

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201194Orig1s000**

**PHARMACOLOGY REVIEW(S)**



FDA Center for Drug Evaluation and Research  
Division of Anesthesia and Analgesia Products  
10903 New Hampshire Avenue, Silver Spring, MD 20993

**ADDENDUM TO NDA 201-194 PHARMACOLOGY TOXICOLOGY REVIEW**

**NDA number:** 201-194  
**Product:** Oxycodone Oral Solution  
**Sponsor:** VistaPharm, Inc.

**Reviewer name:** Elizabeth A. Bolan, Ph.D.  
**Division name:** Division of Anesthesia and Analgesia Products  
**Review completion date:** February 11, 2011

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**Overall Recommendation:** The VistaPharm, Inc. drug substance and drug product specifications are acceptable from a Pharmacology/Toxicology (P/T) perspective. The recommendation from P/T is that NDA 201-194 may be approved with no post-marketing studies.

**Background:** The oxycodone drug substance impurity (b)(4) contains a potentially genotoxic (b)(4) moiety and must therefore be controlled at a level of (b)(4) in the drug substance (see (b)(4) discussion below). In the original NDA, specifications of (b)(4) and (b)(4) were set for (b)(4) in the drug substance and drug product, respectively. These specifications were considered unacceptable. It was communicated to the Applicant that the acceptance specification for the drug substance must be reduced and that the stability specification for the drug product must be reduced or removed entirely, as (b)(4) is not deemed to be a drug product degradant. The drug substance specifications for (b)(4) in the DMF for oxycodone (DMF (b)(4)) were acceptable. However, in spite of numerous communications with the Applicant, VistaPharm's drug substance and drug product specifications listed in the NDA application had not been changed. On the basis of these deficiencies, the original recommendation from P/T was to not recommend approval of NDA 201-194 (See P/T review finalized on January 14, 2011).

The following comments were communicated to the Applicant:

The Applicant must reduce the drug substance acceptance specification for (b)(4) to NMT (b)(4).

The Applicant must either reduce the drug product stability specification for (b) (4) to NMT (b) (4) or remove the specification entirely if the CMC review team concludes that (b) (4) is not a degradant in this formulation.

In Amendment 9 to NDA 201-194 (January 31, 2011), the Applicant submitted updated stability specifications for the drug product with the specification for (b) (4) removed. This is considered acceptable as the Agency has previously determined that (b) (4) is a process impurity and not a drug product degradant. With this amendment, the drug product specifications for NDA 201-194 are considered acceptable from a P/T perspective.

In Amendment 9 (January 31, 2011), the Applicant also submitted updated acceptance specifications for the oxycodone drug substance. The specification for (b) (4) has been set at (b) (4) which is considered acceptable (see (b) (4) discussion below). In this amendment, the Applicant also submitted specifications for several drug substance impurities which were not included the original NDA application (Table 1). The impurity (b) (4) contains an (b) (4) moiety. It is controlled at (b) (4) in the drug substance, which is considered acceptable (Table 1, see (b) (4) discussion below). It should be noted that (b) (4) has been determined not to be an (b) (4) by our CMC group and therefore may be regulated as a typical non-genotoxic impurity. All other impurity specifications, with the exception of (b) (4), meet thresholds set by ICH Q3A and are therefore considered acceptable (Table 1). The specification for (b) (4) is set at (b) (4) by the Applicant. (b) (4), 6- $\alpha$ -oxycodol is a well-characterized human metabolite and the specification will be considered acceptable. Refer to discussion below of 6- $\alpha$ -oxycodol as a metabolite of oxycodone. With this amendment, VistaPharm's proposed acceptance specifications for drug substance impurities for NDA 201-194 are considered acceptable from a P/T perspective.

**Table 1. Oxycodone Drug Substance Impurity Specifications for NDA 201-194 (from Amendment 9): Acceptability and Rationale**

<i>Impurity</i>	<i>VistaPharm Acceptance Specification</i>	<i>Status; Rationale</i>
(b) (4)	(b) (4)	<u>Acceptable</u> ; meets ICH Q3A
(b) (4)	(b) (4)	<u>Acceptable</u> ; meets ICH Q3A
(b) (4)	(b) (4)	<u>Acceptable</u> ; meets ICH Q3A
(b) (4)	(b) (4)	<u>Acceptable</u> ; (b) (4) (see discussion below)
(b) (4)	(b) (4)	<u>Acceptable</u> ; meets ICH Q3A
(b) (4)	(b) (4)	<u>Acceptable</u> ; meets ICH Q3A
(b) (4)	(b) (4)	<u>Acceptable</u> ; see discussion below regarding acceptable levels of (b) (4)
(b) (4)	(b) (4)	<u>Acceptable</u> ; see discussion below regarding acceptable levels of (b) (4)

\*structural alert for mutagenicity

**Acceptable Thresholds for** (b) (4) s

In the original NDA, the Applicant had identified (b) (4) as a drug substance impurity and set the specification at (b) (4). The drug substance impurity (b) (4) contains an (b) (4) moiety which is a structural alert for genotoxicity. The (b) (4) moiety has been demonstrated to be reactive with DNA resulting in genotoxicity and mutagenicity (b) (4)

(b) (4) As potentially genotoxic substances present a safety concern, the Agency maintains that such substances should be tested for their genotoxic potential or reduced to acceptable levels. Current Agency policy on acceptable levels for potentially genotoxic agents is a specification to reflect NMT 1.5 mcg/day. A specification of (b) (4) would need to be set in order to meet the threshold of NMT 1.5 mcg/day for this product when a total daily intake of 100 mg of oxycodone is consumed. The Applicant has controlled (b) (4) in the drug substance with a specification of (b) (4). Although (b) (4) exceeds the specification needed to meet the NMT 1.5 mcg/day threshold typically set for potentially genotoxic substances, it represents reasonable current technological capabilities and is being considered acceptable by the Agency for drug substances containing (b) (4). However, as technological capabilities improve, ultimately the Agency is working toward reaching the NMT 1.5 mcg/day specifications for impurities that are genotoxic structural alerts.

**Six- $\alpha$ -Oxycodol as a Metabolite of Oxycodone**

A major metabolic pathway of oxycodone is *N*-demethylation to noroxycodone (Baldacci, et al., 2004). Oxycodone and noroxycodone both undergo 6-keto reduction to yield 6- $\alpha$ -oxycodol (also called 14-hydroxy dihydrocodeine) as well as 6- $\beta$ -oxycodol (Baldacci, et al., 2004). Six- $\alpha$ -oxycodol has been shown to be produced in rat and rabbit (Ishida, et al., 1982) as well as human (Wey and Thormann, 2002; Baldacci, et al., 2004; Moore, et al., 2003; Baldacci and Thormann, 2005; Lalovic, et al., 2006). Six- $\alpha$ -oxycodol and 6- $\beta$ -oxycodol have been shown to undergo further processing via glucuronidation in the human (Wey and Thormann, 2002). According to Lalovic et al, the 6- $\alpha$  oxycodol metabolite represents 6% of the total dose of oxycodone (Lalovic, et al., 2006). (b) (4)

## Reference List

Baldacci A, Caslavská J, Wey AB and Thormann W (2004) Identification of new oxycodone metabolites in human urine by capillary electrophoresis-multiple-stage ion-trap mass spectrometry. *J Chromatogr A* **1051**:273-282.

(b) (4)

Ishida T, Oguri K and Yoshimura H (1982) Determination of oxycodone metabolites in urines and feces of several mammalian species. *J Pharmacobiodyn* **5**:521-525.

Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY and Shen DD (2006) Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* **79**:461-479.

Moore KA, Ramcharitar V, Levine B and Fowler D (2003) Tentative identification of novel oxycodone metabolites in human urine. *J Anal Toxicol* **27**:346-352.

Wey AB and Thormann W (2002) Capillary electrophoresis and capillary electrophoresis-ion trap multiple-stage mass spectrometry for the differentiation and identification of oxycodone and its major metabolites in human urine. *J Chromatogr B Analyt Technol Biomed Life Sci* **770**:191-205.

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/s/  
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ELIZABETH BOLAN  
02/14/2011

RICHARD D MELLON  
02/14/2011

I concur. NDA 201-194 may be approved from the nonclinical pharmacology toxicology perspective.

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 201-194  
Supporting document/s: 000  
Applicant's letter date: Submit date: 5/4/10  
CDER stamp date: Received date: 5/4/10  
Product: Oxycodone Oral Solution  
Indication: For the relief of moderate to moderately severe pain where the use of an opioid analgesic is appropriate  
Applicant: VistaPharm, Inc.  
Review Division: Division of Anesthesia and Analgesia Products  
Reviewer: Elizabeth A. Bolan, Ph.D.  
Supervisor/Team Leader: R. Daniel Mellon, Ph.D.  
Division Director: Bob Rappaport, M.D.  
Project Manager: Dominic Chiapperino, Ph.D.

*Template Version: December 7, 2009*

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# 1 Executive Summary

## 1.1 Introduction

VistaPharm's oxycodone oral solution drug product is considered a marketed unapproved product. In response to a preIND meeting request, on August 27, 2009 the Agency provided advice to the Applicant regarding their planned NDA submission. From a nonclinical perspective, the Applicant was informed that no new toxicology studies for oxycodone drug substance would be required. However, the NDA application must provide adequate safety qualification for drug substance impurities and drug product degradants that exceed ICH qualification thresholds or have structural alerts for mutagenicity, provide adequate justification for the safety of the excipients in the drug product formulation, and provide adequate characterization of the safety of the container closure system in terms of leachable/extractable testing. The meeting was apparently cancelled by the Applicant following receipt of the preliminary responses. An IND was never submitted by the Applicant prior to NDA submission.

## 1.2 Brief Discussion of Nonclinical Findings

NDA 201-194 for Oxycodone Oral Solution, 5 mg/5 mL (VistaPharm) is being submitted via the 505(b)(2) regulatory pathway with Roxicodone (NDA 21-011) as the referenced product. Oxycodone Oral Solution, 5 mg/5 mL is currently a marketed unapproved product. The applicant is relying on the Agency's findings of safety and efficacy and the pharmacology, pharmacokinetics, and toxicology information in the label of Roxicodone. No nonclinical studies were conducted for this NDA. There are no unique nonclinical issues with this product as compared to Roxicodone or other approved immediate-release oxycodone (OC) products. The drug substance and drug product specification for (b) (4), an impurity with an (b) (4) moiety and structural alert for genotoxicity are not acceptable and must be reduced to NMT (b) (4). The excipients in this formulation are acceptable when the product is used at levels up to the maximum theoretical daily dose of OC (100 mg/day) and do not pose any unique toxicologic concerns. The container closure system is deemed acceptable in terms of leachable/extractable safety justification.

## 1.3 Recommendations

### 1.3.1 Approvability

This NDA can **NOT** be approved from a pharmacology/toxicology perspective.

### 1.3.2 Additional Non Clinical Recommendations

The Applicant must reduce the drug substance acceptance specification for (b) (4) to NMT (b) (4).

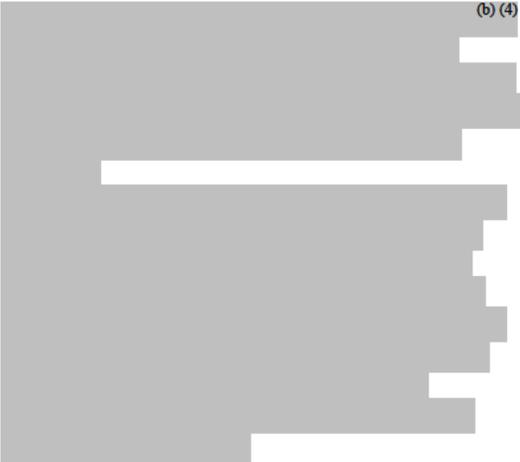
The Applicant must either reduce the drug product stability specification for (b) (4) to NMT (b) (4) or remove the specification entirely if the CMC review team concludes that (b) (4) is not a degradant in this formulation.

### 1.3.3 Labeling

The following recommendations are being proposed for the nonclinical sections of the label. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

**Table 1 Labeling Review**

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
<p><i>(from highlights section)</i>  <b>INDICATIONS AND USAGE</b>                      Oxycodone HCl Oral Solution is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.(1)</p>	<p><i>(from highlights section)</i>  <b>INDICATIONS AND USAGE</b>                      Oxycodone HCl Oral Solution is an <b>opioid agonist immediate release oral formulation of oxycodone hydrochloride</b> indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.(1)</p>	<p>The Established Pharmaceu<b>t</b>ic Class of oxycodone was added as per PLR format.</p>
<p><b>8 USE IN SPECIFIC POPULATIONS</b>  <b>8.1 Pregnancy</b>                      Teratogenic Effects</p> <p>(b) (4)</p> <p>Nonteratogenic Effects</p>	<p><del>Teratogenic Effects</del></p> <p>Category B:                      There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.</p> <p>Teratogenic Effects</p> <p>Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at</p>	<p>(b) (4)</p>

<p>Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.</p>	<p>doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a mg/m<sup>2</sup> basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m<sup>2</sup> basis), respectively was not teratogenic or embryo-fetal toxic (b) (4)</p>  <p>Nonteratogenic Effects</p> <p>Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.</p>	
<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> 	<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p><u>Carcinogenesis</u>          No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.</p>  <p><u>Mutagenesis</u>          Oxycodone hydrochloride was genotoxic in an <i>in vitro</i> mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an <i>in vitro</i> bacterial reverse mutation assay (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) or in an assay for chromosomal aberrations (<i>in vivo</i> mouse bone marrow micronucleus assay).</p> <p><u>Impairment of Fertility</u>          No animal studies to evaluate the effect of oxycodone on male or female fertility have been conducted.</p>	

## 2 Drug Information

### 2.1 Drug

Oxycodone Hydrochloride Oral Solution, 5 mg/5 mL

#### 2.1.1 CAS Registry Number (Optional)

124-90-3

#### 2.1.2 Generic Name

Oxycodone Hydrochloride Oral Solution

#### 2.1.3 Code Name

N/A

#### 2.1.4 Chemical Name

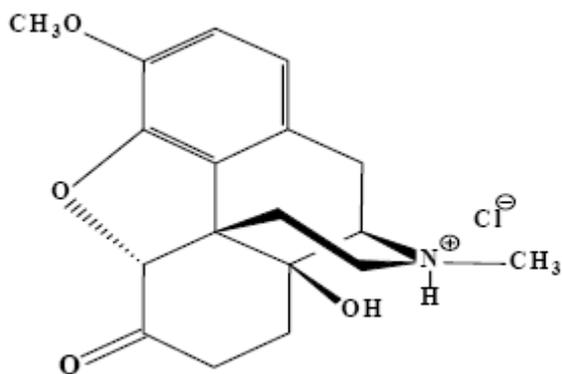
Dihydrohydroxycodeinone, 14-hydroxydihydrocodeinone, 6-deoxy-7,8-dihydro-14-hydroxy-3-O-methyl-6-oxomorphine

#### 2.1.5 Molecular Formula/Molecular Weight

$C_{18}H_{21}NO_4 \cdot HCl$ ; MW 351.83 g/mol

#### 2.1.6 Structure

*Figure 1 Structure of Oxycodone HCl*



## 2.1.7 Pharmacologic class

Opioid agonist

## 2.2 Relevant IND/s, NDA/s, and DMF/s

**Table 2 Relevant IND/s, NDA/s and DMF/s**

<b>IND/NDA/DMF</b>	<b>Drug/Compound</b>	<b>Sponsor</b>	<b>Division</b>	<b>Status</b>
NDA 21-011	Roxicodone	Xanodyne	DAAP	Approved; 505(b)(2) reference
pIND 105,754	Oxycodone oral solution, 5 mg/5 mL	VistaPharm	DAAP	Active
DMF	(b) (4)			
DMF				
DMF				

## 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

The clinical formulation of Oxycodone Oral Solution is a 5 mg/5 mL aqueous solution. The applicant is seeking approval for one low-dose strength of OC (1 mg/mL). The indication proposed for this product is relief of moderate to severe pain where the use of an opioid analgesic is appropriate. The components of the formulation and their functions are detailed in Table 3. Levels of all excipients in the formulation when the product is used at the maximum theoretical daily dose (MTDD) of OC via this formulation are acceptable; refer to Section 2.3.2 for discussion of excipients. Refer to Section 2.4 for a discussion of the MTDD of this product.

**Table 3 Oxycodone Oral Solution 5 mg/5 mL Formulation**

<b>Ingredient</b>	<b>Function</b>	<b>Amount per mL, mg</b>
Oxycodone HCl	active	1.0

Poloxamer 188	(b) (4)
Sodium benzoate	
Citric acid, anhydrous	
Glycerin Natural, (b) (4)	
Sorbitol Solution, 70%	
FD&C Red #40	
Raspberry flavor (b) (4)	

The drug product is stored in 5 mL unit dose cups and 500 mL high density polyethylene (HDPE) bottles. The Applicant has confirmed that the resins used in the manufacturer of these containers comply with 21 CFR 177.1520 and are therefore acceptable for food contact applications. As such, further studies on leachables and extractables are therefore, not necessary. From a toxicology perspective, the container closure is acceptable.

### 2.3.2 Comments on Novel Excipients

All of the excipients in the Oxycodone Oral Solution, 5 mg/5 mL formulation are found in approved drug products and are listed in the FDA Inactive Ingredients Guide (IIG; Table 4) as being present in FDA approved products at a maximum dosage greater than that proposed in this product. However, several of the excipients in the drug product will exceed levels listed in the IIG when the MTDD of OC for this product is consumed. The MTDD for this product is 100 mg/day OC (see section 2.4 for further discussion). Table 4 outlines the levels of excipients in the drug product calculated at the MTDD of OC and the basis of the acceptability of the levels. Refer to discussion of individual excipients below.

#### *Sodium benzoate*

The total daily intake of sodium benzoate would be 100 mg when this product is used at the MTDD of OC via this formulation (Table 4). This level exceeds the value listed in the IIG; however, sodium benzoate is a commonly used food additive. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated sodium benzoate and issued a Summary of Evaluations for sodium benzoate (report # INS 211; 1996) which states that the acceptable daily intake of sodium benzoate is 0-5 mg/kg body weight. For a 60 kg human, the maximum of 300 mg of sodium benzoate would be considered acceptable. Therefore, the levels of sodium benzoate (100 mg at the MTDD of OC) in this product are considered acceptable.

#### *Glycerin natural,* (b) (4)

Glycerin, also referred to as glycerol, is used as a humectant, solvent and sweetener in foods. It is considered GRAS when used in accordance with good manufacturing practice with no maximum level specified. Glycerin is currently categorized by the

American Dietetic Association as a carbohydrate. It has a caloric density similar to sucrose but has a lower glycemic index and different metabolic pathway. The total daily intake of glycerin would be 10 g when the MTDD of OC for this product is consumed and does not present any toxicologic concern (Table 4).

*Sorbitol solution, 70%*

The total daily intake of sorbitol would be 15 g (adjusted for a 70% sorbitol solution) when the MTDD of OC for this product is consumed (Table 4). This level exceeds the value listed in the IIG. Sorbitol is a sugar alcohol and is found in numerous foods as a sweetener. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of sorbitol and established an acceptable daily intake of “not specified”. Sorbitol has also been granted GRAS status without limits by FDA. Sorbitol is listed in 21 CFR §184.1835, and may be used in foods at levels not to exceed good manufacturing practices (up to 99%). The FDA requires a label statement for foods whose reasonably foreseeable consumption may result in the daily ingestion of  $\geq 50$  g of sorbitol to state that excess consumption may have a laxative effect (21CFR §184.1835). The level of sorbitol in this product is less than what could be consumed in a food product and is considered acceptable.

*FD&C Red #40*

FD&C Red #40, under 21 CFR §74.1340, may be used in drugs in amounts consistent with good manufacturing practice. No limits have been set for this coloring agent. It is found in numerous products at similar levels to this product and does not present a toxicologic concern. Therefore, the levels of FD&C Red #40 in this product are considered acceptable.

*Raspberry flavor*

Raspberry flavor (b) (4) is under DMF (b) (4) held by the (b) (4). All the components of Raspberry flavor (b) (4) are considered GRAS and therefore are considered acceptable when the maximum daily dose of OC in this product is consumed. Refer to the pharmacology/toxicology review of DMF (b) (4) submitted to DARRTs on January 13, 2011.

Levels of all excipients in the formulation of Oxycodone Oral Solution, 5 mg/5 mL when used at the MTDD of OC for this product are considered acceptable from the pharmacology/toxicology perspective and do not pose any unique toxicologic concerns.

**Table 4 Levels of Excipients in Oxycodone Oral Solution 5 mg/5 mL**

<b>Excipient</b>	<b>Amount in mg per mL of solution</b>	<b>Total Daily Intake (Amount in mg per 100 mg of oxycodone*)</b>
Poloxamer 188		(b) (4)
Sodium benzoate		
Citric acid, anhydrous		

Glycerin natural, (b) (4)	(b) (4)
Sorbitol solution, 70%	
FD&C Red #40	
Raspberry flavor (b) (4)	

\*Note that 100 mg is the maximum theoretical daily dose of IR OC products (excluding solutions intended only for opioid tolerant individuals). Maximum levels of excipients in the drug product will be calculated based on use of the product at this dose of OC.

### 2.3.3 Comments on Impurities/Degradants of Concern

#### Drug Substance Impurities

The applicant is referencing (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for the Oxycodone HCl drug substance. The applicant notes that during the course of their development program the process of manufacturing the Oxycodone HCl changed. The change included an additional (b) (4) impurity level from (b) (4). Reference is given for both DMF (b) (4) however, the to-be-marketed formulation has the specification of (b) (4) for the (b) (4).

The qualification threshold according to the ICH Q3A (R2) guidance for impurities in the drug substance for a maximum daily dose (MDD) of  $\leq 2$  g/day is 0.15% or 1 mg/day intake, whichever is lower. The applicant has identified (b) (4) as drug substance impurities and set the specifications at (b) (4) respectively (Table 5). The drug substance impurity (b) (4) contains an (b) (4) moiety which is a structural alert for genotoxicity. The (b) (4) moiety has been demonstrated to be reactive with DNA resulting in genotoxicity and mutagenicity (b) (4). As potentially genotoxic substances present a safety concern, the Agency maintains that such substances should be tested for their genotoxic potential or reduced to acceptable levels. Current Agency policy on acceptable levels for potentially genotoxic agents is a specification to reflect NMT 1.5 mcg/day. A specification of (b) (4) would need to be set in order to meet the threshold of NMT 1.5 mcg/day for this product. The applicant has controlled (b) (4) in the drug substance with a specification of (b) (4). Although (b) (4) exceeds the specification needed to meet the NMT 1.5 mcg/day threshold typically set for potentially genotoxic substances, it represents reasonable current technological capabilities and is being considered acceptable by the Agency for drug substances containing (b) (4). However, as technological capabilities improve, ultimately the Agency is working toward reaching the NMT 1.5 mcg/day specifications for impurities that are genotoxic structural alerts. The drug substance specifications in DMF (b) (4) are acceptable. However, in spite of numerous communications with the Applicant, VistaPharm's DS acceptability

specification listed in VistaPharm's application has not been changed as of the date of this review and therefore is not acceptable.

**Table 5 Drug Substance Specifications: Oxycodone HCl**

<b>Impurity</b>	<b>VistaPharm Acceptance Specification</b>	<b>Status</b>
	(b) (4)	Unacceptable as of 1/13/2011
		acceptable

Drug Product Impurities/Degradants

The qualification threshold according to the ICH Q3B (R2) guidance for impurities/degradants in the drug product for a MDD of the drug substance administered per day between 10 mg – 100 mg (MTDD of OC is 100 mg/day for this product) is 0.5% or 200 mcg TDI, whichever is lower. The Applicant has identified (b) (4) as impurities/degradants in the drug product. In spite of numerous communications with the Applicant requesting that the specification be reduced to NMT (b) (4), they have not updated the NDA as of the completion of this review. Therefore, the current specification is not acceptable and must be reduced to NMT (b) (4) or removed entirely as this impurity is not deemed to be a drug product degradant.

**Table 6 Drug Product Specifications: Oxycodone Oral Solution 5 mg/5 mL**

<b>Impurity</b>	<b>Drug product Specification</b>	<b>Status</b>
	(b) (4)	Unacceptable as of 1/13/2011
		acceptable

## 2.4 Proposed Clinical Population and Dosing Regimen

The Oxycodone Oral Solution 5 mg/5 mL drug product is a low-dose liquid formulation of OC intended for oral use in an adult population.

Determination of the maximum daily dose of oxycodone for a low-dose oral solution

The development of tolerance to the effects of opioids results in reduced effectiveness and necessitates increased dosing in order to maintain the desired therapeutic effect. Therefore, no maximum daily dose exists for opioids. The maximum theoretical daily dose (MTDD) of OC must be considered to determine the ICH guideline qualification thresholds for impurity and degradant levels as well as the acceptable levels of total amounts of excipients. The immediate release (IR) tablets and low dose strength solutions (*i.e.* 1 mg/mL) are not typically used in an opioid tolerant population therefore the MTDD is considerably lower than what would be utilized in an opioid tolerant

population with controlled release or high strength solution OC products. The Division consulted the Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE) in order to obtain a sense of the current utilization patterns and trends for low-dose immediate-release OC products to aid in their determination of a maximum theoretical daily dose for this low strength OC-containing product. Using information from SDI's Physician's Drug and Diagnosis Audit (PDDA) database, the consult summarized the dispensed prescriptions of the oral IR tablet and 5 mg/5 mL solution products by strength and daily dose prescribed by office-based physicians in an outpatient setting for years 2007 through 2009. The largest daily dose for the IR tablet was 180 mg/day which accounted for 0.3% of the written prescriptions for 2007-2009. The only daily dose reported for the 5 mg/5 mL solution was 150 mg/day which accounted for 100% of the written prescriptions for years 2007 through 2009 (See OSE consult by Rajdeep Gill dated June 23, 2010). Using the current OC prescribing data provided in the OSE consult as well as their own clinical experiences, the clinicians in DAAP have determined that a reasonable maximum theoretical daily dose of a low dose OC oral solution is 100 mg/day.

## **2.5 Regulatory Background**

NDA 201-194 is for Oxycodone Oral Solution, 5 mg/5 mL which is a marketed unapproved drug. The applicant is submitting this NDA via the 505(b)(2) pathway with Roxycodone (NDA 21-011) as the referenced product.

## **3 Studies Submitted**

### **3.1 Studies Reviewed**

No studies were submitted by the applicant.

### **3.2 Studies Not Reviewed**

No studies were submitted by the applicant.

### **3.3 Previous Reviews Referenced**

Refer to the pharmacology toxicology review for Roxycodone (NDA 21-011) by Dr. Belinda Hayes for information pertaining to sections 4 through 10 of this template.

## **4 Pharmacology**

### **4.1 Primary Pharmacology**

### **4.2 Secondary Pharmacology**

### **4.3 Safety Pharmacology**

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **5.1 PK/ADME**

### **5.2 Toxicokinetics**

## **6 General Toxicology**

### **6.1 Single-Dose Toxicity**

### **6.2 Repeat-Dose Toxicity**

## **7 Genetic Toxicology**

### **7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)**

### **7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells**

### **7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)**

### **7.4 Other Genetic Toxicity Studies**

## **8 Carcinogenicity**

## **9 Reproductive and Developmental Toxicology**

### **9.1 Fertility and Early Embryonic Development**

### **9.2 Embryonic Fetal Development**

### **9.3 Prenatal and Postnatal Development**

## **10 Special Toxicology Studies**

## **11 Integrated Summary and Safety Evaluation**

VistaPharm's Oxycodone Oral Solution 5 mg/5 mL is a marketed unapproved product. NDA 201-194 for Oxycodone Oral Solution 5 mg/5 mL is being submitted via the 505(b)(2) regulatory pathway with Roxycodone (NDA 21-011) as the referenced product. No data were submitted with this NDA. The impurities/degradants are controlled at acceptable levels in both the drug substance and drug product. The excipients used in the Oxycodone Oral Solution 5 mg/ 5mL formulation do not pose any toxicologic concerns when the product is used at levels up to the maximum theoretical daily dose of 100 mg of OC. There are no unique nonclinical issues with this product as compared to other approved immediate-release OC products. The Applicant has not provided acceptable drug substance and drug product specifications with respect to (b) (4) [REDACTED]. This was communicated to the Applicant in the 74-day letter as well as numerous email communications; however, the applicant has not revised the specifications. This is not acceptable and is deemed an approval issue.

## **12 Appendix/Attachments**

Reference List

Baldacci, A., et al. "Identification of new oxycodone metabolites in human urine by capillary electrophoresis-multiple-stage ion-trap mass spectrometry." Journal of chromatography.A 1051.1-2 (2004): 273-82.

(b) (4)

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/s/  
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ELIZABETH BOLAN  
01/14/2011

RICHARD D MELLON  
01/14/2011  
I concur.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 201-194

**NDA/BLA Number:** 201-194    **Applicant:** VistaPharm

**Stamp Date:** May 4, 2010

**Drug Name:** Oxycodone HCl    **NDA/BLA Type:** 505(b)(2)  
Oral Solution

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not Applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not Applicable
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not Applicable
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	Justification of levels of excipients based on the maximum dose of the product was not provided.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 201-194**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	Specifications for (b) (4) in the drug substance and drug product are unacceptable.
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not Applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

Comments for the 74-Day Letter

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

The development of tolerance to the effects of opioids results in reduced effectiveness and necessitates increased dosing in order to maintain the desired therapeutic effect. Therefore, no maximum daily dose exists for opioids. The maximum theoretical daily dose (MTDD) of oxycodone in your formulation must be considered to determine the ICH guideline qualification thresholds for impurity and degradant levels as well as the acceptable levels of total amounts of excipients. Provide clinical use data to establish the MTDD of oxycodone for your product.

Your NDA does not contain adequate information to justify the safety of the drug product formulation. Specifically, your NDA must include justification for the safety of the levels of each excipient when used at the MTDD of oxycodone for your product (see previous comment). Please refer to the FDA Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the NDA 201517 CDER web page at the following: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Your proposed drug substance and drug product specifications of NMT (b) (4) for (b) (4) (b) (4), an impurity that contains an (b) (4) structural alert for genotoxicity, is not adequately justified for safety. As noted in the preNDA meeting minutes, impurities with structural alerts for genotoxicity must be

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 201-194**

reduced to NMT 1.5 mcg/day or adequate safety qualification must be provided. Adequate safety qualification for this impurity must include a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

Elizabeth A. Bolan, PhD	June 30, 2010
_____ Reviewing Pharmacologist	_____ Date
R. Daniel Mellon, Ph.D.	June 30, 2010
_____ Team Leader/Supervisor	_____ Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201194	ORIG-1	VISTAPHARM INC	OXYCODONE HCL SOLUTION

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/s/

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ELIZABETH BOLAN  
06/30/2010

RICHARD D MELLON  
06/30/2010