CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200534Orig1s000

OTHER REVIEW(S)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1698-2: Pharmacokinetic and Safety study in Subjects > 2 years to <17 of age.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	May 2011
	Study/Ttrial Completion:	November 2013
	Final Report Submission:	May 2014
	Other: N/A	

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

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

   Product ready for approval in Adults. Note: the product is currently marketed, but not approved.

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Pharmacokinetic and Safety in Subjects > 2 years to <17 of age.

Required

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

Continuation of Question 4

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

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____
(signature line for BLAs)

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/s/

TANYA D CLAYTON
10/20/2010

LARISSA LAPTEVA
10/20/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1698-1: Pharmacokinetic, Safety and Efficacy study in Subjects from Birth to 2 years of age.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	August 2011
Study/Ttrial Completion:	November 2014
Final Report Submission:	November 2015
Other: N/A	

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

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

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

PK, Safety and Efficacy in Subjects from Birth to 2 years.

Required

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

Continuation of Question 4

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

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

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/s/

TANYA D CLAYTON
10/20/2010

LARISSA LAPTEVA
10/20/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 18, 2010
Application Type/Numbers:	NDA 200534 and NDA 200535
To:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products
Through:	Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis
From:	Kristina A. Toliver, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Oxycodone Hydrochloride Capsules, 5 mg Oral Solution 100 mg/5 mL (20 mg/mL)
Applicant/sponsor:	LeHigh Valley Technologies
OSE RCM #:	2010-749

CONTENTS

1 BACKGROUND

1.1 *INTRODUCTION*

This review responds to a request from the Division of Anesthesia and Analgesia Products (DAAP) dated April 6, 2010 for DMEPA evaluation of the container label and package insert labeling for LeHigh Valley Technologies' Oxycodone Hydrochloride for the potential to contribute to medication errors.

1.2 *REGULATORY HISTORY*

LeHigh Valley Technologies' Oxycodone Hydrochloride capsules and oral solution are marketed, unapproved products. The NDAs for these two formulations were submitted on December 22, 2009. There is no proposed proprietary name for this product at this time.

Postmarketing medication errors associated with unapproved, marketed products are currently under review in OSE 2010-1694.

(b) (4) the 20 mg/mL concentration will be approved this cycle.

1.3 *PRODUCT INFORMATION*

Oxycodone hydrochloride is an opioid agonist indicated for the relief of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate. The usual dose is 5 mg to 15 mg every 4 to 6 hours as needed. The product will be supplied as 100-count bottles of capsules, (b) (4) and 30 mL of the 20 mg/mL solution.

2 METHODS AND MATERIALS

2.1 *LABELS AND LABELING RISK ASSESSMENT*

We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

The Applicant submitted container labels on September 28, 2010 and insert labeling was discussed and revised during a September 29, 2010 labeling meeting (See Appendix A through C for container label and carton labeling images):

(b) (4)

- Container Label: 20 mg/mL oral solution (30 mL)
- Container Label: 5 mg capsules (100-count)

2.2 *ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE*

The AERS search conducted in OSE 2010-1649, DMEPA searched the FDA AERS database to identify post-marketing cases involving single ingredient oxycodone immediate-release products.

3 RESULTS

3.1 *ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE*

The search conducted in OSE 2010-1694 identified one medication error case that is pertinent to the review of the container labels and carton labeling for LeHigh Valley Technologies' oxycodone products. The one case involved a 21-moth old patient who received a prescription for Oxycodone 1 mg/mL, but was dispensed 20 mg/mL. This type of medication error demonstrates the need for the differing product strengths to be readily distinguishable for the proposed product. See our recommendations in Section 4 with regard to this issue.

4 RECOMMENDATIONS

Our evaluation of the proposed container labels and carton labeling dated September 28, 2010 noted areas of needed improvement in order to minimize the potential of medication errors. We provide recommendations on the insert and patient instructions for use labeling in Section 3.1, *Comments to the Division*. Section 4.1 *Comments to the Applicant* contains our recommendations for the carton labeling and container labels. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval (See Appendices A and B for the container labels and carton labeling).

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Bola Adeolu at 301-796-4264.

4.1 *COMMENTS TO THE DIVISION*

Ensure the expression of strength for the 20 mg/mL product strength is expressed as 100 mg/mL (20 mg/mL).

4.2 *COMMENTS TO THE APPLICANT*

A. Oral Solution Container Labels and Carton Labeling

1. Revise the statement of strength for the 20 mg/mL strength to 100 mg/5 mL followed in close proximity by the 20 mg/mL concentration in lesser prominence on all associated labels and labeling. Additionally, remove the spaces that appear before and after the forward slash. The strength and concentration should be presented as follows.

100 mg/5 mL
20 mg/mL

2. [redacted] (b) (4)

   Additionally, the low color contrast of the black font on blue background of the 20 mg/mL concentration makes the product strength difficult to read.

3. Revise the usual dosage statement to read "Dosage and Administration: See package insert" or "…See full prescribing information."

B. 100 mg/5 mL (20 mg/mL) Container Labels and Carton Labeling

1. [redacted] (b) (4)

2. Include the statement "Medication guide to be dispensed to each patient".

3. Include the following boxed statement prominently on the principal display panels of the container labels and carton labeling to ensure that practitioners and patients are aware it is only intended for patients that are opioid tolerant. The Applicant logo may need to be reduced in size or relocated in order to prominently include this statement.

ONLY FOR USE IN PATIENTS WHO ARE OPIOID TOLERANT.

4. Remove the words [redacted] (b) (4) from the labels and labeling.

B. Capsule Container Labels

Revise the usual dosage statement to read "Dosage and Administration: See package insert" or "…See full prescribing information."

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/s/

KRISTINA C ARNWINE
10/18/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER
10/19/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 200534	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Oxycodone Hydrochloride Capsules Dosage Form: Capsules Strengths: 5 mg		
Applicant: Lehigh Valley Technologies, Inc.		
Date of Receipt: Oct. 22, 2009		
PDUFA Goal Date: Oct. 22, 2010	Action Goal Date (if different):	
Proposed Indication(s): moderate to severe pain		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Roxicodone	Safety and efficacy, labeling

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioequivalent study, UPN-1189

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Roxicodone	NDA 21-011	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: Roxicodone Tablets, NDA 21-011

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a different dosage form, capsules and strength, 5 mg. The referenced listed drug is tablets, 15 mg.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Roxicodone Tablest; Oxycodone Tablets. There are also approved generics.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

TANYA D CLAYTON
10/12/2010

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 5, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 200-534** Oxycodone HCl Capsules
NDA 200-535 Oxycodone HCl Oral Solution
Indication: treatment of moderate to severe pain (b) (4) ; the 20 mg/mL strength oral solution should only be used in opioid-tolerant patients
Dosage: capsules 5 mg; oral solution (b) (4) 20 mg/mL oral solution
Form: capsules and oral solution

Sponsor: Lehigh Valley Technologies, Inc.

Materials received: NDA 200-534 and 200-535 (Dec 22, 2009) are located in EDR
Previous IND 78,623, and 78,624

Table of Contents

A. Background:

These two NDAs of previously marketed but unapproved drugs were submitted based on prior agreements with FDA at Pre-IND meeting (Dec 2007), Pre-NDA meeting (March 2009) and Meeting with the DAAP (Feb 2010). Roxicodone® (NDA 21-011), an immediate-release tablet (b) (4) the reference listed drugs (RLD) for the purposes of establishing efficacy in a bioequivalence study performed in the fasted state and evaluation of food effect (study UPN-1189). Study UPN-1189 was a single-dose, five-way crossover study to evaluate the relative bioavailability of an immediate-release oxycodone hydrochloride capsule (5

mg capsule) and an oxycodone oral solution (20 mg/mL) and the effect of food in healthy adult volunteers.

The sponsor's proposed labels for the to-be-marketed products are derived from the Roxicodone® (b) (4) labels, with additional information derived from study UPN-1189.

The sponsor included Postmarketing Safety Data from FDA's Spontaneous Reporting System (SRS Database, from 1 January 1969 through 31 October 1997), the Adverse Events Reporting System (AERS Database, from 1 November 1997 through 31 March 2008). The data show an estimated 6,728 MedWatch reports in which oxycodone is a primary or secondary suspect drug. The sponsor also provided reports of adverse events for oxycodone submitted to the World Health Organization (WHO) from 79 countries from 1968 to 31 December 2008, a total of 16,125 reports.

REMS and Medication Guides

The sponsor developed MedGuides for oral solution formulation. The sponsor will provide instruction on the label of the product package and container to authorized dispensers to provide the Medication Guide to each patient to whom the drug is dispensed. Additionally, the sponsor will submit REMS Assessments to the FDA 18 months, 3 years, and in the 7th year from the date of approval of the REMS.

B. Conclusions and Recommendations

CSS Comments to be relayed to the Sponsor

1. As a Schedule II drug under the CSA, all Schedule II narcotic regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of oxycodone hydrochloride capsules and oral solution should be in place and strictly followed.

2. The sponsor needs to conduct routine surveillance and monitoring of their drug products and report all cases of abuse, and misuse or overdose (intentional or unintentional and leading to death) and relevant information on drug diversion.

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/s/

ALICJA LERNER
10/05/2010

LORI A LOVE
10/06/2010

MICHAEL KLEIN
10/06/2010

MEMORANDUM

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

DATE: September 30, 2010

TO: Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products (DAAP)

FROM: Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 10/1/10
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDAs 200534 and 200535, Oxycodone Hydrochloride Capsules and Oxycodone Hydrochloride Oral Solutions, sponsored by Lehigh Valley Technologies, Inc.

At the request of the Division of Anesthesia and Analgesia Products (DAAP), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study # UPN1189
Title: "A Single-Dose, Five-Way Crossover Study to Evaluate the Relative Bioavailability of an Immediate-Release Oxycodone Hydrochloride Capsule (5 mg Capsule) and an Oxycodone Oral Solution (20 mg/1 mL) and the Effect of Food in Healthy Adult Volunteers"

The clinical and analytical portions of Study UPN1189 were conducted at DecisionLine Clinical Research Corporation, 720 King St. W., Toronto, Ontario, Canada and (b) (4) , respectively.

Clinical Site - DecisionLine Clinical Research Corporation, Toronto, Ontario, Canada

Following inspection of the clinical site (September 13-17, 2010), Form FDA-483 was not issued, and no significant clinical finding was noted.

Analytical Site - (b) (4)

Following inspection of the analytical site (September 15-17 and 20-21, 2010), no Form FDA-483 was issued. There were minor issues regarding documentations for sample processes, but no significant analytical finding was observed.

Conclusion:

Following the inspections of the clinical and analytical sites for the study, DSI recommends that the data from the study UPN1189 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Xikui Chen, Ph.D.

Final Classification:
NAI - DecisionLine Clinical Research Corporation, Toronto, Ontario, Canada
VAI - (b) (4)

cc: DARRTS
DSI/Ball/Haidar
DSI/Yau/Rivera-Lopez/CF
OND/ODEII/DAAP/Bob Rappaport/Tanya Clayton/Ellen Fields
OTS/OCP/DCP2/Suresh Doddapaneni
HFR-NE150/Matthew Palo
HFR-CE1520/Edward McDonald
Draft: XC 9/30/10
Edit: MKY 9/30/10
DSI: (b) (4)
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FACTS: (b) (4)

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CDER DSI PM TRACK

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/s/

XIKUI CHEN
10/01/2010