CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200535Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**200535**
SERIAL NUMBER:	**1**
DATE RECEIVED BY CENTER:	**December 22, 2009**
PRODUCT:	**Oxycodone hydrochloride oral solution ((b) (4) 20 mg/mL)**
INTENDED CLINICAL POPULATION:	**Management of moderate to severe pain (b) (4)**
SPONSOR:	**Lehigh Valley Technologies, Inc.**
DOCUMENTS REVIEWED:	**Modules 2 and 4 of electronic submission**
REVIEW DIVISION:	**Division of Anesthesia and Analgesia Products (DAAP; HFD-170)**
PHARM/TOX REVIEWER:	**Carlic K. Huynh, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Tanya Clayton**
Date of review submission to Document Archiving, Reporting & Regulatory Tracking System (DARRTS):	**October 12, 2010**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The NDA is recommended for approval.

B. Recommendation for nonclinical studies

At this time, there are no recommendations for further nonclinical studies.

C. Recommendations on labeling

The labeling for Lehigh Valley Technology, Inc's oxycodone hydrochloride oral solution will be the same as the referenced drug product, ROXICODONE®.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
(from highlights section) **INDICATIONS AND USAGE** (b) (4)	*(from highlights section)* **INDICATIONS AND USAGE** (b) (4)	This is fine as the Sponsor is using the PLR format.
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Pregnancy Category B: *Teratogenic effects* (b) (4)	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** *Teratogenic effects* Pregnancy Category B: (b) (4)	The proposed labeling is from the referenced Roxicodone label. The edits were completed to place the human statement first as per the MHT pregnancy labeling initiative.

(b) (4)	(b) (4)	
Nonteratogenic effects Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and / or withdrawal symptoms, either at birth and / or in the nursery.	There are no adequate and well-controlled studies of oxycodone in pregnant women. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed. Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a mg/m^2 basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m^2 basis), respectively was not teratogenic or embryo-fetal toxic. Nonteratogenic Effects Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	
(b) (4)	(b) (4)	The proposed labeling is from the Roxicodone label and therefore acceptable.
Mutagenesis Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay	*Mutagenesis* Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay	

(Salmonella typhimurium and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay). *Impairment of Fertility*	*(Salmonella typhimurium* and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay). *Impairment of Fertility* (b) (4)	

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The Sponsor did not submit any new nonclinical studies in this NDA. The Sponsor is relying up the Agency's previous findings for safety and efficacy to ROXICODONE®. The levels of the impurities and degradents from the drug substance and drug product specifications sent by the Sponsor are deemed adequate. Analysis of the excipients at the maximum theoretical daily dose (MTDD) indicates that the exposures of the exicipients do not represent a safety concern in the formulations. The components of the container closure system appear to be appropriately cited in the CRF as indirect food contact material and as such there are no safety issues pending CMC issues.

B. Pharmacologic activity

Oxycodone is a semi-synthetic opioid. It is a full opioid receptor agonist whose principal therapeutic action is analgesia. Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6, a pathway that may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants). The precise mechanism of the analgesic action of oxycodone is unknown but is thought to involve CNS opioid receptors. Oxycodone in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. It produces respiratory depression by direct action on brain stem respiratory centers. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to clinical use as the Sponsor is relying upon the Agency's previous findings for safety and efficacy to ROXICODONE®.

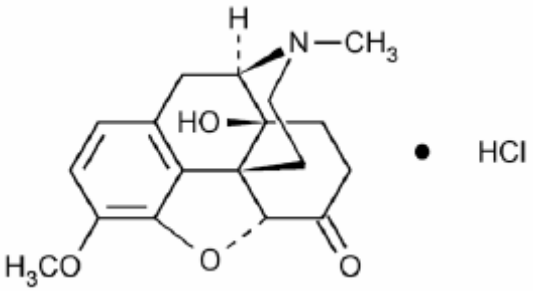
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	200535
Review number:	1
Sequence number/date/type of submission:	SDN 1 / submit and receive date December 22, 2009; SDN 3 / submit and receive date February 23, 2010; SDN 5 / submit and receive date March 30, 2010; SDN 6 / submit and receive date April 5, 2010; SDN 10 / submit date August 19, 2010, receive date August 20, 2010; SDN 13 / submit and receive date September 21, 2010 / 505(b)(2) type NDA
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Lehigh Valley Technologies, Inc. 514 N. 12th Street Allentown, PA 18105
Manufacturer for drug substance:	(b) (4)
Reviewer name:	Carlic K. Huynh, Ph.D.
Division name:	Division of Anesthesia and Analgesia Products (DAAP)
HFD #:	170
Review completion date:	October 12, 2010

Drug:

Trade name:
Generic name: oxycodone hydrochloride
Code name:
Chemical name: 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS registry number: 124-90-3
Molecular formula/molecular weight: $C_{18}H_{21}NO_4 \cdot HCl$/351.83
Structure:



Relevant INDs/NDAs/DMFs:
The development program for this drug product was conducted under IND 78,624 submitted by Glenmark Generics Inc. for the indication of moderate to severe pain and has been active since May 17, 2008.

The referenced drug for this 505(b)(2) NDA is ROXICODONE® (NDA 21-011; Xanodyne Pharmaceuticals, Inc.).

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
21-011	Roxicodone (oxycodone hydrochloride tablets)	DAAP	5, 15, 30 mg (oral)	AP	8/31/2000	Moderate to severe pain	Xanodyne
200-534	Oxycodone Oral Capsules	DAAP	5 mg	Pending		Moderate to severe pain	Lehigh Valley

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
(b) (4)			2/4/2003	Specification for (b) (4) which is acceptable.
			4/14/2008	See CMC review and PT review.
			4/2/1974	See CMC review.
			9/4/1975	See CMC review.
			12/14/1989	See CMC review.
			11/15/1971	See CMC review.
			7/11/1975	See CMC review.
			7/8/2003	See CMC review.

Drug class: opioid agonist

Intended clinical population: Management of moderate to severe pain (b) (4) . It is noted that the (b) (4) oral solution, 20 mg/mL, is reserved for opioid-tolerant patients.

Clinical formulation:

The composition of oxycodone HCl oral solutions ((b) (4) 20 mg/mL) is in the following table:

Component	(b) (4) 20 mg/mL (mg/mL)	(%w/v)	Function
Oxycodone hydrochloride, USP	(b) (4)		Active (analgesic)
Citric acid anhydrous, USP			(b) (4)
Sodium citrate dihydrate, USP			
Sodium benzoate, NF			
Saccharin sodium, USP			
(b) (4)			
D&C Yellow #1((b) (4)			
Sorbitol solution (b) (4) USP			
Natural/Artificial Berry Flavor			
(b) (4)			
Purified Water, USP			
			(b) (4)

[2] Complies with 21 CFR 74.1340

(b) (4) and complies with 21 CFR 74.1710

[4] The qualitative composition and specification has been provided by the DMF holder; see section 3.2.P.1.

-- Not Applicable

All ingredients are listed in the Inactive Ingredient Guide (IIG) as being present in FDA approved drug products at a maximum dosage greater than that proposed in this product, with the exception of the berry flavor which is not currently listed in the IIG. Natural and Artificial Berry Flavor (b) (4), DMF (b) (4) has been reviewed by the CMC review team and was deemed acceptable. Due to the development of tolerance and based on clinical use data, DAAP have determined that a reasonable maximum theoretical daily dose (MTDD) of oxycodone in an opioid tolerant individual is 1.5 g/day. Opioid tolerant patients are given the 20 mg/mL strength oxycodone oral solution and therefore the safety assessment of the excipients for the 20 mg/mL concentration will be based on 1.5 g of oxycodone via this product. (b) (4)

The exposure of the excipients to patients taking the (b) (4) 20 mg/mL strength oxycodone oral solutions at the MTDD is illustrated the following table:

Ingredients	(b) (4)	Exposure in 20 mg/mL strength oral solution at the MTDD of 1.5 g/day (mg)	IIG maximum potency limit (oral)
No. of doses to MTDD		75	
Oxycodone HCl		(b) (4)	N/A
Citric acid anhydrous, USP			500 mg

Sodium citrate dehydrate, USP	(b) (4)	300 mg
Sodium benzoate, NF		60 mg
Saccharin sodium, USP		20 mg
(b) (4)		73.2 mg
D&C Yellow #10 (b) (4)		331 mg
Sorbitol (b) (4) USP		337.28 mg
Natural and Artificial Berry Flavor (b) (4)		Not listed in IIG; therefore novel excipient
Purified Water, USP		N/A
Total (mg)		

(b) (4)

(b) (4) The amount of D&C Yellow #10 is (b) (4) mg at the MTDD for the 20 mg/mL strength oral solution. The IIG maximum potency limit for D&C Yellow #10 is 331 mg in oral products, which exceeds the amount in the formulation. Moreover, D&C Yellow #10, under 21 CFR 74.1710, may be used in drugs in amounts consistent with good manufacturing practice. The amount of sodium citrate dehydrate at the MTDD (b) (4). The IIG maximum potency limit for sodium citrate dehydrate is 300 mg, which exceeds the amount in the formulation. Moreover, sodium citrate, under 21 CFR §184.1754, may be used in foods without limitation other than current good manufacturing practice. Citric acid, under 21 CFR §184.1033, may be used in foods without limitation other than current good manufacturing practice and the levels at the MTDD do not exceed the maximum potency in the IIG. Thus, the proposed levels of these excipients in these products do not appear to represent a safety concern.

As noted in the table above, the remaining excipients exceed the IIG maximum potency limits at the MTDD of the (b) (4) oral solutions. Therefore, a safety assessment was completed for these levels.

Sodium benzoate, under 21 CFR §184.1733, may be used in foods at levels that do not exceed good manufacturing practice (0.1%). At the MTDD, the amount of sodium benzoate in the (b) (4) 20 mg/mL strength oral solution is (b) (4) , which meets the good manufacturing practices. Moreover, according to the Hazardous Substances Data Bank (HSDB), the maximum daily dose of sodium benzoate should not exceed 10 g. In fact, the IIG maximum potency limit for sodium benzoate is 60 mg in oral products, which exceeds the amount of sodium benzoate in the 20 mg/mL strength oral solution. Furthermore, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) determined that the acceptable daily intake of sodium benzoate is 0-5 mg/kg. At the MTDD, the amount of sodium benzoate (b) (4) . Thus, the proposed levels of sodium benzoate in these products do not appear to represent a safety concern.

Saccharin sodium, under 21 CFR §180.37, may be used as a sweetening agent in beverages in amounts not to exceed 12 mg of saccharin per fluid ounce (29.5 mL or 0.4 mg/mL). In processed foods, saccharin can be used in amounts not to exceed 30 mg per serving. There is no clear maximum daily dose listed in the regulations. The Joint FAO/WHO expert committee on food additives has set an acceptable daily intake (ADI) for saccharin of 5 mg/kg body weight (300 mg for a 60 kg person). The ADI is a conservative value and is based on a dose that is 100 fold below the NOEL in animal studies. Specifically, the ADI for saccharin is largely based on results of a 2-generation long-term feeding study in rats, where no relevant toxicological effects were noted in rats fed a diet of 1% saccharin (equivalent to 500 mg/kg/day = HED of 80.6 mg/kg or 4839 mg/60 kg person (Schoenig et al., 1985; Squire 1985; European Commission Scientific Committee for Food, 1997). At the MTDD, the daily dose of saccharin ((b) (4) (b) (4)) exceeds this ADI . However, the MTDD of saccharin via this product it is still almost 10-times below the rat NOAEL based on body surface area. Further, in order to exceed the 5 mg/kg (300 mg/60 kg person) ADI via use of this product exclusively, (b) (4) (b) (4) It is noted that the daily exposure of (b) (4) to saccharin in the (b) (4) formulation at the MTDD is lower than the daily exposure to saccharin in other approved products. Therefore, the amount of saccharin in (b) (4) formulations does not appear to represent any safety concerns even at the MTDD.

Sorbitol, under 21 CFR §184.1835, may be used in foods at levels not to exceed good manufacturing practices (up to 99%). Sorbitol is a sugar alcohol that is used as a sugar substitute. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of sorbitol and has concluded that an acceptable daily intake (ADI)

does not need to be specified. [redacted], a person could consume [redacted] of sorbitol, [redacted]. As per 21CFR §184.1835, "The label and labeling of food whose reasonably foreseeable consumption may result in daily ingestion of 50 grams of sorbitol shall bear the statement: 'Excess consumption may have a laxative effect'." Given the fact that opioids such as oxycodone produce constipation[1], the exposure to <50 grams of sorbitol via these drug product formulations is not likely to pose clinical adverse effects.

Natural and Artificial Berry flavor ([redacted]) is not currently in any FDA-approved drug product and is therefore deemed novel. The safety of this excipient is reviewed under DMF [redacted] to [redacted] (see the CMC and nonclinical review of DMF [redacted]). In brief, there are no safety concerns with Natural and Artificial Berry flavor ([redacted]) in these formulations at the MTDD.

Thus, there are no safety concerns with the excipients in these formulations even taking into consideration the MTDD.

The sponsor has proposed the following drug substance specifications:

Impurity	**Proposed Specification**	**ICH Q3A(R2) qualification threshold (MDD ≤ 2 g/day)**	**Reviewer's Assessment**
[redacted]	[redacted]	Below ICH, as this contains a structural alert for mutagenicity	Acceptable
10-hydroxyoxycodone		0.15% or 1 mg, whichever is lower	Acceptable
7,8-dihydro-8β,14-dihydroxycodineon		0.15% or 1 mg, whichever is lower	Acceptable, this compound does not contain a structural alert for mutagenicity
Oxymorphone/ noroxymorphone		0.15% or 1 mg, whichever is lower	Acceptable
6-α-oxycodol		0.15% or 1 mg, whichever is lower	Acceptable
[redacted]		Below ICH, as this contains a structural alert for mutagenicity	Acceptable
Hydrocodone		0.15% or 1 mg, whichever is lower	Acceptable
Unknown impurity		0.15% or 1 mg,	Acceptable

[1] Ordóñez Gallego et al., 2007 is a review paper that examined various clinical studies conducted with oxycodone. They summarized various adverse effects of oxycodone, the most common being constipation.

		whichever is lower	
(b) (4)	(b) (4)	Class 3, low toxic potential to man; no health-based exposure limit needed	Acceptable, as per ICHQ3C

The sponsor has proposed the following drug product stability specifications for (b) (4) the 20 mg/mL strength solutions:

Impurity	**Proposed Specification**	**ICH Q3B(R2) qualification threshold (MDD >100 mg - 2 g)**	**Reviewer's Assessment**
(b) (4)	(b) (4)	0.2% or 3 mg, whichever is lower	Acceptable
Unknown impurity	(b) (4)	0.2% or 3 mg, whichever is lower	Acceptable

Thus, the levels of the impurities and degradants in the drug substance and drug product specifications are acceptable as they meet ICH Q3A(R2) and ICH Q3B(R2) thresholds.

Route of administration: oral

Extractables/Leachables:
The following table represents the proposed container closure system for the oxycodone HCl oral solutions in this NDA:

Strength	Container Closure	Supplier	DMF/LOA
(b) (4)			
20 mg/mL	**Bottle:** 30-mL, white HDPE bottle **Closure:** 20-mm CR cap Heat-induced innerseal **Calibrated oral syringe**: Barrel: 18-mm × 89-mm (b) (4) Plunger: 15-mm × 95-mm HDPE with white colorant Ink: blank ink (b) (4) (b) (4)	(b) (4)	(b) (4)

There were no extractables/leachables testing submitted by the Sponsor. However, in discussions with the Chemistry, Manufacture, and Control (CMC) review team, the components of the container closure system for these oxycodone oral solutions are cited appropriately in the CFR for indirect food contact materials (see CMC review). It is noted that DMF (b) (4) has been active since November 15, 1971, DMF (b) (4) has been active since July 11, 1975, and DMF (b) (4) has been active since July 8, 2003. Thus, there are no safety issues at this time from a nonclinical pharmacology toxicology perspective pending any issues that may be raised by the CMC review team (see CMC review).

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 200-535 are owned by Lehigh Valley Technologies, Inc. or are data for which Lehigh Valley Technologies, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 200-535 that Lehigh Valley Technologies, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Lehigh Valley Technologies, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 200-535.

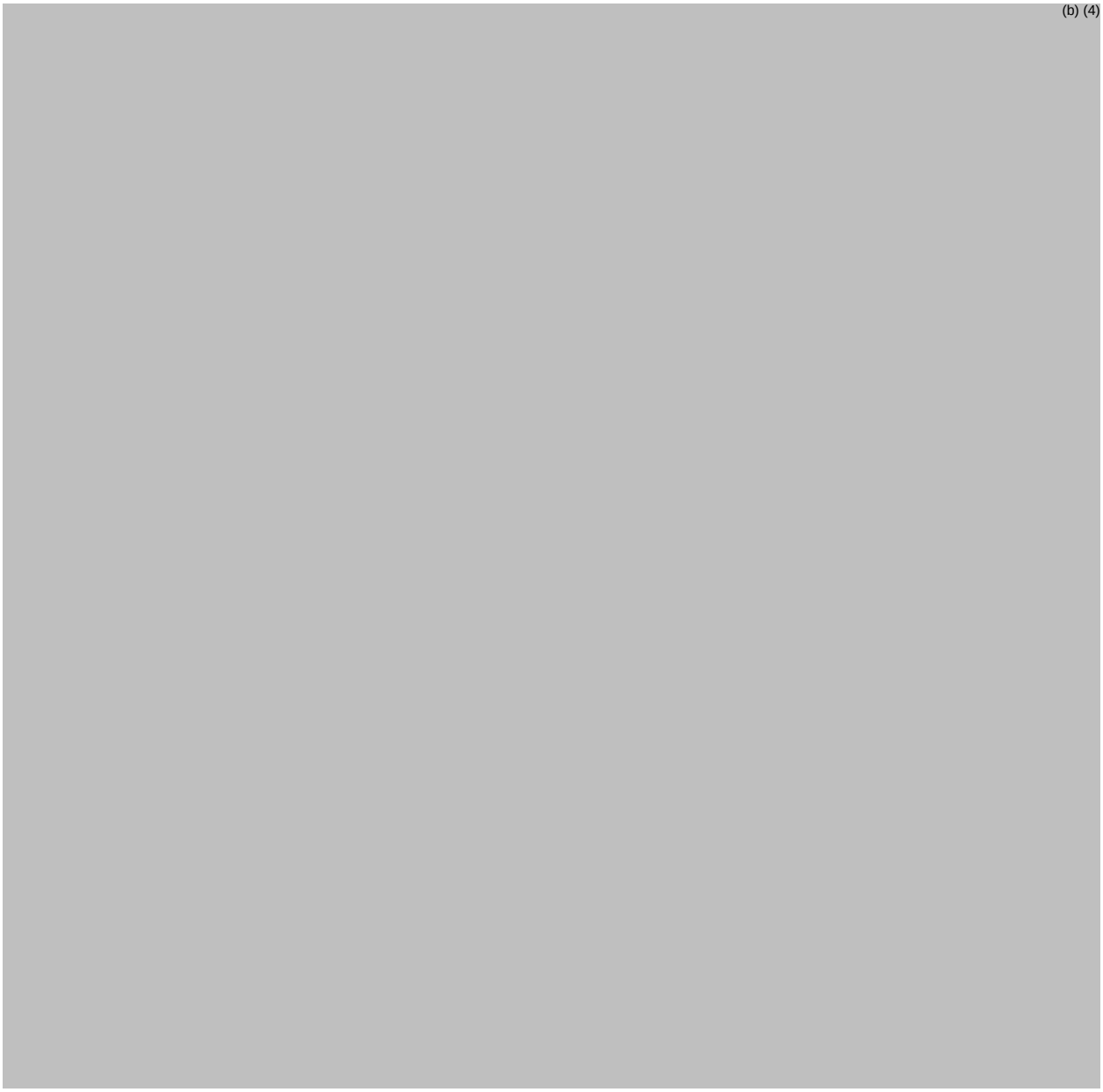
Studies reviewed within this submission:
The Sponsor did not conduct any new nonclinical studies for this NDA submission.

Studies not reviewed within this submission:
None.

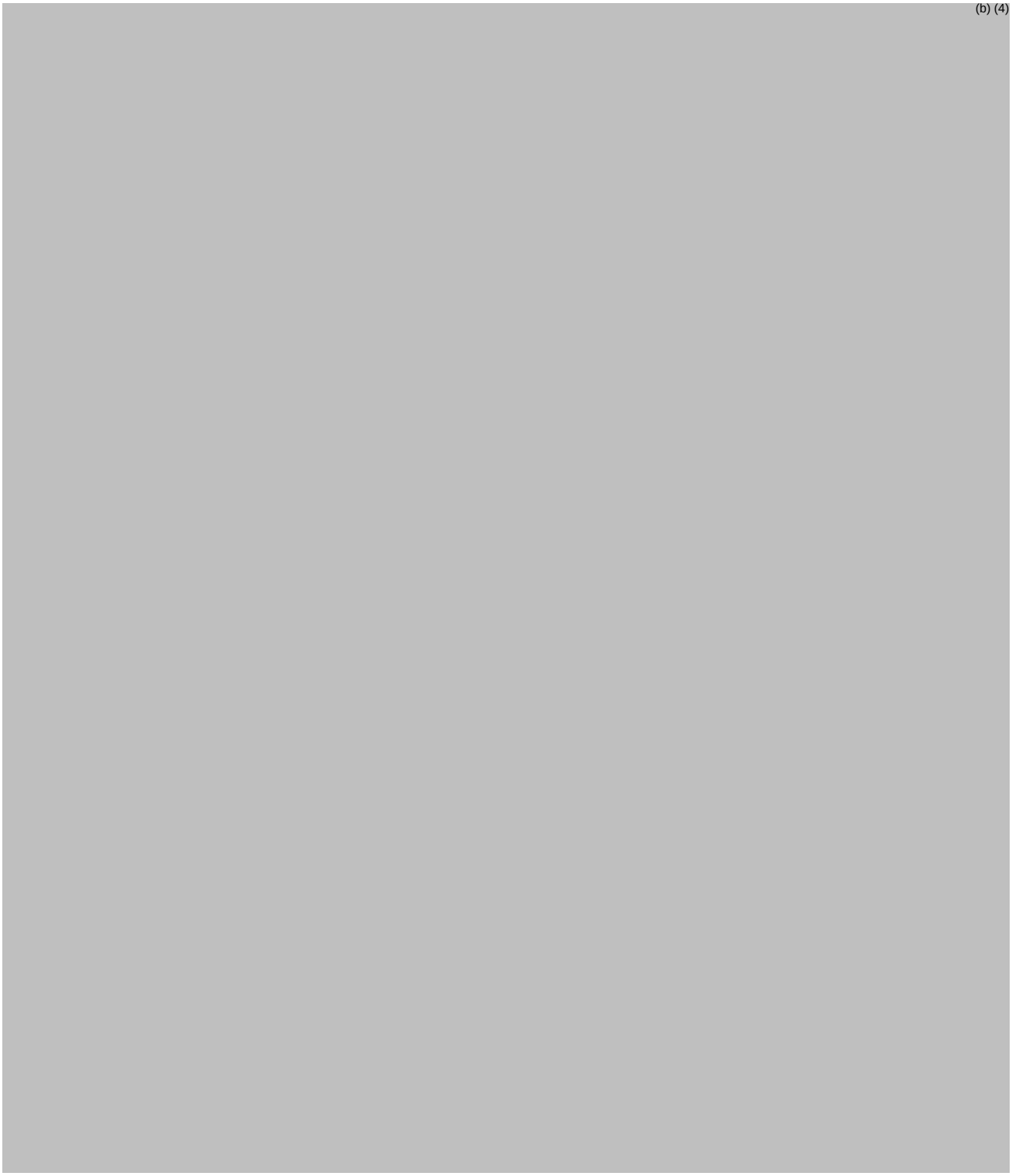
2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Oxycodone is a semi-synthetic opioid. It is a full opioid receptor agonist whose principal therapeutic action is analgesia. Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6, a pathway that may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants). The precise mechanism of the analgesic action of oxycodone is unknown but is thought to involve CNS opioid receptors. Oxycodone in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. It produces respiratory depression by direct action on brain stem respiratory centers. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla.



5 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page



2.6.6.2 Single-dose toxicity

There were no single-dose toxicity studies submitted in this NDA.

2.6.6.3 Repeat-dose toxicity

There were no repeat-dose toxicity studies submitted in this NDA.

2.6.6.4 Genetic toxicology
There were no genetic toxicology studies submitted in this NDA.

2.6.6.5 Carcinogenicity
There were no carcinogenicity studies submitted in this NDA.

2.6.6.6 Reproductive and developmental toxicology
There were no reproductive and developmental toxicology studies submitted in this NDA.

2.6.6.7 Local tolerance
There were no local tolerance studies submitted in this NDA.

2.6.6.8 Special toxicology studies
There were no special toxicology studies submitted in this NDA.

2.6.6.9 Discussion and Conclusions
See "overall conclusions and recommendations" below.

2.6.6.10 Tables and Figures
None.

2.6.7 TOXICOLOGY TABULATED SUMMARY
None.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
The drug product subject in this NDA is oxycodone hydrochloride, (b) (4) 20 mg/mL, from Lehigh Valley Technology, Inc. The Sponsor is relying upon the Agency's previous findings for safety and efficacy to ROXICODONE®. From a nonclinical pharmacology toxicology perspective, there are no safety concerns and this NDA is recommended for approval.

Unresolved toxicology issues (if any):

Recommendations:
This NDA is recommended for approval.

Suggested labeling:
The sponsor has proposed the same language as the referenced product labeling, ROXICODONE®. Minor edits have been made to the ROXICODONE® label to comply with the PLR format (see "Executive Summary" above) and current pregnancy labeling practices. This is acceptable; however, it is noted that the Sponsor has proposed

a single label for the capsules as well as the liquid oral solutions (being reviewed under NDA 200-535).

APPENDIX/ATTACHMENTS

References

European Commission Scientific Committee for Food. Opinion on saccharin and its sodium, potassium and calcium salts. Annex III to Document III/5157/97, 1-8. 1997.

Ordóñez Gallego A, González Barón M, and Espinosa Arranz E. Oxycodone: a pharmacological and clinical review. Clin Transl Oncol, 2007; 9:298-307.

Schoenig GP, Goldenthal EI, Geil RG, Frith CH, Richter WR and Carlborg FW (1985) Evaluation of the dose response and in utero exposure to saccharin in the rat. Food Chem Toxicol 23:475-490.

Squire RA (1985) Histopathological evaluation of rat urinary bladders from the IRDC two-generation bioassay of sodium saccharin. Food Chem Toxicol 23:491-497.

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

/s/

CARLIC K HUYNH
10/12/2010

RICHARD D MELLON
10/12/2010
I concur.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 200534 and 200535	**Applicant: Lehigh Valley Technologies, Inc.**	**Stamp Date: December 22, 2009**
Drug Name: Oxycodone HCl oral capsule and solution	**NDA/BLA Type: 505(b)(2)**	**DAARP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF): **Fileable**

(b) (4)

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?	X		The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included referenced nonclinical studies. The Sponsor is also proposing to rely upon the literature as well as the Agency's previous finding of safety for Roxicodone® for nonclinical support.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			Not applicable. At the time of the filing review, the Sponsor is proposing to rely upon the published scientific literature as well as the Agency's previous findings of safety for Roxicodone® for toxicology

				studies.
6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	X		This NDA contains excipients that are found in the FDA IIG. The amount of excipients in this formulation is below the maximum potency limits.
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			Not applicable. The Sponsor has not conducted any animal studies in support of this NDA.
8	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. The Sponsor has not conducted any animal studies in support of this NDA.
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?			Not applicable. The Sponsor did not conduct any new nonclinical studies in support of this NDA.
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The referenced labels do not contain exposure margins; therefore, they will be incorporated into the label during this review cycle based on the dosage form. This need not be a filing issue.
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	X		The Sponsor has submitted specifications for the drug substance and drug product in module 3. Adequate specifications for the (b) (4) are provided. The specifications for (b) (4) will need to be discussed during review as there is a difference in opinion regarding

				the maximum daily dose for these products.
12	Has the sponsor addressed any abuse potential issues in the submission?	X		The Sponsor provides discussion on the addiction potential of oxycodone HCl.
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This is a 505(b)(2) New Drug Application (NDA) submitted to support a Rx.
14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	X		FILING ISSUES: There are no filing issues at this time.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Comments to Sponsor:
Please provide the following information:

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, 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) in both NDA 200534 and 200535 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, 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. NDA 200535 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.

Reviewing Pharmacologist: _____
Date

Team Leader: _____
Date

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

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

/s/

CARLIC K HUYNH
02/26/2010

RICHARD D MELLON
02/26/2010