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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**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 204031
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Product: XARTEMIS XR (Oxycodone
HCl/Acetaminophen
Extended-Release Tablets)
Indication: Management of (b) (4) acute
pain where the use of an opioid analgesic is
appropriate
Applicant: Mallinckrodt, Inc.
Review Division: Division of Anesthesia, Analgesia, and Addiction
Products
Reviewer: Elizabeth A. Bolan, PhD
Supervisor/Team Leader: R. Daniel Mellon, PhD
Division Director: Bob Rappaport, MD
Project Manager: Dominic Chiapperino, PhD

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1 Executive Summary

1.1 Introduction

Mallinckrodt has submitted NDA 204031 for COV795, a combination oxycodone/acetaminophen extended-release formulation. The product is planned to be available in one strength of 7.5/325 mg/mg oxycodone/acetaminophen, respectively. The indication sought by the Applicant is management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. The Applicant is submitting NDA 204031 via the 505(b)(2) regulatory pathway with Roxicodone (NDA 21011) and Ultracet (NDA 21123) as the referenced products. The Applicant is relying on the Agency's findings of safety and the relevant pharmacology, pharmacokinetics, and toxicology information in the labels of the referenced products and on published literature. No new nonclinical studies with oxycodone or acetaminophen or the combination were required for this NDA. The excipients in the formulation can be found in higher amounts in approved chronic use drug products and do not pose any novel toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. There are no unique nonclinical issues with this product as compared to other oral formulations of its individual components, oxycodone and acetaminophen.

1.2 Brief Discussion of Nonclinical Findings

No new toxicology studies with oxycodone or acetaminophen were required for or submitted with NDA 204031.

1.3 Recommendations

1.3.1 Approvability

The recommendation from pharmacology/toxicology is that NDA 204031 be approved with no post-marketing studies and upon agreement on the proposed drug product labeling.

1.3.2 Additional Non Clinical Recommendations

There are no additional nonclinical recommendations for NDA 204031.

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 reviewApplicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
<i>(from highlights section)</i> 1. INDICATIONS AND USAGE	<i>(from highlights section)</i> 1. INDICATIONS AND USAGE	The Established

<p>(b) (4)</p>	<p>XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for the management of (b) (4) pain where use of an opioid analgesic is appropriate. (1)</p>	<p>Pharmacologic Class (EPC) of OC was added as per PLR format. Acetaminophen (APAP) does not have an EPC so it was not included.</p>
	<p>USE IN SPECIFIC POPULATIONS</p> <ul style="list-style-type: none"> • Pregnancy: Based on animal data, may cause fetal harm. (8.1) 	<p>As per the Maternal Health Team pregnancy labeling initiative, the standard language for a Pregnancy Category (PC) C drug was added to the Highlights section. Oxycodone single-entity products are designated PC B and oral APAP does not have a PC at this time. Since the combination of OC and APAP has not been studied this product should be designated a PC C.</p>
<p>7.4. Mixed Agonist/Antagonist Opioid Analgesics Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with (b) (4) opioid agonist analgesic (b) (4) XARTEMIS.</p>	<p>7.4. Mixed Agonist/Antagonist Opioid Analgesics Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with an (b) (4) opioid agonist analgesic such as XARTEMIS XR.</p>	<p>The descriptor (b) (4) was removed because it is unclear what (b) (4) means in a pharmacologic sense.</p>
<p>8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy <i>Pregnancy Category C</i> (b) (4) There have been no adequate and well-controlled studies of XARTEMIS in pregnant women. (b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy</p> <p>Pregnancy Category C Risk Summary (b) (4) There are (b) (4) no adequate and well-controlled studies of XARTEMIS XR tablets or oxycodone/acetaminophen in pregnant women. (b) (4)</p> <p>Epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital</p>	<p>The Applicant's proposed labeling for OC in this section is from the current Roxycodone label.</p> <p>The summary of the human APAP data from the literature will be reviewed and edited by the MHT. The text inserted here is from a previous literature</p>

<p>(b) (4)</p>	<p>malformations. No data exist for oxycodone use in pregnancy but neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss. No reproductive or developmental studies in animals were conducted with the combination of oxycodone and acetaminophen. The following data are based on findings from studies performed with the individual components. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation. Reproductive studies in rats and rabbits with doses of oxycodone greater than clinical doses did not show any teratogenic or embryo-fetal toxic effects. (b) (4)</p> <p><u>Human Data</u> Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery. Two large population based studies have evaluated the safety of acetaminophen in pregnant women during the first trimester; neither study showed an increased risk of developing fetal abnormalities.</p>	<p>review.</p> <p>The summary of the nonclinical APAP data from the literature is from a general literature review conducted by R. Daniel Mellon. This review is included as Appendix 1.</p> <p>The addition of an overall risk summary statement was added to comply with the Maternal Health Team's Pregnancy Labeling and Lactation Rule initiative and as per OND current labeling recommendations. In addition, to comply with this initiative, the information in Section 8.1 was reorganized. The headings (b) (4) were deleted and the information was reorganized into Human Data and Animal Data sections.</p>
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<p>(b) (4)</p>	<p>(b) (4)</p> <p><u>Animal Data</u> No reproductive or developmental studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.</p> <p>Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times (b) (4) the maximum human daily dose (MHDD) of 4 grams/day based on a body surface area comparison (b) (4) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations (b) (4).</p> <p>When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison. In a continuous breeding study, pregnant mice (b) (4) received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating</p>	<p>This sentence was deleted because it duplicates one of the Burdan papers already described in the previous paragraph (see Appendix 1)</p> <p>The findings from the Neto paper described in Dr. Mellon's literature review were added (Neto, et al., 2004).</p>
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	<p>pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.</p> <p>(b) (4)</p> <p>Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults based on a body surface area comparison (b) (4) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg based on body surface area comparison), it was non teratogenic or embryo-fetal toxic.</p>	
<p>12. CLINICAL PHARMACOLOGY 12.1. Mechanism of Action Oxycodone HCl is (b) (4) opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all (b) (4) opioid agonists, there is no ceiling effect to analgesia.</p>	<p>12. CLINICAL PHARMACOLOGY 12.1. Mechanism of Action Oxycodone HCl is an (b) (4) opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all (b) (4) full opioid agonists, there is no ceiling effect to analgesia.</p>	<p>The words (b) (4) were removed. See above for rationale.</p>
<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenesis</i></p> <p>(b) (4)</p> <p>Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of</p>	<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>No carcinogenicity, mutagenicity, or fertility studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.</p> <p><u>Carcinogenesis</u> No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.</p> <p>(b) (4)</p>	<p>The Applicant's proposed labeling for OC in this section is from the current Roxicodone label.</p> <p>The APAP data described in the Applicant's proposed labeling for this section are from the literature.</p>

<p>carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.2-1.4 times the MHDD, (b) (4)</p>	<p>(b) (4)</p> <p>Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.2-1.4 times the MHDD, based on a body surface area comparison (b) (4)</p>	<p>(b) (4)</p>
<p><u>Mutagenesis</u></p> <p>(b) (4)</p> <p>Oxycodone hydrochloride was genotoxic in an in vitro mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) or in an assay for chromosomal aberrations (in vivo mouse bone marrow micronucleus assay). Acetaminophen was not mutagenic in the bacterial reverse mutation assay (b) (4)</p> <p>In contrast, acetaminophen tested positive (b) (4)</p> <p>In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on (b) (4)). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on (b) (4)), suggesting a threshold effect. (b) (4)</p>	<p><u>Mutagenesis</u></p> <p>Oxycodone hydrochloride was genotoxic in an in vitro mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) or in an assay for chromosomal aberrations (in vivo mouse bone marrow micronucleus assay). Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test) (b) (4). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges and chromosomal aberrations in in vitro assays using Chinese hamster ovary cells.</p>	<p>(b) (4)</p>
<p><u>Impairment of Fertility</u></p> <p>(b) (4)</p> <p>In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of</p>	<p>In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). (b) (4)</p>	<p>(b) (4)</p>

<p>acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on (b) (4)) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing. Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on (b) (4)) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.</p>	<p>(b) (4)</p> <p>—In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison (b) (4)), suggesting a threshold effect. (b) (4)</p> <p>Impairment of Fertility No animal studies to evaluate the effect of oxycodone on male or female fertility have been conducted.</p> <p>Oxycodone</p> <p>(b) (4)</p> <p>In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface comparison (b) (4)) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.</p> <p>Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison (b) (4)) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.</p>	
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2 Drug Information

2.1 Drug

XARTEMIS (code name COV795) contains two active ingredients, oxycodone HCl and acetaminophen

Oxycodone Hydrochloride

CAS Registry Number: 124-90-3

Generic Name: Oxycodone hydrochloride

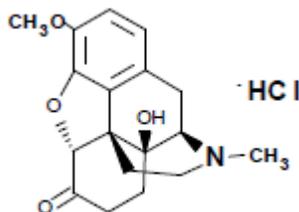
Code Name: N/A

Chemical Name: (5 α)-14-hydroxy-17-methyl-3-(methoxy)-4,5-epoxymorphinan-6-one

Molecular Formula/Molecular Weight: C₁₈H₂₁NO₄•HCl; MW 351.83 g/mol

Structure or Biochemical Description:

Figure 1 Structure of oxycodone hydrochloride



Pharmacologic Class: Opioid agonist (Established Pharmacologic Class)

Acetaminophen

CAS Registry Number: 103-90-2

Generic Name: Acetaminophen

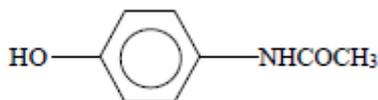
Code Name: APAP

Chemical Name: N-acetyl-p-aminophenol

Molecular Formula/Molecular Weight: C₈H₉NO₂; MW 151.16 g/mol

Structure:

Figure 2 Structure of acetaminophen



Pharmacologic Class: Non-opioid, non-salicylate analgesic (no Established Pharmacologic Class exists for acetaminophen)

2.2 Relevant INDs, NDAs, and DMFs

Table 2 Relevant INDs, NDAs, and DMFs

<i>IND/NDA/DMF</i>	<i>Drug/Compound</i>	<i>Sponsor</i>	<i>Division</i>	<i>Status</i>
IND 104702	COV795	Mallinckrodt	DAAAP	Active
NDA 21011	Roxicodone	Mallinckrodt	DAAAP	Approved, 505(b)(2) reference for oxycodone
NDA 21123	Ultracet	Janssen	DAAAP	Approved, 505(b)(2) reference for acetaminophen
DMF 6930	Oxycodone HCl	Mallinckrodt	ONDQA	Acceptable
DMF 5326	Acetaminophen	Mallinckrodt	ONDQA	Acceptable
DMF (b) (4)	(b) (4)	(b) (4)	ONDQA	Acceptable

2.3 Drug Formulation

COV795 is a multilayer extended-release formulation of oxycodone hydrochloride (OC) and acetaminophen (APAP) which is intended for twice daily dosing. The Applicant is seeking approval for one strength of COV795 (7.5 mg OC/325 mg APAP). The indication sought for this product is (b) (4) acute pain where the use of an opioid analgesic is appropriate. The Applicant purports abuse-deterrent properties of the COV795 product due to its resistance to crushing/pulverizing as well as resistance to extraction and injection (i.e., a gel is formed that cannot be injected). Refer to the Controlled Substance Staff review for assessment of the abuse-deterrent characteristics.

The product is comprised of an immediate-release layer and an extended-release layer. The immediate-release layer contains (b) (4)% of the total OC dose and (b) (4)% of the total APAP dose and the extended-release layer contains (b) (4)% of the total OC dose and (b) (4)% of the total APAP dose. The quantitative composition of each layer of COV795 and function of each component is presented in Table 3. The acceptability and rationale of the total daily intake of each excipient when the maximum daily dose of this product is consumed is detailed in Table 4. Refer to Section 2.6 for a discussion of the maximum daily dose (MDD) of this product.

Table 3 Quantitative composition of COV795 (reproduced from NDA)

IR Layer							
Ingredient	Grade	Role	mg in Tablet	w/w %			
Oxycodone HCl ¹	USP	Active	1.875	0.197%			
Acetaminophen	USP	Active	162.500	17.073%			
Hydroxypropyl Cellulose (b) (4)	NF			(b) (4)			
Microcrystalline Cellulose (b) (4)	NF						
Croscarmellose Sodium (b) (4)	NF						
Colloidal Silicon Dioxide (b) (4)	NF						
Magnesium Stearate	NF						
Pregelatinized Starch (b) (4)	NF						
Citric Acid Anhydrous Powder	USP						
Edetate Disodium	USP						
(b) (4)							
Polyethylene Oxide (Polyox (b) (4) molecular weight = (b) (4)	NF				Controlled Release Polymer		(b) (4)
(b) (4)							

Table 4 Acceptability of levels of excipient for COV795

<i>Ingredient</i>	<i>Total mg/tablet</i>	<i>Total mg at MDD of COV795</i>	<i>Acceptable? (Rationale)</i>
Hydroxypropyl cellulose (b) (4)			Yes (IID)
Microcrystalline cellulose (b) (4)			Yes (IID)
Croscarmellose sodium			Yes (IID)
Colloidal silicon dioxide			Yes (IID)
Magnesium stearate			Yes (IID)
Pregelatinized starch			Yes (IID)
Citric acid, anhydrous powder			Yes (IID)
Edatate disodium			Yes (IID)
Polyethylene oxide (Polyox) (b) (4)			Yes (IID)
(b) (4)			Yes (IID*)

IID= FDA Inactive Ingredients Database

(b) (4)

2.4 Comments on Novel Excipients

All of the excipients, with the exception of (b) (4), are listed in the FDA Inactive Ingredients Database (IID; Table 4) and are used in approved chronic drug products at levels greater than those in COV795 when calculated for the MDD of APAP. (b) (4) is used as part of the (b) (4) on the drug product and is not listed in the IID. The Applicant has referenced the DMF (b) (4) for (b) (4). The individual components of (b) (4) are listed in Table 5 (NOTE: These are proprietary data and must be redacted for public postings). The individual components of (b) (4) all can be found in the IID and are used in approved chronic drug products at levels greater than those for COV795 when calculated for the MDD of the product.

Table 5 Components of (b) (4)

<i>Ingredient</i>	<i>w/w (%)</i>
(b) (4)	

2.5 Comments on Impurities/Degradants of Concern

Oxycodone Drug Substance Impurities

The MDD of the OC component of this product is 90 mg (see Determination of Maximum Daily Dose in Section 2.6). The qualification threshold according to ICH Q3A(R2) for a MDD of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant is referencing Mallinckrodt’s DMF 6930 for the oxycodone hydrochloride drug substance. The drug substance impurity specifications are presented in the table below.

The drug substance impurities 14-hydroxycodeinone (14-HC) and codeinone each contain an (b) (4) which is a structural alert for genotoxicity. The (b) (4) has been demonstrated to be reactive with DNA resulting in genotoxicity and mutagenicity (Eder E, et al., 1990; Eder E, et al., 1993). 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. As recommended in the December 2008 Draft FDA Guidance for Industry entitled “Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches”, acceptable levels for potentially genotoxic agents is NMT 1.5 mcg/day. The DMF holder for the oxycodone hydrochloride drug substance has shown that 14-HC and codeinone are qualified for genotoxic potential. The studies as well as the formal reviews are in DMF 6930. Since codeinone and 14-HC have been deemed non-genotoxic, acceptable levels of the impurities for DMF 6930 will be based on specifications as per ICH Q3A(R2) and ICH Q3B(R2) for levels of an ordinary non-genotoxic impurity. The current specifications for codeinone and 14-HC proposed by the Applicant for the drug substance are acceptable (Table 6).

The specifications for 6-oxycodol and noroxycodone exceed the thresholds set by ICH Q3A(R2) (Table 6). However, both 6-oxycodol and noroxycodone have been shown to be human metabolites of OC. The major metabolic pathway of OC is (b) (4) which accounts for (b) (4) % of the OC dose (b) (4). Oxycodone also undergoes (b) (4) reduction to yield (b) (4). The threshold set for qualification of impurities according to ICH Q3A(R2) is 0.15%. The Applicant is proposing specifications of (b) (4) % and (b) (4) % for 6-oxycodol and noroxycodone, respectively. Since 6-oxycodol and noroxycodone are produced in the body at levels much greater than the specifications proposed, the specifications can be considered acceptable from a pharmacology/toxicology perspective.

All other impurities in the OC drug substance meet qualification thresholds as per ICH Q3A(R2). The drug substance specifications for all of the impurities in the OC drug substance, as outlined in Table 6 are acceptable from the pharmacology toxicology perspective.

Table 6 Drug substance specifications: oxycodone HCl

<i>Impurity</i>	<i>Acceptance Specification</i>	<i>Acceptable?</i>
Oxymorphone	(b) (4)	Yes

(b) (4)	(b) (4)	Yes
		Yes
6-Oxycodol*		Yes
14-Hydroxycodone**		Yes
Hydrocodone		Yes
Codeinone**		Yes
Noroxycodone*		Yes

*human metabolite

**structural alert for mutagenicity

Acetaminophen Drug Substance Impurities

The MDD of the APAP component of this product is 4 g (see Determination of Maximum Daily Dose in Section 2.6). The qualification threshold according to ICH Q3A(R2) for a MDD of >2 g/day is 0.05%. Mallinckrodt’s DMF 5326 is being referenced for the APAP drug substance. The Applicant has identified (b) (4) as drug substance impurities and set the specifications at (b) (4)%, respectively (Table 7). The impurities (b) (4) both contain a structural alert for mutagenicity. Drug Master File 5326 contains the same specifications for these impurities and has been previously found adequate by the Agency for numerous APAP drug products. Therefore, although the specifications for these drug substance impurities would exceed the proposed NMT 1.5 mcg/day threshold for potentially genotoxic substances, based on the long history of use in approved APAP products, this will not be deemed a deficiency in the DMF. The drug substance specifications in Table 7 for the impurities in the APAP drug substance are acceptable from the pharmacology toxicology perspective.

Table 7 Drug substance specifications: acetaminophen

(b) (4)	Acceptance Specification	Acceptable?
(b) (4)	(b) (4)	Yes
		Yes

Drug Product Impurities/Degradants

The drug product is comprised of two active ingredients that have different MDDs. The MDD for the OC component of this product is 90 mg due to the presence of the APAP in this drug product combination. The qualification threshold according to ICH Q3B(R2) for a MDD of a drug substance administered per day between 10 mg – 100 mg is 0.5% or 200 mcg total daily intake (TDI), whichever is lower. The MDD for the APAP component of this product is 4 g. The qualification threshold according to ICH Q3B(R2) for a MDD of a drug substance administered per day >2 g is 0.15%.

The Applicant has set drug product stability specifications for (b) (4), Related Substance (b) (4) and (b) (4) (Table 8). The source of the drug product degradant, the stability specifications, and the acceptability of the specifications are presented in the table below. Related Substance (b) (4) has been identified as (b) (4)

(b) (4)

and the structure is shown in Figure 3. The specifications for the OC-derived degradants are below the qualification thresholds set by ICH Q3B(R2) and are considered acceptable from the pharmacology toxicology perspective.

As noted previously in this review, (b) (4) contains a structural alert for mutagenicity. Although the stability specification set by the Applicant of (b) (4) % would exceed the NMT 1.5 mcg/day threshold for potentially genotoxic compounds, it is within the specification of the referenced product, Ultracet, and it is in compliance with the requirements in the USP monograph titled “Acetaminophen with Tramadol Hydrochloride Tablets.” The stability specification of (b) (4) % for (b) (4) is considered acceptable from the pharmacology toxicology perspective.

Table 8 Drug product stability specifications for COV795

<i>Source</i>	<i>Impurity/Degradant</i>	<i>Specification</i>	<i>Acceptable?</i>
Oxycodone		(b) (4)	Yes
			Yes
APAP			Yes

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant plans to market one strength of COV795 (7.5 mg OC and 325 mg APAP). The product is intended to be dosed at two tablets twice daily for a total daily dose of 30 mg OC and 1300 mg APAP. The product will be labeled for acute use only. The maximum daily dose of acetaminophen for prescription products is 4 g. Based on the maximum dose of 4 g for acetaminophen in this product, 12 tablets of COV795 could be consumed. For 12 tablets, the maximum daily dose of the oxycodone component of COV795 would be 90 mg.

2.7 Regulatory Background

The IND for COV795 (IND 104702) was originally submitted in 2010. The proposed clinical PK/BA protocols were allowed to proceed. At the time of the safety meeting the formulation was not finalized and the strengths under development were (b) (4)

The Division provided written responses as well as non-hold comments to the Sponsor. The responses and comments from pharmacology toxicology included recommendations on the acceptable maximum daily dose of the product (based on the MDD of 4 g for acetaminophen), and comments regarding acceptable levels or qualification of excipients and impurities/degradants. It was also noted that if the levels of OC and APAP were below those of the referenced products for the use of this product no toxicology studies would be required for the two active ingredients. On January 13, 2011, the Agency announced that drug manufacturers must limit the strength of APAP in prescription drug products to 325 mg per tablet, capsule, or other dosage unit¹. In October of 2011 written responses were provided to the Sponsor in lieu of an “End of Phase 1/Pre-Phase 3” meeting. The Division provided guidance regarding the appropriate 505(b)(2) references, product labeling for the nonclinical sections of the label and reiterated the comments on impurities and excipients. The Division also re-confirmed that no nonclinical toxicology studies would be needed for the two active ingredients. A Pre-NDA meeting with the Sponsor was held in December of 2012. The Sponsor confirmed that they plan to market a 7.5 mg OC/325 mg APAP formulation intended to be dosed at two tablets twice daily. No nonclinical issues were discussed at the Pre-NDA meeting. In May of 2013, NDA 204031 for COV795 was submitted via the 505(b)(2) pathway with Roxicodone (NDA 21011) and Ultracet (NDA 21123) as the referenced products.

3 Studies Submitted

3.1 Studies Reviewed

Table 9 Studies reviewed

¹ See Federal Register 76(10):2691-2697.

Study Title	Study Report #	EDR Location
Fluoroscopic Evaluation of Gastrointestinal Transit and Erosion of Oxycodone HCl/ APAP Gastroretentive Dosage Form in Beagle Dogs (non-GLP)	IAC-983	4.2.1.3
Pharmacokinetic Evaluation of Oxycodone HCl/Acetaminophen (ER Formulations) Following a Single Oral Dose in Beagle Dogs (non-GLP)	0130/09/131-E	4.2.2.2
(b) (4) Assessment	1500-13-003	4.2.3.7.7
Related Substance (b) (4) Assessment	1500-13-005	4.2.3.7.7

3.2 Studies Not Reviewed

All studies submitted were reviewed.

3.3 Previous Reviews Referenced

No previous reviews have been referenced.

4 Pharmacology

4.1 Primary Pharmacology

Oxycodone is a semisynthetic opioid with highest affinity for the mu opioid receptor but it also shows weak affinity for the kappa 2 opioid receptor. It is thought that OC exerts its primary pharmacodynamic effect of analgesia through activation of the mu opioid receptor. Acetaminophen is an analgesic and antipyretic with an exact mechanism that is not completely understood. Extensive clinical experience exists with OC and APAP, both as individual compounds, and as the combination.

4.2 Secondary Pharmacology

The secondary pharmacologic effects of mu opioid agonists such as OC include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility, and physical dependence.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

Fluoroscopic Evaluation of Gastrointestinal Transit and Erosion of Oxycodone HCl/APAP Gastroretentive Dosage Form in Beagle Dogs (Study IAC-983)

Gastrointestinal transit and tablet erosion of four different formulations of OC/APAP were assessed in beagle dogs in a non-GLP study. The test formulations included two different strengths of OC/APAP (15 mg OC/500 mg APAP and 30 mg OC/500 mg APAP) and two formulations with 6- or 8-hour release rates for each strength. Other than the release rate time (i.e., 6 or 8 hours) no details on the exact formulations used were provided. The amount of OC in the tablet seemed to have an effect on erosion (Table 10). Within the same formulation, the tablets with 30 mg OC had about a 2 hour increase in erosion time as compared to tablets containing 15 mg OC. No gastrointestinal transit endpoints were measured in this study. This study was conducted early in product development and was not designed to support the safety of the to-be-marketed formulation of COV795.

Table 10 Early formulation tablet erosion time in dogs

Dog #	Tablet Erosion Time (hrs)			
	15/500	15/500	30/500	30/500
	6 hr tablet	8 hr tablet	6 hr tablet	8 hr tablet
1	3.25	7.25	7.25	7.75
2	3.00	7.25	4.25	9.25
3	5.25	6.75	7.25	8.25
4	4.75	6.25	7.75	8.75
5	3.75	4.75	6.75	7.25
Mean ± SD	4.00 ± 0.97	6.45 ± 1.04	6.65 ± 1.39	8.25 ± 0.79

Pharmacokinetic Evaluation of Oxycodone HCl/Acetaminophen (ER Formulations) Following a Single Oral Dose in Beagle Dogs (Study 0130/09/131-E)

This non-GLP study evaluated the pharmacokinetic profile of five different prototype formulations of COV795 after single doses in beagle dogs after a single oral administration. The formulations contained 15 or 30 mg OC with 500 mg APAP. The levels of excipients in each formulation were varied in order to provide different release characteristics. Quantitative composition of each formulation was provided for this study. Percocet (7.5 mg OC/325 mg APAP) was used as the reference compound. This study was conducted early in product development in order to identify which of the

prototype formulations possessed the most favorable PK attributes. Since this study was not designed to support the safety or define the PK profile of the to-be-marketed formulation of COV795, it will not be described in further detail in this review.

6 General Toxicology

No general toxicology studies were needed to support the safety of either of the active ingredients or any of the components of the formulation.

7 Genetic Toxicology

The summary of the genetic toxicology studies conducted with the two active ingredients are detailed in the product labels of the referenced products and will be used for the product labeling in this product. All of the genetic toxicology studies described in the labels of the referenced products are from the literature.

8 Carcinogenicity

No carcinogenicity studies have been conducted for OC. The findings from the mouse and rat carcinogenicity studies with APAP, conducted by the National Toxicology Program, will be included in the product label.

9 Reproductive and Developmental Toxicology

The summary of reproductive and developmental toxicology studies conducted with the two active ingredients are detailed in the product labels of the referenced products and will be used for the product labeling in this product. As per the Maternal Health Team pregnancy labeling initiative, a Risk Summary was added to the Pregnancy section of the label and the information in the section was reorganized (refer to labeling review table for details; Table 1).

10 Special Toxicology Studies

No special toxicology studies were conducted.

11 Integrated Summary and Safety Evaluation

Mallinckrodt's NDA 204031 for COV795 is being submitted via the 505(b)(2) regulatory pathway with Roxicodone (NDA 21011) and Ultracet (NDA 21123) as the referenced products. No toxicology data for either active ingredient were required or submitted with this NDA. The impurities/degradants are controlled at acceptable levels in both the drug substances and the drug product. The excipients used in the COV795 formulation do not pose any toxicologic concerns when the product is used at levels up to the

maximum theoretical daily dose of 4 g of APAP. There are no unique nonclinical issues with this product as compared to other approved OC/APAP combination products.

Reference List

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- Neto JA, Oliveira-Filho RM, Simoes MJ, Soares JM, Jr. and Kulay L, Jr. (2004) Long-term acetaminophen (paracetamol) treatment causes liver and kidney ultra-structural changes during rat pregnancy. *Clin Exp Obstet Gynecol* **31**:221-224.

12 Appendix 1

Nonclinical Recommendations for Acetaminophen Rx Labeling

The following labeling recommendations for acetaminophen are based upon a review of the literature completed by R. Daniel Mellon, Ph.D.

Recommended Labeling	Rationale/Comment
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy <i>Pregnancy Category C</i></p> <p>[Human data to be provided by Maternal Health Review Team]</p>	<p>The Agency has not officially assigned a pregnancy category for a single entity oral acetaminophen drug product. Based on the existing animal data, a Pregnancy Category C would be appropriate. However, as per 21CFR§201.57 if animal studies demonstrated adverse effects (other than decrease in fertility) but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus then the drug may be given a Pregnancy Category B with appropriate CFR language.</p>
<p>Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations.</p>	<p>The statement regarding bone effects in the rat model represents collective review of the data reported in the studies from Burdan (2000, 2001, and 2003).</p>
<p>When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.</p>	<p>These rat data regarding liver and kidney toxicity are from Neto et al (2004).</p>
<p>In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0%</p>	<p>The mouse data are from the NTP reproductive toxicology study as</p>

Recommended Labeling	Rationale/Comment
<p>acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.</p>	<p>summarized by Reel et al. (1992).</p>
<p>13 NONCLINICAL TOXICOLOGY</p>	
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><u>Carcinogenesis.</u> Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).</p>	<p>Based on current CDER ECAC standards, the mononuclear cell leukemia findings were deemed significant. However, the ECAC concluded that the finding is considered to have limited relevance to humans. We elected to leave the “equivocal” statement in the labeling, as that is what the NTP concluded at the time and is how the results were described in the study report.</p>
<p><u>Mutagenesis.</u> Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges</p>	<p>Findings from the Ames and in vitro chromosomal aberrations assays are from the studies conducted by the NTP. Although there are several studies in the literature that suggest the same</p>

Recommended Labeling	Rationale/Comment
<p>and chromosomal aberrations in in vitro assays using Chinese hamster ovary cells.</p> <p>In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.</p>	<p>conclusion, the NTP studies are the most definitive studies and result in the same basic message.</p> <p>The NTP has not conducted an in vivo assay for chromosomal damage. There are, however, numerous reports, as summarized in several articles (Rannug, et al., 1995; Bergman, et al., 1996) that demonstrate positive findings for clastogenicity in both animals and humans. The summary article (Bergman et al. 1996) suggests that there should be a threshold for these effects and that they likely occur at hepatotoxic doses. Definitive concurrence with such a conclusion would require careful evaluation of the underlying data that are not available to the Agency. The proposed labeling reflects the results for the pivotal in vivo study described in the Bergman review. Since the data are consistent with the carcinogenicity study results, and the study was apparently completed for the German regulatory authorities, the reported results will be included in product labeling.</p>
<p><u>Impairment of fertility.</u> In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this</p>	<p>To date, the results of the fertility endpoints from Reel et al. (1992) serve as the primary data on fertility.</p>

Recommended Labeling	Rationale/Comment
<p>dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.</p> <p>Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.</p>	<p>The statement regarding testicular findings is derived from studies in rats by Boyd and Hogan (1968) and Jacqueson et al (1984) which reported decreased testicular weights and spermatogenesis following dosing of acetaminophen at 1.2 times the MHDD for longer than 30-days.</p> <p>There are data in the rat reporting effects on sexual behavior, sperm parameters, early implantation, and fertility at doses that are also only 1.2 fold the maximum human dose (Ratnasooriya and Jayakody, 2000).</p> <p>Ultrastructural changes in the testes have been reported after a single dose of oral APAP (1.6 times the MHDD) to the male rat by Yano et al. (2002).</p>

Genetic Toxicology of APAP. There are numerous studies in the literature that report positive genotoxicity findings for acetaminophen. As summarized in one review article of the genotoxic effects of acetaminophen (Rannug, et al., 1995), “[a]n overall evaluation of the data indicates that genotoxic effects of paracetamol contribute to the total burden of genetic damage observed in humans.” Given the widespread use of acetaminophen, careful consideration of these findings must be made in order to provide as accurate information as possible for product labeling.

The United States National Toxicology Program (NTP) has conducted in vitro mutagenicity and clastogenicity studies on APAP (National Toxicology Program, 1993). The results of the NTP studies indicate that acetaminophen tests negative as a mutagen; however, it tests positive as a clastogen in vitro (induced sister chromatid exchanges and chromosomal aberrations in CHO cells). These data are available to the public, employed current protocols and were conducted in accordance with Good Laboratory Practices (GLPs). These findings also should be included in product labeling. Although there are numerous published studies that support the conclusion that APAP is clastogenic in vitro (Ibrulj, et al., 2007), the results of the NTP studies provide adequate data to support such a statement in the product labeling.

As per current standards, positive in vitro clastogenicity results must be further assessed via an adequate in vivo study which can also provide information with respect to a potential No Observed Effect Level (NOEL) for clastogenicity. The NTP has not conducted an in vivo assay for clastogenicity, such as the micronucleus assay. Although there are many references to in vivo clastogenicity studies in the literature (for reviews see (Rannug, et al., 1995; Bergman, et al., 1996)), the cited studies that would most closely resemble current study protocols are not publically available. However, as results from in vivo studies provide data regarding a potential threshold for clastogenicity, results from adequate in vivo studies should also be included in the product labeling.

Shortly after the Rannug article was published, three European Regulators (Medical Products Agency in Sweden, Federal Institute for Drugs and Medical Devices in Germany and Medicines Control Authority in Norway) published a second review on the subject of the genotoxicity and carcinogenicity of acetaminophen (Bergman, et al., 1996). This summary review cites several studies that were apparently conducted at the request of the German regulatory authorities to more definitively characterize the in vivo clastogenic potential of acetaminophen. These original studies are not available as

(b) (4)
However, according to Bergman, they were published by (b) (4).
(b) (4). This citation was obtained by the review team and determined to be an abstract of a presentation. As this reference did not provide actual data, it normally would not be used to inform product labeling. Bergman et al. conclude that there is “convincing evidence that genotoxic effects of paracetamol appear only at dosages inducing pronounced liver and bone marrow toxicity and that the threshold level for genotoxicity is not reached at therapeutic dosages.” The Bergman paper conclusion that the genotoxic effects of the acetaminophen only occur at doses that exceed the hepatotoxic doses in the rat model is illustrated in the diagram below, reproduced from that article.

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Collectively the existing genotoxicity data support the conclusion that acetaminophen is clastogenic, the effect is dose-dependent, and a NOEL can be obtained that provides an apparent safety margin based on body surface area comparisons. Ideally, a safety margin would be based on exposure data, and therefore, if at all possible, the pivotal study reports referenced by Bergman would be reviewed by the Agency. However, the proprietary data could not be obtained; therefore, these results cannot be independently verified. However, as this finding is key to the conclusion that a NOEL for clastogenicity exists, and the study was conducted by the German regulatory authorities, the finding should be reported in the labeling. Due to the lack of toxicokinetic data, the exposure comparison must be made based on a body surface area comparison. According to the Bergman summary, 3 x 250 mg/kg (4500 mg/m²) dose of acetaminophen (4 hour intervals) did not result in an increase in micronuclei formation. In contrast, either 3 x 500 or 1 x 1500 mg/kg dose (9000 mg/m²) resulted in an increase in micronuclei formation. The NOEL dose for clastogenicity as defined in the studies reported in Bergman et al. (4500 mg/m²) is 1.8 times the maximum daily dose of APAP (4000 mg/60 kg = 2467 mg/m²) based on a body surface area comparison.

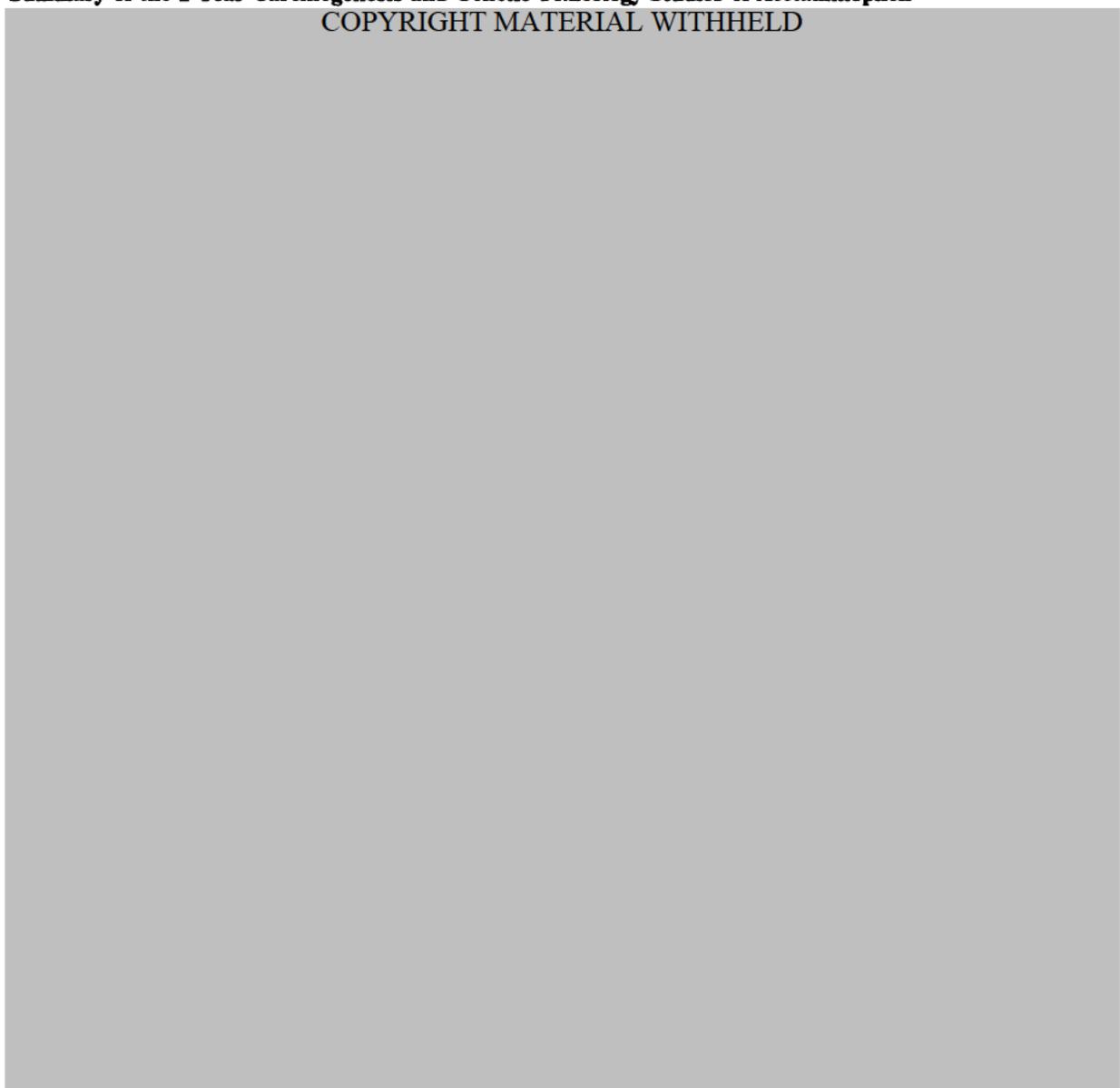
Oshida and colleagues examined the in vivo effects of APAP in the comet assay (Oshida, et al., 2008). These investigators treated mice with 12, 60, or 300 mg/kg APAP, IP and examined the liver, kidney, and bone marrow for evidence of DNA damage via the comet assay and examined cytotoxicity via hematology and clinical chemistry parameters. The high dose of APAP produced a positive response in the liver only, suggesting a threshold for genotoxicity, however, the effect also correlated with cytotoxicity. Therefore, the positive comet assay results may be due to cytotoxicity rather than genotoxicity. Based on a body surface area basis, the NOEL of 60 mg/kg

(180 mg/m²) provides an exposure margin of 0.07. The high dose of 300 mg/kg (900 mg/m²) provides an exposure margin of 0.36, suggesting that the hepatotoxicity or genotoxicity occurs at clinically relevant exposures. However, given the uncertainty if the finding is due to cytotoxicity or actual genotoxicity in this study, this study is not recommended to be included in the product labeling.

Carcinogenicity of APAP. Studies conducted by the NTP to evaluate the carcinogenic potential of acetaminophen can be used to support oral acetaminophen drug product prescription labeling. The study reports are available publically. The NTP study reports do not contain toxicokinetic data; therefore, the exposure margins for the product labeling will have to be based on body surface area comparisons for the label. The summary of the study results are reproduced from the NTP report in the table below:

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Acetaminophen

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Mean daily doses of APAP consumed were calculated based on mean food consumption over the course of the above studies in order to determine the exposure margin that should be included in the product labeling, as summarized in the table below:

Mean Dose (mg/kg)/Day APAP consumption (NTP Studies)

Group	600 ppm	3000 ppm	6000 ppm	6000 ppm (mg/m ²)	Exposure Margin* (HD = 6000 ppm)
Male Rats	30	149	295	1770	0.7
Female Rats	33	163	318	1908	0.8
Male Mice	91	448	1010	3030	1.2
Female Mice	114	603	1187	3561	1.4

*Exposure margin based on body surface area comparison to the maximum adult human dose of 4000 mg/day (2466.6 mg/m² for an average 60 kg person) for the high dose (HD) group.

Based on the results of this study, the NTP panel concluded that there was no evidence of carcinogenic activity in male rats. The NTP concluded that there was equivocal evidence of carcinogenic activity of acetaminophen in female rats based on an increase in the incidence of mononuclear cell leukemia that reached statistical significance in the high dose group. There was no evidence of carcinogenic activity of acetaminophen in male or female mice.

The results of this study were discussed by the Executive Carcinogenicity Assessment Committee (ECAC) on February 2, 2010. Based upon current CDER criteria, the mononuclear cell leukemia noted in the female rats were significant rather than equivocal; however, the ECAC specifically noted that the NTP F344 rat strain is known to have a high background incidence of certain tumors, including mononuclear cell leukemia (Haseman, et al., 1998; Caldwell, 1999; Ishmael and Dugard, 2006). In fact, the NTP has discontinued use of the F344/N rat strain and began using a commercial source of the F344 rat (King-Herbert and Thayer, 2006). In terms of the finding regarding the increased incidence of mononuclear cell leukemia, the ECAC minutes note that "The committee recommended that the labeling of the product describe the results of the studies but note that this is of limited relevance."

Effects on Fertility. A review of the literature identified three publications that provide some data relevant to fertility studies (Boyd and Hogan, 1968; Jacqueson, et al., 1984; Lamb, 1997). Boyd and Hogan administered acetaminophen via oral gavage to Wistar rats at doses of 500 mg/kg to 4000 mg/kg for 100 days. The publication notes that changes in testicular weight were not noted for treatment durations of less than one month. In animals that survived the 100 day treatment, decreased testicular weights were noted even at the lowest dose tested (500 mg/kg corresponds to 3000 mg/m²) which is only 1.2 times the maximum human dose of 4000 mg/day on a body surface area comparison. The decrease in weight of the testes was attributed to "almost complete atrophy of spermatogenic tissue." A NOAEL for testicular changes following longer than 1 month treatment was not obtained.

Studies conducted by Jacqueson and colleagues report that a 70-day treatment of male rats with 500 mg/kg dose of APAP resulted in a similar decrease in testicular weight, an increase in testicular cytosol glutathione transferase activity and of lipid peroxides. The authors note that the treatment did not result in decreased testicular glutathione levels; therefore, the toxicity can not be readily attributed to a mechanism similar to APAP-induced hepatotoxicity (Jacqueson, et al., 1984).

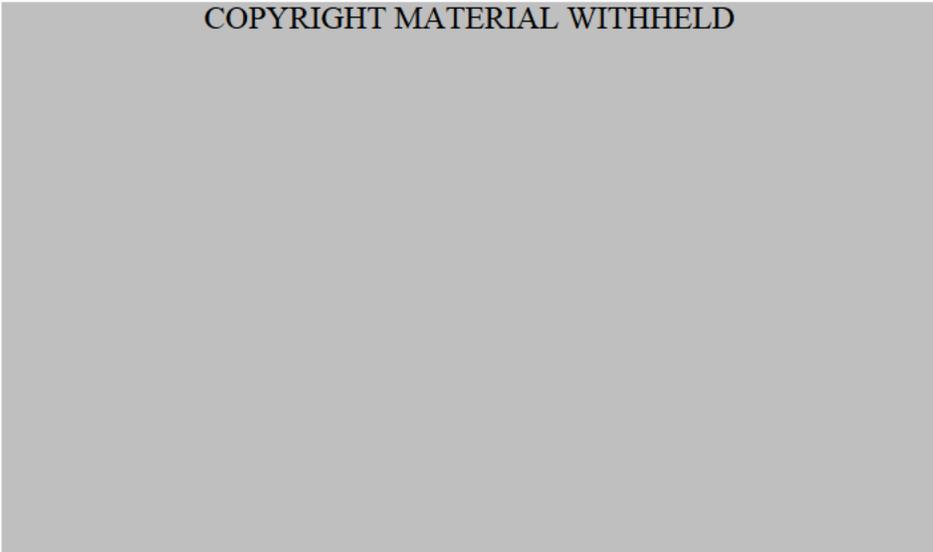
Although changes in testicular weight following 30-day treatment with 500 mg/kg APAP to rats was not noted by Boyd and Hogan (1968) and Jacqueson et al. (1984), a literature search conducted by the review team notes that this dose has also been reported to result in impairment of libido, sexual vigor/performance, fertility index, implantation index and number of implantation sites in the rat (Ratnasooriya and Jayakody, 2000). The authors administered either 500 or 1000 mg/kg APAP to male rats via oral gavage for 30 consecutive days and then examined their sexual behavior and fertility via interactions with untreated females. The 500 mg/kg dose (3000 mg/m²) reduced sexual behavior parameters, reduced vaginal sperm counts, impaired sperm motility, and reduced fertility (pregnancy rate, implantation index and fertility index). This dose is 1.2 times the human maximum daily dose based on a body surface area comparison. Time course studies using 1000 mg/kg APAP demonstrated a reduction in ejaculated sperm number as measured by vaginal sperm counts following treatment for 17 days; whereas no effects were noted on Day 3 or Day 7. Based on these results, a NOEL levels of adverse effects on male sexual behavior and fertility was not established.

Yano et al. reported that a single dose of APAP (650 mg/kg = 3990 mg/m²) administered orally to the male rat produced ultrastructural changes in the testes when measured 5, 10, and 15 days following treatment (Yano and Dolder, 2002). These changes included deformed seminiferous tubules, dilated blood vessels, edema of interstitial tissue, advanced spermatids with unusual amounts of residual cytoplasm, and well developed endoplasmic reticulum and Golgi complexes. A NOEL was not reported for these effects, which were noted with a dose that is 1.6 times the maximum human daily dose on a body surface area basis.

The NTP conducted a continuous breeding study in Swiss CD-1 mice which were given APAP at 0.0, 0.25, 0.5, and 1.0% in feed (National Toxicology Program, 1984;Reel, et al., 1992;Lamb, 1997). These doses resulted in exposures estimated from food consumption of 357, 715, and 1430 mg/kg/day (Reel, et al., 1992). Although designed as a continuous breeding study, this study reports that continuous exposure of mice to up to 1.0% APAP indirectly (in utero and lactational exposure) and directly from Day 28 (weaning) to Day 74 ± 10 had no significant effect on mating or fertility. Although there was no significant difference in sperm motility or sperm density in the cauda epididymis between 0 and 1.0% APAP groups, there was a significant increase in the percentage of abnormal sperm from the cauda epididymis relative to controls (see table below reproduced from the publication). Of note, based on the Lamb et al. summary, only the high dose group and control group appear to have been evaluated for sperm parameters; therefore, a NOEL level for sperm effects can not be obtained via this

study. The high dose tested, 1430 mg/kg (4290 mg/m²) is 1.7 times the maximum daily dose of APAP (4000 mg/60 kg = 2467 mg/m²) based on a body surface area comparison.

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Cumulative exposure to APAP appeared to reduced fecundity of mating pairs, since 6 of 19 high-dose pairs failed to produce a fifth litter and of the 13 mating pairs that did produce a litter, there was a reduction in the number of live pups born (Reel, et al., 1992).

Effects on Embryo-Fetal Development. Information in the published domain can be used to inform the Pregnancy section of acetaminophen product labeling (Lambert and Thorgeirsson, 1976;Lubawy and Garrett, 1977;Reel, et al., 1992;Laub, et al., 2000;Burdan, 2000;Neto, et al., 2004). As a single entity oral prescription drug label for acetaminophen has not previously been approved by the Agency, it appears as though a Pregnancy Category for oral acetaminophen has never been officially designated. Given the long history of clinical use of oral APAP during pregnancy, the nonclinical review team recognizes that there may be adequate and well-controlled clinical studies with oral acetaminophen to justify a Pregnancy Category ^(b)₍₄₎ for oral drug products. However, this must be confirmed via review of the large amount of published clinical literature. The reader is referred to the Maternal Health Team Consult Response for evaluation of the existing human data and product labeling recommendations regarding the clinical effects of oral APAP on pregnancy.

The published nonclinical literature identified by the review team is summarized below:

Lambert and Thorgeirsson report no teratogenic effect of acetaminophen in B6 and AK strains of mice treated from Gestation Day 6 through 13 with APAP does of 100 and 250 mg/kg via IP injection. Based on a body surface area comparison, the dose of 250 mg/kg in a mouse (750 mg/m²) is only 0.3-times the maximum recommended human

dose of 4000 mg/60 kg person (2466.6 mg/m²). However, as the parameters examined were not described in the publication, it is not possible to confirm the adequacy of the study (Lambert and Thorgeirsson, 1976).

Lubawy and Garrett report that there were no adverse effects of 125 mg/kg or 250 mg/kg APAP when administered to pregnant rats from Gestation Day 8 through 19. However, this study does not appear to examine visceral or skeletal malformations and therefore cannot be considered an adequate embryo-fetal development study (Lubawy and Garrett, 1977). Based on a body surface area comparison, the dose of 250 mg/kg in a rat (1500 mg/m²) is only 0.6-times the maximum recommended human dose of 4000 mg/60 kg person (2466.6 mg/m²).

As referenced above in the fertility discussion, Reel et al. report the results of NTP's continuous breeding study in mice; however, these studies do not appear to have been designed to specifically monitor for visceral or skeletal malformations (Reel, et al., 1992). The authors, however, report a decreased number of live pups in the fifth litter. Assessment of the F1 mice from the fourth and fifth litter indicated that pup weights at birth were not affected by APAP treatment; however, body weights of the F1 mice during the lactational and postweaning periods were depressed in a dose-related manner, as noted in the table below (reproduced from the Reel et al. publication).

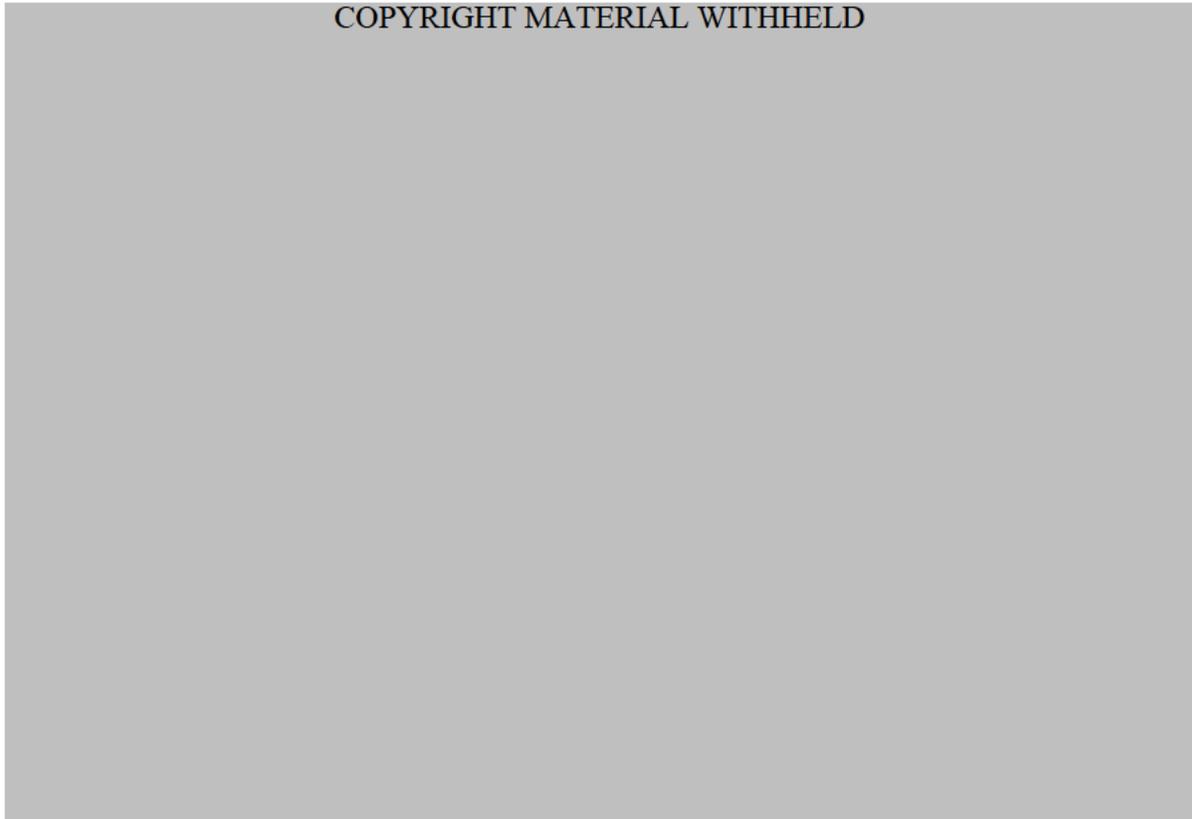
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Laub et al. administered APAP to female mice only during the first few days of gestation; therefore this study cannot be deemed an embryo-fetal development study since dosing did not cover the period of organogenesis. This study did suggest that APAP doses of 800 or 1430 mg/kg did not affect the development of preimplantation embryos (Laub, et al., 2000). Based on a body surface area comparison, the dose of 1430 mg/kg in a mouse (4290 mg/m²) is 1.7-times the maximum recommended human dose of 4000 mg/60 kg person (2466.6 mg/m²).

Buridan treated pregnant Wistar rats via oral gavage with 3.5, 35, or 350 mg/kg APAP from Gestation Day 8 to 14 and examined macroscopically for external malformation and for skeletal malformations (Buridan, 2000). The author concludes that the APAP

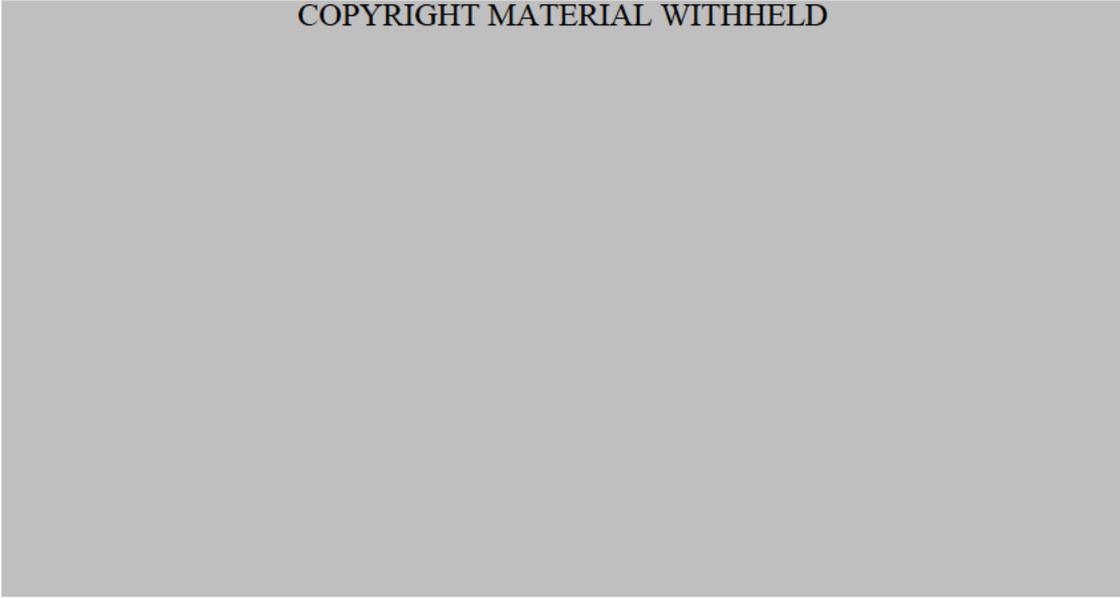
treatment did not lead to statistically significant differences in bone anomalies; however, there were some dose-related increases in the incidence of reduced ossification that exceeded control levels. Historical control data was not discussed in this publication. The highest dose tested (350 mg/kg = 2100 mg/m²) is only 0.85-times the maximum recommended human dose of 4000 mg/60 kg person (2466.6 mg/m²) based on body surface area. Although visceral malformations were not evaluated in this study, the treatment duration was consistent with a standard embryo-fetal development study. The skeletal variations reported in this publication are reproduced in the table below (emphasis added by reviewer).

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Although not reviewed by the Applicant, Burdan published a second article that contributes to the understanding of the potential embryo-fetal effects of APAP. In the subsequent study (Burdan, et al., 2001), Burdan reported decreased weight and length of Gestation Day 21 fetuses removed from the dams treated with 350 mg/kg APAP compared to those removed from the controls or the low dose, respectively (see table below, reproduced from the publication).

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Burdan has also examined the potential external, visceral, and skeletal effects of the combination of APAP and caffeine (doses of APAP are the same as in the two previous studies). The author reports no evidence of malformations in any group (Burdan, 2003). Collectively, the work of Burdan and colleagues suggests that treatment of the rat during organogenesis results in evidence of fetotoxicity (reduced fetal weight and length), statistically insignificant increases in altered bone morphology, but no evidence of external, visceral, or skeletal malformations. None of the studies that examined APAP alone demonstrated evidence of maternal toxicity; however, the top dose represents only 0.85-times the maximum recommended human daily dose on a body surface area basis.

Neto et al. treated pregnant rats via oral gavage with 0, 125, 500, or 1500 mg/kg APAP from Gestation Day 1 to term pregnancy and examined the effects on maternal and fetal liver and kidney via light and electron microscopy. As this study did not examine either visceral or skeletal tissues, it is not an adequate embryo-fetal development study. The two higher doses tested produced necrotic areas in both the liver and kidney in both maternal and fetal tissues (Neto, et al., 2004). Based on a body surface area comparison, the dose of 500 mg/kg in a rat (3000 mg/m²) is only 1.2-times the maximum recommended human dose of 4000 mg/60 kg person (2466.6 mg/m²). The authors report a NOEL for APAP-induced microscopic liver and kidney changes of 125 mg/kg. Based on a body surface area comparison, the dose of 125 mg/kg in a rat (750 mg/m²) is only 0.3-times the maximum recommended human dose of 4000 mg/60 kg person (2466.6 mg/m²). The study supports the conclusion that in the rat model, APAP treatment will produce both maternal and fetal liver and kidney histopathology at a dose between 125 and 500 mg/kg (between 0.3 and 1.2-times the maximum recommended human dose based on body surface area). This does not represent a "high dose" and indicates that the rat model is unlikely to provide an adequate safety margin via the oral

route of administration to justify a Pregnancy Category ^(b)₍₄₎ based on nonclinical data. In the absence of adequate clinical data with an oral APAP formulation, these adverse findings would dictate a Pregnancy Category C.

Effects of Pre- and Postnatal Development. Pre- and postnatal developmental data have been reported by Reel et al.; however, this study did not include comparable endpoints as a dedicated pre- and postnatal development study. Liver and kidney findings were reported by Neto et al. as described above (Neto, et al., 2004). As the effects reported in Neto et al. represent adverse effects on the fetus, they should be included in the product labeling and support a Pregnancy Category C, unless superseded by adequate human data.

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Ref Type: Report

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/s/

ELIZABETH BOLAN
10/25/2013

RICHARD D MELLON
10/25/2013

I concur with Dr. Bolan's recommendation that, from a nonclinical pharmacology toxicology perspective, NDA 204031 may be approved with the recommended labeling.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204031 Applicant: Mallinckrodt, Inc. Stamp Date: 5/28/13

**Drug Name: Oxycodone HCl NDA/BLA Type: 505(b)(2)
and Acetaminophen CR
Tablets**

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).	X		
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?	X		
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?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² 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		Justification for impurity/degradant specifications in excess of ICH thresholds is included in the NDA.
11	Has the applicant addressed any abuse potential issues in the submission?			Defer to CSS
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____

Pharm Tox has no comments for the 74-day letter.

Elizabeth A. Bolan, Ph.D. 6/27/13

 Reviewing Pharmacologist Date

R. Daniel Mellon, Ph.D. 6/27/13

 Team Leader/Supervisor Date

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/s/

ELIZABETH BOLAN
06/27/2013

RICHARD D MELLON
06/27/2013