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Christopher Hilfiger, Regulatory Project Manager

FDA Attendees	Title
Bob A Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Ellen Fields, MD	Clinical Team Leader
Elizabeth Kilgore, MD	Medical Officer
Carlic Huynh, PhD	Pharm/Tox Reviewer
Dan Mellon, PhD	Pharm/Tox Team Leader
Ali Al-Hakim, PhD	ONDQA Branch Chief
Danae Christodoulou, PhD	CMC Reviewer
Glenmark Attendees	**Title**
William McIntyre, PhD	Executive Vice President, Regulatory Affairs
Anthony Maffia, III	Director, Regulatory Affairs
(b) (4)	Consultant, Managing Director
	Clinical Pharmacology Consultant
	Chemistry Consultant
	Project Manager
	Chemistry Consultant

Question 1.

Glenmark would like the FDA's feedback regarding the proposed specifications for the drug substance and drug product, especially as they relate to the tightened specifications for low (b) (4) *in the drug substance and absence of a specified limit for this impurity in the drug product.*

FDA Response:

The drug substance and the drug product specifications will be assessed at the time of NDA submission as per ICH Guidelines Q3A and Q3B. The total daily exposure of impurities with structural alerts for mutagenicity should be limited to NMT 1.5 mcg.

Question 2.

Glenmark is (b) (4) *for NDA approval. Is this plan acceptable to FDA?*

FDA Response:

No. You must include primary stability data on drug product batch(es) manufactured with low (b) (4) **API in your NDA submission. Provide comparative batch analysis data on release and stability for drug product manufactured from high and low** (b) (4) **API.**

Question 3.

Is the extent and type of overall stability data for the commercial and other NDA batches of drug product sufficient to support filing of the NDA? Is the plan for providing updated stability information during the course of the review acceptable?

FDA Response:

Regarding the 5-mg capsules, you must include primary stability data on drug product manufactured with low (b) (4) **API. See response to Question 2.**
The expiration dating will be assessed at the time of NDA review, based on ICH Q1E guidelines, i.e., real time stability data on primary and supporting NDA batches, and statistical analysis evaluation, as applicable.

Question 4.

Is the extent and type of overall stability data for the registration batches of drug product sufficient to support filing of the NDA? Is the plan for providing updated stability information during the course of the review acceptable?

FDA Response:

We strongly recommend that you submit the maximum available stability data for your primary stability batches at the time of NDA submission, or at least in the early part of the review cycle (first three months for a standard priority submission). While every effort

will be made to review any stability amendments to the NDA, their review will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, per GRMP guidelines, we may not be able to review amendments submitted to the NDA during the review cycle.

Question 5.

(b) (4)

FDA Response:

- **If there are existing patents or exclusivity for a product referenced in a 505(B)(2) application, we may not be able to approve the application until such patents or exclusivity expire.** (b) (4)
- **The** (b) (4) **capsule will have the same indication as the immediate-release oxycodone reference product unless you can provide additional support for any differences.**
- **The** (b) (4) **oral solution (20 mg/mL) is not appropriate for use as the first opioid or in non-opioid- tolerant patients. Therefore, this must be reflected in the indication.**
- **The ISE must include a discussion of why reliance on the reference product is adequate to support the efficacy of your product.**

Question 6.

Does the Division agree that the plan for restricting comprehensive search of the worldwide literature for safety information to that published after August 2000, the date of the most recently approved Roxicodone® label?

FDA Response: Yes

Question 7.

Does the Division agree that no pediatric studies are needed in support of the planned NDA?

FDA Response:

No. The requirements for pediatric studies based on PREA state that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of

administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. (63 FR 66632) Your products represent new dosage forms.

Single- and multiple-dose PK, efficacy and safety studies in the appropriate pediatric age groups will be required.

Additional Clinical Pharmacology Comments:

- **It appears that you have assessed the (1) relative bioavailability of the 5-mg capsules and 20-mg/mL solution products to (b) (4) Roxicodone® (b) (4) and (2) effect of food on the 5-mg capsules. However, data were not submitted in the meeting package and we are unable to assess if appropriate bridging has been established between your products and the products you will rely upon for the 505 (b)(2) linkage. As stated during the pre-IND meeting, additional clinical/PK studies may be required if the relative bioavailability data does not establish an appropriate bridge between your products to the reference products.**
- **We remind you that if you are planning to seek a (b) (4) , submit (b) (4) in the NDA with all supportive information.**
- **The effect of food was determined only with your capsule product. If you think that this information also applies to the solution formulations, provide justification in the NDA.**

Additional CMC Comments:

For the oral solution, provide a leachables/extractables evaluation of your container/closure system with the drug product in the NDA, with characterization and assay of any new impurities and degradants. With regards to extractables and leachables testing, consult the FDA Guidance document "Container Closure Systems for Packaging Human Drugs and Biologics," USP <661>, and the PQRI leachables/extractables recommendations to the FDA found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf. Refer to the non-clinical comments regarding the safety evaluation of your leachables/extractables.

Provide a list of all manufacturing facilities, in alphabetical order, statement about their cGMP status and whether they are ready for inspections. For all foreign sites, provide a name contact with telephone number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.

Non-clinical Comments:

- **Adequate safety qualification should be provided for any new excipients. Please refer to Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical**

Excipients (May 2005) which is available on the CDER web page at the following address: http://www.fda.gov/cder/guidance/5544fnl.pdf.

- **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICHQ3A(R2) and ICHQ3B(R2).**
  - **Adequate qualification must include:**
    - **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.**
    - **Repeat dose toxicology of appropriate duration to support the proposed indication.**
  - **Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic impurities unless otherwise justified.**
  - **It is noted that you have listed a specification of (b) (4) (b) (4) for potentially genotoxic impurities or degradation products throughout the meeting package. The correct specification for potentially genotoxic impurities or degradation products is NMT 1.5 mcg/day.**

- **The NDA submission must contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).**

- **The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/2853dft.pdf. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).**

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

literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Regulatory Comment:

You must submit a separate NDA for each formulation of oxycodone. However, you may combine the labels for each product into one label. For further information please refer to Guidance for Industry Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees http://www.fda.gov/cder/guidance/5469fnl.htm.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 78623	GLENMARK GENERICS INC USA	OXYCODONE HCL CAPSULES
IND 78624	GLENMARK GENERICS INC USA	OXYCODONE HCL SOLUTION

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

/s/

CHRISTOPHER M HILFIGER
03/31/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND (b) (4)
PIND (b) (4)
PIND 78,623
PIND 78,624

Glenmark Pharmaceuticals, Inc., USA
750 Corporate Drive
Mahwah, NJ 07430

Attention: William McIntyre, Ph.D.
Executive Vice President, Regulatory Affairs

Dear Dr. McIntyre:

Please refer to your Pre-Investigational New Drug Applications (PINDs) for your morphine sulfate tablets and solution, and oxycodone HCl capsules and solution products.

We also refer to the Type B, Pre-IND meeting between representatives of your firm and FDA on December 6, 2007. The purpose of the meeting was to provide you with feedback on the questions in your October 25, 2007 meeting package, which were specifically related to your preparations for submission on an IND for your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Meeting Date: December 6, 2007
Time: 3:00 PM EST
Location: Teleconference
Applications: PIND (b) (4); (b) (4); 78,623; and 78,624
Regulatory Status: Presubmission
Products: - Morphine sulfate tablets and solution (PIND (b) (4), PIND (b) (4))
- Oxycodone HCl capsules and solution (PIND 78,623, PIND 78,624)
Proposed Indication: Treatment of moderate-to-severe pain
Sponsor: Glenmark Pharmaceuticals, Inc.
Type of Meeting: Type B- Pre-IND (PIND)
Meeting Chair: Sharon Hertz, M.D., Deputy Director
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Kimberly Compton, Project Manager, DAARP

Industry Representatives	**Title**
William McIntyre, Ph.D.	Executive Vice President, Regulatory Affairs, Glenmark Pharmaceuticals, Inc.
Anthony Maffia, III	Senior Manager, Regulatory Affairs, Glenmark Pharmaceuticals, Inc.
(b) (4)	
FDA	**Title**
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Mary Purucker, MD, PhD	Medical Team Leader, DAARP
Belinda Hayes, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAARP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead (PAL), Office of New Drug Quality Assessment (ONDQA)
Janice Weiner, J.D., M.P.H.	Regulatory Counsel, Office Of Regulatory Policy
Tanya Clayton	Regulatory Project Manager, DAARP
Kim Compton	Regulatory Project Manager, DAARP

Meeting Objective:
The purpose of the meeting was to provide the sponsor with feedback on questions from their October 25, 2007, meeting package, which were specifically related to their preparations for submission of an IND for these products.

Background:
On December 4, 2007 (prior to the December 6, 2007 meeting) the Agency forwarded to the firm the comments and responses to the questions posed by the sponsor in their October 25, 2007, meeting package. The sponsor requested further discussion of Morphine Question 6/ Oxycodone Question 7, Morphine and Oxycodone Questions 8, 9, and 10 as well as the both the Additional Regulatory Comments for Oxycodone and the Regulatory Comments for both Morphine and Oxycodone at the meeting.

Presented below are the Agency comments related to the sponsor's background material and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**.

As the discussions consisted of one on-going discussion of basic underlying issues surrounding these applications, all Discussion which took place at the meeting is captured in one location following the "Regulatory Comments for both Morphine and Oxycodone" below.

Meeting:

Chemistry Questions

Morphine and Oxycodone Question 1
Does the Division agree that the information to be submitted in the IND appears adequate to support the proposed trial?

FDA Response (Morphine and Oxycodone)
Yes. Refer to Additional Chemistry Comments below for further information.

Discussion
There was no further discussion of this issue.

Oxycodone Question 2
Do the tentative tests and specifications for the drug substances appear adequate?

FDA Response (Oxycodone)
Yes. As you proposed, the specifications for impurities should be tightened at the time of the NDA.

Harmonize your acceptance specifications for the drug substance, with your supplier's specifications. Refer to the ICH Q3A Guidance to establish limits for impurities in the drug substance. Structural alerts for mutagenicity, i.e., (b) (4) **should be limited to NMT 1.5 mcg/day, as per the EMEA Guideline.**

Discussion
There was no further discussion of this issue.

Morphine Question 2/ Oxycodone Question 3
Do the tentative tests and specifications for the two drug products appear adequate?

FDA Response (Morphine and Oxycodone)
No. Specifications for the drug products should include impurities/degradants at release and on stability. Monitor, identify and qualify any new degradents in the drug products. Refer to ICH Q3B Guidance and the EMEA Guideline for structural alerts, as discussed above.

Include (b) (4) in the specifications of the Oral Solutions.

Oxycodone is known to exhibit multiple polymorphs. Monitor the polymorphic form in the drug product during development of your solid oral formulation. Provide crystallographic data to support suitability of the morphic form for the manufacturability and performance of the drug product.

Discussion
There was no further discussion of this issue.

Additional Chemistry Comment
Provide a DMF reference and LoA (if applicable) for the non-pharmacopeial excipients D&C Yellow #10 and Natural/Artificial Berry Flavor. Include the supplier and specifications/CoAs in your INDs.

Also, please refer to the Nonclinical comments below for further information regarding novel excipients.

Discussion
There was no further discussion of this issue.

Nonclinical Questions

Morphine Question 3/Oxycodone Question 4
Is Glenmark's plan [whereby the sponsor refers to their intent to rely on the Agency's prior judgment of safety as well as on publicly available information for nonclinical support of their applications] *acceptable to the Agency?*

FDA Response (Morphine and Oxycodone)
Yes, you may rely upon studies not conducted by or for you and to which you have not obtained a right of reference or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug) to support your nonclinical development program. Please also see Additional Regulatory Comments following the Response to Question 10.

Discussion
There was no further discussion of this issue.

Morphine Question 4/Oxycodone Question 5
Does the Agency agree that no additional toxicology studies will be required for approval?

FDA Response (Morphine and Oxycodone)
In principal, yes. Include copies of all referenced literature citations your NDA submission.

- **Adequate safety qualification must be provided for any new excipients. Refer to *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients* (May 2005) which is available on the CDER web page at the following http://www.fda.gov/cder/guidance.htm.**

- **Regarding Impurities**

  - **Opioid drug products derived from thebaine (phenanthrene-derivatives) may contain impurities, such as (b) (4), containing an (b) (4) moiety. It is a structural alert for mutagenicity. The specification of this impurity in the drug substance may not exceed the acceptable specifications of NMT 1.5 mcg/day (b) (4) in an opioid tolerant patient. If it exceeds this specification, adequate safety qualification should be provided. Adequate qualification would include:**

    - **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.**

    - **Repeat-dose toxicology of 90-day duration in the most appropriate species to support the proposed chronic indication.**

    - **Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.**

- **Your NDA/IND submission should contain information on potential leachables and extractables from the drug delivery system. Provide your**

justification for the safety of potential exposure to the study subjects, supporting data/literature references. Complete characterization of leachables and extractables should be submitted with the NDA

Discussion
There was no further discussion of this issue.

Clinical Pharmacology Questions

Morphine Question 5/Oxycodone Question 6
Is the design of the proposed study [whereby the sponsor refers to single-dose bioavailability/bioequivalence studies for each product comparing the proposed products to an approved reference products] *acceptable?*

FDA Response (Morphine and Oxycodone)
Yes.

Discussion
There was no further discussion of this issue.

Morphine Question 6/Oxycodone Question 7
Does the Agency agree that no additional pharmacokinetic studies are needed?

FDA Response (Morphine tablet)
Whether additional PK studies are required will be based on a review of data obtained with the formulation, including *in vitro* release and dissolution.

See Response to Morphine Questions #7 and 10, and the Regulatory Comments related to Morphine below.

FDA Response (Morphine and Oxycodone solutions)
Clarify whether you plan to request a [redacted] If so, provide justification.

For further discussion, see the Regulatory Comments related to Oxycodone following Question # 10 below.

Discussion
See discussion following "Regulatory Comments for both Morphine and Oxycodone" below.

Morphine Question 7

(b) (4)

[redacted]

(b) (4)

Discussion
There was no further discussion of this issue.

Clinical Questions

Morphine and Oxycodone Question 8
Is the design of the study [whereby the sponsor refers to their plan (b) (4) *adequate to demonstrate efficacy?*

FDA Response (Morphine and Oxycodone)
The proposed study design does appear adequate to support a finding of efficacy. The full protocol must be reviewed before final comments can be provided.

However, you may wish to explore the labeling for the products you plan to reference for your 505(b)(2) application to see whether there is adequate information to support the labeling for your products. Additional clinical efficacy studies may not be necessary unless you wish to support a claim or dosing regimen not present in the referenced product labeling.

Discussion
See discussion following "Regulatory Comments for both Morphine and Oxycodone" below.

Morphine and Oxycodone Question 9
Does the Agency agree that no additional clinical studies will be required to demonstrate efficacy?

FDA Response (Morphine and Oxycodone)
As long as you do not seek to support claims for which the Agency has not previously made a finding of efficacy or safety, oxycodone clinical efficacy or safety studies are not required.

Discussion
See discussion following "Regulatory Comments for both Morphine and Oxycodone" below.

Morphine Question 10

(b) (4)

[redacted]

Additional Regulatory Comments for Oxycodone

A 505(b)(2) application would be an acceptable approach for these Oxycodone products at this time based on the information provided.

Your pre-IND briefing package suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for (b) (4) Roxycodone (NDA 21-011), Roxycodone SR (NDA 20-932; listed in the discontinued section of the Orange Book), Combunox (NDA 21-378), and Percodan (NDA 07-337) for support of safety and/or efficacy. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug.

Regulatory Comments for both Morphine and Oxycodone

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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

<u>Post Meeting Note</u>
With reference to the above discussion, it also should be noted that a filed 505(b)(2) application under review may be subject to any (unexpired) exclusivity granted to a subsequently approved NDA.

<u>Discussion</u>
Dr. Hertz stated that unless the sponsor wanted to support specific labeling language with their proposed (b) (4) studies, such studies would not be necessary. The sponsor can rely upon the Agency's finding of safety and/or effectiveness (b) (4) and then provide dosing information based upon appropriate sources such as published literature. If the sponsor wishes to use information from other products (b) (4) then they will need to identify the products as additional listed drugs relied upon and comply with applicable regulatory requirements.

Dr. Hertz stated that the firm will need to establish a link or "bridge" to demonstrate the appropriateness of reliance on any referenced product(s) with a relative bioavailability (BA) study.

Dr. Hertz clarified that, although the Division does not make exclusivity determinations, only applications which require new clinical studies to support approval are eligible for 3-year exclusivity. The proposed clinical studies are not required for approval.

Ms. Weiner clarified that a 505(b)(2) application which relies on the Agency's finding of safety and/or effectiveness for a listed drug may rely on that finding as described in product labeling, but may not rely upon the summary basis of approval or an FDA reviewer's summary for the listed drug even if publicly available. A sponsor may rely upon the Agency's finding of safety and/or effectiveness for a listed drug to the extent that they demonstrate that such reliance is scientifically appropriate, which is why bridging studies are necessary. It is the sponsor's responsibility to provide any necessary data to support the differences between the listed drug relied upon and the proposed drug product.

Dr. Hertz stated that the firm should provide information to demonstrate why referenced safety labeling is relevant to their product (e.g., relative BA study) and, therefore, why they feel the Agency's prior findings are relevant to the product(s) in question.

Ms. Weiner stated that the sponsor will need to provide a bridge supporting the scientific appropriateness of reliance for each listed drug or published literature used to support elements of their proposed 505(b)(2) applications.

Dr. Hertz stated that if the firm relies on a modified-release dosing formulation, then they will need to specify which portions of those applications they wish to rely on. Justification would be needed to support not conducting a relative BA study and she noted that it would be difficult to establish such a link for these products by providing a scientific rationale in lieu of a relative BA study. The best approach would be to conduct a relative BA study.

Dr. Rappaport stated that if the sponsor wanted to use information from immediate-release and extended-release products in their proposed product labels, they could conduct one three-arm study comparing the three formulations. Dr. Hertz clarified that the firm would need a relative BA study, not a bioequivalence study, noting the difference between the two terms. There is an expectation that the pharmacokinetics for these products would look different from the (b) (4) extended-release formulations.

Regarding the oxycodone preparations, Dr. Hertz stated that there are both oral immediate-release and extended-release preparations approved, but noted that the path for relative BA would be the same as that discussed above for morphine. The sponsor would need to comply with applicable regulatory requirements, including an appropriate patent certification, for each listed drug relied upon.

Dr. Rappaport noted that the only indication which could be granted to these applications would be for the treatment of moderate to severe pain with no other language included in the indication.

Ms. Weiner stated that if there is a pharmaceutically equivalent product, the sponsor would need to identify the product as one of their referenced drugs, noting that the sponsor has selected a pharmaceutical alternative (capsule), so it appears acceptable as the referenced product.

With reference to the last paragraph of the Regulatory Comments for both Morphine and Oxycodone, Dr. Hertz stated that the Division would not refuse to file an application because another application for a pharmaceutically equivalent product was under review but had not yet been approved. Since all applications are confidential, the Agency could not even acknowledge that another application was in-house. Dr. Hertz also noted that sponsors of 505(b)(2) applications pay user fees, but was unsure if the user fee would be refunded if a pharmaceutically equivalent product was approved after the 505(b)(2) application had been submitted, but before a filing decision had been made. She referred the sponsor to the user fee office for clarification of this issue.

Additional Clinical Comments

1. **As a Schedule II drug under the CSA, all Schedule II regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of study drug must be in place and strictly followed during any clinical studies conducted.**

2. **To provide information and data related to abuse, misuse, diversion and overdose of the product, submit descriptions of all reports and details, including narratives, of an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies. Additionally, provide any available epidemiological data on abuse, misuse, diversion and overdose on their currently marketed morphine and Oxycodone products.**

   Discussion
   There was no further discussion of this issue.

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The sponsor understands that no clinical trials are needed if appropriate bridging to approved products is established (such as with a relative BA study).

2. If a relative BA study is completed, comparing the products to (b) (4) extended-release formulation, the sponsor is limited to using the information in those labels to support approval of their proposed product and in their labeling.

3. The sponsor understands that they will be allowed to reference information in the labels of approved products only if a link (e.g., relative BA study) is established.

4. The sponsor understands that utilizing a scientific rationale in lieu of a relative BA study is highly unlikely to be a path to approval of these products.

5. The sponsor understands that, provided there are no other pharmaceutically equivalent products approved as of the day of submission of their applications, new 505(b)(2) applications will be accepted for submission, however applications that were already in-

house may still be approved after new applications are accepted and before a filing decision is made.

Linked Applications	Sponsor Name	Drug Name
IND (b) (4)	GLENMARK PHARMS	MORPHINE SULFATE IR TABLETS
IND (b) (4)	GLENMARK PHARMA	MORPHINE SULFATE ORAL SOLUTION
IND 78623	GLENMARK PHARMS INC	OXYCODONE HCL CAPSULES
IND 78624	GLENMARK PHARMS INC	OXYCODONE HCL SOLUTION

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/s/

TANYA D CLAYTON
01/04/2008
signing for Kimberly Compton