CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200535Orig1s000

CHEMISTRY REVIEW(S)

Oxycodone Hydrochloride Oral Solution
NDA 200535

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

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

Indication: For management of moderate to severe pain (b) (4) .

Presentations: The oral solution is available in 20 mg/mL. The 20 mg/mL drug product is a yellow, berry flavored liquid, packaged in 30-mL white HDPE bottles with a window stripe, CR closures and heat-induction inner seal. It is supplied in an individual carton together with an accompanying calibrated oral syringe, separately packaged.

EER Status: Acceptable as of Jan 7, 2010

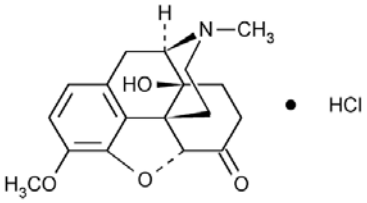
Consults: **EA** – Granted
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology – Acceptable.
Biopharmaceutics – Acceptable, with PMC
Quality Microbiology – Acceptable

Original Submission: 22-Dec-2009

Post-Approval CMC Commitments:
The applicant has committed to submit a prior-approval supplement by Mar 31, 2011, with validated analytical method for the content of *Burkholderia cepacia* and adequate data-reflecting regulatory specifications.

The applicant has also committed that due to the pending development of the analytical method and acceptance criteria for *Burkholderia cepacia*, any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior-approval supplement with adequate supporting data.

Drug Substance: Oxycodone hydrochloride drug substance is a white crystalline powder, soluble in water and slightly soluble in alcohols. It is derived from the opioid alkaloid, thebaine and it is manufactured by (b) (4), in a DEA-registered manufacturing facility in (b) (4). Chemically, oxycodone hydrochloride is (5*R*,*9R*,13*S*,14*S*)-4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride (salt) with a molecular mass of 351.82. ($C_{18}H_{21}NO_4$. HCl)



The manufacturing and controls are referenced to DMF (b) (4) held by (b) (4). The drug substance for the related NDA 200-534 (Oxycodone Hydrochloride capsules) is sourced from a different manufacturer, (b) (4).

The drug substance contains trace amounts of (b) (4) impurities, (b) (4) Drug substance with these specifications was used during the development and it is used for the commercial drug product. Other attributes for drug substance controls were revised several times during the course of this review, and the last version of drug substance specifications, submitted in amendment dated Oct 1, 2010, has acceptable controls for identification, assay, individual and total impurities, water content, and residual solvents.

The drug substance specifications has acceptable controls for Description, Identification, Assay, Specific Rotation, Residue on Ignition, Related Substances, (b) (4), Chloride content, Residual Solvents, (b) (4). Note that the sponsor has provided adequate justification for deletion of microbial testing in the drug substance but is however controlled in the drug product.

The container closure is stored in tightly sealed (b) (4) bags (b) (4). The (b) (4) are secured under controlled conditions required for a DEA Schedule II narcotic drug substance. A retest period of (b) (4) is established by (b) (4) but LVT tests the drug substance annually.

Conclusion: The drug substance is satisfactory.

Drug Product:

(b) (4). The 20 mg/mL drug product is a yellow, berry flavored liquid, packaged in 30-mL white HDPE bottles with a window stripe, CR closures and heat-induction inner seal. Each 1 mL of oral yellow solution contains 20 mg of oxycodone hydrochloride, USP and the following inactive ingredients: citric acid anhydrous, D&C Yellow #10, natural/artificial berry flavor, purified water, sodium citrate dihydrate, sodium benzoate, saccharin sodium, and sorbitol. It is supplied in an individual carton together with an accompanying (separately overwrapped) 1 mL calibrated oral syringe. The oral solution is manufactured and released by Lehigh Valley Technologies, Inc. in Allentown, PA. (b) (4), is

an alternate packager for the drug product. The intended commercial manufacturing batch size for oxycodone hydrochloride USP, is (b) (4) for the 20 mg/mL strength.

The proposed 20 mg/mL drug product was originally supplied with a (b) (4) closure designed to be kept in the vial solution during the use period. A change to the container closure was submitted in amendment dated Sep 8, 2010. It included change of the (b) (4) to the calibrated 1 mL oral dosing syringe, co-packaged with the vial in one carton. Since the (b) (4) was used during bioequivalence studies, the applicant provided a short bridging dose accuracy studies comparing the amount of drug product delivered with the syringe and with the (b) (4).

The applicant has submitted a bioavailability/bioequivalency studies for 20 mg/mL product (b) (4)

(b) (4) However, based on the statement from the applicant, the (b) (4) was used in the bioavailability and bioequivalency studies.

The proposed post-approval agreement with the applicant is based on the recommendation from the Microbiology review team.

The currently proposed expiry period of two years is supported by the submitted stability data however, any further extension of the expiry period has to be achieved *via* a prior-approval (PA) supplement due to the limited data, and method for controls of microbial limits.

One additional formulation of oxycodone hydrochloride capsule (5 mg) is the subject of an NDA 200-534 (Lehigh Valley Technologies).

Conclusion: The drug product is acceptable.

Additional Items:
Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:
From a CMC perspective, the application is recommended for **approval for the 20 mg/mL strength formulation**.

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/s/

PRASAD PERI
10/18/2010
Recommend approval for the 20 mg/mL strength from CMC perspecive

CHEMISTRY REVIEW

NDA 200-535

Oxycodone Hydrochloride (oxycodone hydrochloride) Solution, (b) (4) 100 mg/5 mL

Lehigh Valley Technologies, Inc.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division I

Division of Anesthesia and Analgesia Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-535
2. REVIEW #: 1
3. REVIEW DATE: 14-Oct-2010
4. REVIEWER: Eugenia M. Nashed
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Stamp Date	Comments
Original NDA	22-Dec-2009	22-Dec-2009	2 CMC filing safety comments sent on Feb 18, 2010, and 6 additional CMC comments forwarded in the 74 day letter on Mar 5, 2010.
Amendment	23-Feb-2010	23-Feb-2010	Response to CMC filing safety comments (LOAs to supporting DMFs and BSE/TSE statement for gelatin capsules).
Amendment	03-Mar-2010	03-Mar-2010	Change in the reference listed drug (RLD) – (b) (4)
Amendment	30-Mar-2010	30-Mar-2010	Partial response to 6 CMC comments forwarded on Mar 5, 2010 (74 day letter).
Amendment	05-Apr-2010	05-Apr-2010	Additional response/data to 6 CMC comments requested on Mar 5, 2010 (74 day letter).
Amendment	16-Aug-2010	16-Aug-2010	Partial response to deficiencies discussed during teleconference on Jul 12, 2010, and IR letter dated Jul 22, 2010.
Amendment	19-Aug-2010	20-Aug-2010	Additional response/data to deficiencies discussed during teleconference on Jul 12, 2010, and IR letter dated Jul 22, 2010.
Amendment	02-Sep-2010	02-Sep-2010	Updated Labeling
Amendment	08-Sep-2010	08-Sep-2010	Change in the dosing unit from a (b) (4) to a calibrated syringe
Amendment	21-Sep-2010	21-Sep-2010	Additional data to support request for the change in dosing unit from a (b) (4) to a calibrated syringe

Amendment	28-Sep-2010	29-Sep-2010	Response to CMC comments discussed during teleconference on Sep 23, 2010, and forwarded in IR letter dated Sep 23, 2010.
Amendment	01-Oct-2010	04-Oct-2010	Additional response to CMC comments discussed during teleconference on Sep 23, 2010, and forwarded in IR letter dated Sep 23, 2010.
Amendment	07-Oct-2010	12-Oct-2010	Response to IR letter dated Oct 6, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Lehigh Valley Technologies, Inc.

Address: 514 North 12th Street, Philadelphia, PA 18102

Representative: Catherine Clark, Director, U.S. Regulatory Affairs

Telephone: (610) 782-9780 Fax: (610) 782-9781

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Oxycodone Hydrochloride Oral Solution
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

PHARMACOL. CATEGORY: Management of moderate to severe pain

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: (b) (4) 20 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __x__Rx (Schedule II) ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	1	Adequate	09/07/2010	Current with annual report and updated list of firms provided
	V			4	N/A		Meets Federal Regulations under 21 CFR, 174-186
	V			4	N/A		Meets Federal Regulations under 21 CFR, 174-186
	V			4	N/A		Meets Federal Regulations under 21 CFR, 175 105, 176 170 and 176 180
	III			4	N/A		The same syringe used under NDA 22-195 (Morphine Sulfate Oral Solution, 20 mg/mL. (b) (4) comply with (b) (4) .

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Chemistry Review Data Sheet

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 78623			Pending		
IND 78624			Pending		
NDA 21-011		Roxicodone (oxycodone hydrochloride) Tablets	Approved		On the market, the same indication.

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	200-534	Lehigh Valley	Pending NDA for Oxycodone hydrochloride capsules, 5 mg

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EES	GMP status of the manufacturing and testing facilities	Jan 6, 2010	Jun 3, 2010	Acceptable.
Pharm/Tox	Safety of impurities and excipients (flavoring)	May 23, 2006	Oct, 12, 2010	PT team recommends approval
DDMAC	Labeling	Jan 31, 2006	Pending	
EA				Waiver requested and granted; drug product already on the market
Microbiology	(b) (4) , Microbial control limits for drug product	Sep 15, 2010	Pending	Microbiology team recommends approval with post-approval agreement to develop validated method for control of *B. cepacia,* and submit PA supplement by Mar 31, 2010.

The Chemistry Review for NDA 200-535

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Oxycodone hydrochloride solution, 20 mg/mL, is recommended for **approval** from the CMC perspective, based on the agreement on microbial controls provided by the applicant (Amendments dated Oct 7, Oct 1, and Sep 28, 2010) and recommendation from the Microbiology review team (Oct 14, 2010) – refer to section I.B., below in this review. The acceptable safety of the drug substance and drug product impurities is addressed in the PharmTox reviews dated Oct 12, 2010 – for summary, refer to section II. A., below.

(b) (4)

The overall EER status for this NDA is acceptable (AC) as of Jun 3, 2010. The supporting DMFs have adequate status as of Oct 12, 2010.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Agreements

We acknowledge the acceptance criteria established for controls on microbial limits in the drug product and remind you of the agreement to submit a prior-approval supplement by Mar 31, 2011, with validated analytical method for the content of *Burkholderia cepacia* and adequate, data-reflecting regulatory specifications, as outlined in the following agreement.

1. You agree to submit the method (or methods) that will be used for the demonstration of the absence of *Burkholderia cepacia* in Oxycodone Hydrochloride Oral Solution drug product(s). You should provide sufficient data to validate the ability of the assay to detect *Burkholderia cepacia* if present, as well as document the limit(s) of detection. The USP General Chapters <1227> VALIDATION OF MICROBIAL RECOVERY FROM PHARMACOPEIAL ARTICLES and <1223> VALIDATION OF ALTERNATIVE MICROBIOLOGICAL METHODS may provide useful guidance.

The currently approved expiry period for the drug product is 24 months, (b) (4). Due to the pending development of the analytical method and acceptance criteria for *Burkholderia cepacia*, any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior-approval supplement with adequate supporting data. Note that all stability data should be carried with drug product samples retained in the container closure approved for marketing, including the child-resistant closure.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The oxycodone hydrochloride drug substance is a white crystalline powder, soluble in water and slightly soluble in alcohols. It is derived from the opioid alkaloid, thebaine and it is manufactured by (b) (4), in DEA-registered manufacturing facility in (b) (4). The manufacturing and controls are supported by DMF (b) (4), which has an acceptable status. The drug substance for the related NDA 200-534 (Oxycodone Hydrochloride Oral Capsules, 5 mg, review pending) is sourced from a different manufacturer, (b) (4).

The drug substance contains trace amounts of (b) (4) impurities, (b) (4). (b) (4) Drug substance with these specifications was used during the development and it is used for the commercial drug product. Other attributes for drug substance controls were revised several times during the course of this review, and the last version of drug substance specifications, submitted in amendment dated Oct 1, 2010 (see copy reproduced in section S.4.1 of this review), has acceptable controls for identification, assay, individual and total impurities (acceptable based on PT review dated Oct 12, 2010), water content, and residual solvents.

(b) (4) (b) (4) The 20 mg/mL drug product is a yellow, berry-flavored liquid, packaged in 30-mL white HDPE bottles with a window stripe, CR closures and heat-induction innerseal. It is supplied in an individual carton together with an accompanying (separately overwrapped) 1 mL calibrated oral syringe. The oral solution is manufactured and released by Lehigh Valley Technologies, Inc.

The originally proposed 20 mg/mL drug product was supplied with a (b) (4) closure designed to be kept in the vial solution during the use period. A change to the container closure was submitted in amendment dated Sep 8, 2010. It included change of the (b) (4) to the calibrated 1 mL oral dosing syringe, co-packaged with the vial in one carton. Since the (b) (4) was used during bioequivalence studies, the applicant provided a short bridging dose accuracy studies comparing the amount of drug product delivered with the syringe and with the (b) (4). The results are considered adequate for the proposed change in

the container closure and are discussed in the drug product container closure section of this review.

The applicant has submitted a bioavailability/bioequivalency studies for 20 mg/mL product (b) (4) [redacted] However, based on the statement from the applicant, the [redacted] was used in the bioavailability and bioequivalency studies.

Drug product controls were revised several times during the course of NDA review (five IR letters and two teleconferences with the applicant) and need additional revisions in the microbial limit controls, i.e., development of the method, method validation and acceptance criteria for the content/absence of *Burkholderia cepacia*. The proposed post-approval agreement with the applicant is based on amendments submitted on Oct 7, Oct 1, and Sep 28, 2010, and it is specified in section I.B. of this review, in accord with the recommendation from the Microbiology review team.

The currently proposed expiry period of two years is supported by the submitted stability data (revised data in submission dated Oct 1, 2010), however any further extension of the expiry period has to be achieved *via* a prior-approval (PA) supplement due to the incomplete data, specifications and method for controls of microbial limits.

B. Description of How the Drug Product is Intended to be Used

The proposed drug product is an immediate-release oral solution 20 mg/mL [redacted] of oxycodone hydrochloride in a solution of standard excipients and has pH 3- 4. For the 20 mg/mL the formulation includes citric acid, sodium citrate, sodium benzoate [redacted], D&C yellow #10, saccharin sodium, sorbitol solution [redacted] Berry Flavor [redacted], and water. The drug product is dosed by a syringe and it is used for management of moderate to severe pain [redacted]. An oral capsule formulation of oxycodone hydrochloride (5 mg) is a subject of pending NDA 200-534.

C. Basis for Approvability or Not-Approval Recommendation

The original NDA application lacked adequate data and information to assure safety and quality controls for the drug product. Five IR letters (Feb 18, Mar 5, Jul 22, Sep 23, and Oct 7, 2010) with CMC comments were forwarded to the applicant, and the major deficiencies (extractables/leachables from the [redacted], impurities, microbial limits, and stability data) were discussed during teleconferences on Jul 12, and Sep 23, 2010. The last version of Drug substance and Drug product specifications submitted on Oct 1, and Oct 7, 2010, respectively, is acceptable for the approval recommendation from the CMC perspective with a post-approval agreement to develop a validated method and specifications documenting the

absence of *Burkholderia cepacia*. This is recommended by the Microbiology review team (Review dated Oct 14, 2010). The prior-approval (PA) supplement will be submitted by Mar 31, 2010. Based on the above agreement the 20 mg/mL drug product is recommended for approval. (b) (4)

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

EUGENIA M NASHED
10/15/2010

PRASAD PERI
10/15/2010
I concur

INITIAL QUALITY ASSESSMENT

Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment

Division of Anesthesia and Analgesia Products

OND Division:	Anesthesia and Analgesia Products
NDA:	**200-534** and **200-535**
Applicant:	Lehigh Valley Technologies, Inc.
Stamp date:	December 22, 2009 and Feb 23, 2010 Amendment
PDUFA Date:	June 22, 2010
Trademark:	None
Established Name:	Oxycodone HCl
Dosage Form:	Capsules, containing 5 mg oxycodone HCl (NDA 200-534) Solution, (b) (4) 100 mg oxycodone HCl per 5 mL (NDA 200-535)
Route of Administration:	Oral
Indication:	Management of moderate to severe pain
CMC Reviewer:	Eugenia M. Nashed, Ph.D.

Pharmaceutical Assessment Lead: Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

Two NDAs are submitted as 505(b)(2) applications for oxycodone hydrochloride (oxycodone HCl), with reference to the approved drugs, Roxicodone® IR tablets, NDA 21-011 (Roxane Labs) [redacted]. Pre-IND meeting for these applications was held on 6 Dec 2007, and pre-NDA meeting correspondence took place on 31 Mar 2009, when the acceptance criteria for [redacted] impurities and extend of the required stability data were discussed, in addition to other issues.

The proposed drug products are immediate-release formulations containing oxycodone HCl for management of moderate to severe pain where the use of an opioid analgesic is appropriate. The NDA 200-534 is for hard gelatin capsules containing 5 mg of oxycodone HCl per capsule ([redacted]), and NDA 200-535 describes [redacted] 20 mg/mL (for opioid-tolerant patients) of oxycodone HCl. Both drug products are manufactured by the NDA applicant, Lehigh Valley Technologies, Inc.

The oxycodone HCl drug substance is sourced from [redacted] for NDA 200-534 (Capsules), and it is sourced from [redacted] for NDA 200-535 (Oral Solutions). The initial drug substance for capsules which was used for formulation development, clinical and primary stability batches was supported by [redacted] DMF [redacted]. This drug substance had an interim specification of [redacted].

NDA 200-534 drug product is formulated as Size #4, yellow and white hard gelatin capsules which contain a powdered blend of oxycodone HCl and several standard excipients, 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. Substantial formulation changes are noted during development.

NDA 200-535 drug product is formulated as oral solution containing, in addition to oxycodone HCl, several standard excipients, [redacted]% of sorbitol [redacted]%, USP, saccharin sodium, USP, citric acid anhydrous, USP, sodium citrate dihydrate, USP, sodium benzoate, NF, natural/artificial berry flavor [redacted] (DMF [redacted]), and [redacted] D&C Yellow #10 colorant (20 mg/mL). Formulation changes are noted during development.

Numerous CMC deficiencies were discussed during the NDA Filing meeting on Feb 18, 2010. A request regarding missing LOAs to several DMFs and lack of statement regarding BSE/TSE safety of the used gelatin was forwarded to the applicant on Feb 18, 2010. The applicant's response received by e-mail on Feb 19, 2010 (hard copy on Feb 23, 2010) is considered sufficient from the CMC perspective to file both NDAs for review. Summary of remaining CMC issues to be addressed during NDA review include additional release and stability attributes, additional stability data, compatibility of the formulations, extractables and leachables data for the container closures containing liquid formulations, acceptance criteria for impurities and PT and Micro consults.

In summary, both NDA applications are Acceptable for Filing from a CMC perspective, based on the data submitted in the original NDA and in Feb 23, 2010, amendment. CMC comments for the 74-day letter are listed in Section D of this review.

B. Review, Comments and Recommendations

Drug Substance

The drug substances manufacturing processes and controls are referenced to Drug Master Files as follows:

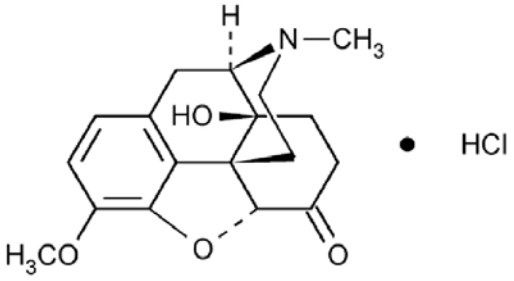
Oxycodone HCl

DMF (b) (4), (b) (4) (NDA 200-534 commercial batches only; development and stability batches were sourced from (b) (4) DMF (b) (4))

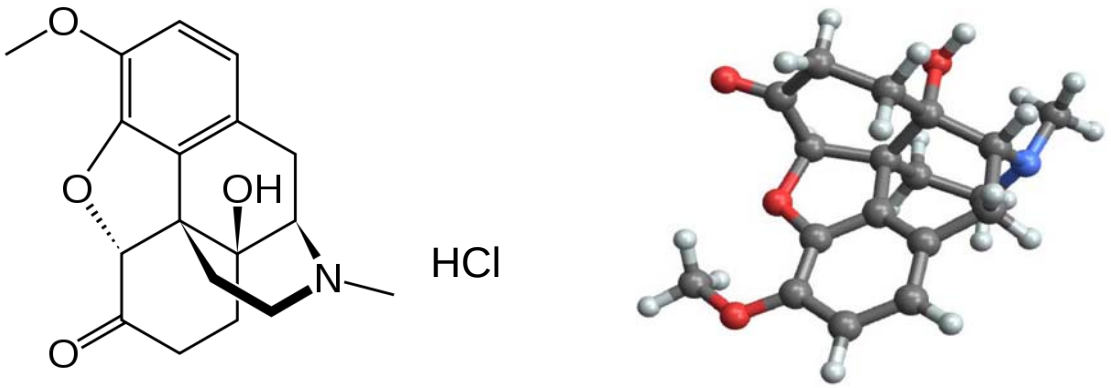
DMF (b) (4), (b) (4) (NDA 200-535)

Molecular Structure, Chemical Name, Molecular Formula and General Properties

Chemical Structure/Properties of Oxycodone Hydrochloride

Chemical Structure	
Molecular Formula	$C_{18}H_{21}NO_4 \cdot HCl$
Relative Molecular Mass	351.82

The molecule contains four chiral centers with the indicated absolute configuration (in parentheses) at C5 (R), C9 (R), C13 (S), and C14 (S). Refer to simplified 3D structure depicted below.



(5*R*,9*R*,13*S*,14*S*)-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride

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C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer will review issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the product's life-cycle:

1. The comparability of the drug substance(s) from two different suppliers, DMF (b) (4) (oxycodone HCl, (b) (4)) and DMF (b) (4) (oxycodone HCl, (b) (4)) will be reviewed and evaluated.

2. Impact of the physical properties of drug substance and adequacy of controls applied to monitor polymorphic form(s) of the drug substances will be assessed during review of both DMFs and NDAs, as any potential polymorphic conversion may influence the solubility and dissolution of the drug substance.

3. The amounts and specifications of compendial excipients in the formulation. Evaluation of the suitability of pharmacopeial specifications of excipients for drug product manufacturability, quality and performance.

4. Formulation changes during development and their impact on the quality and performance of the commercial drug products. Compatibility of the final formulation after review of the requested data.

5. In-process blend uniformity, stratified sampling and in-process content uniformity according to the FDA "Guidance for Industry: Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment".

6. The dissolution method will be evaluated for discriminatory ability and robustness, after review of the requested dissolution data.

7. Adequacy of the proposed controls for drug product, after receiving of the requested resubmission of specifications and batch analyses. Acceptability of the proposed limits for identified and unidentified impurities/degradants in the drug product. Proposed acceptance criteria will be assessed in consultation with the Toxicology Division.

8. Review of results for extractables and leachables after receiving the requested data.

9. The proposed expiration dating of 24 months in view of the submitted stability data will be assessed as per ICH Q1E.

D. Comments for 74-day Letter:

NDA 200-534

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

2. Provide data on compatibility studies for the proposed commercial drug product formulation. Alternatively, provide precise references to the appropriate sections of the US-approved reference drug product(s).

3. 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.

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

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

6. Provide updated stability data for the commercial drug product formulation to support the requested expiry period. Submit revised stability specifications, as requested for drug product above. Provide data collected according to the revised protocol for each testing interval.

NDA 200-535

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

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

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

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

5. Provide (b) (4)

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

E.

Recommendation for fileability: The NDA is recommended for filing from the CMC perspective, based on pre-NDA agreements and submitted NDA data. Data for 3 registration batches for capsules with 9 months of long term storage conditions and 6 months of accelerated storage conditions were submitted along with supportive data (up to 24 months) for older drug product batches. Also, data for 3 registration batches for each solution presentation were provided. Although additional testing attributes need to be added to the pending release and stability testing programs, the NDA is suitable for evaluation and assessment based on the current FDA and ICH guidelines for submitting CMC information for the New Drug Applications. See below, a step by step summary evaluation of the required parameters for the NDA submission.

Recommendation for Team Review: The NDA is not recommended for team review, since it is a 505(b)(2) application, the drug substances are not NMEs, the formulation does not include novel excipients and the manufacturing process for the drug product does not present unusual complexity.

Consults

Specifications for impurities will be evaluated in consultation with the Toxicology reviewer.
No statistical consult was deemed necessary. The proposed expiration dating will be evaluated during review after the update for pending stability data is submitted.

NDA Number: 200-534 and 200-535	**Supplement Number and Type:**	**Established/Proper Name:** **Oxycodone HCl Capsules** **Oxycodone HCl Solution**
Applicant: Lehigh Valley Technologies, Inc.	**Letter Date: 12/22/09**	**Stamp Date: 12/22/09**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Clarifications and communications with OC.
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	Clarifications and communications with OC.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF(s) (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF(s) (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF(s) (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF(s) (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solid Oral Dosage Form) Micro consult for (b) (4) for the solutions

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Original NDA and Amendment dated Feb 23, 2010

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2		(b) (4)		API
	2				API
	2				Capsule
	2				Container Closure
	3				Container Closure
	3				Container Closure

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		Based on data submitted in NDA and Feb 23, 2010, Amendment
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Several potential review issues are listed in Section D of the IQA, above

{See appended electronic signature page}

Eugenia Nashed, Ph.D.
Senior CMC Reviewer 02-19-2010
Division of Pre-Marketing Assessment #1, Branch #2
Office of New Drug Quality Assessment

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief 02-19-2010
Division of Pre-Marketing Assessment #1, Branch #2
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION [redacted] (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/

EUGENIA M NASHED
03/02/2010

PRASAD PERI
03/02/2010
I concur