CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200534Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Review # 2 *(Addendum to Initial Review)* Office of New Drugs Quality Assessment			
Application No.:	NDA 200-534	**Reviewer:** Minerva Hughes, PhD	
Submission Date:	22 Dec 2010		
Division:	Division of Anesthesia and Analgesia Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Lehigh Valley Technologies	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	None proposed	**Date Assigned:**	22 Jul 2010
Generic Name:	Oxycodone hydrochloride, capsule	**Date of Review:**	13 October 2010 *Review # 2*
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate	**Type of Submission:** Original New Drug Application *(Type 7 marketed drug without an approved application)* 28 Sept 2010 Response to Information Request	
Formulation/strengths	Capsule, 5 mg		
Route of Administration	Oral		

RECOMMENDATION:

The dissolution method and specifications are inadequate for product quality control. NDA 200-534 is recommended for approval with the following post-approval commitments, which should be conveyed to the applicant.

1. The dissolution method and specifications in the application is accepted only on an interim basis. As a Phase 4 agreement, you are required to develop a new dissolution method based on unit sampling that is sufficiently discriminating to assure product quality control. A full dissolution method development and validation report, in accordance with applicable ICH, FDA and USP guidelines should be submitted within 1 year of receipt of the action letter for review. Please note that the development of an in-process disintegration test does not preclude the requirement for an acceptable dissolution method for product release. Proposed dissolution tolerances should be based on data and sufficiently justified. You are also reminded that the dissolution method is a two part process comprised of the dissolution step and the determinative step. Your HPLC method for assaying dissolution samples should be appropriately validated. Validation data (specificity, accuracy, linearity, range, method repeatability, intermediate precision, etc.) should be clearly presented in the dissolution method development report.

BACKGROUND:

Reference is made to the initial Biopharmaceutics Quality Review dated 27 August 2010 by this reviewer regarding NDA 200-534. A teleconference was held on 23 September 2010 between FDA and Lehigh Valley Technologies to discuss outstanding deficiencies from all review disciplines which may preclude an approvable action for NDA 200-534. Regarding the dissolution method, the applicant was informed that (b) (4) was not acceptable and a commitment to implementing unit sampling is needed before approval. Biopharmaceutics acknowledged the applicant's previous communications with the primary CMC reviewer regarding dissolution as well as the applicant's commitment to develop a suitable dissolution method for quality control. The applicant was advised that a full method development

report, outlining the discriminating potential for the dissolution method, should be submitted for review.

After the teleconference, biopharmaceutics review comments of 27 August 2010 were conveyed to the applicant. The applicant's responses to the 27 August 2010 FDA comments (submission 28 September 2010) are summarized and evaluated in this report.

BIOPHARMACEUTIC INFORMATION:

- *Applicant's response (summarized) Biopharmaceutic Review Comment # 1 on dissolution sampling and specification*: The applicant agrees to unit sampling for dissolution testing but proposes to keep the interim specifications (b) (4) . The applicant acknowledged that the dissolution method was not suitable for quality control and plans to work on developing either a revised method that permits a more controlled release rate or developing an in-process disintegration test for quality control. The applicant commits to submitting a Prior Approval Supplement within 1 year of the action letter to address the dissolution method deficiencies.

  Reviewer's Evaluation: *Acceptable.* The applicant's proposal to maintain the interim specification in tandem with developing a more discriminating method is accepted. Tighter specification may be more appropriate based on the limited data; however, quality assurance is only possible through adequate methods, which the applicant has committed to developing. The applicants submitted two options for addressing the deficiencies regarding the dissolution method: Option 1 - develop a more discriminating method and Option 2 – gather profile information at short time points in conjunction with developing a disintegration test for in-process quality control. It is not clear if the applicant plans to pursue only one of the listed options, or if the applicant plans to develop a discriminating method either with or without the addition of an in-process disintegration test. The addition of an in-process disintegration test does not obviate the requirement for the development of a discriminating dissolution method and suitable specifications.

- *Biopharmaceutics Review Comment #2 on dissolution method development report:* Not conveyed to the applicant. This reviewer was not involved in the clearance of the 28 September 2010 information request forwarded to the applicant. The final document in DARRTs lists Comment #1 twice and Comment #2 was omitted. This comment was a request for a full method development report.

  Reviewer's Evaluation: No response to evaluate. Information is summarized above for inclusion in the action letter.

- *Applicant's response (summarized) Biopharmaceutics Review Comment # on discrepancies between the HPLC method LOQ and dissolution linearity range:* The applicant noted that there was (b) (4) .

  Reviewer's Evaluation: *Not acceptable.* (b) (4)
  (b) (4)

(b) (4)

Signatures *(electronic signature appended)*
Biopharmaceutics Reviewer
Biopharmaceutics Team Leader or Supervisor
Office of New Drugs Quality Assessment

cc: Angelica Dorantes, Tonya Clayton, Eugenia Nashed

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

/s/

MINERVA HUGHES
10/13/2010

PATRICK J MARROUM
10/13/2010

CLINICAL PHARMACOLOGY REVIEW

NDA: 200534	Submission Date(s): December 22, 2009
Brand Name	N/A
Generic Name	Oxycodone Hydrochloride capsule
Reviewer	Wei Qiu, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND division	Division of Anesthesia and Analgesia Products
Sponsor	Lehigh Valley Technologies, Inc.
Relevant IND(s)	N/A
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Oral capsules; 5 mg
Indication	Management of moderate to severe pain where use of an opioid analgesic is appropriate.

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1 Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, original NDA 200535 submitted on December 22, 2009 is acceptable provided that (a) DSI inspection finds the data from pivotal BE study UPN-1189 acceptable and (b) agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Lehigh Valley Technologies, Inc. (LVT) submitted this 505(b)(2) NDA for Oxycodone Hydrochloride Capsules, 5 mg for the management of moderate to severe pain where use of an opioid analgesic is appropriate. Sponsor has been marketing this product without an approved NDA.

Oxycodone is an opioid analgesic that was first synthesized in 1916. Single-ingredient oxycodone hydrochloride immediate-release oral tablets are approved in the US in strengths ranging from 5 mg to 30 mg for management of moderate to severe pain where the use of an opioid analgesic is appropriate. Sponsor initially planed to rely on the Agency's previous findings of the safety and efficacy of Roxicodone® (NDA 21-011; immediate-release oxycodone tablet) (b) (4) as the reference drugs. (b) (4)

The clinical and clinical pharmacology database for this NDA consists of a single bioavailability/bioequivalence study (study UPN-1189). This is a single-dose, five-period 4-way crossover study in healthy volunteers to establish bioequivalence to Roxicodone® IR tablet, assess the effect of food on the capsules, (b) (4). The oral solution is another dosage form currently marketed by LVT without an approved NDA and is the subject of a separate NDA (NDA 200535).

***Bioequivalence*: comparison with Roxicodone® IR tablet**
Single oral dose of the 15 mg oxycodone capsules (3 x 5 mg) is bioequivalent to a 15 mg Roxicodone® tablet (1 x 15 mg) under fasting condition. The point estimate of the geometric mean ratio (Oxycodone IR capsule/Roxicodone® IR tablet) for Cmax, AUCt and AUCinf are 99.5%, 97.8%, and 97.2%, respectively. The corresponding 90% CIs are 91.4 - 108.2%, 93.0 - 102.9%, and 91.8 – 102.9%, respectively.

Food Effect: High fat breakfast decreased oxycodone Cmax by 14% and increased oxycodone AUC0-t and AUCinf by 21 and 23%, respectively. The point estimates of the geometric means ratios (fed/fasting) for Cmax, AUCt, AUCinf are 85.9%, 120.6%, and 122.7%, respectively. The corresponding 90% confidence intervals are 74.7 – 98.6%, 105 – 138.5%, and 106 – 141.9%, respectively. These changes in Cmax and AUC can be considered to be not clinically significant and the product can be taken without regard to meals.

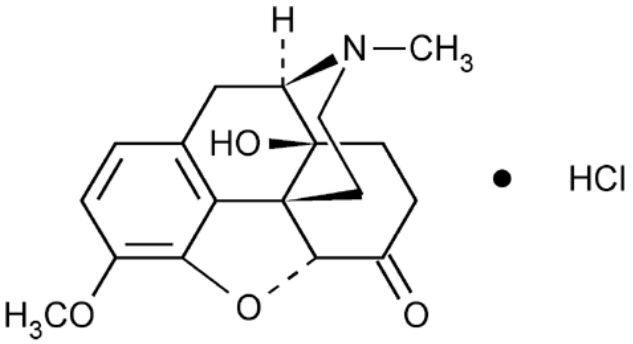
At the time of finalizing this review, DSI inspection of study UPN-1189 is pending and an addendum to this review will be written if DSI audit finds significant issues affecting the acceptability of the data.

2 Question Based Review

2.1 General Attributes of the Drug

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?*

Table 1 Physical-Chemical Properties of Oxycodone Hydrochloride

Drug Name	Oxycodone Hydrochloride
Chemical Name	4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
Structure	
Molecular Formula	C18H21NO4·HCl
Molecular Weight	351.82
Melting Point	218°C -223°C (range not to exceed 2°C)
Appearance	White to off-white, fine crystalline powder
Solubility	Up to 0.18 g/mL in water (pH 6.5-6.6); ~0.10 g/mL in water (pH>6.6)

The components and composition of the drug product, oxycodone hydrochloride capsule 5 mg, is listed in **Table 2**.

Table 2 Components and Composition of Oxycodone Hydrochloride Capsules, 5 mg

Ingredient	Mg/capsule	Function
Oxycodone hydrochloride, USP	(b) (4)	Active (analgesic)
Microcrystalline cellulose, NF	(b) (4)	(b) (4)
Lactose anhydrous, NF	(b) (4)	
Pre-gelatinized starch, NF	(b) (4)	
Sodium starch glycolate, NF		
Colloidal silicon dioxide, NF		
Magnesium stearate, NF		
Sodium lauryl sulfate, NF		
Theoretical weight		

(b) (4)

2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Oxycodone is a pure agonist opioid whose principle therapeutic action is analgesic. Oxycodone capsule is indicated for the management of moderate to severe pain where the use of an opiod analgesic is appropriate.

3. What are the proposed dosage(s) and route(s) of administration?

Oxycodone capsules are immediate-release oral formulation.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of oxycodone in general?

Oxycodone is generally well absorbed following oral administration with an approximately 60% to 87% absorption. Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone. The formation of noroxycodone is mainly medicated by CYP3A4 and the formation of oxymorphone is mediated by CYP2D6. Oxycodone and its metabolites are excreted primarily via the kidney. Apparent elimination half-life of oxycodone is 3.5 to 4 hours.

2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

The activity is primarily due to the parent compound oxycodone. Oxycodone concentrations were measured as well as its metabolites, noroxycodone and oxymorphone.

2.3 Intrinsic Factors

1. What is the pediatric plan?

In line with the Agency's current policy with respect to pure opioids, sponsor would be required to conduct pharmacokinetics studies in all ages. Efficacy studies will be required in children up to 2 years of age. At this time, sponsor is requesting deferral of pediatric studies since adult studies are complete and ready for approval. This seems reasonable and the required pediatric studies will have to be conducted as post marketing requirements.

2.4 Extrinsic Factors

Two articles related to drug-drug interactions with oxycodone were published subsequent to the approval of the reference Roxicodone Tablets Product. These articles are: (1) Hagelberg NM et al., Voriconazole drastically increases exposure to oral oxycodone. Eur J Clin Pharmacol. 2009;65:263-271 and (2) Nieminen TH et al., Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009;110:1371-1378. Since the findings from these studies are relevant to all oxycodone products, Agency has been incorporating these findings into oxycodone package inserts as appropriate. As such, package insert of this product will also be updated with these metabolism and drug drug interaction data.

2.5 General Biopharmaceutics

1. *Is the proposed oxycodone oral capsule bioequivalent to the reference immediate release oral tablet following single dose administration?*

When administered as a 15 mg dose in the fasted state, the oxycodone plasma concentration-time profiles for test capsule and reference IR tablets are similar (Figure 1). The statistical analysis results for the assessment of bioequivalence between proposed oxycodone capsules and the reference oxycodone IR tablet are presented in the Table 2. Results showed that the ratio of the geometric means for log transformed Cmax and AUC values as well as its corresponding confidence intervals fell within the range of 80% to 125%. The tmax values are similar. It is concluded that the proposed oxycodone capsule (3 x 5 mg) is bioequivalent to the reference oxycodone tablet (1 x 15 mg) under fasting condition.

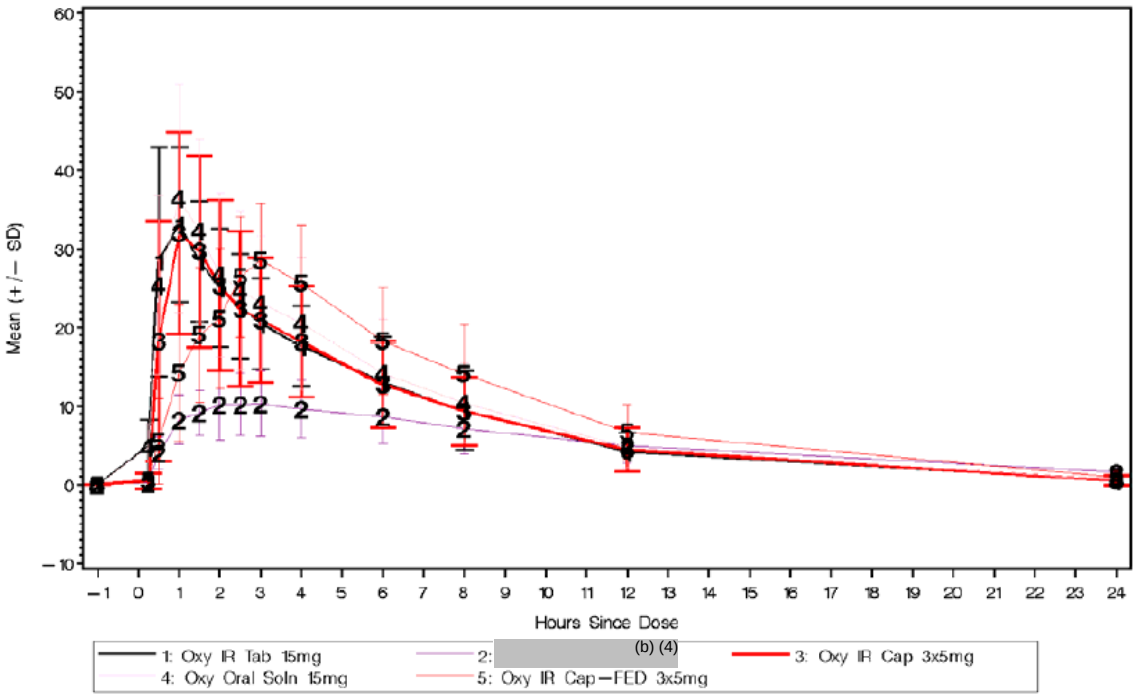


Figure 1 Mean Oxycodone plasma concentration (ng/mL) time profiles

Table 2 Mean (%CV) PK parameter of oxycodone following single oral administration of 15 mg oxycodone capsules (3 x 5 mg) and 15 mg Roxicodone tablet under fasted condition in healthy adults subjects (UPN-1189) (N = 25)

Parameter	Oxy IR capsule 15 mg (3 x 5 mg) Fasted (Treatment C, N = 25)	**Roxicodone® IR Tablet 15 mg (1 x 15 mg) Fasted (Treatment A, N = 25)**
AUClast (ng.h/ml)	**190.1 (30.8)**	193.6 (30.4)
AUCinf (ng.h/mL)	**192.4 (32.7)**	196.5 (31.3)
Cmax (ng/mL)	**37.1 (36.1)**	36.3 (27.4)
T1/2 (h)	**3.90**	4.15
Tmax (h)[a]	**1.00 (0.50 – 6.00)**	1.00 (0.50 – 6.00)
CL/F (L/hr)	**77.1**	74.8
Kel (1/hr)	**0.18**	0.18
Vd/F (L)	**420**	439
Geometric Mean Ratio (capsule/tablet) % (90% CI)		
AUClast	97.8 (93.0 – 102.9)	
AUCinf	97.2 (91.8 – 102.9)	
Cmax	99.5 (91.4, 108.2)	

[a] tmax reported as median (range)
Source: Table 6 and 11 of study UPN-1189 report.

(b) (4)

Noroxycodone is the major circulating metabolite of oxycodone, with a lower exposure as compared to the parent compound, oxycodone. The rate and extents of absorption of noroxycodone following single dose administration of a 15 mg oxycodone capsule dose and 15 mg Roxicodone tablet under fasting condition are equivalent (Table 3). Another metabolite, oxymorphone was also measured but the concentrations were very low relative to the parent compound for all the treatments (e.g., approximately 2% of the exposure to parent compound).

Table 3 Mean (%CV) PK parameter of noroxycodone following single oral administration of 15 mg oxycodone capsules (3 x 5 mg) and 15 mg Roxicodone® tablet under fasted condition in healthy adults subjects (UPN-1189) (N = 25)

Parameter	Oxy IR capsule 15 mg (3 x 5 mg) Fasted (Treatment C, N = 25)	**Roxicodone® IR Tablet 15 mg (1 x 15 mg) Fasted (Treatment A, N = 25)**
AUClast (ng.h/ml)	**160.6 (33.9)**	162.8 (33.0)
AUCinf (ng.h/mL)	**177.2 (37.6)**	179.4 (34.7)
Cmax (ng/mL)	**20.9 (32.4)**	20.7 (24.4)
T1/2 (h)	**6.41**	6.48
Tmax (h)[a]	**1.00 (0.50 – 6.00)**	1.00 (0.50 – 6.00)
Kel (1/hr)	**0.11**	0.11
Geometric Mean Ratio (capsule/tablet) % (90% CI)		
AUClast	98.4 (95.1 – 101.9)	
AUCinf	98.1 (94.5 – 101.7)	
Cmax	99.1 (90.4, 108.6)	

[a] tmax reported as median (range)
Source: Table 7 and 12 of Study UPN-1189 report.

2. Does food affect the bioavailability of oxycodone from the capsules?

High fat breakfast delayed oxycodone tmax by about 2 hrs and the oxycodone peak concentration was decreased by about 14%. The extent of absorption is increased by about 23% (Table 4). For the metabolite noroxycodone, Cmax and AUC values were decreased by about 40% and 15%, respectively (Table 5). It should be noted the major activity of oxycodone is due to oxycodone itself. Overall, these exposure changes due to food effect can be considered to be not clinically significant.

Table 4 Mean (%CV) Plasma Pharmacokinetic Parameters of Oxycodone following single oral administration of 15 mg oxycodone Capsules (3 x 5 mg) under fasted and fed conditions in healthy adults subjects (Study UPN-1189) (N = 25) and Statistical Analysis

Parameter	Oxy IR capsules Fasted (N = 25)	**Oxy IR capsules High-Fat Fed (N = 25)**
AUClast (ng.h/ml)	**190.1 (30.8)**	227.8 (28.8)
AUCinf (ng.h/mL)	**192.4 (32.7)**	234.0 (30.2)
Cmax (ng/mL)	**37.1 (36.1)**	30.7 (22.4)
T1/2 (h)	**3.90**	4.05
Tmax[a] (h)	**1.00 (0.50 – 6.00)**	3.00 (1.50 – 6.00)
CL/F (L/hr)	**77.1**	62.5
Kel (1/hr)	**0.18**	0.18
Vd/F (L)	**420**	356
Geometric Mean Ratio (Fed/Fasted) (%) (90% CI)		
AUClast	120.6 (105 – 138.5)	

AUCinf	122.7 (106.0 – 141.9)	
Cmax	85.9 (74.7 – 98.6)	

a Median (Range)
Source: Table 6 and 15 of study UPN-1189 report.

Table 5 Mean (%CV) Plasma Pharmacokinetic Parameters of Noroxycodone following single oral administration of 15 mg oxycodone Capsules under fasted and fed conditions in healthy adults subjects (Study UPN-1189) (N = 25) and Statistical Analysis

Parameter	Oxy IR capsules Fasted (N = 25)	**Oxy IR capsules High-Fat Fed (N = 25)**
AUClast (ng.h/ml)	**160.6 (33.9)**	137.1 (35.4)
AUCinf (ng.h/mL)	**177.2 (37.6)**	159.0 (30.2)
Cmax (ng/mL)	**20.9 (32.4)**	12.3 (26.5)
T1/2 (h)	**6.41**	6.77
Tmax[a] (h)	**1.00 (0.50 – 6.00)**	3.00 (2.00 – 8.00)
Kel (1/hr)	**0.11**	0.11
Geometric Mean Ratio (Fed/Fasted) (%) (90% CI)		
AUClast	84.8 (72.3 – 99.5)	
AUCinf	88.4 (73.8 – 105.9)	
Cmax	59.8 (52.1 – 68.6)	

a Median (Range)
Source: Table 7 and 16 of study UPN-1189 report.

2.6 Analytical Section

1. What bioanalytical methods are used to assess concentrations?

A validated LC-MS/MS method was used for the determination of oxycodone, noroxycodone, and oxymorphone in humam plasma. The established lower limit of quantitation (LLOQ) were 0.50 ng/mL for oxycodone, 0.25 ng/mL for noroxycodone and 0.025 ng/mL for oxymorphone. The maximum 68 days storage for study samples at -70^{o}C until analysis does not exceed the 97 days storage stability established at -40^{o}C and -70^{o}C during assay validation.

QC samples for oxycodone were 1.50, 15.00, 50.00, and 80.00 ng/mL; QC samples for noroxycodone were 0.75, 7.50, 25.00, and 40.00 ng/mL; QC samples for oxymorphone were 0.075, 0.75, 2.50, and 4.00 ng/mL. The assays were demonstrated to be accurate and precise.

Table 4 Summary of Accuracy and Precision Data for Oxycodone, Noroxycodone, and Oxymorphone (Report 08-0096-upn-1189-tsrpt-01)

Analyte	%RE Range	%CV Range
Oxycodone	0.8 to 3.3	5.4 to 6.4
Noroxycodone	0.7 to 1.4	2.5 to 4.2
Oxymorphone	0.5 to 1.3	2.7 to 4.9

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

4 Appendix

4.1 Clinical Pharmacology Filing Memo

7 Pages of a Clinical Pharmacology and Biopharmaceutics Filing form has been removed, a duplicate of this review dated 3/1/10 can be found at the end of this review section.

4.2 Individual Study Synopsis

Following is the synopsis as reported in the NDA submission;

2. SYNOPSIS

Name of Sponsor: Glenmark Generics, Inc. **Names of Finished Products:** Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg **Name of Active Ingredient:** oxycodone hydrochloride	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(for National Authority Use Only)*

Study 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

Investigator

Myroslava Romach, MSc, MD, FRCPC

Study Center

DecisionLine Clinical Research Corporation
720 King St. W., Suite 700
Toronto, Ontario, Canada
M5V 2T3

Publication (reference)

None at the time of report publication.

Study Period	**Phase of Development**
24 Jul 2008 (first subject check-in) to 27 Aug 2008 (last pharmacokinetic sample collected)	1

Objectives

Primary

- To determine the relative bioavailability of a single 15 mg dose of oxycodone (3 × 5 mg immediate-release [IR] capsules, Glenmark) relative to a pharmaceutical alternative, a single 15 mg dose of an approved IR oxycodone tablet (1 × 15 mg tablet, Roxicodone®, Xanodyne Pharmaceuticals, Inc.).
- To determine the relative bioavailability of a single 15 mg dose of an oxycodone oral solution (0.75 mL × 20 mg/mL, Glenmark), relative to a pharmaceutical alternative, a single 15 mg dose of an approved IR oxycodone tablet (1 × 15 mg tablet, Roxicodone®, Xanodyne Pharmaceuticals, Inc.).

(b) (4)

Name of Sponsor: Glenmark Generics, Inc. **Names of Finished Products:** Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg **Name of Active Ingredient:** oxycodone hydrochloride	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(for National Authority Use Only)*

- To determine the relative bioavailability of a single 15 mg dose of an oxycodone oral solution (0.75 mL × 20 mg/mL, Glenmark), as compared to a single 15 mg dose of IR oxycodone capsules (3 × 5 mg IR capsules, Glenmark).
- To determine the effect of food (high-fat meal) on the pharmacokinetics of IR oxycodone capsules (3 × 5 mg IR capsules, Glenmark), as compared to the pharmacokinetics of IR oxycodone capsules (3 × 5 mg IR capsules, Glenmark) when administered in a fasted state.

Secondary

- To assess the safety and tolerability of two new IR oxycodone hydrochloride formulations, a 5 mg capsule strength (dosed as a single 15 mg dose) and a 20 mg/mL concentrated oral solution (dosed as a single 15 mg dose), when administered to healthy volunteers as single doses in a fasted or fed state

Methodology

This was an open-label, single-center, single-dose, five-way crossover study that assessed the relative bioavailability of two new IR oxycodone formulations in healthy volunteers and evaluated food effects when IR oxycodone hydrochloride capsules (3 × 5 mg capsules) were administered to healthy volunteers in fasted and fed states. Eligible subjects were randomly assigned to one of four pre-determined treatment sequences wherein they received each of the following treatments in a fasted state (one per treatment period): a single dose of a 15 mg IR oxycodone tablet (reference 1); (b) (4) (b) (4); a single 15 mg dose of oral IR oxycodone capsules (3 × 5 mg capsules) (test); and a single 15 mg dose of (0.75 mL of 20 mg/mL) oxycodone oral solution (test). In the fifth treatment period, all subjects were to receive a single 15 mg dose of IR oxycodone capsules (3 × 5 mg capsules) after completing a high-fat breakfast (test). A 7-day washout period (approximate) separated each treatment period.

Number of Subjects (planned & analyzed)

Planned: 35 subjects were to be enrolled, in order to have 24 subjects complete the study.

Analyzed: 35 subjected were enrolled and 25 subjects completed the study.

Subjects and Main Criteria for Inclusion

Subjects were non-smoking, male or female volunteers, 18 to 55 years of age (inclusive). Subjects were to be in good general health (as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory results (with particular emphasis on risk factors for renal or hepatic impairment). Subjects were also to have hemoglobin ≥ 12 g/dL and a body mass index between 18 and 32 kg/m^2 at screening.

Name of Sponsor: Glenmark Generics, Inc. **Names of Finished Products:** Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg **Name of Active Ingredient:** oxycodone hydrochloride	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(for National Authority Use Only)*

Study Treatments (including dose, mode of administration, and batch numbers)

Treatment A: (Reference 1)	Roxicodone® IR 15 mg tablet for oral administration (oxycodone hydrochloride). Manufacturer: Xanodyne Pharmaceuticals, Inc; Lot #: 757873A.
Treatment B: (Reference 2)	[redacted] (b) (4)
Treatment C: (Test)	Oxycodone hydrochloride IR capsules 15 mg dose (3 × 5 mg capsules), for oral administration. Manufacturer: Lehigh Valley Technologies Inc.; Lot #: OH-003-07.
Treatment D: (Test)	Oxycodone hydrochloride oral solution 15 mg dose (0.75 mL of 20 mg/mL [redacted] (b) (4) Manufacturer: Lehigh Valley Technologies Inc.; Lot #: SB-OH-004
Treatment E: (Test, fed)	Oxycodone hydrochloride IR capsules 15 mg dose (3 × 5 mg capsules), administered after a high-fat breakfast. Manufacturer: Lehigh Valley Technologies Inc.; Lot #: OH-003-07.

Duration of Treatment

Approximately 4 weeks (exclusive of the 28-day screening period)

Study Endpoints

The pharmacokinetic parameters of interest for assessing relative bioavailability were

- The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration (AUC_{0-t})
- The area under the plasma concentration versus time curve from time 0 to infinity (AUC_{0-inf})
- The maximum observed plasma concentration (C_{max})
- The time of the maximum observed plasma concentration (T_{max})

The criteria for bioequivalence [redacted] (b) (4) and for absence of a food effect were a 90% confidence interval (CI) for the ratio of test to reference least square mean (LSM) of ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} for parent and metabolites within 0.80 to 1.25, representing a maximum of 20% difference (FDA Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Products-General Considerations, March 2003).

T_{max} while not a primary endpoint was also analysed as an important parameter in pain relief. Absence of an effect was based on a two-tailed p-value.

Name of Sponsor: Glenmark Generics, Inc. **Names of Finished Products:** Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg **Name of Active Ingredient:** oxycodone hydrochloride	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(for National Authority Use Only)*

Safety monitoring/assessments included:

- adverse events
- vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- pulse oximetry
- clinical laboratory tests (hematology, chemistry, and urinalysis)
- physical examination

Statistical Methods (Data Analysis)

Descriptive statistics for all calculated pharmacokinetic parameters (mean, median, standard deviation, range) were generated for oxycodone, noroxycodone, and oxymorphone. These statistics were calculated separately for each of the four oxycodone doses administered in the fasted state and for the oxycodone dose administered under the fed condition. Geometric mean and geometric coefficient of variation were provided for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Analysis of variance (ANOVA) was performed on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} for oxycodone and its metabolites. The ANOVA model included sequence, treatment (dosing condition), and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance; all other main effects were tested using the residual error (error mean square). Each ANOVA included calculation of the LSM, the difference between treatment LSM, and the standard error associated with the difference. These were done using the SAS® general linear model (GLM) procedure. Ninety (90%) percent CIs for the ratio of test and reference were calculated for each parameter, consistent with the two one-sided tests approach.

T_{max} was presented from nonparametric analysis (Walsh Averages and appropriate quantile (or P value) of the Wilcoxon Signed Rank Test).

Name of Sponsor: Glenmark Generics, Inc.	**Individual Study Table Referring to Part of the Dossier:**	*(for National Authority Use Only)*
Names of Finished Products: Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg	Volume: Page:	
Name of Active Ingredient: oxycodone hydrochloride		

Summary of Results

Pharmacokinetic Results:

	Oxy IR Tab 15 mg Reference 1 N=25	(b) (4)	Oxy IR Cap 3 × 5 mg Test 1 N=25	Oxy Oral Soln 15 mg Test 2 N=25	Oxy IR Cap-FED 3 × 5 mg Test 3 N=25
Oxycodone					
C_{max} (ng/mL)					
Mean	36.2924		37.1364	38.5484	30.6956
CV (%)	27.4		36.1	30.2	22.4
T_{max} (h)					
Median	1.0000		1.0000	1.0000	3.0000
Range	0.500 - 6.000		0.500 - 6.000	0.500 - 4.000	1.500 - 6.000
AUC_{0-t} (ng·h/mL)					
Mean	193.5574		190.1378	212.4236	227.7834
CV (%)	30.4		30.8	32.8	28.8
AUC_{0-inf} (ng·h/mL)					
Mean	196.5110		192.4113	214.3104	234.0531
CV (%)	31.3		32.7	34.2	30.2
Noroxycodone					
C_{max} (ng/mL)					
Mean (SD)	20.6916		20.9220	22.6824	12.3024
CV (%)	24.4		32.4	21.5	26.5
T_{max} (h)					
Median	1.0000		1.0000	1.0000	3.0000
Range	0.500 - 6.000		0.500 - 6.000	0.500 - 4.000	2.000 - 8.000
AUC_{0-t} (ng·h/mL)					
Mean (SD)	162.7627		160.6511	178.7348	137.1148
CV (%)	33.0		33.9	33.5	35.4
AUC_{0-inf} (ng·h/mL)					
Mean (SD)	179.3877		177.2561	194.7932	158.9650
CV (%)	34.7		37.6	36.6	41.4

Note: (b) (4)

Source: Table 14.2.2.1 and 14.2.2.2

The relative bioavailability of oxycodone IR capsules is high. The rate and extent of absorption of the capsules and the oral solution are the same, with respect to oxycodone and noroxycodone.

Co-administration with food delays absorption (T_{max} occurs at 3 hours); peak oxycodone concentrations are lower (by 17%) than when the IR capsule is given in the fasted state. The extent of absorption is increased by about 17%. Effects are more pronounced for the metabolite (noroxycodone): peak concentrations are 41% lower and the extent of absorption is decreased, rather than increased, by about 10%.

Name of Sponsor: Glenmark Generics, Inc. **Names of Finished Products:** Oral Oxycodone Solution (20 mg/1 mL) Immediate-release Oxycodone Hydrochloride Capsule, 5 mg **Name of Active Ingredient:** oxycodone hydrochloride	**Individual Study Table Referring to Part of the Dossier:** Volume: Page:	*(for National Authority Use Only)*

Oxycodone IR capsules and oral solution are equivalent in rate and extent of exposure to Roxicodone®. This applies to both oxycodone and noroxycodone. (b) (4)

(b) (4)

Safety Results:

- The most common adverse events pertained to the central nervous system (including psychiatric events) and the gastrointestinal system. Of these, the most common adverse events were euphoric mood, somnolence, dizziness, and nausea. (b) (4)

(b) (4)

- Adverse events were mild or moderate in intensity. Six subjects (17%) had nausea and vomiting, resulting in the discontinuation of 2. Two additional subjects discontinued (11% overall); the other reasons for discontinuation included dizziness and nausea in 1 subject and diarrhea, headache, and dizziness in 1 subject. There were no serious adverse events.
- Pulse oximetry was performed post dosing. No oxygen saturation readings were below 90%. The effects on blood pressure and pulse in this study were minimal and no subject had clinically significant changes.
- There was no effect on clinical laboratory results.

Conclusions

The current study demonstrated that the rate and extent of exposure to oxycodone was equivalent for Glenmark's proposed 5 mg oxycodone capsules and oxycodone oral solution. Additionally, the proposed dosage forms were equivalent in extent of exposure to (b) (4) oxycodone IR tablets 15 mg (Roxicodone®) (b) (4). As expected, food effects were present when the IR formulation was administered after a high-fat meal. Oxycodone was well tolerated in this study, and the safety profile was consistent with what would be expected for an opioid drug.

Date of Report	17 FEB 2009

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

/s/

WEI QIU
10/12/2010

SURESH DODDAPANENI
10/12/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200534	**Reviewer:** Minerva Hughes, PhD	
Submission Date:	22 Dec 2010		
Division:	Division of Anesthesia and Analgesia Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Lehigh Valley Technologies	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	None proposed	**Date Assigned:**	22 Jul 2010
Generic Name:	Oxycodone hydrochloride, capsule	**Date of Review:**	27 Aug 2010
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate	**Type of Submission:** Original New Drug Application *(Type 7 marketed drug without an approved application)*	
Formulation/strengths	Capsule, 5 mg		
Route of Administration	Oral		

SUBMISSION:

Oxycodone is a synthetic opioid analgesic approved in the United States for the treatment of moderate to severe pain, either as a single-ingredient or combination drug product. It has been in clinical use since 1917. Lehigh Valley Technologies (LVT) is submitting NDA 200-534 for the use of oxycodone hydrochloride in pain management in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The drug product is a hard gelatin capsule consisting of an opaque yellow cap imprinted with "LV" and an opaque white body imprinted "901". Each capsule contains 5 mg oxycodone hydrochloride and the inactive ingredients microcrystalline cellulose NF, lactose anhydrous NF, pre-gelatinized starch NF, sodium starch glycolate NF, colloidal silicon dioxide NF, magnesium stearate NF, and sodium lauryl sulfate NF.

BIOPHARMACEUTIC INFORMATION:

Biopharmaceutics information in the application included the following:

1. A five-way, single-dose, crossover study to establish bioequivalence of the proposed immediate-release capsule to Roxicodone (referenced listed drug, tablet formulation) – reviewed by the clinical pharmacology reviewer.
2. Dissolution method and specifications – covered by this review.

RECOMMENDATION:

There is insufficient data in the application to permit a thorough review of the selected dissolution method and proposed dissolution specification for quality control and performance. The applicant has committed to providing the Agency with additional dissolution data by 31 March 2011, and a final Biopharmaceutics' assessment is deferred until additional data are received. These deficiencies will not preclude an approval recommendation from Biopharmaceutics if the applicant agrees to the following recommended changes and additional data requests. If an approval action is not issued for other reasons, the following data should be submitted as part of the applicant's complete response.

At this time, the following comments should be conveyed to the applicant.

1. You have indicated that additional dissolution data will be available by 31 March 2011 to permit a thorough review of the dissolution method and specifications and have submitted a proposal for an interim dissolution specification. Although limited, the dissolution profile data in the application

(b) (4)

2. Reference is made to USP <1092> and ICH Q2A for guidelines on acceptable validation characteristics for the dissolution procedure and HPLC analysis method. The method validation report submitted in the application was limited to only the HPLC determinative step. Submit a full method development and validation report for the dissolution method which accounts for product specific parameters such as media selection, sampling (automatic versus manual), agitation, etc.

(b) (4)

Signatures *(electronic signature appended)*
Biopharmaceutics Reviewer
Biopharmaceutics Team Leader or Supervisor
Office of New Drugs Quality Assessment

cc: Angelica Dorantes, Tonya Clayton, Eugenia Nashed

REVIEWER'S NOTES

1.0 INTRODUCTION

NDA 200-534 was submitted by Lehigh Valley Technologies (LVT) on 22 December 2009 for the use of oxycodone hydrochloride, formulated as a 5 mg immediate release (IR) capsule, in the treatment of moderate to severe pain. Oxycodone hydrochloride 5 mg capsules were previously marketed by LVT without an approved application. As such, the safety, efficacy, and quality of the product has not been confirmed. As part of ongoing FDA surveillance of unapproved marketed drugs, a number of manufacturers of unapproved narcotics, which included those of 5 mg oxycodone hydrochloride capsules, were notified that an approved NDA was required and were requested to cease distribution.

As oxycodone hydrochloride is not a new molecular entity, LVT is relying on FDA's prior findings of safety and efficacy for the reference listed drug (RLD) Roxicodone (NDA 21-011), a 15 mg IR tablet, for marketing approval. A single-dose, five-period crossover study (UPN-1189) in healthy volunteers was completed to demonstrate bioequivalence with respect to the extent and rate of absorption. Of note, Roxicodone is a different dosage form with different standards for strength, purity, identity, and quality. The two drug products may not be considered pharmaceutical equivalents.

As part of the CMC Quality review, Biopharmaceutics was consulted to review the adequacy of the dissolution method and specifications for quality control and performance. The following submissions were reviewed in support of this assessment.

Submission(s) Reviewed	Document Date
Original Submission	22 Dec 2010
Amendment – Response to CMC information request from Day 74 Letter	5 April 2010
Amendment – Response to CMC information request of 23 July 2010	16 Aug 2010
Amendment – Additional responses to CMC information request of 23 July 2010	19 Aug 2010

The above referenced CMC information requests were issued by the primary CMC reviewer Eugenia Nashed as part of the initial filing and on going quality review. These CMC requests included the following comments from Dr. Nashed relevent to the dissolution method and specification, and thus, considered in this review.

- 5 Mar 2010, Day 74 Letter:

Provide detailed description of the dissolution method to include testing apparatus and exact experimental conditions, in addition to a reference to USP chapter <711>. Justify the adequacy of the selected dissolution conditions and provide dissolution profiles obtained during release and stability testing of the commercial formulation of the capsules. Submit adequate data for commercial formulation to support the proposed acceptance criteria for capsule dissolution.

- 23 Jul 2010, CMC Information Request:

Upgrade the analytical method for drug product dissolution to demonstrate dissolution profile acceptable as a base for control of capsules' quality, as discussed during teleconference on July 12, 2010. The establishing of adequate dissolution method for

controlling quality is particularly important due to the lack of formal compatibility studies for drug product ingredients. Due to the limit data available during the response submission you may want to propose an interim (b) (4) *Dissolution acceptance criteria, e.g.,* (b) (4) *(Q) of the labeled amount dissolved in 30 min, and additional testing for Dissolution Profile with data reported at method-derived intervals, e.g., 10, 15, 30 and 45 min. Also, specify, in a footnote, the final date by which adequate amount of data will be submitted for re-evaluation of the interim acceptance criteria.*

2.0 BIOPHARMACEUTICS QUALITY ASSESSMENT

2.1. Drug Product Composition

The drug product was formulated to closely match an unapproved 5 mg oxycodone capsule manufactured by (b) (4), the competitor at the time, with respect to appearance, composition, and dissolution properties. The proposed commercial formulation is summarized in the table below.

Table 3.2.P.1:1
Composition of Oxycodone Hydrochloride Capsules, 5 mg

Component	Composition		Function
	mg/capsule	%/capsule	
Oxycodone hydrochloride, USP	(b) (4)		Active (analgesic)
Microcrystalline cellulose, NF			(b) (4)
Lactose anhydrous, NF			
Pre-gelatinized starch, NF			
Sodium starch glycolate, NF			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF			
Sodium lauryl sulfate, NF			
Theoretical weight			
Imprinted size # 4 hard gelatin capsule (b) (4) imprinted with edible black ink)			

[1]The proposed drug product, oxycodone hydrochloride capsules, 5 mg, contains an overage (b) (4) for the drug substance. The overage of the drug substance compensates for moisture content of the drug substance. See Section 3.2.P.2.2.2.

Source: Applicant submitted information. NDA 200-534 Section 3.2.P.1

Reviewer's Comments: (b) (4) is no longer marketed by the manufacturer. The application also does not contain comparative dissolution studies using (b) (4) oxycodone product.

2.2. Drug Product Regulatory Specification

The proposed drug product regulatory specification is included for informational purposes and is summarized in the table below.

Table 3.2.P.5:1
Proposed Regulatory Specifications of Oxycodone Hydrochloride Capsules, 5 mg

Test	Specification	Method
Appearance[1, 2]	(b) (4)	Visual; TM-047
Identification (release only)		TM-031
Dissolution	(b) (4)	TM-031 USP <711>
Uniformity of dosage units (release only)		TM-031
Assay (HPLC)[1, 2]		TM-031
Related substances[1, 2, 3]		TM-032
Container closure[1, 2]		TM-047
Water content[1]		TM-040

[1] Performed for stability testing
[2] (b) (4)
[3] Reporting threshold = 0.1% (ICHQ3B)
NMT = Not more than

Source: Applicant submitted information. NDA 200-534 Section 3.2.P.5. specifications as of NDA amendment 5 Apr 2010.

Refer to the primary CMC Reviewer's review for comments regarding the acceptability of the proposed specification. Comments regarding the dissolution specification are outlined in the subsequent sections.

2.3. Dissolution Method and Specification

2.3.1. Specification

The applicant initially proposed a dissolution specification in accordance with USP <711> guidelines (b) (4) as follows:

- o (b) (4)

Capsules were evaluated at release and on stability according to the above criterion. A comparative dissolution profile graph was provided in NDA Section 2.7.1.1.2 depicting the dissolution profile ((b) (4)) for Lot OH-003-07/clinical, OH-008-08/registration, OH-009-08/registration, and OH-010-08/registration); data used to generate the curves were not submitted for review.

Figure 2.7.1:1
Dissolution Profiles of Four Different Oxycodone HCl Capsules, 5 mg Batches Manufactured by LVT

(b) (4)

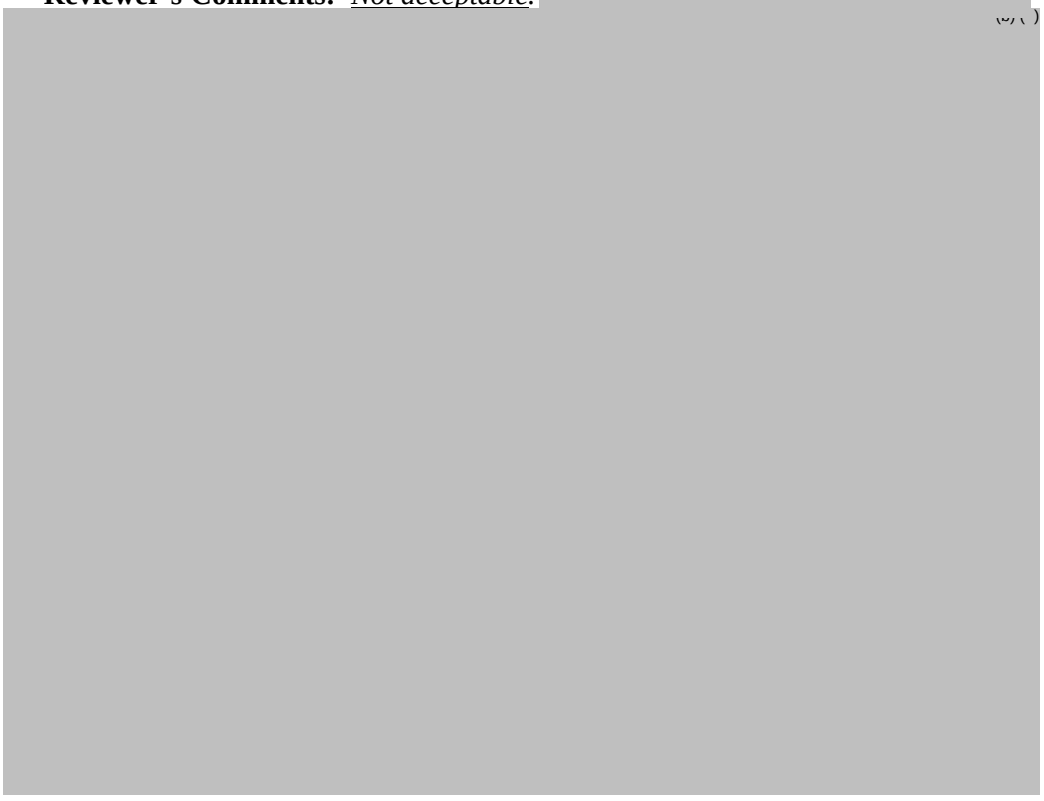
Source: Applicant submitted information. NDA 200-534 Section 2.7.1.

The dissolution specification was revised in amendment 19 Aug 2010 to the following interim specification based on advice sent by the primary CMC reviewer.

- (b) (4)

The applicant notes that additional dissolution data will not be available until 31 March 2011 for re-evaluation of the interim specification.

Reviewer's Comments: *Not acceptable.* (b) (4)



(b) (4)

2.3.2. Method Validation Data

The dissolution method developed by the applicant is as follows.

(b) (4)

Submitted method validation data are summarized below.

Dissolution Method Validation			
Parameter	**Test**	**Acceptance Criteria**	**Result**
System Suitability	(b) (4)		
Precision			

Dissolution Method Validation			
Parameter	**Test**	**Acceptance Criteria**	**Result**
	(b) (4)		
Linearity/Range			
Accuracy/Recovery (b) (4)			
Ruggedness			
Solution Stability			
Robustness			
Sampling/Manual			
(b) (4)			

Reviewer's Comments: *Major deficiencies noted.* The applicant's dissolution method validation data are limited to only the HPLC step in the process, which is the same method used for assay. As reviewed, the method validation data does not appear to fully comply with current guidelines (i.e., ICH Q2A, FDA Draft Guidance, USP <1092>). The applicant (b) (4) , so information on method variability is not clear for all validation parameters. The following observations were made with respect to the HPLC validation data.

- Method robustness does not account for effects from variations in mobile phase composition and detection wavelength.
- The concept of ruggedness as evaluated by the applicant provides incomplete information on method precision. Replicate samples and injections were not performed. Intra-analyst variability was not assessed.
- No information provided on the composition or age of placebo solutions used to determine interference.
- (b) (4)

The applicant provides no information regarding the validation of the dissolution procedure itself. The proposed dissolution conditions are common and appear reasonable for the product, but this should be adequately supported by data. It is this reviewer's expectation that product specific dissolution parameters such as media selection, stirring rate, sampling time, sampling method (automatic or

manual), or the need for any specific protocols (b) (4) are adequately justified and validated to ensure suitability under normal conditions of variation. (b) (4)

(b) (4)

Since the HPLC method is the same as used for assay and content uniformity, the acceptability of method validation is covered by the CMC Reviewer. Comments specific to sensitivity for use as a determinative step for dissolution will be conveyed by this review.

2.3.3. Justification Specifications

Dissolution specifications were revised on 19 August 2010 to an interim (b) (4) specification as described above. The applicant states that the specifications were justified because it is supported by the limited data and was advised by FDA in CMC information request letter of 26 July 2010 (*note: letter signatory date is 23 July 2010*).

Reviewer's Comments: *Major Deficiencies noted*. The proposed specification was an interim proposal suggested by FDA; however, the use of (b) (4) is not acceptable. Previous FDA advice was incosistent with current FDA and USP thinking on the topic.

2.3.4. Batch Analysis/Stability Data

Stability data were submitted for the following drug product lots.

(b) (4)

[redacted]

3.0 REGULATORY ISSUES AND COMMENTS FOR APPLICANT

Interim dissolution specifications were proposed by the CMC Reviewer before an assessment by Biopharmaceutics. The proposed interim specification had tighter limits for (b) (4) dissolution, which were to be re-evaluated after additional data are submitted to the NDA. The applicant has indicated in their 19 August 2010 amendment that additional dissolution data will be submitted on 31 March 2011, after the PDUFA goal date for NDA 200-534. Consequently, Biopharmaceutics is unable to issue a final recommendation for the dissolution specification during this review cycle. At this time, the following comments should be conveyed to the applicant.

1. You have indicated that additional dissolution data will be available by 31 March 2011 to permit a thorough review of the dissolution method and specifications and have submitted a proposal for an interim dissolution specification. Although limited, the dissolution profile data in the application (b) (4)

(b) (4)

[redacted]

2. Reference is made to USP <1092> and ICH Q2A for guidelines on acceptable validation characteristics for the dissolution procedure and HPLC analysis method. The method validation report submitted in the application was limited to only the HPLC determinative step. Submit a full method development and validation report for the dissolution method which accounts for product specific parameters such as media selection, sampling (automatic versus manual), agitation, etc.

3. (b) (4)

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

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

/s/

MINERVA HUGHES
08/27/2010

PATRICK J MARROUM
08/29/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**200534**	**Brand Name**	**Oxycodone Hydrochloride Capsules, 5 mg**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	
Medical Division	**DAARP**	**Drug Class**	**Opioid analgesic**
OCP Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Management of moderate to severe pain where use of an opioid analgesic is appropriate**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Oral capsule**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**Dec 22, 2009**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review	**July 22, 2010**	**Sponsor**	**Lehigh Valley Technologies, Inc.**
Medical Division Due Date	**Aug 22, 2010**	**Priority Classification**	**Standard**
PDUFA Due Date	**Oct 22, 2010**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies	**x**			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**1**		**Request deferral**
Literature References				
Total Number of Studies		**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the final formulation was used in support of the NDA and the intended commercial product, oxycodone hydrochloride capsules, 5 mg.
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	biopharmaceutics section of the NDA legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		LVT is requesting a deferral of the need for studies in children 16 years of age and younger on the grounds that adult studies are completed and ready for approval whereas the Pediatric Plan is not yet fully formulated and studies have not yet been initiated in pediatric patients. Sponsor intends to submit the PK study protocol within 6 months after approval of the NDAs.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the clinical pharmacology section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

DSI inspection should be conducted with the Study UPN 1189.

Title of the study: 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
Study Clinical Site: Decision Line Clinical Research Corporation
720 King St. W., Suite 700
Toronto, Ontario, Canada M5V 2T3
T: 416-963-5602
F: 416-963-9732
Study Analytical Site:

(b) (4)

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Lehigh Valley Technologies, Inc. (LVT) submitted a 505(b) (2) NDA for Oxycodone Hydrochloride Capsules, 5 mg for the management of moderate to severe pain where use of an opioid analgesic is appropriate.

Oxycodone is an opioid analgesic that was first synthesized in 1916. Single-ingredient oxycodone hydrochloride immediate-release oral tablets are approved in the US in strengths ranging from 5 mg to 30 mg for management of moderate to severe pain where the use of an opioid analgesic is appropriate. Sponsor plans to rely on the agency's finding of the safety and efficacy of oxycodone as reflected in the approved product of Roxicodone® (NDA 21-011), an immediate-release tablet, (b) (4) the chosen reference listed drugs.

Sponsor conducted a single-dose, five-period crossover study UPN-1189 in healthy volunteers to establish bioequivalent to the tablet RLD, assess the effect of food on the capsules, and assess the bioavailability relative to the (b) (4) RLD and an oral solution. The oral solution is another dosage form developed by LVT and is the subject of a separate NDA (NDA 200535). Sponsor concluded that the proposed capsule is bioequivalent to the approved immediate-release RLD, Roxicodone tablet, 15 mg. (b) (4)

Table 1 Components and Composition of Oxycodone Hydrochloride Capsules, 5 mg

Ingredient	Mg/capsule	Function
Oxycodone hydrochloride, USP	(b) (4)	Active (analgesic)
Microcrystalline cellulose, NF	(b) (4)	(b) (4)
Lactose anhydrous, NF	(b) (4)	
Pre-gelatinized starch, NF	(b) (4)	
Sodium starch glycolate, NF		
Colloidal silicon dioxide, NF		
Magnesium stearate, NF		
Sodium lauryl sulfate, NF		
Theoretical weight		

(b) (4)

In study UPN-1189, thirty-five healthy volunteers enrolled in the study, 25 of whom (21 men and 4 women) completed all five periods and were included in the biopharmaceutics analyses. The following treatments were administered to the subjects in a randomly assigned sequence with dosing under fasting condition: LVT's oxycodone IR capsules (3 x 5 mg), LVT's oxycodone oral solution (0.75 mL, 20 mg/mL), Oxycodone IR tablet (1 x 15 mg Roxicodone®), (b) (4) . In the fifth study period, all subjects received LVT's oxycodone IR capsules (3 x 5 mg) administered after a high-fat meal. The proposed capsule formulation was bioequivalent to the Roxicodone oral tablet (Table 2). Food decreased Cmax by 14% and increased AUC by 23%. Tmax was delayed by 2 hours on average (Table 3). According to Roxicodone label, high-fat meal increased AUC of an oral solution by 27% and there was a 1.25 hour delay in Tmax. (b) (4)

(b) (4)

Table 2 Statistical Analysis Summary for Bioequivalence after Single-Dose Oxycodone Capsules (LVT, test) versus Oxycodone IR Tablet (Reference) Administered to Healthy Volunteers under Fasting Conditions, N=25

A: Oxycodone

Parameter (unit)	Geometric Means		% Ratio of Means (%)	90% CI
	Oxycodone Capsules (1 × 15-mg Capsule) (Test)	Roxicodone® (1 × 15-mg IR Tablet) (Reference)		
C_{max} (ng/mL)	34.9	35.1	99.5	(91.4, 108.2)
AUC_{0-t} (ng·h/mL)	181.1	185.0	97.8	(93.0, 102.9)
AUC_{0-inf} (ng·h/mL)	182.2	187.3	97.2	(91.8, 102.9)

Data Source: Table 14.2.4.1.1.1, Table 14.2.4.1.1.2, Table 14.2.4.1.1.3, and Table 14.2.2.1 in the Final Clinical Study Report UPN-1189.

B: Noroxycodone

Parameter (unit)	Geometric Means		% Ratio of Means (%)	90% CI
	Oxycodone Capsules (1 × 15-mg Capsule) (Test)	Roxicodone® (1 × 15-mg IR Tablet) (Reference)		
C_{max} (ng/mL)	19.9	20.1	99.1	(90.4, 108.6)
AUC_{0-t} (ng·h/mL)	152.7	154.9	98.4	(95.1, 101.9)
AUC_{0-inf} (ng·h/mL)	166.7	170.0	98.1	(94.5, 101.7)

Data Source: Table 14.2.4.1.2.1, Table 14.2.4.1.2.2, Table 14.2.4.1.2.3, and Table 14.2.2.2 in the Final Clinical Study Report UPN-1189.

Table 3 Summary Statistical Analysis of the Food Effect for Oxycodone IR Capsules (LVT) Administered to Healthy Adult Volunteers under Fed and Fasted Conditions, N = 25

A: Oxycodone

Parameter (unit)	Geometric Means		% Ratio of Means (%)	90% CI
	Oxycodone Capsules (3 × 5 mg) Fed	Oxycodone Capsules (3 × 5 mg) Fasted		
C_{max} (ng/mL)	30.0	34.9	85.9	(74.7, 98.6)
AUC_{0-t} (ng·h/mL)	218.3	181.1	120.6	(105, 138.5)
AUC_{0-inf} (ng·h/mL)	223.5	182.2	122.7	(106.0, 141.9)

Data Source: Table 14.2.4.2.2 and Table 14.2.2.2 in the Final Clinical Study Report UPN-1189.

B: Noroxycodone

Parameter (unit)	Geometric Means		% Ratio of Means (%)	90% CI
	Oxycodone Capsules (3 × 5 mg) Fed	Oxycodone Capsules (3 × 5 mg) Fasted		
C_{max} (ng/mL)	11.2	22.2	59.8	(52.1, 68.6)
AUC_{0-t} (ng·h/mL)	129.2	152.7	84.8	(72.3, 99.5)
AUC_{0-inf} (ng·h/mL)	147.6	166.7	88.4	(73.8, 105.9)

Data Source: Table 14.2.4.2. and Table 14.2.2.2 in the Final Clinical Study Report UPN-1189.

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(b) (4)

Sponsor submitted a request for pediatric deferral on the basis that adult studies are completed and ready for approval whereas the Pediatric Plan is not yet fully formulated and studies have not yet been initiated in pediatric patients. Sponsor intends to submit PK study protocol within 6 months of NDA approval.

In addition, this reviewer plans to incorporate DDI information with (b) (4) based on published literature to the label as appropriate.

1. Hagelberg NM et al. Voriconazole drastically increases exposure to oral oxycodone. Eur J Clin Pharmacol. 2009;65:263-271.

2. Nieminen TH et al. Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009;110:1371-1378.

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

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/s/

WEI QIU
03/01/2010

SURESH DODDAPANENI
03/01/2010