

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206544Orig1s000

PHARMACOLOGY REVIEW(S)

Memo

To: NDA 206544/Morphobond

From: Karen Davis-Bruno, PhD; Assoc. Director Pharmacology/Toxicology OND IO

Date: 10/1/15

Reference is made to the secondary Pharmacology/Toxicology review written by Dr. Mellon for NDA 206544/Morphabond/Inspirion Delivery Technologies dated 9/14/15. Morphobond is a controlled release morphine product for the management of long term pain (b) (4) alternative treatment options are inadequate. The formulation contains abuse-deterrent properties. DAAAP Pharmacology/Toxicology team has a concern regarding the formulation which contains (b) (4). (b) (4) is present at levels exceeding previous FDA approved drug products based on the intended therapeutic dose of Morphabond. These (b) (4) components are of a sufficiently high molecular weight to show no apparent systemic absorption and no detectable lower molecular weight entities based on prior knowledge with related (b) (4) products. (b) (4) does not therefore, pose a safety concern. However (b) (4) (b) (4) contains a (b) (4) and (b) (4) contains (b) (4). An extensive review of the published literature would support the safety of (b) (4) based on prior experience with (b) (4) respectively. The outstanding concern is the safety of the (b) (4).

The Pharmacology/Toxicology reviews for NDA 206544, recommend additional toxicology studies with (b) (4) to address the concern for (b) (4). These studies include: (b) (4) toxicology in two species, a complete reproductive toxicology battery (fertility, embryo-fetal development (EFD; in rat and rabbit) and rat pre- and post-natal development) as well as a 2-year carcinogenicity study. This is consistent with current guidelines, representing a conservative approach. For instance, a 6-month transgenic mouse carcinogenicity study could be substituted for the recommended 2-year carcinogenicity study. While chronic and reproductive toxicity studies may not be available with (b) (4), their utility seems limited if this compound doesn't achieve appreciable systemic distribution from Morphobond administration. Therefore data establishing the metabolism of (b) (4), as predicted, might allow for establishment of safety based on the safety profile and concentrations of its metabolites. If the goal is to confirm summary information available in published literature a single species chronic toxicity study (6-month rat), might be sufficient to establish safety of chronic dosing in the absence of any product-related histopathology findings at study completion.

(b) (4)

(b) (4) it is appropriate to approve the application for Pharm/Tox and require the submission of this additional safety information as PMRs.

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/s/

KAREN L DAVIS BRUNO
10/01/2015
tertiary P/T review

**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
Secondary Review**

Application number: NDA 206544

Supporting document/s: SDNs 1, 9, 10 and 11

Applicant's letter date: November 21, 2014; August 3, 2015; August 20, 2015; and August 28, 2015

CDER stamp date: November 21, 2014; August 3, 2015; August 20, 2015; and August 28, 2015

Product: Morphabond; Morphine ARER (Morphine sulfate abuse-resistant, extended-release tablets)

Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Applicant: Inspirion Delivery Technologies LLC

Review Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Reviewer: Carlic K. Huynh, PhD

Acting Team Leader: Newton H. Woo, PhD

Supervisor: R. Daniel Mellon, PhD

Division Director: Sharon Hertz, MD

Project Manager: Christopher Hilfiger

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Inspirion submitted NDA 206544 in support of Morphabond, a controlled-release, single-entity morphine drug product for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The formulation is intended to have abuse-deterrent properties. Dr. Carlic Huynh completed the primary pharmacology toxicology review of this NDA and is recommending a complete response.

No new studies for morphine were required to support this 505(b)(2) application which relies in part on the Agency's previous finding of safety for MS Contin. Therefore, the NDA review focuses on the safety of the drug product formulation.

The drug product formulation contains (b) (4) which are considered "new" excipients as defined by the FDA in that they are either used at greater daily doses than other oral drug products or have never been used in FDA-approved drug products to date. (b) (4) is used in other chronic oral drug products approved by the FDA. However, the use in Morphabond is novel in that the total daily dose of the excipient in this formulation will exceed that of any other FDA-approved oral drug product. (b) (4) is novel in that this excipient has not been previously used in any FDA-approved drug product.

(b) (4) are ethylacrylate and methylmethacrylate copolymers. Members of this class of polymers are used in a variety of oral drug products in order to obtain the desired drug-release profile. The ethylacrylate and methylmethacrylate copolymer backbone of both (b) (4) are sufficiently large to preclude systemic absorption following oral administration (the mean molecular weight of (b) (4) is 750,000 Daltons and (b) (4) is 600,000 Daltons) and the Applicant has provided adequate data to support the conclusion that there are no detectable lower molecular weight entities in the polymeric material, that there is no apparent systemic absorption of the polymers and that (b) (4) are adequately controlled. Therefore there are no safety concerns with the polymeric backbone of (b) (4) (b) (4)

However, in addition to differences in molecular weight, these (b) (4) also differ by the presence of the (b) (4) in the product. In the case of (b) (4), the (b) (4); whereas, (b) (4) employs the (b) (4) (b) (4). As the backbone polymethacrylate polymer is not absorbed systemically, and there are older data that have been historically used to support these polymers, the backbone is not believed to present any novel risk to the patients. In contrast, there are considerably less data for the (b) (4) and there are no distribution data for these compounds to directly demonstrate if the (b) (4) are or are not absorbed systemically. Therefore, the NDA review has focused on the safety of the (b) (4) and the (b) (4) when the product is used up to the maximum

theoretical daily dose (MTDD) of morphine (2 grams/day). The Applicant has not conducted toxicology studies for these [REDACTED] compounds. Rather they justify the safety of the [REDACTED] (b) (4) in the drug product formulation as this [REDACTED] (b) (4) was present in the toxicology studies for [REDACTED] (b) (4). This alone is inadequate as there are no fertility and early embryonic development study, pre- and post-natal development study, or carcinogenicity studies with these [REDACTED] (b) (4). To address these issues, the Applicant and Dr. Huynh have conducted a weight-of-evidence review based on literature and data on analogous compounds.

Dr. Huynh has reviewed the existing data on [REDACTED] (b) (4) and concludes that there are adequate data to support the safety of this excipient in the drug product. This is in part based on data with other specific compounds in the class, such as [REDACTED] (b) (4) and [REDACTED] (b) (4). I concur with Dr. Huynh's conclusion that adequate data exist to support the safety of [REDACTED] (b) (4) in the [REDACTED] (b) (4) polymer. This memo will summarize some of the key points of his review.

[REDACTED] (b) (4)
[REDACTED] (b) (4) He recommends that the NDA be designated a complete response and that the following additional toxicology studies be completed to support approval:

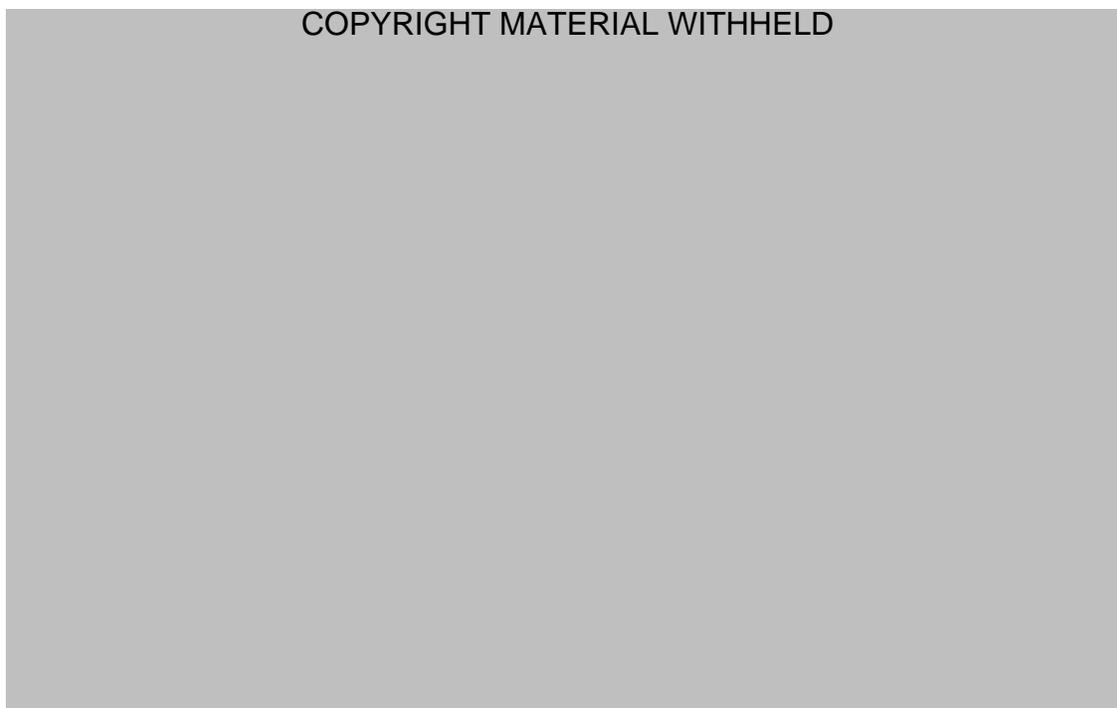
1. Chronic toxicology studies with [REDACTED] (b) (4) in two species (6-month rodent and 9-month nonrodent) are required for a chronic indication.
2. Reproductive and developmental toxicology battery with [REDACTED] (b) (4): fertility and early embryonic development (rat), embryofetal development (rat and rabbit), and pre- and postnatal development studies (rat).
3. A carcinogenicity assessment of [REDACTED] (b) (4) in mice. As per the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.

[REDACTED] (b) (4)
I summarize the existing safety justification for each of these excipients below.

Although there are no definitive toxicology studies of (b) (4), the submitted toxicology studies with (b) (4) and (b) (4) assess the safety of the (b) (4) present in the test article. Therefore, these studies can be used to support the safety of both the polymeric backbone and the (b) (4). The Applicant submitted the following studies with (b) (4): genetic toxicology studies, chronic toxicology studies of 6-month duration in the dog and rat models, and embryo-fetal developmental toxicology studies in the rat and rabbit. As noted by Dr. Huynh, for a novel excipient, the FDA usually recommends the same battery of studies as it does for any other active ingredient unless otherwise justified. The standard study endpoints that are not covered by the data from (b) (4) and (b) (4) include fertility and early embryonic development, pre- and postnatal development, and carcinogenicity studies in two species. These were addressed by the Applicant via reference to literature. Some of the literature referenced by the Applicant included summary reviews from third party organizations such as (b) (4) Review Expert Panels. The Agency does not generally accept these summary reviews as adequate as there is limited detail in the summaries and as the full study reports are not available for review, the findings cannot be independently verified. However, where possible, the original publications were reviewed to determine the general adequacy of the study designs and level of detail to permit reasonable conclusions. In this case, there is adequate information to support the conclusion that data from lower molecular weight (b) (4) are useful to support the safety of higher molecular weight (b) (4). In fact, these lower molecular weight compounds have greater absorption than (b) (4) and there is a clear pattern of decreased toxicity with increasing number of polyethylene units in the compounds. As such, they represent a “worst-case” scenario and likely overestimate the potential for toxicity of (b) (4). This serves as an adequate scientific bridge to support the use of the data on lower molecular weight compounds to justify the safety of (b) (4).

(b) (4)

As noted by Dr. Huynh, although there are no direct data to document that (b) (4) (b) (4) is not absorbed from the gastrointestinal tract; however, given the MW of (b) (4) (b) (4) for (b) (4) (b) (4), it is not anticipated to be absorbed from the gastrointestinal tract intact (b) (4) (b) (4). There are limited absorption and metabolism data for lower molecular weight (b) (4) (b) (4) compounds. The data suggests that increasing number of (b) (4) (b) (4) units attached to the (b) (4) (b) (4) moiety decreases systemic absorption as demonstrated by increases in fecal elimination and decreases in urinary elimination as a function of the number of (b) (4) (b) (4) adducts attached (b) (4) (b) (4) as illustrated below in the figure reproduced from the publication.



These investigators also radiolabeled either the carbons in the (b) (4) (b) (4) chain or the carbons in (b) (4) (b) (4) structure of (b) (4) (b) (4). Radiolabeling studies with the (b) (4) (b) (4) also suggest that the alkylphenol moiety is likely cleaved from the polyethylene chain (b) (4) (b) (4). It is not known if this cleavage takes place in the GI tract or after absorption but it is speculated that this would require oxidation, and therefore is likely occurring after absorption from the GI tract.

(b) (4) (b) (4) provide data to support the conclusion that (b) (4) (b) (4) (MW = (b) (4) (b) (4)) is readily absorbed following vaginal administration. Specifically, radiolabeled material was detected in the plasma and tissues as well as in the milk and plasma of pups who nursed from mothers treated intravaginally with (b) (4) (b) (4). These authors estimate that approximately 0.3% of the intravaginally administered dose is secreted daily in the milk (b) (4) (b) (4) (b) (4) is an FDA approved over-the-counter spermicidal drug product. Given the data suggesting systemic absorption of

this compound following intravaginal administration, the systemic safety of (b) (4) appears to have been already deemed acceptable by the Agency.

Based upon review of the existing data, I do not believe that the levels of (b) (4) in the Morphabond drug product are likely to result in any adverse effects. No further nonclinical studies are warranted.

The following table summarizes the primary safety justification for (b) (4).

| Endpoint | Primary Justification | Comment on Adequacy |
|---|--|-------------------------------|
| General Toxicology in two species | <p>6-month rat and dog studies with (b) (4) and (b) (4), respectively.</p> <p>Published general toxicology studies with (b) (4) in females (b) (4)</p> | Acceptable NOAEL demonstrated |
| Genetic Toxicology | <p>Full battery of studies with (b) (4)</p> <p>Negative genetic toxicology data for other (b) (4) and (b) (4) compounds (b) (4)</p> <p>FDA previous finding of safety for (b) (4) (b) (4) (b) (4)</p> <p>Acceptability of lower MW (b) (4) as indirect food additives as per the CFR.</p> | Acceptable |
| Fertility and Early Embryonic Development | <p>Published female fertility data for (b) (4) (b) (4)</p> <p>Lack of adverse effects in a limited 5-day data on male rats treated with (b) (4) (b) (4)</p> <p>Lack of adverse effects on male reproductive tissues for related alkylphenol polyethylene surfactants (b) (4)</p> <p>FDA previous finding of safety for (b) (4) (b) (4) (CFR) and data to show that (b) (4) is absorbed systemically after intravaginal</p> | Acceptable |

| | | |
|--------------------------------|--|------------|
| | <p>administration (b) (4)</p> <p>Expected limited, if any, systemic absorption (b) (4)</p> | |
| Embryofetal Development | <p>Studies with (b) (4) (rat and rabbit)</p> <p>FDA previous finding of safety for (b) (4) (monographed as per CFR)</p> <p>Expected limited, if any, systemic absorption (b) (4)</p> | Acceptable |
| Pre- and Postnatal Development | <p>Published lactational exposure data for (b) (4) (b) (4)</p> <p>FDA previous finding of safety for (b) (4) (CFR)</p> <p>Expected limited, if any, systemic absorption (b) (4)</p> | Acceptable |
| Carcinogenicity | <p>No hyperplastic effects noted in chronic toxicology studies (b) (4)</p> <p>No evidence of carcinogenicity with similar compounds (b) (4)</p> <p>Published carcinogenicity studies with (b) (4) in female rats and mice (b) (4)</p> <p>FDA previous finding of safety for (b) (4) (CFR)</p> <p>Expected limited, if any, systemic absorption (b) (4)</p> | Acceptable |

Reference List

(b) (4)

Aso S, Sueta S, Kajiwara Y, Morita S, Horiwaki S and Sato T (1999b) Effects on reproduction and fetal development of female rats treated subcutaneously with a surfactant, polyoxyethylene(10)nonylphenyl ether(NP-10), for 15 weeks. *J Toxicol Sci* **24 Suppl 2**:115-128.

(b) (4)

Buzzi R and Wurgler FE (1990) Knowledge-based battery design of short-term tests based on dose information. *Mutat Res* **234**:269-288.

(b) (4)

Drotman RB (1980) The absorption, distribution, and excretion of alkylpolyethoxylates by rats and humans. *Toxicol Appl Pharmacol* **52**:38-44.

European Food Safety Authority (EFSA) (2010) Scientific opinion on the safety of neutral methacrylate copolymer for the purposed uses as a food additive. *EFSA Journal* **8**:1655.

Fiume MM, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks JG, Jr., Shank RC, Slaga TJ, Snyder PW and Andersen FA (2012) Safety assessment of alkyl PEG ethers as used in cosmetics. *Int J Toxicol* **31**:169S-244S.

Inoue H, Yamamoto T, Shoji A, Watari N, Hirouchi Y, Enomoto M and Morita K (1999a) Carcinogenicity test of polyoxyethylene(10)nonylphenyl ether(NP-10) in female B6C3F1 mice. *J Toxicol Sci* **24**:149-166.

(b) (4)

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K and Speck W (1987) Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ Mutagen* 9 Suppl 9:1-109.

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/s/

RICHARD D MELLON
09/14/2015

**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 206544

Supporting document/s: SDNs 1, 9, 10, and 11 (Electronic Document Room Sequence Numbers 0, 8, 9, and 10)

Applicant's letter date: November 21, 2014 (SDN 1), August 3, 2015 (SDN 9), August 20, 2015 (SDN 10), and August 28, 2015 (SDN 11)

CDER stamp date: November 21, 2014 (SDN 1), August 3, 2015 (SDN 9), August 20, 2015 (SDN 10), and August 28, 2015 (SDN 11)

Product: Morphabond; Morphine sulfate abuse-resistant, extended-release tablets; Morphine ARER

Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Applicant: Inspirion Delivery Technologies LLC

Review Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Reviewer: Carlic K. Huynh, PhD

Acting Team Leader: Newton H. Woo, PhD

Supervisor: R. Daniel Mellon, PhD

Division Director: Sharon Hertz, MD

Project Manager: Christopher Hilfiger

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Applicant, Inspirion Delivery Technologies LLC, has developed an abuse-deterrent formulation of morphine sulfate extended-release tablets referred to during development as "Morphine ARER" for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The Applicant has submitted a 505(b)(2) application relying upon the Agency's previous finding of safety for MS Contin (NDA 19516).

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were required to be submitted for morphine sulfate. There were no nonclinical safety concerns with the drug substance and drug product specifications as well as the container closure system as the proposed drug product is formulated as solid oral tablets. With the exception of (b) (4), all excipients in the composition of the proposed drug formulation were determined to be qualified for safety up to the maximum theoretical daily dose (MTDD) of 2 g/day of morphine. Additional data were required to justify the levels of these excipients.

Several nonclinical studies were submitted to justify the levels of (b) (4) (b) (4) at the MTDD of 2 g/day of morphine sulfate, which are (b) (4) (b) (4) and (b) (4), respectively. These studies were submitted with the NDA and also cross-referenced in MF (b) (4). (b) (4) ethyl acrylate and methyl methacrylate copolymers (2:1) (b) (4) molecular weights of 750,000 and 600,000, respectively. The nonclinical studies with (b) (4) (an ethyl acrylate and methyl methacrylate copolymer (2:1) with (b) (4) and MW of 750,000) included an excretion and tissue distribution study evaluating radiolabelled (b) (4), embryofetal developmental toxicology in rat and rabbit with (b) (4), 6-month general toxicology with (b) (4) in the rat and with (b) (4) in the dog, mutagenicity (Ames) with (b) (4), as well as mutagenicity (Ames), micronucleus induction, and mutation at the Thymidine Kinase locus in mouse lymphoma cells with (b) (4) (b) (4)

In the excretion and tissue distribution study, rats were administered a single oral dose of ^{14}C - (b) (4). Approximately 97% of radioactivity was accounted for in the feces. Radioactivity in the various tissues, including the liver, spleen, mesenteric lymph nodes, small and large intestine, and blood, was not significantly different from background with no significant increasing trend of radioactivity in various tissues. (b) (4) does not appear to be absorbed systemically but excreted in feces.

Due to the lack of systemic absorption, reproductive and developmental toxicology studies with (b) (4) were not deemed necessary.

Several genetic toxicology studies were conducted with (b) (4) and the weight of evidence suggests that these (b) (4) copolymers do not have mutagenic or clastogenic potential. A carcinogenic assessment was not conducted with any (b) (4) excipient. However, based on the negative genetic toxicology data, limited systemic exposure, lack of accumulation potential, negative histopathology data from chronic toxicology studies and knowledge of other excipients that are high molecular weight copolymers, a carcinogenicity assessment of (b) (4) is not deemed necessary.

As part of the safety justification of the (b) (4) copolymer backbone, 6-month oral toxicology studies in the rat and dog with (b) (4) were submitted and reviewed. In the rat study, the NOAEL appears to be 2000 mg/kg based on no treatment-related changes in the toxicological endpoints of the study. The rat NOAEL confers an exposure margin of 10.1 for (b) (4) and 35.4 for the (b) (4) (the copolymeric backbone) based on a body surface area comparison. In the dog study, the NOAEL is 500 (or 125) mg/kg due to the decreased body weights (>10%), macroscopic findings (abnormal size, content, area, and color were noted in various organs), organ weight and organ-to-body-weight ratio (in various organs), and histopathological changes (lymphoid aggregation in the gall bladder of females, nephropathy in the kidney of males, and lymphoid hyperplasia in the spleen of males) at the high dose groups. The dog NOAEL confers an exposure margin of 2.1 for (b) (4) and 7.37 for (b) (4) (the copolymeric backbone) based on a body surface area comparison.

Embryofetal studies conducted with (b) (4) in feed in the rat and rabbit were submitted. However, due to the lack of systemic absorption of (b) (4), reproductive and developmental toxicology studies with the copolymeric backbone contained in (b) (4) are not necessary. Nonetheless, these embryofetal studies were reviewed as part of a safety justification for the (b) (4). The carcinogenicity assessment of the (b) (4) backbone is deemed not necessary as per the guidance for industry: *Evaluation of Pharmaceutical Excipients*.

Although the safety of the copolymeric backbone of (b) (4) has been addressed, the safety of the (b) (4) has not been adequately addressed. At the MTDD of 2 g/day of morphine, there are (b) (4) and (b) (4) of the (b) (4) and (b) (4), respectively. Both (b) (4) are considered novel for the oral route of administration and may be systemically absorbed. There are no reproductive and developmental studies with (b) (4) alone and only embryo-fetal development studies conducted in rats and rabbits with (b) (4) containing (b) (4).

In the rat embryofetal study testing (b) (4), both the maternal and fetal NOAELs are 2000 mg/kg due to no treatment-related changes for all toxicological endpoints. At the MTDD of 2 g/day of morphine, which results in (b) (4) of (b) (4), the exposure margin for this level of (b) (4) based on the maternal and fetal NOAEL is 671-fold, based on a body surface area comparison. In the rabbit embryofetal study, both the maternal and fetal NOAELs are 2000 mg/kg due to no treatment-related changes in any toxicological endpoint. At the MTDD of 2 g/day of morphine, which results in (b) (4) of (b) (4), the exposure margin for this level of (b) (4) based on the maternal and fetal NOAEL is 1342-fold, based on a body surface area comparison. There were no other reproductive and developmental toxicology studies with (b) (4) such as the fertility and early embryonic development study as well as the pre- and postnatal development study. However, there are studies with an analogous compound, (b) (4) in the published literature regarding the fertility and pre- and postnatal development in rats that appear adequate and supportive. In addition, a 90-day and 2-year feed studies in rats and dogs with various length analogous (b) (4) compounds showed no clinically relevant toxicological and histopathological findings. There are no genotoxicity studies or a carcinogenicity assessment with (b) (4); however, there is a mouse carcinogenicity assessment of the analogous compound (b) (4) in the published literature. The doses tested in the carcinogenicity assessment of (b) (4) showed that the test compound was noncarcinogenic. The 6-month rat and dog studies with (b) (4) may be used to justify the levels of the (b) (4). The rat NOAEL of 2000 mg/kg yields an exposure margin of 671-fold, based on a body surface area comparison. The dog NOAEL of 125 mg/kg yields an exposure margin of 140-fold, based on a body surface area comparison. Using a weight-of-evidence approach as outlined in the guidance for industry: *Evaluation of Pharmaceutical Excipients*, it was deemed that a carcinogenicity assessment of (b) (4) is not necessary. Overall, the data suggests there is minimal risk with these various length analogous (b) (4) compounds.

(b) (4)

From a nonclinical pharmacology toxicology perspective, the recommendation for the Morphine ARER drug product is a Complete Response (b) (4)

(b) (4)

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, (b) (4)

(b) (4)

(b) (4)

(b) (4)

a Complete Response is recommended at this time.

Deficiency

(b) (4)

Information needed to resolve this deficiency

Complete the following studies:

1. Chronic toxicology studies with (b) (4) in two species (6-month rodent and 9-month nonrodent).
2. Reproductive and developmental toxicology battery with (b) (4): fertility and early embryonic development (rat), embryofetal development (rat and rabbit), and pre- and postnatal development studies (rat).
3. A carcinogenicity assessment of (b) (4) in rats and mice. As per the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.

1.3.2 Additional Non Clinical Recommendations

1.3.3 Labeling

The following labeling changes are recommended:

| <i>Applicant's proposed labeling</i> | <i>Reviewer's proposed changes</i> | <i>Rationale for changes</i> |
|---|---|---|
| <p>INDICATIONS AND USAGE MorphaBond is an opioid agonist (b) (4) indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)</p> | <p>INDICATIONS AND USAGE MorphaBond is an opioid agonist (b) (4) indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)</p> | <p>No changes were necessary as the correct Established Pharmacologic Class for morphine was used.</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>USE IN SPECIFIC POPULATIONS</p> <ul style="list-style-type: none"> Pregnancy: Based on animal data, may cause fetal harm. (8.1) | <p>No changes were necessary. As per the Maternal Health Team labeling initiative, nonclinical pregnancy information with a reference to Section 8.1 was placed in the Highlights section.</p> |
| <p>8.1 Pregnancy Teratogenic Effects (Pregnancy Category C) There are no adequate and well-controlled studies in pregnant women. MorphaBond should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.</p> | <p>8.1 Pregnancy Teratogenic Effects (Pregnancy Category C) There are no adequate and well-controlled studies in pregnant women. MorphaBond should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.</p> | <p>No changes to the content were necessary.</p> <p>The Applicant's proposed labeling is identical to the current MS Contin labeling including an introductory paragraph as per the CFR for Category C drugs and human data to be placed first as per the Maternal Health Team initiative.</p> <p>The Applicant also used a summary of the literature reports describing the effects of morphine on human and animal development.</p> |

| | | |
|---|--|--|
| <p>Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.</p> <p>Nonteratogenic Effects Infants born to mothers who</p> | <p>Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue, and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.</p> <p>Nonteratogenic Effects Infants born to mothers who</p> | |
|---|--|--|

| | | |
|---|--|--|
| <p>have taken opioids chronically may exhibit neonatal withdrawal syndrome [see <i>Warnings and Precautions</i> (5.3)], reversible reduction in brain volume, small size, decreased ventilatory response to CO₂ and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.</p> | <p>have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO₂, and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.</p> | |
| <p>Controlled studies of chronic <i>in utero</i> morphine exposure in pregnant women have not been conducted. Published literature has reported that exposure to morphine during pregnancy in animals is associated with reduction in growth and a host of behavioral abnormalities in the offspring. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis</p> | <p>Controlled studies of chronic <i>in utero</i> morphine exposure in pregnant women have not been conducted. Published literature has reported that exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs, and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis, and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in</p> | |

| | | |
|---|---|--|
| <p>in male offspring were also observed. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, IP) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.</p> | <p>male offspring were also observed. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, IP) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.</p> | |
| <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.</p> <p>Mutagenesis No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the</p> | <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.</p> <p>Mutagenesis No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the</p> | <p>No changes to the content were necessary.</p> <p>The Applicant's proposed labeling is identical to the current MS Contin product labeling.</p> <p>The Applicant used a summary of the literature reports describing the effects of morphine on mutagenicity, clastogenicity, and fertility.</p> |

| | | |
|---|---|--|
| <p>above positive findings, <i>in vitro</i> studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in <i>Drosophila</i>.</p> <p>Impairment of Fertility No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e., testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.</p> | <p>above positive findings, <i>in vitro</i> studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in <i>Drosophila</i>.</p> <p>Impairment of Fertility No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted. Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e., testosterone, luteinizing hormone, (b) (4) serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.</p> | |
|---|---|--|

2 Drug Information

2.1 Drug

CAS Registry Number

6211-15-0

Generic Name

Morphine sulfate

Code Name

IDT-001

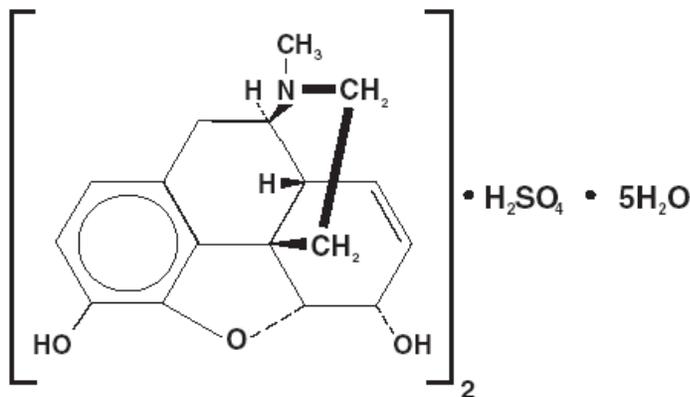
Chemical Name

Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 α ,6 α)-, sulfate (2:1) (salt), pentahydrate7,8-Didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -diol sulfate (2:1) (salt) pentahydrate

Molecular Formula/Molecular Weight

(C₁₇H₁₉NO₃)₂•H₂SO₄•5H₂O / 758.83 g/mol

Structure or Biochemical Description



Pharmacologic Class

Opioid Agonist (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

| NDA# | Drug Name | Div | Strength (route) | Marketing Status | AP Date | Indication | Sponsor |
|-------|--|--------|------------------------------------|------------------|--------------|---|------------------|
| 19516 | MS CONTIN® (Morphine sulfate SR tablets) | DAAAAP | 15, 30, 60, 100, and 200 mg (oral) | AP | May 29, 1987 | The management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time | Purdue Pharma LP |

| IND# | Drug Name | Div | Status | Indication | Sponsor |
|--------|------------------|-------|--------|---|-------------------------------------|
| 115822 | Morphine sulfate | DAAAP | Active | Management of chronic moderate to severe pain | Inspirion Delivery Technologies LLC |

| MF# | Subject of DMF | Holder | Submit Date | Reviewer's Comment |
|------|--|---------------|-------------|--|
| 6967 | Morphine Sulfate as manufactured in Wilmington, Delaware | Noramco, Inc. | May 8, 1987 | LOA provided. Specification for (b) (4) is NMT (b) (4)%, which is acceptable since genetic toxicology studies on (b) (4) (Ames and chrome abs) have been completed and were negative (see nonclinical review dated January 7, 2008). (b) (4) |

2.3 Drug Formulation

The proposed drug product is a smooth surface tablet that the Applicant expects to pass through the body and be excreted intact. Although the Applicant supports this supposition through in vitro dissolution data (b) (4) (b) (4) with simulated gastrointestinal fluid (b) (4) in vivo data in animals or humans (b) (4) (b) (4) (b) (4) have not been provided. (b) (4) (b) (4) The image below was reproduced from the submission:



Figure 8 Composition of Morphine ARER Tablet

The dimensions of morphine ARER tablet strengths are presented in Table 7.

Table 7 Dimensions of Morphine ARER Tablet Strengths

| Strength | Diameter | Width |
|----------|----------|---------|
| 15mg | | (b) (4) |
| 30mg | | |
| 60mg | | |
| 100mg | | |

The following table illustrates the composition of the morphine ARER tablets (data from the Applicant's submission):

| Component | Morphine ARER Tablets | | | |
|--|-----------------------|-------------------|-------------------|--------------------|
| | 15 mg (mg/tablet) | 30 mg (mg/tablet) | 60 mg (mg/tablet) | 100 mg (mg/tablet) |
| (b) (4) | | | | |
| Hypromellose (hydroxypropyl methylcellulose) | | | | (b) (4) |
| Xanthan gum | | | | |
| Microcrystalline cellulose | | | | |
| Sodium alginate | | | | |
| Alginic acid | | | | |
| Mannitol | | | | |

| | | | | |
|--|---------|--|--|--|
| Colloidal silicon dioxide (b) (4) | (b) (4) | | | |
| Magnesium stearate (b) (4) | | | | |
| Lactose monohydrate (b) (4) | | | | |
| Polysorbate 80 (b) (4) | | | | |
| Morphine sulfate | | | | |
| Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4) | (b) (4) | | | |
| Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4) | | | | |
| (b) (4) | | | | |
| (b) (4) | | | | |
| Titanium dioxide ^b (b) (4) | (b) (4) | | | |
| FD&C Blue #1/ (b) (4) | | | | |

| | | |
|--|---------|---------|
| FD&C Blue #2 | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| FD&C Red #40/ | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| FD&C Yellow #6 | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Isopropyl alcohol ^c | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Black iron oxide ^c | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| n-Butyl alcohol ^c | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Propylene glycol ^c | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Ammonium hydroxide | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Total theoretical finished tablet weight | | (b) (4) |
| NA | | (b) (4) |
| a = | | (b) (4) |
| b = | | (b) (4) |
| c = | | (b) (4) |

As shown in the table above, the morphine ARER tablet is made up of a (b) (4) (b) (4) (which contains the active drug morphine), and color coatings (that has printing on it). The (b) (4) copolymers are used (b) (4) (b) (4) is in the (b) (4) (b) (4) whereas (b) (4) is in the (b) (4) (b) (4)

2.4 Comments on Novel Excipients

As with any opioid drug product indicated for chronic use, there is no maximum daily dose listed in the proposed labelling due to the development of tolerance. The development of tolerance necessitates increased doses with time to order to obtain the same desired effect. To establish the safety of the product for opioid-tolerant individuals, the DAAAP has established a “maximum theoretical daily dose (MTDD)” of 2 grams per day as the MTDD for morphine products based on clinical use data.

The following table illustrates the amount of each excipient at the Maximum Theoretical Daily Dose (MTDD) of 2 g/day of morphine sulfate via 20 of the 100 mg ARER tablets and compares the levels to the maximum potency data from the FDA CDER Inactive Ingredients Database (IID):

| Excipient | Maximum Potency in Approved Chronic Oral Products via the FDA IID (mg/dosage form) | Amount at the MTDD of twenty 100 mg ARER tablets (mg) | Coverage Up To the MTDD via IID |
|---|--|---|---------------------------------|
| Hypromellose (hydroxypropyl methylcellulose (b) (4) (b) (4)) | | | (b) (4) |
| Xanthan gum (b) (4) | | | (b) (4) |
| Microcrystalline cellulose (b) (4) (b) (4) | | | (b) (4) |
| Sodium alginate | | | (b) (4) |
| Alginic acid | | | (b) (4) |
| Mannitol (b) (4) | | | (b) (4) |
| Colloidal silicon dioxide (b) (4) | | | (b) (4) |
| Magnesium stearate | | | (b) (4) |
| Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4) | | | (b) (4) |
| Lactose monohydrate (b) (4) (b) (4) | | | (b) (4) |
| Polysorbate 80 (b) (4) | | | (b) (4) |
| Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4) | | | (b) (4) |
| (b) (4) color coating for 100 mg tablet (Gray (b) (4) (b) (4)) | | | (b) (4) |
| (b) (4) | | | (b) (4) |
| Titanium dioxide ^a | | | (b) (4) |
| (b) (4) | | | (b) (4) |
| FD&C Blue #2/ (b) (4) (b) (4) | | | (b) (4) |
| FD&C Red #40/ (b) (4) (b) (4) | | | (b) (4) |
| FD&C Yellow #6/ (b) (4) (b) (4) | | | (b) (4) |
| (b) (4) | | | (b) (4) |
| (b) (4) | | | (b) (4) |

| | | |
|--------------------------------|---------|---------|
| (b) (4) | (b) (4) | (b) (4) |
| Isopropyl alcohol ^b | (b) (4) | (b) (4) |
| Black iron oxide ^b | (b) (4) | (b) (4) |
| n-Butyl alcohol ^b | (b) (4) | (b) (4) |
| Propylene glycol ^c | (b) (4) | (b) (4) |
| Ammonium hydroxide | (b) (4) | (b) (4) |

a = (b) (4)

b = (b) (4)

c = (b) (4) silicon dioxide is in approved chronic use oral products (as listed in the FDA IID) at levels that provides coverage up to the MTDD.

d = Titanium dioxide has been evaluated by JECFA (Joint FAO/WHO Expert Committee on Food Additives) with a "not limited" average daily intake (ADI)¹. Thus, there is coverage of this excipient for up the MTDD of 2 g/day of morphine.

e = FD&C Blue #2/ (b) (4) is in approved oral products as listed in the FDA IID (b) (4) that provides coverage of this excipient in morphine ARER up to the MTDD of 2 g/day.

NG = Listed in the FDA IID without a maximum potency given.

As shown in the table above, the components of each of the colorants used in the different strength morphine ARER tablets are justified. It is noted that (b) (4) Gray (b) (4) is not specifically listed in the FDA IID; however, each of the components are. It is also noted that black iron oxide in the (b) (4) (b) (4) is not listed in the FDA IID; however, (b) (4) is.

As shown in the table above, there are no support for the daily exposures to hypromellose (hydroxypropyl methylcellulose), xanthan gum, (b) (4) (b) (4) at the MTDD of 2 g/day of morphine. The Applicant submitted an excipient safety assessment report in the NDA submission. Safety of these excipients is discussed below.

Hydroxypropyl methylcellulose (CAS 9004-65-3)

Hydroxypropyl methylcellulose may be safely used in food as a food additive according to 21 CFR §172.874. There is no limitation listed in the CFR in terms of dose. An ADI (acceptable daily intake) for hydroxypropyl methylcellulose was established by JECFA (Joint FAO/WHO Expert Committee on Food Additives) of up to 25 mg/kg, which is 1.5 g for an average human weighing 60 kg². The ADI of modified celluloses such as hydroxypropyl methylcellulose should consider the laxative effect of these compounds³. Furthermore, an approved oral drug product contains (b) (4) of hydroxypropyl methylcellulose per tablet and the MTDD of this product is (b) (4) or (b) (4) of the excipient. Thus, the levels of hydroxypropyl methylcellulose in this formulation

¹ http://www.inchem.org/documents/jecfa/jecval/jec_2278.htm

² <http://www.inchem.org/documents/jecfa/jecmono/v17je01.htm>

³ Evaluation of certain food additives and contaminants. Thirty-fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 789. 1990.

(b) (4) of the excipient at the MTDD of 2 g/day of morphine) are adequately justified for safety.

Xanthan Gum (CAS 11138-66-2)

Xanthan gum may be used safely in foods according to 21 CFR §172.695. There is no limitation listed in the CFR in terms of dose. An ADI (average daily intake) for xanthan gum was previously established by JECFA (Joint FAO/WHO Expert Committee on Food Additives) at up to 10 mg/kg, which is 600 mg for an average human weighing 60 kg; however, new data has been presented to further weigh in on the determination of the ADI⁴. New 2-year studies in rats failed to demonstrate carcinogenicity and toxicity attributed to xanthan gum, negative results in reproduction studies in rats, and no toxic effects in short-term studies in rats, rabbits, guinea pigs, and dogs as evaluated by JECFA. It is suggested by JECFA that up to 10-13 grams daily in humans indicated no adverse effects. Thus, the levels of xanthan gum in this formulation (b) (4) of the excipient at the MTDD of 2 g/day of morphine) are adequately justified for safety.

(b) (4)
(b) (4) contains ethyl acrylate and methyl methacrylate copolymer 2:1, 750,000 MW, which is listed in the IID with a maximum potency of (b) (4) per dosage form in an FDA-approved oral tablet product for a chronic indication. The daily dosing regimen for this product is 1 to 2 tablets a day, resulting in up to (b) (4) of the excipient. However, this is significantly less than the amount of this excipient at the MTDD of 2 g/day of morphine via (b) (4) tablets (b) (4) and is therefore considered a novel use of this excipient in this drug product. At the MTDD of 2 g/day of morphine, there is (b) (4) of the (b) (4).

To qualify the total daily amount of (b) (4), the Applicant submitted 6-month toxicology studies evaluating (b) (4) (b) (4) in the rat and (b) (4) in the dog, which are in the DMF (MF (b) (4)). The reader is referred to Section 6 below for a formal review of these studies. The NOAELs obtained are 2000 and 125 mg/kg for the rat and dog, respectively. At the MTDD of 2 g/day of morphine, the rat and dog NOAEL confer an exposure margin of 10.1 and 2.1, respectively.

(b) (4)
(b) (4) is a novel excipient that is not present in any FDA-approved drug products and is not listed in the IID.

(b) (4) contain ethyl acrylate and methyl methacrylate copolymers (2:1). The main differences between these (b) (4) compounds are the (b) (4) used and the molecular weights. (b) (4) is of lower molecular weight than (b) (4) (600,000 vs. 750,000 g/mol). It is noted that the Applicant stated that molar mass fractions below (b) (4) in the (b) (4) was negligible (mean 0.06%; n=6 batches) and there was no fraction below (b) (4). For (b) (4), the (b) (4) is (b) (4) which is also called (b) (4). The

⁴ <http://www.inchem.org/documents/jecfa/jecmono/v21je13.htm>

(b) (4) for (b) (4) The (b) (4)
(b) (4) is also known as (b) (4) as per the European
Pharmacopeia and (b) (4) as per the USP. Other synonyms include (b) (4)

At the MTDD of 2 g/day of morphine ARER via (b) (4), the level of (b) (4)
(b) (4) is (b) (4) which would result in delivery of (b) (4) of the (b) (4). As
(b) (4) is not in the IID, the safety of this excipient must be justified by
evaluation of both the backbone of the ethyl acrylate and methyl methacrylate
copolymers (2:1) and the (b) (4). The 6-month
toxicology studies with (b) (4) backbone in the rat and dog were reviewed
(the reader is referred to Section 6 below). The NOAELs obtained are 2000 and 125
mg/kg for the rat and dog, respectively. At the MTDD of 2 g/day of morphine, the rat
and dog NOAEL confer an exposure margin of 35.4 and 7.37, respectively, for the
copolymer backbone.

Information regarding (b) (4) are in MF (b) (4)
submitted by (b) (4). The
Applicant has a letter of authorization (LOA) to this DMF⁵. MF (b) (4) contains toxicity
data in support of (b) (4) and the Applicant also submitted the pivotal
toxicology studies to the NDA (see table below in Section 3 Studies Submitted). These
studies include repeat-dose general toxicology studies of various durations, embryonic
fetal development studies, and mutagenicity studies for the various (b) (4)
(b) (4) which are reviewed in Sections 6, 7, and 9. It is noted that
there are no carcinogenicity studies for any (b) (4). Rather, the Applicant provided a
weight-of-evidence justification why these studies are not necessary. The Applicant is
leveraging the data for (b) (4) for a 6-month nonrodent toxicology study.
(b) (4) contains ethyl acrylate and methyl methacrylate copolymer (2:1)
with a molecular weight of 750,000 g/mol and (b) (4).
Thus, (b) (4) are all similar to
one another.

The following table illustrates the quality attributes of these (b) (4) copolymers
discussed in this review (reproduced from from the Applicant's submission):

⁵ See the MF review for further information and discussions regarding (b) (4).

(b) (4)



(b) (4)



(b) (4)



(b) (4)



Ethyl acrylate (CAS 140-88-5)

Ethyl acrylate was not mutagenic in an Ames test using *S. typhimurium* strains TA98, TA100, and TA1537 without metabolic activation (Ishidate et al., 1981). In another study, 0.001 to 5.0 mcL/plate of ethyl acrylate was tested for mutagenic potential using strains TA1535, TA1537, TA98, TA100, and *Saccharomyces cerevisiae* strain D4 with and without metabolic activation and negative (Industry Acrylate Testing Group (IATG) 1982). In a L5178T TK+/- mouse lymphoma assay, ethyl acrylate tested at concentrations of 20 to 27.5 mcg/mL was determined to be mutagenic and clastogenic without metabolic activation (Moore et al., 1988). Similar findings were reported in two other studies in which ethyl acrylate was mutagenic without metabolic activation (Ciaccio et al., 1998; Dearfield et al., 1991). In an in vivo micronucleus test, ethyl acrylate administered as two IP doses 24 hours apart at doses of 112.5 to 1800 mg/kg resulted in increased MPEs. At all doses, the ratio of PCEs to NCEs was significantly increased (Przybojewska et al., 1984). The effect of ethyl acrylate on DNA damage in forestomach squamous epithelium was determined in an alkaline elution assay and was observed at single oral doses of 0.1% to 4.0% to not induce DNA damage (Morimoto et al., 1990).

In inhalational carcinogenicity studies, rats and mice were exposed to 6 hours per day to air containing 25 or 75 ppm ethyl acrylate for 27 months or to 225 ppm for 6 months followed by a 21-month recovery period. Mean body weight of rats and mice of the 75 and 225 ppm groups were significantly decreased throughout the study. No neoplasms were observed in rats or mice (Miller et al., 1985). In oral carcinogenicity studies, rats and mice dosed by gavage with 100 or 200 mg/kg ethyl acrylate in corn oil five times per week for 103 weeks (NTP 1986) resulted in cell papillomas and squamous cell carcinomas of the nonglandular stomach. It was described that these findings occurred at the site of chemical deposition in both male and female rats and mice in a dose and concentration dependent manner. Ethyl acrylate also caused irritation of the gastric nonglandular stomach mucosa in male and female rat and mice. It is noted that ethyl acrylate was labeled by IARC as “possibly carcinogenic to humans” based largely upon oral gavage studies in rats and mice (reported in 1986 by NTP) that produced tumors only of the forestomach. However, in 2000 NTP removed ethyl acrylate from its list of carcinogens and switched it to “reasonably anticipated to be a human carcinogen” based on the notion that the forestomach tumors were only when the chemical was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation. Doses of ethyl acrylate that induced tumors in the described carcinogenicity studies were 100 and 200 mg/kg/day, which is (b) (4) higher than the level of ethyl acrylate associated with the morphine ARER at the MTDD based on a body surface area comparison basis.

Therefore, the specification for ethyl acrylate is acceptable.

Methyl methacrylate (CAS 93-33-3)

Methyl methacrylate was nonmutagenic with or without metabolic activation in a Salmonella assay (Zeiger et al., 1990) but was positive with and without metabolic activation in a chromosomal aberration assay and SCE assay and was positive without metabolic activation in a mouse lymphoma assay.

Methyl methacrylate has not been tested in a dedicated carcinogenicity assessment but was evaluated in a chronic toxicology study via administration in drinking water up to 2000 ppm for 104 weeks (Borzelleca et. al, 1964). No abnormalities or lesions related to methyl methacrylate were identified and therefore the highest concentration of 2000 ppm was identified as the NOAEL. This is approximately (b) (4) higher than the level of methyl methacrylate associated with morphine ARER at the MTDD based on a body surface area comparison. In addition, several inhalational studies with methyl methacrylate (NTP, 1986) and closely related acrylates have not demonstrated any tumors in animals. It is noted that IARC 1994 gave the following evaluation for methyl methacrylate “there is inadequate evidence in humans for the carcinogenicity of methyl methacrylate. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals” and overall “methyl methacrylate is not classifiable as to its carcinogenicity to humans.”

The European Scientific Committee on Food has established a tolerable daily intake of methyl methacrylate of 0.1 mg/kg/day⁶ which correlates to 6 mg/day for a 60 kg person. This level is (b) (4) higher than the level of methyl methacrylate that could be consumed when this drug product is dosed up the MTDD.

Therefore, the specification for methyl methacrylate is acceptable.

(b) (4)

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⁶ http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_42.pdf



Overall Conclusions for the Safety of (b) (4)

| Excipient Components | Amount at the MTDD of twenty 100 mg ARER tablets (mg) | Qualified Up To the MTDD? |
|--|---|---------------------------|
| (b) (4) | | |
| Ethyl acrylate and methyl methacrylate copolymer 2:1 | | (b) (4) |
| (b) (4) | | |
| | | |
| | | |
| | | |
| (b) (4) | | |
| Ethyl acrylate and methyl methacrylate copolymer 2:1 | | (b) (4) |
| (b) (4) | | |
| | | |
| | | |

As stated earlier, the safety of the copolymeric backbone of (b) (4) (b) (4) has been addressed. Designated NOAELs identified in the repeat-dose toxicity studies in rats and dogs yield adequate safety margins. It was demonstrated that there is a lack of systemic exposure to (b) (4) and therefore reproductive and developmental toxicology studies are waived for the copolymeric backbone contained in (b) (4). In addition, based on a weight of evidence approach as outline in the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, a carcinogenicity assessment for the polymeric backbone was not deemed necessary (See Table below).

| Study or Literature Justification | Criteria | Meet Criteria? |
|--|---|---|
| B14-855500; B16-901500; B18-54000; Cosmetic Ingredient Review ⁸ | Negative genetic toxicology data | Yes |
| B06-101328 | Limited systemic exposure | Yes |
| None | Absence of accumulation based on nonclinical and clinical PK data | Yes. Although not definitely demonstrated, due to the large MW of the molecule and limited systemic |

⁸ Fiume MZ. Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients. *International Journal of Toxicology*, 2000;21(Suppl.3):1-50.

| | | |
|---|--|--|
| | | exposure after single administration, it is not expected that this excipient will accumulate significantly. |
| B05-101327; B17-53990 | Negative histopathology data from chronic toxicology studies | Yes |
| There are numerous FDA-approved oral drug products containing ethyl acrylates; methyl acrylates, and other acrylate-based polymers. | Knowledge of other excipients in the same class | Yes. However it should be noted that to our knowledge there are no carcinogenicity studies for acrylate polymers. Studies have been completed on the more reactive monomers that make up the polymers. See the risk assessment for the monomers for further details. |

As both (b) (4) are considered novel for the oral route of administration, the Applicant has attempted to justify the safety of the (b) (4) (b) (4), at the levels found at the MTDD of 2 g/day of morphine, which is (b) (4) (b) (4) respectively (summary of the data is shown in the table below). (b) (4) appears to be systemically absorbed whereas (b) (4) is not predicted to be systemically absorbed due to the differences in their molecular weights. There are no reproductive and developmental studies with (b) (4) alone and only embryo-fetal development studies conducted in rats and rabbits with (b) (4) (b) (4) containing (b) (4). There are published reproductive and developmental studies with an analogous compound, (b) (4) in rats that appear to resemble the portions of the standard fertility and the pre- and postnatal reproductive and developmental toxicology studies; however, they do not characterize male fertility or in utero effects on post-natal development. There is a published mouse and rat carcinogenicity assessment of an analogous compound, (b) (4). However, these studies only tested female animals. With respect to (b) (4), there are no assessments of the developmental and reproductive toxicology battery or the genetic toxicology battery in (b) (4). In addition, (b) (4) is likely to be absorbed due to its lower molecular weight.

Summary of studies submitted with the NDA

| Study | (b) (4) | (b) (4) (studies published in the literature) | (b) (4) (studies published in the literature) |
|-------------|---------|--|--|
| Chronic rat | 6-month | Summaries | Summaries of 3- |

| | | | | | |
|---|---|--|---------|---|--|
| | | | | of 3-month and 2-year oral studies in rats with various analogous compounds | month feed study with analogous compounds (b) (4) |
| Chronic dog | | | 6-month | Summaries of 3-month studies and 2-year oral studies in dogs with various analogous compounds | Summaries of 3-month feed study with analogous compound (b) (4) - (b) (4) |
| Fertility and Early Embryonic Development | | | | Female fertility only (b) (4) & Male sperm assessments (b) (4) | Summary of a multigenerational rat study with analogous compound (b) (4) |
| Embryo-fetal Rat | X | | | | Summary of a multigenerational rat study with analogous compound (b) (4) |
| Embryo-Fetal Rabbit | X | | | | |
| Pre- and Postnatal | | | | Possible lactational exposure only (b) (4) | Summary of a multigenerational rat study with analogous compound (b) (4) |
| Carcinogenicity | | | | Mouse & Rat (female only with (b) (4); Rat and Dog with various analogous | Summaries of two 2-year feed studies in rats with analogous compound (b) (4) |

| | | | | | |
|--|--|--|--|-----------|--|
| | | | | compounds | |
|--|--|--|--|-----------|--|

Regarding a carcinogenic assessment of (b) (4), based on a weight of evidence approach as outline in the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, a carcinogenicity assessment for (b) (4) was not deemed necessary (See Table below).

| Criteria | Study or Literature Justification | Meet Criteria? |
|---|--|---|
| Negative genetic toxicology data | B14-855500; B16-901500; B18-54000; Lambert et. al, 2004; Meyer et. al, 1988; Buttar et. al, 1986; Johnson et. al, 2004 | Yes |
| Limited systemic exposure | B06-101328 | Yes. Although not definitely demonstrated, due to the large MW of the molecule and predicted limited systemic exposure, it is not expected that this excipient will accumulate significantly. |
| Absence of accumulation based on nonclinical and clinical PK data | None | Yes. Although not definitely demonstrated, due to the large MW of the molecule and limited systemic exposure after single administration, it is not expected that this excipient will accumulate significantly. |
| Negative histopathology data from chronic toxicology studies | B05-101327; B17-53990; CIR, 1983; CIR, 2015; Inoue et. al, 1999a; Inoue et. al, 1999b; Smyth and Calandra 1969 | Yes |
| Knowledge of other excipients in the same class | (b) (4) is FDA-approved for use as a spermicide; carcinogenicity assessments with (b) (4) in female rats and mice, | Yes |

Regarding a carcinogenic assessment of (b) (4), based on a weight of evidence approach as outline in the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, a carcinogenicity assessment for (b) (4) was deemed necessary (See Table below).

| Criteria | Study or Literature Justification | Meet Criteria? |
|----------|-----------------------------------|----------------|
|----------|-----------------------------------|----------------|

| | | |
|---|---|---|
| Negative genetic toxicology data | (b) (4) are not mutagenic or carcinogenic as per CIR 1988 review; Zeiger et. al, 1987 and Buzzi and Wurgler 1990 demonstrated that (b) (4) is negative for genetic toxicity | No studies with (b) (4) were submitted. However, structurally similar compounds do not appear to be genotoxic and (b) (4) is in FDA approved dermal products. |
| Limited systemic exposure | None | No. Although no toxicokinetic studies have been performed, the molecular weight of (b) (4) is (b) (4), which suggests the potential for some absorption. What is absorbed is likely lower molecular weight compounds that appear to be renally excreted. |
| Absence of accumulation based on nonclinical and clinical PK data | None | No. Although no toxicokinetic studies have been performed, the molecular weight of (b) (4) is (b) (4), which suggests the potential for absorption. There are no reports suggesting accumulation of (b) (4) in toxicology studies with similar chemical structures. |
| Negative histopathology data from chronic toxicology studies | CIR 1999; CIR 2012 (90-day feed studies in rats and dogs with (b) (4) as well as 90-day feed studies in rats with (b) (4) and 2-year feed studies in rats with (b) (4) | No. Summary data suggestion no preneoplastic lesions, but cannot be independently verified. |
| Knowledge of other excipients in the same class | CIR 1999; CIR 2012 (90-day feed studies in rats and dogs with (b) (4) as well as 90-day feed studies in rats with (b) (4) and 2-year feed studies in rats with (b) (4) | Yes. There no oral carcinogenic assessments in both rats and mice for (b) (4). There is a published summary of unpublished data for (b) (4) suggesting no tumors, but these data cannot be independently verified. |

As shown in the table above, there are no genetic toxicity studies performed with (b) (4) and the likelihood of absorption of (b) (4), the carcinogenicity assessment of (b) (4) in both rats and mice is deemed necessary.

2.5 Comments on Impurities/Degradants of Concern Drug Substance

Information on the drug substance, morphine sulfate, is supplied via reference to the data in MF 6967. The following table illustrates the drug substance specifications (adapted from the Applicant's submission):

| Impurity | Acceptance Criteria | Reviewer's Comments |
|-----------------|----------------------------|----------------------------|
| (b) (4) | | |

(b) (4)

Normally, these specifications would normally have to be lowered to meet ICH Q3A(R2) qualification thresholds. However, MF 6967 has been used in a number of products with the same drug substance impurity profile (see MF 6967 quality review dated (b) (4) (b) (4)). Thus, there is clinical experience with these levels of the drug substance impurities and there are no nonclinical concerns with the drug substance specifications. The proposed drug substance specifications are acceptable.

Drug Product

The drug product specifications for the Morphine ARER tablets are illustrated in the following table (from the Applicant's submission):

| Test | Acceptance Criterion | | | | Analytical Procedure |
|--|----------------------|-------|-------|-------|----------------------|
| | 100 mg | 60 mg | 30 mg | 15 mg | |
| (b) (4) | | | | | |
| HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia. | | | | | |



The proposed specifications for the 15, 30, and 60 mg strength ARER tablets are acceptable.

Since the MTDD of 2 g/day of morphine will be achieved by taking twenty of the 100 mg ARER tablets, the following table illustrates the drug product specifications of the 100 mg ARER tablets only (adapted from the Applicant's submission):

| Degradant | Acceptance Criteria | Reviewer's Comments |
|------------------|----------------------------|----------------------------|
| (b) (4) | | |

The drug product specifications are acceptable.

Container Closure System

As this drug product is formulated into tablets, a drug-specific assessment of the extractables and leachables from the container closure system will not be required as long as the container closure system is acceptable to the CMC review team via reference to indirect food additive regulations in 21 CFR §174-186.

2.6 Proposed Clinical Population and Dosing Regimen

As with the MS CONTIN®, morphine sulfate is not intended for use as an as-needed analgesic due to risks of addiction, abuse, and misuse with opioids. Rather it is intended only for use when daily, around-the-clock, long-term opioid treatments (b) (4) (b) (4) and alternative treatment options are inadequate (b) (4). In this respect, the proposed label for this morphine sulfate ARER product is similar to MS CONTIN®. This morphine product is planned to be marketed as 15, 30, 60, 100 mg tablets with the following prescribed use: For use as the first analgesic, take the 15 mg tablet orally every (b) (4) 12 hours. For use in opioid tolerant patients, the starting dose is 15 mg orally every 12 hours, followed by titration of increasing doses of morphine to achieve adequate analgesia with minimal adverse reactions. Patients who are opioid tolerant are those receiving at least 60 mg of oral morphine for one week or longer. Discontinuation of morphine sulfate should involve a gradual downward titration of dose to prevent the signs and symptoms of withdrawal in a physically-dependent patient. Proposed labeling states that the safety and effectiveness in pediatric patients below the age of 18 have not been established.

2.7 Regulatory Background

The Applicant is submitting NDA 206544 via the 505(b)(2) regulatory pathway and is relying upon the Agency's previous findings of safety for MS CONTIN® to support the proposed clinical study using their formulation of morphine sulfate ARER oral tablets.

The active ingredient, morphine sulfate, was originally approved in 1941. The referenced drug product, morphine sulfate (MS CONTIN®) was approved on May 29, 1987.

There was no preIND meeting for this particular drug product; however, the Agency provided advice regarding the requirements for a proposed drug delivery platform, on February 16, 2010. At that time, advice was given regarding the need for adequate safety justification for the novel excipients, and the proposed drug product and drug substance specifications.

The initial IND for this drug product, Morphine Sulfate ARER, was submitted on September 14, 2012 (IND 115822) and the proposed study was allowed to proceed. The IND has been active since October 14, 2012.

3 Studies Submitted

3.1 Studies Reviewed

The following table illustrates the studies that were submitted in this NDA and reviewed:

| Study Title | Study Number |
|--|--------------|
| Investigation of the Effect of 2837D Administered in the Food on the Pregnant Rat and the Foetus | B03-101325 |
| Examination on the Influence 2837E on the Pregnant Rabbit and the Foetus by Administration in the Diet | B04-101326 |
| 6-Month Toxicity of 2837D in Sprague-Dawley Rats by Administration in the Diet | B05-101327 |
| ¹⁴ C- (b) (4): The Excretion and Tissue Distribution of Radioactivity After Oral Administration to Rats | B06-101328 |
| (b) (4) Assessment of Mutagenic Potential by the "Ames Test" | B07-100072 |
| Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells with (b) (4) | B14-855500 |
| Salmonella Typhimurium Reverse Mutation Assay with (b) (4) | B16-901500 |
| Report B17-53990: (b) (4) 26 Week Oral Toxicity Study in Dogs Followed by a 3 Week Recovery Period | B17-53990 |
| Report B18-54000: (b) (4) Micronucleus Test in Mice | B18-54000 |

It is noted that in the in the Applicant's Excipient Safety Assessment Report, the Applicant has confirmed that (b) (4) was the former name for (b) (4) (b) (4)

3.2 Studies Not Reviewed

The studies outlined below were evaluated for relevance to the NDA submission but not formally reviewed because they were not deemed necessary for approval (see table below):

(b) (4)



3.3 Previous Reviews Referenced

There were no previous reviews referenced.

4 Pharmacology

4.1 Primary Pharmacology

There were no new primary pharmacology studies with morphine submitted in this NDA or required for this 505(b)(2) application.

4.2 Secondary Pharmacology

There were no new secondary pharmacology studies with morphine submitted in this NDA or required for this 505(b)(2) application.

4.3 Safety Pharmacology

There were no new safety pharmacology studies with morphine submitted in this NDA or required for this 505(b)(2) application.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no new nonclinical pharmacokinetics or ADME studies with morphine submitted in this NDA or required for this 505(b)(2) application.

The Applicant submitted an excretion and tissue distribution assessment of radiolabeled (b) (4) in this NDA. The study is cross-referenced in MF (b) (4). It is noted that the Applicant has confirmed that (b) (4) is the former product name for (b) (4).

Title: ^{14}C - (b) (4): **The Excretion and Tissue Distribution of Radioactivity After Oral Administration to Rats** (b) (4)

Study Number: B06-101328

Rats were administered a single oral dose (55 to 75 mg) of (b) (4) that was labeled with ^{14}C (Code 4297-17) and as shown to have a specific radioactivity of 0.17 mCi/mg. There was no information given regarding the purity of the test article. The radioactivity level was measured in feces and urine for 7 days post dose as well as in the blood, liver, kidney, mesenteric lymph nodes, spleen, small intestine, and large intestine at 1, 3, 7, and 14 days post dose. This excretion and tissue distribution study was conducted in 1974 prior to Good Laboratory Practices (GLP). A number of GLP deficiencies were noted, which included a lack of detailed description/characterization of the test article and lack of ability to verify the report findings against the raw data. However, this type of study is not normally required as a core GLP study and the results appear to be scientifically reasonable.

Adult Charles River CD strain male rats weighing 240-270 g at the beginning of dosing were used in this study. Urine samples were collected at intervals of 24 hours. The ^{14}C - (b) (4) was supplied as a film, which was approximately 20 to 30 mcm thick, and was inserted into the cut-end of a flexible cannula which was passed into the stomach. The film was expelled by injecting water through the cannula. There is no description of how the film was placed in the flexible cannula (e.g. tightly rolled into a ball, laid flat, or cut into small pieces). In discussions with the CMC Review Team, the

(b) (4) compound is a waxy material, from which a film can be made, which usually requires additional excipients. In an email dated August 17, 2015, the Applicant confirms that (b) (4). The Applicant also disclosed that during the manufacturing process of the tablets, both (b) (4) copolymers are (b) (4) and that upon (b) (4), a film is formed on the tablet. As such, the film preparation in this study is appropriate because it is representative of the film that is formed as part of the manufacturing process of (b) (4) copolymers on to the tablets. Radioactivity was measured in the urine and feces at 24 hour intervals over a period of 7 days. The rats were sacrificed afterwards and the liver, lung, spleen, kidney, mesenteric lymph nodes, small intestine, and large intestine were removed for radiochemical analysis.

Excretion Study results:

The following table illustrates the excretion of radioactivity in the urine of rats following oral administration of ^{14}C - (b) (4) (from the Applicant's submission):

TABLE 4 : The excretion of radioactivity, expressed as per cent of dose, in the urine of rats following the oral administration of ^{14}C - (b) (4).

| Rat | Dose μCi | Per-cent excretion on day | | | | | | | Total |
|-----|------------------------|---------------------------|--------|--------|-----|--------|--------|-----|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| 1 | 10.14 ¹⁾ | 0.006 | 0.0029 | 0.0024 | NIL | NIL | NIL | NIL | 0.0113 |
| 2 | 11.34 | 0.0065 | 0.0028 | 0.003 | NIL | NIL | NIL | NIL | 0.0123 |
| 3 | 11.05 | 0.0038 | 0.0034 | NIL | NIL | NIL | NIL | NIL | 0.0072 |
| 4 | 12.52 ²⁾ | 0.0045 | 0.0033 | 0.002 | NIL | NIL | 0.0008 | NIL | 0.0106 |
| 5 | 10.94 | 0.0033 | 0.0006 | 0.0003 | NIL | 0.0005 | NIL | NIL | 0.0047 |

1) 59,6 mg

2) 73,6 mg

As shown in the table above, an average of 0.0092% of ^{14}C - (b) (4) was collected in the urine within 7 days of administration, with most of the radioactivity excreted into the urine within 3 days of administration.

The following table illustrates the excretion of radioactivity in the feces of rats following oral administration of ^{14}C - (b) (4) (from the Applicant's submission):

TABLE 6 : The excretion of radioactivity, expressed as per cent of dose, in the faeces of rats after the oral administration of ^{14}C - (b)(4)

| Rat | Dose μCi | Per-cent of dose excreted on day | | | | | | Total |
|-----|------------------------|----------------------------------|------|------|------|------|------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6+7 | |
| 1 | 10.08 | 7.8 | 85.4 | 0.7 | 0.2 | 0.09 | 0.07 | 94.3 |
| 2 | 11.34 | 10.3 | 82.2 | 0.7 | 0.3 | 0.1 | 0.0 | 93.6 |
| 3 | 11.05 | 100.3 | 0.7 | 0.3 | 0.3 | 0.07 | 0.01 | 101.7 |
| 4 | 12.52 | 0.3 | 1.3 | 98.5 | 0.03 | 0.4 | 0.7 | 101.2 |
| 5 | 10.94 | 93.3 | 0.7 | 0.4 | 0.3 | 0.09 | 0.2 | 95.0 |

As shown in the table above, an average of 97.16% of ^{14}C - (b)(4) was in the feces within 7 days of administration.

The results of this excretion study indicate that the majority of radioactivity (approximately 97%) is excreted in the feces while a minimal amount (0.0092%) is excreted in the urine.

Tissue Distribution Study results:

To investigate the rate of elimination of radioactivity from the tissues of dosed animals, 9 male rats weighing 270-320 g of body weight were administered a single oral dose of ^{14}C - (b)(4). Groups of 3 animals were sacrificed after 24 hours, 3 days, and 14 days and the liver, kidney, spleen, mesenteric lymph nodes, small intestine, large intestine, and cardiac blood (3 to 4 mL) were removed and underwent radiochemical analysis.

The following tables illustrate the tissue distribution of radioactivity at 24 and 72 hours as well as at 7 and 14 days following oral administration of ^{14}C - (b)(4) in rats (from the Applicant's submission):

TABLE 7 : Radioactivity in the tissues of rats 24 hours after a single oral dose of ^{14}C -^{(b) (4)} film.

DOSE : Rat 1, 66.89 mg, 11.37 μCi ; Rat 2, 62.30 mg, 10.59 μCi ; Rat 3, 54.88 mg, 9.33 μCi .

| Rat | Tissue | Wet Weight (g) | Background ¹ | Absolute ² | Mean | Corrected ³ | Mean |
|-----|------------------------|----------------|-------------------------|-----------------------|------|------------------------|------|
| 1 | Liver | 15.0 | 281 | 187/235 | 211 | -70 | -40 |
| 2 | | 15.0 | | 266/214 | 240 | -41 | |
| 3 | | 12.5 | | 280/267 | 274 | -7 | |
| 1 | Kidney | 2.85 | 234 | 150/163 | 157 | -77 | -25 |
| 2 | | 2.80 | | 223/231 | 227 | -9 | |
| 3 | | 2.60 | | 243/249 | 246 | +12 | |
| 1 | Spleen | 0.88 | 157 | 204/211 | 208 | +51 | +24 |
| 2 | | 0.80 | | 194/155 | 175 | +18 | |
| 3 | | 0.60 | | 147/172 | 160 | +3 | |
| 1 | Mesenteric lymph nodes | 0.35 | 194 | 239/204 | 222 | +28 | 0 |
| 2 | | 0.50 | | 200/174 | 187 | -7 | |
| 3 | | 0.50 | | 169/179 | 174 | -20 | |
| 1 | Small Intestine | 6.10 | 159 | 223/194 | 209 | +50 | +25 |
| 2 | | 6.00 | | 212/196 | 204 | +45 | |
| 3 | | 5.50 | | 154/121 | 138 | -21 | |
| 1 | Large Intestine | 1.60 | 176 | 213/217 | 215 | +39 | +12 |
| 2 | | 1.40 | | 161/151 | 156 | -20 | |
| 3 | | 1.30 | | 189/197 | 193 | +17 | |
| 1 | Blood (ml) | 0.5 | 44 | 112/93 | 103 | +59 | +37 |
| 2 | | 0.5 | | 71/64 | 68 | +24 | |
| 3 | | 0.5 | | 63/83 | 73 | +29 | |

¹ counts per minute per 100 mg of solubilised tissues from control animals

² counts per minute per 100 mg of solubilised tissues from dosed animals

³ counts per minute per 100 mg of solubilised tissues from dosed animals after correcting for background activity (Column 4).

TABLE 8 : Radioactivity in the issues of rats 72 hours after single oral dose of ^{14}C -^{(b)(4)} Film

DOSE : Rat 1, 58.88 mg, 10.01 μCi ; Rat 2, 65.40 mg, 11.12 μCi ; Rat 3, 63.23 mg, 10.75 μCi .

| Rat | Tissue | Wet Weight (g) | Background ¹ | Absolute ² | Mean | Corrected ³ | Mean |
|-------------|------------------------|----------------------|-------------------------|-------------------------------|-------------------|------------------------|------|
| 1 2 3 | Liver | 15.0 14.0 13.0 | 281 | 251/288 235/186 230/236 | 270 211 233 | -11 -70 -48 | -43 |
| 1 2 3 | Kidney | 2.7 2.5 3.0 | 234 | 296/266 215/173 180/245 | 281 194 213 | +47 -40 -21 | -5 |
| 1 2 3 | Spleen | 0.60 0.50 0.80 | 157 | 168/150 192/133 193/178 | 159 163 186 | +2 +6 +29 | +12 |
| 1 2 3 | Mesenteric lymph nodes | 0.70 1.00 0.80 | 194 | 254/259 300/257 169/188 | 257 279 179 | +63 +85 -15 | +44 |
| 1 2 3 | Small intestine | 6.2 5.2 6.0 | 159 | 206/171 227/265 204/201 | 189 246 203 | +30 +87 +44 | +54 |
| 1 2 3 | Large intestine | 1.5 1.2 1.1 | 176 | 184/185 199/163 137/146 | 185 181 142 | +9 +5 -34 | -7 |
| 1 2 3 | Blood (ml) | 0.5 0.5 0.5 | 44 | 46/40 51/58 51/60 | 43 55 56 | -1 +11 +12 | +7 |

¹ counts per minute per 100 mg of solubilised tissues from control animals

² counts per minute per 100 mg of solubilised tissues from dosed animals

³ counts per minute per 100 mg of solubilised tissues from dosed animals after correcting for background activity (Column 4).

TABLE 9 : Radioactivity in the tissues of rats 7 days after a single oral dose of ^{14}C -^{(b)(4)} film.

DOSE : Rat 1, 59.63 mg, 10.14 μCi ; Rat 2, 66.73 mg, 11.34 μCi ; Rat 3, 65.0 mg, 11.05 μCi ;
Rat 4, 73.63 mg, 12.52 μCi ; Rat 5, 64.33 mg, 10.94 μCi .

| Rat | Tissue | Wet Weight (g) | Background ¹ | Absolute ² | Mean | Corrected ³ | Mean |
|-----|------------------------|----------------|-------------------------|-----------------------|------|------------------------|------|
| 1 | Liver | 11.4 | 281 | 321/300 | 311 | +30 | +7 |
| 2 | | 12.0 | | 274/258 | 266 | -15 | |
| 3 | | 13.1 | | 294/269 | 282 | +1 | |
| 4 | | 10.7 | | 319/336 | 328 | +47 | |
| 5 | | 10.9 | | 265/242 | 254 | -27 | |
| 1 | Kidney | 2.77 | 234 | 163/177 | 170 | -64 | -7 |
| 2 | | 2.80 | | 287/267 | 277 | +43 | |
| 3 | | 2.75 | | 281/293 | 287 | +53 | |
| 4 | | 2.90 | | 246/259 | 253 | +19 | |
| 5 | | 2.72 | | 154/146 | 150 | -84 | |
| 1 | Spleen | 0.65 | 157 | 200/185 | 193 | +36 | +14 |
| 2 | | 0.68 | | 165/139 | 152 | -5 | |
| 3 | | 0.95 | | 138/147 | 143 | -14 | |
| 4 | | 0.55 | | 184/190 | 187 | +30 | |
| 5 | | 0.50 | | 174/187 | 181 | +24 | |
| 1 | Mesenteric lymph nodes | 0.40 | 194 | 240/221 | 231 | +37 | +93 |
| 2 | | 0.42 | | 264/282 | 273 | +79 | |
| 3 | | 0.45 | | 465/438 | 452 | +258 | |
| 4 | | 0.39 | | 275/248 | 262 | +68 | |
| 5 | | 0.45 | | 211/218 | 215 | +21 | |
| 1 | Small intestine | 6.3 | 159 | 144/160 | 152 | -7 | +33 |
| 2 | | 6.6 | | 221/193 | 207 | +48 | |
| 3 | | 6.85 | | 201/198 | 200 | +41 | |
| 4 | | 5.90 | | 232/190 | 211 | +52 | |
| 5 | | 7.60 | | 191/186 | 189 | +30 | |
| 1 | Large intestine | 1.30 | 176 | 163/145 | 154 | -22 | -6 |
| 2 | | 1.25 | | 192/177 | 185 | +9 | |
| 3 | | 1.45 | | 184/164 | 174 | -2 | |
| 4 | | 1.20 | | 148/127 | 138 | -38 | |
| 5 | | 1.45 | | 195/201 | 198 | +22 | |
| 1 | Lung | 1.8 | 168 | 168/174 | 171 | +3 | +2 |
| 2 | | 1.9 | | 136/158 | 147 | -21 | |
| 3 | | 1.4 | | 182/165 | 174 | +6 | |
| 4 | | 1.6 | | 178/181 | 180 | +12 | |
| 5 | | 1.8 | | 183/177 | 180 | +12 | |

¹ counts per minute per 100 mg of solubilised tissues from control animals

² counts per minute per 100 mg of solubilised tissues from dosed animals

³ counts per minute per 100 mg of solubilised tissues from dosed animals after correcting for background activity (Column 4).

TABLE 10 : Radioactivity in the tissues of rats 14 days after a single oral dose of ^{14}C -(b) (4) film.

DOSE : Rat 1, 75.65 mg, 12.86 μCi ; Rat 2, 57.56 mg, 9.79 μCi ; Rat 3, 62.57 mg, 10.64 μCi .

| Rat | Tissue | Wet Weight (g) | Background ¹ | Absolute ² | Mean | Corrected ³ | Mean |
|-------------|------------------------|------------------------|-------------------------|-------------------------------|-------------------|------------------------|------|
| 1 2 3 | Liver | 18.0 15.85 14.70 | 281 | 338/325 280/275 301/292 | 332 278 297 | +51 -3 +16 | +21 |
| 1 2 3 | Kidney | 3.3 3.4 2.8 | 234 | 222/242 198/180 255/261 | 232 189 258 | -2 -45 +24 | -8 |
| 1 2 3 | Spleen | 0.80 0.70 0.65 | 157 | 131/102 180/195 150/135 | 117 188 143 | -40 +31 -14 | -8 |
| 1 2 3 | Mesenteric lymph nodes | 1.20 1.25 1.25 | 194 | 157/172 137/140 247/237 | 165 139 242 | -29 -55 +48 | -12 |
| 1 2 3 | Small intestine | 6.65 5.90 6.25 | 159 | 167/182 130/134 101/121 | 175 132 111 | +16 -27 -48 | -20 |
| 1 2 3 | Large intestine | 1.85 2.00 1.80 | 176 | 169/198 150/162 166/148 | 184 156 157 | +8 -20 -19 | -10 |
| 1 2 3 | Blood (ml) | 0.5 0.5 0.5 | 44 | 43/38 50/51 52/59 | 41 51 56 | -3 +7 +12 | +5 |

¹ counts per minute per 100 mg of solubilised tissues from control animals

² counts per minute per 100 mg of solubilised tissues from dosed animals

³ counts per minute per 100 mg of solubilised tissues from dosed animals after correcting for background activity (Column 4).

As shown in the tables above, minimal radioactivity due to ^{14}C -(b) (4) was detected in various tissues at the timepoints analyzed. At 24 hours post dose, no radioactivity was detected in the liver, kidney, or mesenteric lymph nodes; however, minimal radioactivity was detected in the spleen, small intestine, large intestine and blood.

At 72 hours post dose, no radioactivity was detected in the liver, kidney, and large intestine; however minimal radioactivity was detected in the spleen, mesenteric lymph nodes, small intestine, and blood. The amount of radioactivity in the small intestine and blood has decreased from the 24 hour post dose timepoint.

At 7 days post dose, no radioactivity was detected in the kidney and large intestine; however, there is radioactivity in the liver, spleen, mesenteric lymph nodes, small intestine, and lung. The levels of radioactivity in the mesenteric lymph nodes are greater than in the previous timepoints. This is primarily driven by data from one of the 5 animals tested.

At 14 days post dose, no radioactivity was in the kidney, spleen, mesenteric lymph nodes, small intestine, and large intestine; however, minimal radioactivity was present in the liver and blood. Shown below is a summary of the corrected radioactivity level in various tissues over time.

Corrected Tissue Radioactivity* Over Time

| Tissue | Day 1 | Day 3 | Day 7 | Day 14 |
|-----------------------|-------|-------|-------|--------|
| Liver | -40 | -43 | 7 | 21 |
| Kidney | -25 | -5 | -7 | -8 |
| Spleen | 24 | 12 | 14 | -8 |
| Mesenteric Lymph Node | 0 | 44 | 93 | -12 |
| Small Intestine | 25 | 54 | 33 | -20 |
| Large Intestine | 12 | -7 | -6 | -10 |
| Blood | 37 | 7 | | 5 |

*Counts per minute per 100 mg of solubilized tissue from dose animals after correcting for background activity

As seen in the Table above, there were no significant trends over time. Radioactivity levels in all tissues were comparable to the background levels. The results of this excretion and tissue distribution study indicate that (b) (4) is not absorbed and is excreted in the feces.

5.2 Toxicokinetics

There were no toxicokinetics studies with morphine submitted in this NDA.

6 General Toxicology

There were no new general toxicology studies with morphine submitted and reviewed in this NDA.

Repeat-dose 6-month general toxicology studies in the rat and dog were submitted in this NDA with (b) (4), respectively, and reviewed. These studies were also cross-referenced in MF (b) (4).

6.2 Repeat-Dose Toxicity

Study title: 6-Month Toxicity of 2837 D in Sprague-Dawley Rats by Administration in the Diet (2837 D = (b) (4))

Study no.: B05-101327
Study report location: Module 4 of the Electronic Submission
Conducting laboratory and location: (b) (4)
Date of study initiation: Approximately February 1962 (no specific date given)
GLP compliance: See GLP compliance evaluation below
QA statement: None
Drug, lot #, and % purity: 2837 D is (b) (4) which has been confirmed to be the former product name for (b) (4). As this study was done prior to GLP, the lot # and purity was not provided.

Key Study Findings

- Sprague-Dawley rats were given 0, 500, and 2000 mg/kg of (b) (4) via the diet for 6 months.
- This study was done prior to GLP. The Applicant included a GLP evaluation to determine GLP deficiencies, which noted that there was a lack of detail description/characterization of the test article and there was a lack of verification that the raw data match the final report. The report concludes that this study can be used to support the safety of the test article (2837 D) up to 2000 mg/kg in rats because the study appears to be well-controlled and includes detailed tables and figures of the individual animal data results. However, it would be difficult to extrapolate these findings to any substance manufactured today without knowledge of the exact composition and description of the test article.
- All rats survived to the scheduled necropsy.
- There were no treatment-related changes in clinical signs (including behavioral changes), body weights, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, gross pathology, and organ weights.
- It is noted that histopathology was done with the 2000 mg/kg dose group only. The observations of slight fatty degeneration in the liver and trace microliths in the kidney at the 2000 mg/kg dose group do not appear to be detrimental to health and are not biologically significant because the liver processes fats on a regular basis and tiny stones pass through the kidney regularly.
- However, histopathology was not performed in the control, 500 mg/kg dose groups, and recovery groups in this study, making interpretation of the histopathology findings difficult.
- The Applicant's NOAEL is 2000 mg/kg.

- Taken together, the LOAEL is likely 2000 mg/kg because there were no toxicological signs (such as body weight, hematology, clinical chemistry, and macroscopic observations) and the only histopathological changes observed at the 2000 mg/kg dose group were in the kidney (trace microliths) and liver (slight fatty degeneration), which were not believed to be biologically significant.
- The human equivalent dose is 19459.5 mg of (b) (4) in an average human weighing 60 kg based on a body surface area comparison. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) and an exposure margin of 10.1 for the excipient.
- The human equivalent dose is 19459.5 mg of (b) (4) (copolymer backbone) in an average human weighing 60 kg based on a body surface area comparison. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) (b) (4) and an exposure margin of 35.4 to the copolymeric backbone.

Methods

Doses: 0, 500, and 2000 mg/kg
 Frequency of dosing: Daily
 Route of administration: Oral via diet
 Dose volume: Unknown (rats ate feed containing (b) (4) (b) (4) until they were satiated)
 Formulation/Vehicle: The test compound is in the feed. See below for the contents of the food given to each rat
 Species/Strain: Rats/Sprague-Dawley
 Number/Sex/Group: 20/sex/group
 Age: 39 days (males), 43 days (females)
 Weight: 100 to 105 grams
 Satellite groups: No toxicokinetics group
 Unique study design: No recovery group, histopathology was done on the high dose group (2000 mg/kg) only, and no toxicokinetics.
 Deviation from study protocol: There were no deviations from this protocol.

The following table illustrates the study design (from the Applicant's submission):

| Group/sex | 2837 D dosage in mg/kg body wt/day in the feedstuff | Treated food in g/kg body wt/day | Number of animals | Rat no. |
|-----------------------------------|---|----------------------------------|-------------------|------------------|
| (I) male rats female rats | 500 | 5 | 20 20 | 1 - 20 1 - 20 |
| (II) male rats female rats | 2000 | 20 | 20 20 | 1 - 20 1 - 20 |
| (III) male rats female rats | Controls | 20 (Blank preparation) | 20 20 | 1 - 20 1 - 20 |

The following table illustrates the contents of the food for each rat without (b) (4)
(b) (4) (from the Applicant's submission):

Standardised powdered food (b) (4)
(b) (4)

ANALYSIS (mean values)

| | |
|-----------------------------|--------|
| Crude protein | 19.2% |
| Crude fibre | 5.3% |
| Crude fat | 4.0% |
| Ash | 6.5% |
| H ₂ O | 10.8% |
| N-free extractive substance | 54.2% |
| | <hr/> |
| | 100.0% |

| | | | |
|-------------------------|-------------------|-------------------------------|-------------------|
| Lysine | 11 000 mg/kg ± 5% | Tryptophan | 2 900 mg/kg ± 15% |
| Methionine | 5 700 mg/kg ± 15% | Arginine | 9 100 mg/kg ± 5% |
| Cystine | 3 500 mg/kg ± 15% | Glycine | 12 200 mg/kg ± 5% |
| Vitamin A | 10 000 IU/kg | Pantothenic acid | 21.5 mg/kg |
| Vitamin D | 1 000 IU/kg | Pyridoxine | 5.2 mg/kg |
| Vitamin E | 37.2 mg/kg | Folic acid | 0.9 mg/kg |
| Vitamin B ₁ | 3.7 mg/kg | Choline | 1 302.3 mg/kg |
| Vitamin B ₂ | 14.5 mg/kg | Nicotinic acid | 69.8 mg/kg |
| Vitamin B ₁₂ | 20.1 µg/kg | | |
| Chlorine | 2 800 mg/kg | Manganese | 42 mg/kg |
| Sodium | 1 200 mg/kg | Iron | 262 mg/kg |
| Potassium | 4 600 mg/kg | Zinc | 20 mg/kg |
| Calcium | 13 700 mg/kg | Copper | 7.4 mg/kg |
| Phosphorus | 9 350 mg/kg | Cobalt | 180 µg/kg |
| Sulphur | 1 250 mg/kg | Iodine | approx. 14 mg/kg |
| Barley | 45% | (b) (4) yeast, dried | 5% |
| Oats, rough-ground | 18% | (b) (4) green meal | 4% |
| Maize, rough-ground | 10% | Wheat germ, crushed | 3% |
| Fish meal | 6% | Mineral and active substances | 3% |
| Meat meal | 6% | | <hr/> |
| | | | 100% |

1000 g of this feedstuff contains an additional:

| | | | |
|----------------------------|--------------|----------------------------|-----------|
| Vitamin A | 10 000 IU/kg | Vitamin B ₆ HCl | 10 mg/kg |
| Vitamin D | 200 IU/kg | Vitamin B ₁₂ | 10 µg/kg |
| Vitamin E ₃ | 100 mg/kg | Calcium pantothenate | 10 mg/kg |
| Vitamin K | 5 mg/kg | Nicotinamide | 15 mg/kg |
| Vitamin C | 20 mg/kg | Choline chloride | 300 mg/kg |
| Vitamin B ₁ HCl | 30 mg/kg | Folic acid | 3 mg/kg |
| Vitamin B ₂ | 10 mg/kg | | |

The test compound, (b) (4), is sprayed onto the food pellets (at a ratio of 1:10) and allowed to dry prior to feeding to the rats. The food stuffs were sprayed with water and dried prior to feeding the control rats.

GLP compliance evaluation report was performed by the Applicant. The report notes that there were multiple deficiencies from a GLP standpoint but points out 2 deficiencies, 1) there is a lack of detail description/characterization of the test article and 2) there is a lack of verification that the raw data match the final report. However, the report does conclude that this study can be used to support the safety of the test article (2837 D) up to 2000 mg/kg in rats because the study appears to be well-controlled and includes detailed tables and figures of the individual animal data results. However, the test article (film) used in this study, namely 2837 D, has been confirmed to be (b) (4) and that this formulation is acceptable because oral gavage formulations that may be in a different state are routinely used to demonstrate the safety of solid oral products.

Observations and Results

Mortality

The behavior and general condition of the rats were monitored daily. All rats survived until the end of treatment.

Clinical Signs

The behavior and general condition of the rats were monitored daily. Additionally, after 26 weeks of treatment, auditory function was tested by means of a simple noise test and the teeth were inspected. There were no changes to the outward appearance and behavior of the rats. The feces were normal and there were no signs of infectious disease in the rats. There were no changes to auditory function reported. The teeth were normal.

Body Weights

Body weight was measure once weekly and was also used as the basis for calculating the daily amounts of dosing of (b) (4). Presumably, the body weights were taken at the beginning of the week to calculate the amount of (b) (4) for daily dosing for that week. Body weights were not affected by dosing of (b) (4) as illustrated in the following table (from the Applicant's submission):

| Date/Zeitpunkt Week/Woche | Group/Gruppe (I) 500 mg 2837 D/kg K. G. p. o. | | Group/Gruppe (II) 2000 mg 2837 D/kg K. G. p. o. | | Group/Gruppe (III) Kontrolle | |
|------------------------------|--|-----|--|-----|---------------------------------|-----|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| | vorher | 103 | 102 | 102 | 102 | 102 |
| 1 | 139 | 128 | 141 | 129 | 140 | 126 |
| 2 | 186 | 146 | 190 | 145 | 188 | 144 |
| 3 | 216 | 162 | 220 | 160 | 220 | 158 |
| 4 | 252 | 181 | 251 | 178 | 246 | 176 |
| 5 | 271 | 198 | 274 | 196 | 270 | 194 |
| 6 | 298 | 211 | 296 | 210 | 292 | 208 |
| 7 | 314 | 220 | 316 | 219 | 320 | 210 |
| 8 | 320 | 228 | 328 | 230 | 328 | 221 |
| 9 | 341 | 238 | 340 | 236 | 342 | 231 |
| 10 | 356 | 246 | 357 | 244 | 360 | 240 |
| 11 | 370 | 250 | 371 | 249 | 374 | 248 |
| 12 | 384 | 254 | 384 | 256 | 388 | 257 |
| 13 | 394 | 258 | 396 | 261 | 399 | 264 |
| 14 | 402 | 261 | 406 | 264 | 410 | 264 |
| 15 | 411 | 264 | 416 | 265 | 420 | 267 |
| 16 | 418 | 268 | 421 | 269 | 430 | 270 |
| 17 | 426 | 269 | 430 | 270 | 436 | 271 |
| 18 | 432 | 272 | 440 | 273 | 448 | 272 |
| 19 | 440 | 274 | 444 | 275 | 450 | 270 |
| 20 | 451 | 276 | 455 | 275 | 460 | 274 |
| 21 | 454 | 276 | 461 | 278 | 466 | 276 |
| 22 | 462 | 275 | 466 | 279 | 470 | 276 |
| 23 | 463 | 280 | 467 | 280 | 472 | 277 |
| 24 | 472 | 281 | 473 | 280 | 476 | 278 |
| 25 | 475 | 281 | 476 | 280 | 481 | 278 |
| 26 | 476 | 284 | 480 | 283 | 485 | 280 |

Note = body weights were measured in grams

K.G. = body weight

Kontrolle = Control

Vorher = before (body weights were taken at the beginning of the Week)

Food Consumption

Food consumption was determined daily. Food consumption was consistent between the groups as shown in the following table (from the Applicant's submission):

| Date/Zeitpunkt Week/Woche | Group/Gruppe (I) 500 mg 2837 D/kg K.G. p. o. | | Group/Gruppe (II) 2000 mg 2837 D/kg K.G. p. o. | | Group/Gruppe (III) Kontrolle | |
|------------------------------|---|-----|---|-----|---------------------------------|-----|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| | 1 | 131 | 130 | 128 | 118 | 121 |
| 2 | 111 | 120 | 108 | 109 | 116 | 109 |
| 3 | 101 | 101 | 106 | 102 | 103 | 101 |
| 4 | 96 | 100 | 94 | 101 | 93 | 97 |
| 5 | 94 | 92 | 95 | 96 | 95 | 91 |
| 6 | 89 | 91 | 86 | 98 | 91 | 86 |
| 7 | 92 | 90 | 86 | 90 | 90 | 85 |
| 8 | 84 | 90 | 82 | 90 | 91 | 80 |
| 9 | 79 | 84 | 76 | 84 | 88 | 78 |
| 10 | 76 | 80 | 78 | 81 | 82 | 76 |
| 11 | 75 | 78 | 75 | 84 | 84 | 72 |
| 12 | 74 | 76 | 72 | 85 | 81 | 71 |
| 13 | 69 | 79 | 74 | 76 | 76 | 74 |
| 14 | 64 | 71 | 68 | 77 | 74 | 70 |
| 15 | 71 | 72 | 70 | 72 | 71 | 71 |
| 16 | 64 | 70 | 69 | 70 | 69 | 69 |
| 17 | 68 | 68 | 64 | 76 | 65 | 68 |
| 18 | 62 | 60 | 62 | 70 | 64 | 67 |
| 19 | 65 | 60 | 61 | 69 | 60 | 70 |
| 20 | 58 | 63 | 60 | 65 | 60 | 60 |
| 21 | 61 | 62 | 64 | 66 | 67 | 62 |
| 22 | 64 | 68 | 58 | 70 | 61 | 58 |
| 23 | 62 | 61 | 56 | 60 | 58 | 61 |
| 24 | 63 | 65 | 61 | 58 | 56 | 64 |
| 25 | 67 | 67 | 64 | 56 | 61 | 62 |
| 26 | 64 | 62 | 60 | 57 | 67 | 63 |

Note = food consumption was measured in grams

K.G. = body weight

Kontrolle = Control

Ophthalmoscopy

After 26 weeks of treatment, the eyes were examined. There were no pathological findings found during eye exams that were conducted prior to autopsy.

ECG

An ECG was not performed in this study.

Hematology

Blood samples for hematology and clinical chemistry were taken from the tail vein prior to treatment and after 6, 13, 18, and 26 weeks of treatment in 10 rats/sex/group. The following hematology parameters were measured (from the Applicant's submission):

| | | |
|--------------------------------|--|-------------------------------------|
| Haemoglobin content | Determination of haemoglobin by conversion to cyanhaemoglobin by the method of BETKE and SAVELSBERG. | g/100 ml of blood |
| Erythrocytes) Leucocytes) | With Coulter counter, model D. | Millions/cu.mm. Thousands/cu.mm. |
| Differential blood picture | As per the method of PAPPENHEIM. | |
| Haematocrit value | With haematocrit capillary tubes by the method of HEDIN. | % (v/v) of whole blood |

The following tests were carried out only after the 26th week of treatment:

| | | |
|------------------|---|-------------------------|
| Thrombocytes | As per the method of MIYAKE and BLACHER. | 100 000/cu.mm. of blood |
| Reticulocytes | With brilliant cresyl blue dye. | % of erythrocytes |
| Prothrombin time | With thromboplastin as per the method of FIECHTER [Schweiz. med. Wschr., 21, 259 (1940)]. | Sec. |
| Coagulation time | As per the method of BURKER. | Sec. |

The following table illustrates the changes in hematology during the study (data from the Applicant's submission):

| Parameter | Males | | | Females | | |
|---------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| | Control | 500 mg/kg | 2000 mg/kg | Control | 500 mg/kg | 2000 mg/kg |
| Pretreatment | | | | | | |
| Hemoglobin | 14.7 ± 0.8 | 14.5 ± 0.8 | 14.8 ± 1.1 | 14.5 ± 0.6 | 14.8 ± 0.5 | 14.6 ± 1.1 |
| Erythrocytes | 7.3 ± 0.4 | 7.2 ± 0.4 | 7.3 ± 0.4 | 7.2 ± 0.4 | 7.4 ± 0.3 | 7.3 ± 0.5 |
| Leucocytes | 12.1 ± 2.1 | 11.6 ± 2.4 | 11.3 ± 2.2 | 12.0 ± 2.5 | 11.5 ± 2.8 | 11.1 ± 2.1 |
| % Neutrophils | 11.1 | 10.2 | 10.5 | 10.6 | 10.1 | 9.9 |
| Segmented Stab form | 1.7 | 1.6 | 2.3 | 1.3 | 1.7 | 1.9 |
| % Basophils | 0 | 0 | 0 | 0 | 0 | 0 |
| % Eosinophils | 0 | 0 | 0 | 0.2 | 0.1 | 0.4 |
| % Monocytes | 0 | 0 | 0 | 0 | 0 | 0.1 |
| % Lymphocytes | 87.2 | 88.2 | 87.2 | 87.9 | 88.1 | 87.7 |
| % Hematocrit | 42.5 ± 2.3 | 42.7 ± 2.8 | 43.0 ± 3.0 | 42.6 ± 2.5 | 43.8 ± 2.5 | 43.0 ± 2.5 |
| Week 6 | | | | | | |
| Hemoglobin | 15.3 ± 0.8 | 15.6 ± 1.0 | 15.5 ± 0.9 | 15.1 ± 0.7 | 15.5 ± 0.7 | 15.1 ± 0.8 |
| Erythrocytes | 7.7 ± 0.4 | 7.8 ± 0.5 | 7.7 ± 0.4 | 7.6 ± 0.3 | 7.7 ± 0.4 | 7.6 ± 0.4 |
| Leucocytes | 12.3 | 10.7 | 12.0 | 11.3 | 11.9 | 12.1 |

| | | | | | | |
|---|---------------|---------------|---------------|---------------|---------------|---------------|
| | ± 2.3 | ± 2.0 | ± 2.7 | ± 1.9 | ± 2.4 | ± 2.2 |
| % Neutrophils Segmented Stab form | 11.8 1.5 | 10.0 1.3 | 10.8 2.3 | 9.8 2.1 | 11.5 1.4 | 10.0 1.5 |
| % Basophils | 0 | 0 | 0 | 0 | 0 | 0 |
| % Eosinophils | 0.3 | 0.1 | 0.1 | 0 | 0 | 0 |
| % Monocytes | 0 | 0 | 0.1 | 0 | 0 | 0.1 |
| % Lymphocytes | 86.4 | 88.6 | 86.7 | 88.1 | 87.1 | 88.4 |
| % Hematocrit | 44.6 ± 1.7 | 45.3 ± 2.2 | 45.6 ± 2.5 | 44.7 ± 2.6 | 45.2 ± 1.8 | 44.6 ± 2.1 |
| Week 13 | | | | | | |
| Hemoglobin | 15.5 ± 0.9 | 16.1 ± 0.9 | 15.7 ± 0.7 | 15.4 ± 0.8 | 16.0 ± 0.6 | 15.5 ± 0.7 |
| Erythrocytes | 7.7 ± 0.5 | 8.1 ± 0.5 | 7.8 ± 0.3 | 7.7 ± 0.4 | 7.9 ± 0.2 | 7.7 ± 0.4 |
| Leucocytes | 11.5 ± 1.9 | 12.3 ± 3.0 | 11.5 ± 2.8 | 11.9 ± 3.1 | 12.8 ± 1.3 | 11.7 ± 2.0 |
| % Neutrophils Segmented Stab form | 10.7 1.5 | 10.3 1.5 | 11.4 1.4 | 10.4 1.3 | 10.5 1.4 | 10.7 1.6 |
| % Basophils | 0 | 0 | 0 | 0 | 0 | 0 |
| % Eosinophils | 0 | 0.2 | 0.2 | 0 | 0 | 0.2 |
| % Monocytes | 0 | 0.1 | 0 | 0 | 0 | 0.1 |
| % Lymphocytes | 87.8 | 87.9 | 87.0 | 88.3 | 88.1 | 87.4 |
| % Hematocrit | 45.6 ± 2.1 | 45.8 ± 1.6 | 45.9 ± 1.7 | 44.9 ± 1.7 | 46.4 ± 1.4 | 45.6 ± 2.6 |
| Week 18 | | | | | | |
| Hemoglobin | 15.4 ± 0.8 | 15.5 ± 0.7 | 15.6 ± 0.5 | 15.7 ± 1.0 | 16.0 ± 0.8 | 15.6 ± 0.6 |
| Erythrocytes | 7.7 ± 0.4 | 7.8 ± 0.3 | 7.8 ± 0.3 | 7.8 ± 0.6 | 8.0 ± 0.4 | 7.8 ± 0.3 |
| Leucocytes | 11.9 ± 2.6 | 11.9 ± 2.1 | 11.6 ± 3.0 | 11.5 ± 2.9 | 11.7 ± 2.0 | 12.2 ± 2.0 |
| % Neutrophils Segmented Stab form | 10.4 2.1 | 9.8 1.8 | 11.2 1.6 | 10.7 1.6 | 11.2 1.5 | 10.7 1.3 |
| % Basophils | 0 | 0 | 0 | 0 | 0 | 0 |
| % Eosinophils | 0 | 0 | 0.3 | 0 | 0 | 0 |
| % Monocytes | 0 | 0 | 0 | 0.2 | 0 | 0 |
| % Lymphocytes | 87.5 | 88.4 | 86.9 | 87.5 | 87.3 | 88.0 |
| % Hematocrit | 45.2 ± 1.8 | 44.9 ± 2.5 | 45.5 ± 1.4 | 45.0 ± 2.6 | 45.5 ± 1.7 | 45.5 ± 1.6 |
| Week 26 | | | | | | |
| Hemoglobin | 15.4 ± 0.8 | 15.9 ± 0.6 | 15.9 ± 0.7 | 15.8 ± 0.9 | 16.3 ± 0.7 | 15.8 ± 0.9 |
| Erythrocytes | 7.8 ± 0.5 | 7.9 ± 0.3 | 7.9 ± 0.3 | 7.9 ± 0.5 | 8.2 ± 0.3 | 7.8 ± 0.4 |
| Leucocytes | 12.0 ± 2.4 | 11.3 ± 3.1 | 11.2 ± 2.3 | 10.9 ± 2.8 | 10.7 ± 2.4 | 11.4 ± 2.8 |
| % Neutrophils Segmented Stab form | 10.7 2.1 | 10.7 1.4 | 10.8 1.4 | 11.3 1.6 | 10.9 1.8 | 8.1 2.1 |
| % Basophils | 0 | 0 | 0 | 0 | 0 | 0 |
| % Eosinophils | 0.1 | 0 | 0.1 | 0.1 | 0 | 0.3 |
| % Monocytes | 0 | 0 | 0 | 0.2 | 0 | 0 |
| % Lymphocytes | 87.1 | 87.9 | 87.7 | 86.8 | 87.3 | 87.5 |
| % Hematocrit | 45.2 | 45.7 | 46.3 | 45.9 | 46.1 | 45.6 |

| | | | | | | |
|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | ± 1.8 | ± 1.3 | ± 1.6 | ± 1.7 | ± 1.5 | ± 1.8 |
| Prothrombin time | 13.5 ± 1.4 | 13.1 ± 1.6 | 13.2 ± 1.5 | 13.3 ± 1.0 | 13.0 ± 1.2 | 12.8 ± 1.4 |
| % Reticulocytes | 15.2 ± 4.6 | 15.4 ± 5.7 | 15.6 ± 5.8 | 17.8 ± 5.9 | 14.6 ± 5.0 | 17.8 ± 6.8 |
| Thrombocytes | 6.42 ± 0.70 | 6.25 ± 0.71 | 6.22 ± 1.03 | 6.47 ± 0.55 | 6.26 ± 0.80 | 6.60 ± 0.63 |
| Blood clotting time | 169.0 ± 19.1 | 163.0 ± 22.1 | 169.0 ± 20.3 | 168.0 ± 14.8 | 169.0 ± 14.5 | 170.0 ± 18.3 |

It is noted that each hematology parameter is expressed with ± standard deviation.

In females at Week 26, there was a decrease in the % neutrophil (segmented and stab form) from 12.9 in the controls to 10.2 in the 2000 mg/kg dose group, which represents a 20.9% decrease. Additionally, there was also a 200% increase in the % eosinophils in the 2000 mg/kg dose group at Week 26 in females. These changes were only observed during Week 26. Decreases in neutrophils and increases in eosinophils are a sign of infection, which may not be attributed to the administration of (b) (4). There were no further treatment-related changes in hematology.

Clinical Chemistry

The following clinical chemistry parameters were measured (from the Applicant's submission):

| | | |
|-------------------------------------|--|-----------------------|
| SGPT activity | Test kit from (b)(4) (b)(4), as per the method of WROBLEWSKI et al. [Proc. Soc. exp. Biol. Med., 91, 569 (1956)] | mU/ml of serum |
| Auto-Analyzer SMA 12/micro methods | | |
| Glucose | As per the method of BROWN [Diabetes, 10, 60 - 62 (1961)] and BITTNER and McCLEARY [Amer. J. Clin. Path., 11, 423 (1963)], modified. | mg/100 ml of serum |
| BUN | As per the method of MARSH et al. [Clin. Chem., 11, 624 - 627 (1965)], modified. | mg/100 ml of serum |
| Alkaline phosphatase activity | Test kit from (b)(4) (b)(4), as per the method of BESSEY et al. [J. Biol. Chem., 164, 321 (1946)]. | mU/ml of serum |

The following tests were carried out only after the 26th week
of treatment:

| | | |
|-------------------------|--|-----------------------|
| Sodium) Potassium) | Flame photometry. | mEq/l of serum |
| Chloride | As per the method of SKEGGS, jun. and HOCHSTRASSER [Clin. Chem., 10, 918 - 936 (1964)]. | mEq/l of serum |
| Calcium | As per the method of KESSLER and WOLFMAN [Clin. Chem., 10, 686 - 703 (1964)]. | mEq/l of serum |
| Uric acid | As per the method of SOBRINHO- SIMOES [J. lab. clin. Med., 65, 665 - 668 (1965)], modified as per MUSSER and ORTIGOZA [Techn. Bull. of the Registry of Med. Techs., 34, 21 - 25 (1966)] and serum pretreatment as per NISHI [Clin. Chem., 13, 12 - 18 (1967)]. | mg/100 ml of serum |
| Total protein | Standard automated methods using a modified biuret reaction. | g/100 ml of serum |
| SGOT activity | As per the method of MORGEN- STERN et al. [Clin. Chem., 12, 95 - 111 (1966)]. | mU/ml of serum |
| Total bilirubin | As per the method of JENDRASSIK and GROF [Biochem. Z., 81, 297 (1938)] and GAMBINO and SCHREIBER [Automation in Analytical Chemistry, Technicon Symposia (1964)]. | mg/100 ml of serum |
| CO ₂ | Standard automated methods | mEq/l of serum |

The following table illustrates the changes in clinical chemistry in this study (data from the Applicant's submission):

| Parameter | Males | | | Females | | |
|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Control | 500 mg/kg | 2000 mg/kg | Control | 500 mg/kg | 2000 mg/kg |
| Pretreatment | | | | | | |
| Glucose | 131.6 ± 19.5 | 128.5 ± 15.3 | 130.5 ± 18.0 | 128.8 ± 20.0 | 131.0 ± 13.6 | 130.4 ± 12.1 |
| SGPT | 8.4 ± 2.5 | 8.9 ± 2.1 | 8.1 ± 1.6 | 8.8 ± 3.5 | 9.1 ± 2.0 | 8.9 ± 2.1 |
| BUN | 17.2 ± 2.6 | 17.3 ± 2.1 | 17.7 ± 2.5 | 17.9 ± 3.3 | 17.1 ± 2.2 | 17.4 ± 2.1 |
| ALP | 216.6 ± 22.5 | 215.9 ± 29.5 | 211.4 ± 28.8 | 181.0 ± 18.3 | 184.6 ± 16.6 | 176.2 ± 20.3 |
| Week 6 | | | | | | |
| Glucose | 123.5 ± 16.4 | 124.6 ± 15.5 | 128.9 ± 16.7 | 126.7 ± 19.2 | 129.5 ± 21.4 | 131.5 ± 16.1 |
| SGPT | 9.0 ± 2.2 | 8.9 ± 2.3 | 9.1 ± 1.7 | 9.2 ± 2.2 | 8.5 ± 1.8 | 9.2 ± 1.9 |
| BUN | 16.9 ± 1.9 | 18.2 ± 2.4 | 17.3 ± 2.3 | 17.0 ± 2.4 | 17.1 ± 1.9 | 17.4 ± 2.7 |
| ALP | 208.3 ± 24.2 | 207.4 ± 20.9 | 206.8 ± 21.6 | 153.8 ± 16.3 | 147.4 ± 13.8 | 153.2 ± 17.5 |
| Week 13 | | | | | | |
| Glucose | 123.6 ± 22.9 | 125.7 ± 16.5 | 128.5 ± 20.2 | 127.4 ± 18.0 | 131.0 ± 14.0 | 129.4 ± 13.3 |
| SGPT | 9.4 ± 2.2 | 8.4 ± 1.8 | 10.0 ± 2.4 | 8.4 ± 3.1 | 9.2 ± 2.3 | 9.0 ± 2.4 |
| BUN | 17.1 ± 2.1 | 17.4 ± 1.7 | 17.7 ± 3.0 | 17.2 ± 1.6 | 18.0 ± 3.5 | 17.4 ± 1.8 |
| ALP | 163.4 ± 18.7 | 166.3 ± 15.2 | 168.6 ± 15.5 | 134.4 ± 15.7 | 138.9 ± 20.7 | 136.8 ± 15.5 |
| Week 18 | | | | | | |
| Glucose | 130.3 ± 21.0 | 128.2 ± 16.8 | 138.3 ± 13.7 | 128.0 ± 22.3 | 131.3 ± 19.5 | 130.4 ± 16.9 |
| SGPT | 9.5 ± 2.7 | 8.6 ± 2.1 | 8.5 ± 2.1 | 9.0 ± 2.7 | 8.1 ± 2.8 | 8.2 ± 2.9 |
| BUN | 17.0 ± 1.8 | 17.7 ± 3.1 | 17.9 ± 3.0 | 17.7 ± 1.9 | 16.9 ± 1.7 | 18.3 ± 3.2 |
| ALP | 145.2 ± 18.7 | 142.6 ± 20.3 | 142.8 ± 18.5 | 109.5 ± 16.6 | 114.1 ± 19.9 | 114.8 ± 15.2 |
| Week 26 | | | | | | |
| Glucose | 130.1 ± 16.6 | 131.3 ± 20.2 | 126.3 ± 19.2 | 134.6 ± 13.7 | 126.6 ± 19.1 | 129.9 ± 17.4 |
| SGPT | 9.3 ± 1.9 | 8.3 ± 2.2 | 9.5 ± 2.7 | 8.7 ± 2.0 | 8.8 ± 3.0 | 9.0 ± 1.7 |
| BUN | 16.9 ± 1.9 | 17.8 ± 1.8 | 17.4 ± 1.6 | 17.0 ± 1.9 | 16.9 ± 1.5 | 16.5 ± 2.8 |
| ALP | 114.0 ± 20.7 | 110.4 ± 18.3 | 117.2 ± 22.0 | 93.7 ± 17.3 | 93.8 ± 15.3 | 96.3 ± 17.3 |
| SGOT | 68.2 ± 10.0 | 77.4 ± 14.6 | 71.2 ± 14.6 | 72.6 ± 9.1 | 75.3 ± 10.9 | 68.0 ± 10.2 |
| Total Bilirubin | 0.24 ± 0.05 | 0.24 ± 0.07 | 0.23 ± 0.05 | 0.23 ± 0.05 | 0.25 ± 0.07 | 0.22 ± 0.04 |
| Sodium | 149.8 | 150.0 | 148.9 | 149.3 | 149.8 | 149.8 |

| | | | | | | |
|-----------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | ± 2.1 | ± 2.0 | ± 1.1 | ± 2.8 | ± 2.4 | ± 2.1 |
| Potassium | 5.4 ± 0.5 | 5.3 ± 0.3 | 5.4 ± 0.4 | 5.3 ± 0.3 | 5.4 ± 0.4 | 5.4 ± 0.4 |
| Chloride | 105.3 ± 5.9 | 104.1 ± 3.0 | 103.8 ± 4.9 | 105.5 ± 4.1 | 107.3 ± 4.5 | 106.3 ± 3.7 |
| Calcium | 4.8 ± 0.4 | 4.9 ± 0.3 | 4.8 ± 0.3 | 4.9 ± 0.3 | 4.9 ± 0.2 | 4.9 ± 0.3 |
| CO ₂ | 23.8 ± 3.5 | 23.9 ± 2.1 | 24.4 ± 2.4 | 24.1 ± 3.9 | 23.4 ± 2.8 | 24.4 ± 3.2 |
| Total Protein | 6.4 ± 0.4 | 6.5 ± 0.6 | 6.3 ± 0.3 | 6.4 ± 0.5 | 6.5 ± 0.4 | 6.5 ± 0.4 |
| Uric Acid | 2.6 ± 0.7 | 2.4 ± 0.5 | 2.5 ± 0.5 | 2.3 ± 0.5 | 2.5 ± 0.5 | 2.5 ± 0.6 |

ALP = alkaline phosphatase (a liver enzyme)

SGPT = serum glutamic-pyruvic transaminase or alanine aminotransferase (ALT), a liver enzyme

BUN = blood urea nitrogen

SGOT = serum glutamic oxaloacetic transaminase (a liver and heart enzyme)

It is noted that each clinical chemistry parameter is expressed with \pm standard deviation. There were no treatment-related changes in clinical chemistry.

Urinalysis

Urine samples were collected in metabolism cages prior to treatment and after 6, 13, 18, and 26 weeks of treatment in 10 rats/sex/group. The following urinalysis parameters were measured (from the Applicant's submission):

Colour

Specific gravity

pH

Protein

Acetic acid boiling test

Ketone bodies

Acetest, (b) (4)

Glucose

Haemoglobin

Bilirubin

Combi-Uristix, (b) (4)

The urinary sediment was examined for:

E = epithelial cells

L = leucocytes

R = erythrocytes

B = organisms (e.g. worms' ova, bacteria)

C = casts

A = anorganic material

There were no treatment-related changes in urinalysis.

Gross Pathology

Following sacrifice after 26 weeks of treatment, an autopsy and macroscopic examination was conducted. Organs were then collected, weighed, and prepared for microscopic examination. There were no pathological findings in the gross pathology.

Organ Weights

Following the autopsy and macroscopic examination, 11 organs were then collected, weighed, and prepared for microscopic examination. The following table illustrates the organ weight changes after 26 weeks of treatment in this study (data from the Applicant's submission):

| Organ | Males | | | Females | | |
|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | Control | 500 mg/kg | 2000 mg/kg | Control | 500 mg/kg | 2000 mg/kg |
| Heart | 1.22 ± 0.14 | 1.20 ± 0.16 | 1.19 ± 0.13 | 0.89 ± 0.10 | 0.85 ± 0.09 | 0.84 ± 0.11 |
| Liver | 12.6 ± 1.2 | 12.4 ± 1.5 | 12.4 ± 1.3 | 8.4 ± 0.7 | 8.2 ± 0.8 | 8.1 ± 0.7 |
| Lungs | 1.80 ± 0.19 | 1.87 ± 0.21 | 1.78 ± 0.20 | 1.46 ± 0.13 | 1.46 ± 0.09 | 1.45 ± 0.11 |
| Spleen | 0.65 ± 0.11 | 0.66 ± 0.12 | 0.68 ± 0.11 | 0.53 ± 0.08 | 0.53 ± 0.08 | 0.52 ± 0.09 |
| Kidney Left | 1.35 ± 0.17 | 1.31 ± 0.15 | 1.32 ± 0.14 | 0.88 ± 0.07 | 0.88 ± 0.09 | 0.89 ± 0.16 |
| Right | 1.35 ± 0.17 | 1.31 ± 0.14 | 1.31 ± 0.13 | 0.88 ± 0.07 | 0.88 ± 0.09 | 0.87 ± 0.23 |
| Adrenal Left | 0.024 ± 0.005 | 0.023 ± 0.004 | 0.024 ± 0.005 | 0.034 ± 0.006 | 0.035 ± 0.006 | 0.034 ± 0.006 |
| Right | 0.025 ± 0.005 | 0.022 ± 0.005 | 0.024 ± 0.005 | 0.033 ± 0.005 | 0.036 ± 0.006 | 0.034 ± 0.006 |
| Thymus | 0.48 ± 0.09 | 0.49 ± 0.10 | 0.48 ± 0.06 | 0.42 ± 0.09 | 0.42 ± 0.07 | 0.42 ± 0.07 |
| Pituitary | 0.011 ± 0.002 | 0.010 ± 0.002 | 0.011 ± 0.002 | 0.009 ± 0.002 | 0.009 ± 0.002 | 0.009 ± 0.001 |
| Gonads Left | 1.86 ± 0.16 | 1.84 ± 0.13 | 1.82 ± 0.13 | 0.053 ± 0.009 | 0.051 ± 0.012 | 0.048 ± 0.006 |
| Right | 1.84 ± 0.18 | 1.86 ± 0.11 | 1.82 ± 0.12 | 0.053 ± 0.011 | 0.052 ± 0.009 | 0.049 ± 0.005 |
| Thyroid | 0.036 ± 0.006 | 0.035 ± 0.003 | 0.035 ± 0.004 | 0.027 ± 0.008 | 0.025 ± 0.005 | 0.026 ± 0.007 |
| Brain | 2.01 ± 0.09 | 2.01 ± 0.13 | 2.02 ± 0.09 | 1.94 ± 0.06 | 1.93 ± 0.10 | 1.92 ± 0.11 |

It is noted that these are absolute organ weights expressed in grams ± standard deviation. There were no organ-to-body-weight or organ-to-brain-weight ratios determined in this study. There were no treatment-related changes in the absolute organ weights.

Histopathology

Microscopic examination was done in 10 rats of each sex that received the highest dose of (b) (4) (2000 mg).

Adequate Battery

The following organs were examined microscopically (from the Applicant's submission):

| | | |
|-----------|----------------------|------------------------|
| heart | brain | urinary bladder |
| lung | prostate/uterus | bone marrow |
| liver | stomach | trachea |
| spleen | duodenum | aorta |
| kidney | jejunum | oesophagus |
| adrenal | ileum | pancreas |
| thymus | colon | mesenteric lymph nodes |
| pituitary | rectum | peripheral nerve |
| gonads | salivary gland | skeletal muscle |
| thyroid | eye with optic nerve | |

According to Redbook 2000⁹, this study does not assess several tissues in evaluated in in standard chronic rodent toxicity studies, including cecum, cervix, epididymis, gall bladder, mammary gland, seminal vesicle, skin, spinal cord (cervical, mid-thoracic, and lumbar), and vagina.

Peer Review

There was a Study Pathologist but there was no indication that this study was peer reviewed. A Pathologist Report was not included in the Final Study report.

Histological Findings

The following table illustrates the histopathological changes in this study (data from the Applicant's submission):

| Finding | 2000 mg/kg dose | |
|--|-----------------|---------|
| | Males | Females |
| Liver Slight localized guttate fatty degeneration | 2/10 | 1/10 |
| Kidney Microliths, trace | 0/10 | 3/10 |

Histopathology was done with the 2000 mg/kg dose groups only with no microscopic examination of the control or the low dose groups. At the 2000 mg/kg dose, slight localized guttate fatty degeneration was observed in the liver of 2/10 males and 1/10 females and trace microliths was observed in the in the kidney of 3/10 females only. Fatty degeneration of the liver is the deposition of fat globules in the liver. As the liver functions to constantly make and break down fatty tissue, this observation may be dismissed. A microlith is a very small kidney stone that is normally passed without

⁹ Available at <http://www.cfsan.fda.gov/guidance.html>

causing problems. As such, this observation may be dismissed. It is noted that histopathology was not performed in the control, 500 mg/kg dose groups, and recovery groups in this study.

Special Evaluation

There is no special evaluation in this study.

Toxicokinetics

Toxicokinetics were not examined in this study.

Dosing Solution Analysis

Dosing solution analysis was not conducted in this study. However, the amount of ^{(b) (4)} ingested in each group was measured and shown in the following table (from the Applicant's submission):

| Date/Zeitpunkt Week/Woche | Group/Gruppe (I) 500 mg 2837 D/kg K.G. p. o. | | Group/Gruppe (II) 2000 mg 2837 D/kg K.G. p. o. | |
|------------------------------|---|-----|---|------|
| | ♂ | ♀ | ♂ | ♀ |
| 1 | 545 | 540 | 2130 | 1970 |
| 2 | 425 | 460 | 1690 | 1850 |
| 3 | 455 | 420 | 1970 | 1870 |
| 4 | 475 | 495 | 1770 | 1980 |
| 5 | 490 | 460 | 2020 | 1900 |
| 6 | 475 | 495 | 1810 | 2040 |
| 7 | 515 | 495 | 2000 | 1840 |
| 8 | 455 | 500 | 1910 | 2000 |
| 9 | 470 | 465 | 1850 | 1870 |
| 10 | 480 | 475 | 2050 | 1930 |
| 11 | 495 | 485 | 1900 | 2080 |
| 12 | 490 | 490 | 1950 | 2020 |
| 13 | 465 | 520 | 2060 | 1790 |
| 14 | 465 | 450 | 1840 | 2030 |
| 15 | 555 | 510 | 2060 | 1870 |
| 16 | 450 | 485 | 1970 | 1940 |
| 17 | 530 | 485 | 1860 | 2150 |
| 18 | 455 | 440 | 1940 | 1840 |
| 19 | 525 | 500 | 1970 | 1970 |
| 20 | 450 | 525 | 1970 | 1880 |
| 21 | 525 | 490 | 2140 | 2030 |
| 22 | 525 | 550 | 1810 | 2120 |
| 23 | 485 | 450 | 1930 | 1700 |
| 24 | 510 | 530 | 2180 | 1930 |
| 25 | 530 | 515 | 2100 | 1930 |
| 26 | 480 | 465 | 1880 | 2040 |

K.G. = body weight

As shown in the table above, the 500 mg/kg dose group received within 10% of the dose for all weeks with the exception of Week 2 in the males and Weeks 3 and 18 in the females. The 2000 mg/kg dose group received within 10% of the dose for all weeks with the exception of Weeks 2 and 4 in the males and Weeks 13 and 23 in the females.

Study title: (b) (4) **26 Week Oral Toxicity Study in Dogs Followed by a 3 Week Recovery Period**

Study no.: B17-53990
 Study report location: Module 4 of the Electronic Submission
 Conducting laboratory and location: (b) (4)
 Date of study initiation: November 16, 2006
 GLP compliance: Yes. Signature provided on October 31, 2007
 QA statement: Yes. Signature provided on October 31, 2007
 Drug, lot #, and % purity: (b) (4), lot # B060232001, approximately 22.7% of (b) (4) (b) (4) dry substance in each pellet (this was the amount of (b) (4) in each pellet and not the purity of the (b) (4) (b) (4). A COA for (b) (4) was supplied and indicated that the cellulose coated pellets manufactured to be administered via capsules contained 40.3% of (b) (4). The purity of (b) (4) was not determined in the final study report.

Key Study Findings

- Beagle dogs were administered 0, 200, 500, and 1000 mg/kg of (b) (4) (b) (4) once daily via an oral pellet for 7 days/week for a total of 26 weeks. It is noted that the actual doses given were 0, 50, 125, and 250 mg/kg since each pellet contains approximately 22.7% (b) (4).
- All dogs survived to the scheduled necropsy.
- There were no treatment-related changes in clinical signs and observations, food consumption, ophthalmoscopic examination, ECG, hematology, clinical chemistry, urinalysis, and fecal occult blood.
- No toxicokinetics were performed in this study.
- There was an approximately 10% decrease in the body weights of the high dose male dogs during the treatment phase as well as a 11.7% decrease in the high dose recovery female dogs.

- Macroscopically, abnormal size, content, area, and color were noted in general. These changes in the gall bladder, lymph nodes (female), mammary area (female), thyroid (female), urinary bladder (female), and uterus (female) occurred in the high dose dogs during the treatment period. In the recovery dogs, gall bladder, mammary (female) and lymph nodes (females) were also observed in the high dose dogs. Delayed observations include the colon, lungs, prostate, and thymus in the high dose recovery males, as well as the gall bladder, ovaries, stomach, urinary bladder, and uterus in the high dose recovery females.
- The absolute organ weight changes include the right adrenal in the high dose males during the treatment period as well as the epididymis and prostate in the high dose recovery males and the pituitary in the high dose recovery females.
- The organ-to-body-weight ratio changes include the prostate and right testis in the high dose recovery males as well as the heart the right thyroid in the high dose recovery females.
- Histopathological findings include the gall bladder (lymphoid aggregations) in the high dose females, kidneys (nephropathy) and spleen (lymphoid hyperplasia) in the high dose males, and tonsils (congestion) in both the high dose males and females.
- No histopathology was performed in the recovery dogs.
- The NOAEL is 500 (or 125) mg/kg due to the body weight, macroscopic, organ weight, organ-to-body-weight ratio, and histopathological changes at the high dose groups.
- This is in contrast to the Applicant's NOAEL of 1000 (or 250) mg/kg.
- The human equivalent dose of the NOAEL is 4054 mg o (b) (4) in an average human weighing 60 kg based on a body surface area comparison. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) and an exposure margin of 2.1 for the excipient. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) and an exposure margin of 7.37 for the copolymeric backbone.

Methods

Doses: 0, 200, 500, and 1000 mg/kg/day but the actual doses were 0, 50, 125, and 250 mg/kg/day (see table below)

Frequency of dosing: Once daily, 7 days/week for 26 consecutive weeks

Route of administration: Oral capsule

Dose volume: 1 oral capsule a day

Formulation/Vehicle: Cellulose pellets coated with the test item that was supplied by (b) (4)

Species/Strain: Dogs/Beagle dogs

Number/Sex/Group: 4/sex/group

Age: Approximately 24 weeks

Weight: 6 to 9 kg

Satellite groups: 3/sex/group for the 2 recovery groups (control and high dose)

Unique study design: Body weight gain, organ-to-brain-weight ratios, toxicokinetics, and histopathology in the recovery dogs were not performed or determined in this study.

Deviation from study protocol: There were no significant protocol amendments described in the final study report

The following table illustrates the treatment groups (from the Applicant's submission):

| Group Number | Treatment (mg/kg/day) ⁺ | Expected [°] Dose levels (mg/kg/day) [#] | Actual ^{°°} Dose levels (mg/kg/day) [#] | Level | Dog Numbers | | | |
|--------------|------------------------------------|--|---|---------|-------------|---------|----------------|---------|
| | | | | | Main Phase | | Recovery phase | |
| | | | | | M (even) | F (odd) | M (even) | F (odd) |
| 1 | 0 | 0 | 0 | Control | 2-8 | 1-7 | 10-14 | 9-13 |
| 2 | 200 | 45 | 50 | Low | 16-22 | 15-21 | | |
| 3 | 500 | 114 | 125 | Medium | 24-30 | 23-29 | | |
| 4 | 1000 | 227 | 250 | High | 32-38 | 31-37 | 40-44 | 39-43 |

⁺ : in terms of coated pellets as supplied
[#] : in terms of (b) (4) dry substance
[°] : Calculated on the basis of the analytical declaration supplied by (b) (4) pertaining to test item formulation
^{°°} : Calculated on the basis of the formulation analysis performed at (b) (4) (see section 3.2)

As shown in the table above, the actual dose levels of (b) (4) is approximately 22.7% of the treatment dose because there is approximately 22.7% of (b) (4) in each pellet.

Observations and Results

Mortality

Mortality checks were conducted twice daily. All dogs survived to the scheduled necropsy.

Clinical Signs

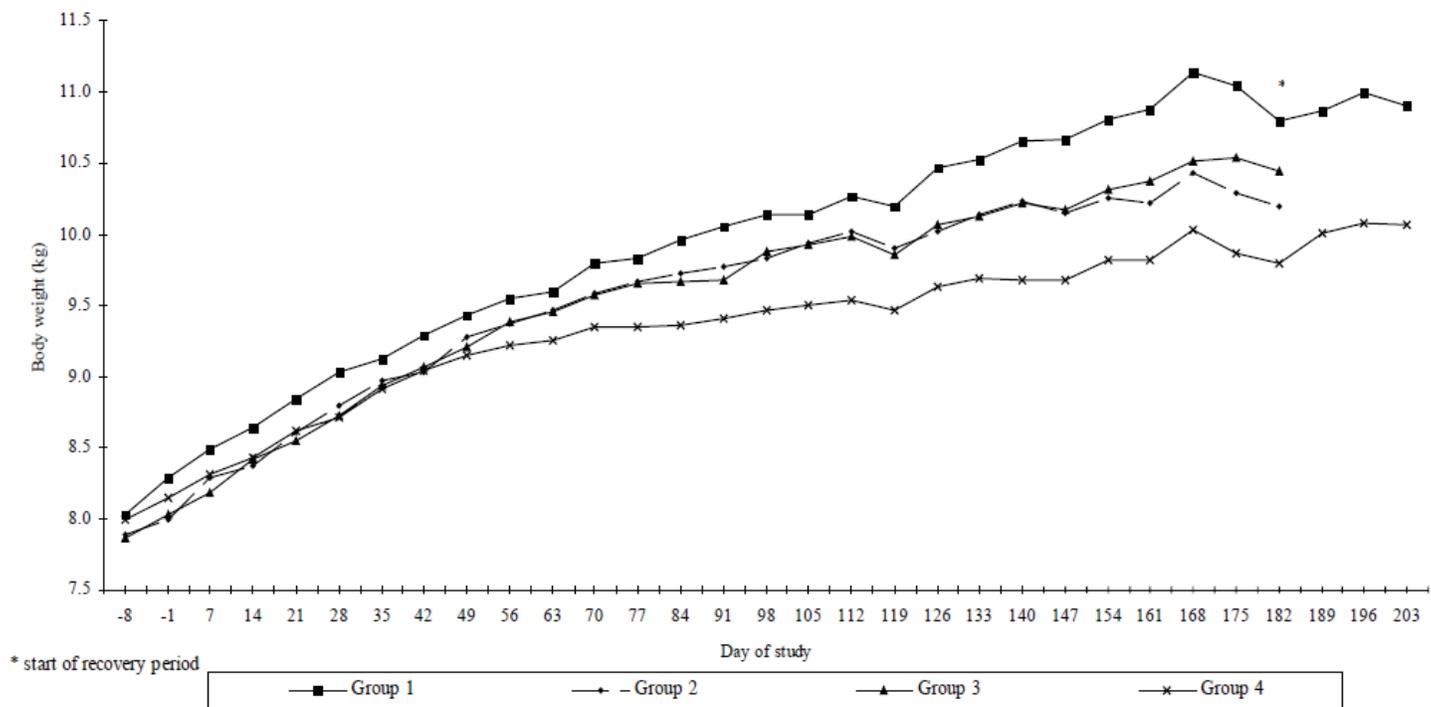
Observations for each dog for signs of reaction to treatment were made daily, at dosing, and at 2 and 4 hours post dose. Pre-dosing, 2 h post dose, and 4 h post dosing observations include liquid feces, soft feces, and mucoid feces occurring sporadically in all male dose groups and throughout the study. In females, liquid feces and mucoid feces were observed in all female dose groups and throughout the study. Fecal observations in both males and females are dismissed as being treatment-related due to the sporadic nature of the events. Emesis occurred in 1 high dose female on Day 32 at 2 h post-dose with no further incidence of this observation and thus emesis does not represent a safety concern. Thus, there were no treatment-related changes in pre- and post-dose observations.

In addition, clinical signs were made prior to the start of treatment, once weekly during the treatment and recovery periods, and whenever possible at 7 day intervals. In males, decreased motor activity was observed in 1 control male only and reddened conjunctiva of the eyes was observed in 1 low-dose male only. The control male with decreased motor activity was also observed with hemorrhagic diarrhea and received Buscopan® for pain associated with a mass in the abdominal area on Days 30, 31, and 32 and following these 3 days of therapy, the health conditions of this control male improved. There was no dose-dependency in these observations and as such, can be dismissed. There were no treatment-related changes in clinical signs in the recovery males. In females, hair loss was observed in 1 high dose female. Hair loss is not considered detrimental to health or represents a safety concern and as such, can be dismissed. Urogenital observations (vulvar discharge, reddened vulva, and swollen vulva) were observed in all females. These urogenital observations were observed in 1 dog each from the high dose group in the recovery group. These observations are dismissed as there was no dose-dependency and since they were present in all main study dogs, they are not considered a delayed observation.

Body Weights

Each dog was weighed on the day prior to the start of treatment, at weekly intervals during the treatment and recovery periods, and prior to necropsy. Body weight gains were not determined.

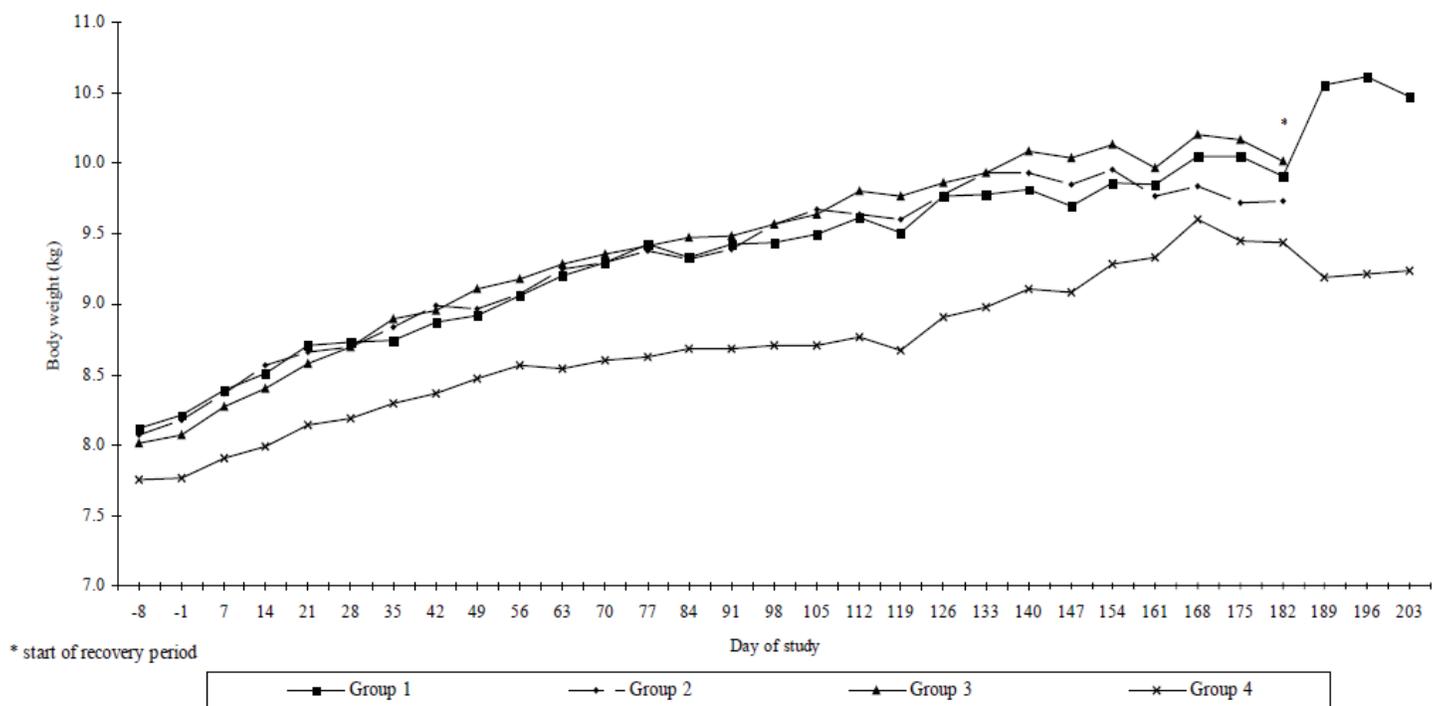
The following graph illustrates the body weights of the male dogs during the treatment and recovery phases (from the Applicant's submission):



As shown in the table above, the body weights of the (b) (4) treatment groups were lower than the control group throughout the treatment phase. At Day 168, there was a decrease in body weight by 6.42, 6.96, and 9.97% in the low-, mid-, and high-dose groups, respectively, compared to control. The decrease in the high-dose group on Day 168 was statistically significant. At the end of the treatment phase on Day 182, there was a decrease in body weight by 5.46, 3.23, and 9.23% in the low-, mid-, and high-dose groups, respectively, compared to control. None of these changes on Day 182 were statistically significant. The decreases in body weight in the high dose group are biologically significant as the decrease was approximately 10%.

During the recovery phase, there was a steady increase in body weights in the high dose group; however, at the end of the 3-week recovery phase, there was a decrease in body weight by 7.64% in the high dose group compared to the control. This change is not statistically significant and is not biologically significant as the decrease was less than 10%.

The following table illustrates the body weights of the female dogs during the treatment and recovery phases (from the Applicant’s submission):



As shown in the table above, the body weight of the high dose (b) (4) treatment group was lower than the control throughout the treatment period. However, from Days 35 to 154, the body weights of the low- and mid-dose groups were greater than control. From Days 35 to the end of study, the body weight of the mid-dose group was greater than control. On Day 119, there was an increase in body weight by 0.936 and 2.67% in the low- and mid-dose groups, respectively, as well as a decrease in body weight by 8.83% in the high dose group compared to control. The changes on Day 119 were not statistically significant. On Day 182, there was an increase in body weight by 1.07% in the mid dose group as well as a decrease in body weight by 1.86 and 4.79% in the low- and high dose groups, respectively, compared to control. The changes on Day 182 were not statistically significant. The changes in body weight in the females were not biologically significant as none of the changes were greater than 10%.

During the recovery phase, there was a decrease in body weight during the first week of recovery followed by a steady increase in body weight to the end of the recovery phase. By the end of recovery, there was a decrease in body weight by 11.7% in the high dose group compared to control. This change is statistically significant and is biologically significant as the change is greater than 10%.

Thus, there appears to be treatment-related decreases in body weights of the high dose males during the treatment phase and in the body weights of the high dose females during the recovery phase.

Food Consumption

The weight of food consumed was recorded daily throughout the study. There were no treatment-related changes in food consumption.

Ophthalmoscopy

Ophthalmoscopic examinations were given to each dog prior to the start of treatment and during Weeks 12 and 25. Ophthalmoscopic examinations were performed and interpreted by a veterinarian. There were no treatment-related findings in ophthalmoscopy.

ECG

Electrocardiography was performed once prior to treatment. During Weeks 12 and 26, electrocardiography was performed prior to dosing and at approximately 2 hours post dose. Electrocardiography was performed and interpreted by a veterinarian.

There were episodes of sinus respiratory arrhythmia, sinus wandering pacemaker, some PR interval of high duration, sinoatrial block, some T-waves of high amplitude, R-waves of high amplitude, sinus bradycardia, and right and left deviation of mean electrical axis (QRS) that occurred sporadically in all groups. The interpreting veterinarian did not have any concerns with these findings as they were occasional, spontaneous, or were viewed as common age-related observations in dogs.

Thus, there were no treatment-related changes in myocardial electrical activity detected by electrocardiography.

Hematology

Blood, urine, and fecal samples were collected for each dog after overnight fasting once prior to the start of treatment, once during Weeks 13 and 26 of treatment, and at the end of recovery. Blood was collected via the jugular vein. Urine and fecal samples were collected from the metabolism cage or from the pen.

The following hematology and coagulation parameters were examined (from the Applicant's submission):

Erythrocyte sedimentation rate
Haematocrit
Haemoglobin
Red blood cell count
Reticulocyte count
Mean red blood cell volume
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
White blood cell count
Differential leucocyte count - Neutrophils
- Lymphocytes
- Eosinophils
- Basophils
- Monocytes
- Large unstained cells

Abnormalities of the blood film
Platelets
Prothrombin time
Activated partial thromboplastin time

At Week 13, there was a decrease in the red blood cell count by 7.84% in the male high dose group only compared to control. At Week 26, there was a decreased in the red blood cell count by 6.83% in the male high dose group only compared to control. In the recovery males, the decrease in the red blood cell count (by 13.9%) remained in the high dose. This decrease in the red blood cell count is statistically significant and was observed in the recovery males. However, the red blood cell count in the high dose males were within normal limits for Beagle dogs of this age (Derelanko 2008).

There were no further treatment-related changes in hematology in the males. There were no treatment-related changes in hematology in the females.

Clinical Chemistry

The following clinical chemistry parameters were examined (from the Applicant's submission):

Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Urea
Creatinine
Glucose
Total bilirubin
Total cholesterol
Total protein
Albumin
Globulin (protocol deviation)
Albumin/Globulin ratio
Sodium
Potassium
Calcium
Chloride

At Week 13, there was a decrease in the ALP by 32.9% in the male low-dose group only compared to control. There was an increase in total bilirubin by 38.0% in the female mid dose only compared to control. The changes in ALP and total bilirubin were not dose-dependent and as such, can be dismissed.

At Week 26, there was a decrease in total bilirubin by 48.1% in the male low dose group only compared to control. There was an increase in urea by 27.0% in the male mid dose group only compared to control. The changes in the total bilirubin and urea were not dose-dependent and as such, can be dismissed.

In the recovery males, there was an increase in sodium by 1.12% in the high dose group compared to control. The sodium levels in the recovery male control and high-dose groups were slightly above the normal ranges described in Derelanko (2008); however, there is a $\pm 2.8\%$ range described in Derelanko (2008) and since the increase in the sodium levels in the high dose recovery males falls within this range, the sodium levels in the high dose recovery males can be dismissed.

There were no further treatment-related changes in clinical chemistry.

Urinalysis

The following urinalysis parameters were examined (from the Applicant's submission):

Appearance
 Volume
 Specific gravity
 pH
 Protein
 Total reducing substances
 Glucose
 Ketones
 Bilirubin
 Urobilinogen
 Blood
 Epithelial cells
 Leukocytes
 Erythrocytes
 Crystals
 Spermatozoa and precursors
 Other abnormal components

Additionally, fecal occult blood was determined from the fecal samples.

At Week 13, there was a decrease in the specific gravity by 2.29% and 1.23% in the female low- and high-dose groups, respectively, compared to control. However, the specific gravity at Week 13 was within normal ranges for Beagle dogs (Derelanko 2008). At Week 26, there was a decrease in the specific gravity by 1.16% in the male low dose group only compared to control. The changes in the specific gravity were not dose-dependent at Week 26 and as such, can be dismissed. The urine volume in males varied greatly between all dose groups; however, the urine volume was within normal ranges for Beagle dogs (Derelanko 2008).

There were no further treatment-related changes in urinalysis.

There were no treatment-related changes in the fecal occult blood.

Gross Pathology

Following the scheduled necropsy at the end of Week 26 for the main study dogs and at the end of Week 29 for the recovery dogs, detailed examination of the external surfaces and orifices as well as the organs in the internal cavities was conducted. The following table illustrates the macroscopic observations in either sex in both the treatment and recovery periods (data from the Applicant's submission):

| | Males | | | | Females | | | |
|-------------------------------|---------|----------|----------|-----------|---------|----------|----------|-----------|
| | Control | Low Dose | Mid Dose | High Dose | Control | Low Dose | Mid Dose | High Dose |
| <i>Treatment Period</i> N = 4 | | | | | | | | |

| | | | | | | | | |
|--|--------|------------|------------|--------|--------|------------|------------|--------|
| Cecum: White granular content | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Colon: White granular content | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| Gall Bladder: Abnormal size Abnormal content | 0 1 | 0 1 | 0 0 | 0 1 | 0 1 | 0 0 | 0 2 | 1 2 |
| Mammary Area Abnormal color Abnormal size | 0 0 | 0 0 | 0 0 | 0 0 | 2 2 | 3 3 | 1 2 | 3 3 |
| Pituitary Cysts | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| Spleen Abnormal area Abnormal shape | 0 2 | 0 3 | 1 3 | 1 2 | 0 2 | 0 3 | 2 1 | 0 3 |
| Thyroid Abnormal size | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Urinary Bladder Abnormal color | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Uterus Abnormal area | N/A | N/A | N/A | N/A | 0 | 0 | 0 | 1 |
| Lymph Nodes Abnormal color | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Submandibular Lymph Nodes Abnormal color | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| <i>Recovery Period N = 3</i> | | | | | | | | |
| Colon Abnormal color | 0 | N/A | N/A | 1 | 0 | N/A | N/A | 0 |
| Gall Bladder Abnormal area Abnormal contents | 0 1 | N/A N/A | N/A N/A | 0 1 | 0 1 | N/A N/A | N/A N/A | 1 2 |
| Lungs Abnormal area | 0 | N/A | N/A | 1 | 0 | N/A | N/A | 0 |
| Mammary Area Abnormal color Abnormal size | 0 0 | N/A N/A | N/A N/A | 0 0 | 0 0 | N/A N/A | N/A N/A | 1 1 |
| Ovaries Abnormal size | N/A | N/A | N/A | N/A | 0 | N/A | N/A | 2 |
| Pituitary Cyst | 1 | N/A | N/A | 0 | 0 | N/A | N/A | 1 |
| Prostate Abnormal size | 0 | N/A | N/A | 1 | N/A | N/A | N/A | N/A |
| Stomach Abnormal color | 0 | N/A | N/A | 0 | 0 | N/A | N/A | 1 |
| Thymus | | | | | | | | |

| | | | | | | | | |
|-----------------------------------|-----|-----|-----|-----|---|-----|-----|---|
| Abnormal size | 0 | N/A | N/A | 1 | 0 | N/A | N/A | 0 |
| Urinary Bladder Abnormal color | 0 | N/A | N/A | 0 | 0 | N/A | N/A | 1 |
| Uterus Abnormal size | N/A | N/A | N/A | N/A | 0 | N/A | N/A | 2 |
| Lymph Nodes Abnormal color | 0 | N/A | N/A | 0 | 0 | N/A | N/A | 1 |

In general, the gross pathological observations include noting abnormal size, color, area, shape, and contents of the organ. The findings at the gall bladder (males), mammary area, spleen, lymph nodes, and submandibular lymph nodes during the treatment period do not show a clear dose-dependency and as such, can be dismissed.

There was an increase incidence of abnormal size and content in the gall bladder of high dose females during the treatment period. There were increased incidences of abnormal size, color, and area in the thyroid, urinary bladder, and uterus, respectively, in the high dose females during the treatment period.

The white content observed in the colon and cecum in the low- and mid-dose males and females during the treatment period are considered to be remnants of the formulation. There was an increase incidence of cysts in the pituitary in the high dose females compared to the control females during the treatment and recovery periods. Cysts are water filled sacs that usually resolve on their own and as such, do not represent a safety concern.

In the recovery dogs, abnormal contents in the gall bladder of the high dose dogs that were observed during the treatment period were also observed in the recovery high dose dogs. The observations in the mammary area in the females during the treatment period were also observed in the high dose recovery females. The abnormal color of the lymph nodes observed in the females during the treatment period was also observed in the high dose recovery females.

Delayed observations in the recovery dogs include the colon, lungs, prostate, and thymus in high dose males as well as the gall bladder (abnormal area), ovaries, stomach, urinary bladder, and uterus (abnormal size).

Organ Weights

At the scheduled necropsy, organs were collected and weighed. See table in the histopathology section below for the list of organs weighed. The following table illustrates the changes in absolute and relative organ weights in either sex during both the treatment and recovery periods (data from the Applicant's submission):

| Absolute Organ Weights (g) in Beagle Dogs Treated with (b) (4) Via | | | | | |
|--|-----|---------|----------|----------|-----------|
| Organ | Sex | Control | Low Dose | Mid Dose | High Dose |

| <i>Treatment Phase</i> | | | | | |
|---|-----|---------|---------------------|---------------------------|----------------------------|
| Right Adrenal | M | 0.6548 | 0.6460 | 0.5323 (↓18.7%) | 0.5360 (↓18.1%) |
| <i>Recovery Phase</i> | | | | | |
| Left Epididymis | M | 1.8150 | N/A | N/A | 1.4633 (↓19.4%) |
| Right Epididymis | | 1.7417 | N/A | N/A | 1.5077 (↓13.4%) |
| Prostate | | 11.312 | N/A | N/A | 3.801 (↓66.4%) |
| Pituitary | F | 0.0660 | N/A | N/A | 0.0587 (↓11.1%) |
| Organ-to-Body-Weight Ratio (%) in Beagle Dogs Treated with [REDACTED] Via Oral Administration ^{(b) (4)} | | | | | |
| Organ | Sex | Control | Low Dose | Mid Dose | High Dose |
| <i>Treatment Phase</i> | | | | | |
| Right Epididymis | M | 0.01382 | 0.02319 (↑34.6%) | 0.01642 | 0.01708 |
| <i>Recovery Phase</i> | | | | | |
| Prostate | M | 0.1032 | N/A | N/A | 0.0378 (↓63.4%) |
| Right Testis | | 0.05818 | N/A | N/A | 0.07922 (↑36.2%) |
| Heart | F | 0.6843 | N/A | N/A | 0.7894 (↑15.4%) |
| Right Thyroid | | 0.00412 | N/A | N/A | 0.00526 (↑27.7%) |

As shown in the table above, there were a number of absolute organ weight and organ-to-body ratio changes in the dogs during both the treatment and recovery periods.

The absolute organ weight of the right adrenal was decreased by 18.7% and 18.1% in the mid- and high-dose males during the treatment phase, which does not represent a clear dose-dependency. There are no macroscopic and histopathologic correlates to the decrease in the absolute organ weight of the right adrenal. Moreover, this decrease was not observed in the recovery males (see below). Thus, this finding at the mid dose can be dismissed. However, regarding the decrease at the high dose, the decrease of greater than 10% in the absolute organ weight of any organ is considered biologically significant.

There was no microscopic correlation to these absolute organ weight changes during the treatment period.

There were no changes in the absolute organ weight of the right adrenal in the recovery males. However, there were a number of delayed observations in the absolute organ weights in the recovery dogs that were not seen during the treatment period. There

were decreases in the absolute organ weights of the left and right epididymis and prostate in the high dose recovery males and in the pituitary in the high dose recovery females, compared to control.

There were no treatment-related changes in the absolute organ weight and organ-to-body weight ratio in females during the treatment period.

The right epididymis organ-to-body weight ratio increased by 34.6% in the low dose group only, compared to control. This finding can be dismissed as there was no dose dependency.

There was no microscopic correlation to these organ-to-body weight ratio changes during the treatment period.

There were no changes in the organ-to-body-weight ratio of the right epididymis in the recovery males. However, there were a number of delayed observations in the organ-to-body-weight ratio in the recovery dogs that were not seen during the treatment period. There was a decrease in the organ-to-body-weight ratio of the prostate as well as an increase in the right testis in the high dose recovery males and an increase in the heart and right thyroid in the high dose recovery females, compared to control.

There were no further treatment-related changes in the absolute organ weight and the organ-to-body-weight ratio in either sex in both the treatment and recovery periods.

Histopathology

Adequate Battery

The following organs and tissues were collected, weighed, and examined microscopically (from the Applicant's submission):

| Organs / Tissues | Weight | Fixation Preservation | Microscopic Examination |
|------------------------------------|--------|--------------------------|----------------------------|
| Abnormalities | | ✓ | ✓ |
| Adrenal glands | ✓ | ✓ | ✓ |
| Aorta | | ✓ | ✓ |
| Bone marrow (from sternum) | | ✓ | ✓ |
| Brain | ✓ | ✓ | ✓ |
| Caecum | | ✓ | ✓* |
| Colon | | ✓ | ✓* |
| Duodenum | | ✓ | ✓* |
| Epididymides | ✓ | ✓ | ✓ |
| Eyes | | ✓ | ✓ |
| Femur with joint | | ✓ | ✓ |
| Gall bladder | | ✓ | ✓ |
| Heart | ✓ | ✓ | ✓ |
| Ileum (including Peyer's patches) | | ✓ | ✓* |
| Jejunum | | ✓ | ✓* |
| Kidneys | ✓ | ✓ | ✓ |
| Larynx | | ✓ | § |
| Liver | ✓ | ✓ | ✓ |
| Lungs (including mainstem bronchi) | ✓ | ✓ | ✓ |
| Lymph nodes - peribronchial | | ✓ | ✓ |
| Lymph nodes - mesenteric | | ✓ | ✓ |
| Mammary area | | ✓ | ✓ |
| Oesophagus | | ✓ | ✓ |
| Optic nerves | | ✓ | ✓ |
| Ovaries | ✓ | ✓ | ✓ |
| Oviducts | | ✓ | ✓ |
| Pancreas | | ✓ | ✓ |
| Parathyroid glands ^a | | ✓ | ✓ |
| Pituitary gland | ✓ | ✓ | ✓ |
| Prostate gland | ✓ | ✓ | ✓ |
| Rectum | | ✓ | ✓* |
| Salivary glands | ✓ | ✓ | ✓ |
| Sciatic nerve | | ✓ | ✓ |
| Skeletal muscle | | ✓ | ✓ |
| Skin | | ✓ | ✓ |
| Spinal column | | ✓ | |
| Spinal cord | | ✓ | ✓ |
| Spleen | ✓ | ✓ | ✓ |
| Stomach | | ✓ | ✓* |
| Testes | ✓ | ✓ | ✓ |
| Thymus (where present) | ✓ | ✓ | ✓ |
| Thyroid gland | ✓ | ✓ | ✓ |
| Tongue | | ✓ | ✓ |
| Trachea | | ✓ | ✓ |
| Ureters | | ✓ | ✓ |
| Urinary bladder | | ✓ | ✓ |
| Uterus – cervix | ✓ | ✓ | ✓ |
| Vagina | | ✓ | ✓ |

* : Multiple locations (three) were taken.

§ : not examined as no signs of toxicity or target organ involvement were observed.

^a : weighed and preserved with thyroid gland.

This is an adequate battery of tissues to collect, weight, and examine microscopically.

Peer Review

There was no separate Pathologist Report in this Final Study Report. There was only one Study Pathologist on this study and it does not appear that this study was peer reviewed.

Histological Findings

The following table illustrates the histopathological findings in either sex during both the treatment and recovery phases (data from the Applicant's submission):

| N = 4 | Males | | | | Females | | | |
|--|---------|----------|----------|-----------|---------|----------|----------|-----------|
| | Control | Low Dose | Mid Dose | High Dose | Control | Low Dose | Mid Dose | High Dose |
| <i>Treatment Period</i> | | | | | | | | |
| Gall Bladder Lymphoid aggregations | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 3 |
| Kidneys Nephropathy | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| Mammary Area Glandular hyperplasia | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 2 |
| Secretory activity | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 1 |
| Pituitary Cranio-pharyngeal cysts | 0 | 0 | 2 | 1 | 2 | 2 | 1 | 3 |
| Skin Chronic inflammation | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Spleen Lymphoid hyperplasia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Urinary Bladder Vascular degenerative changes | 1 | 0 | 2 | 2 | 0 | 0 | 1 | 0 |
| Uterus Hydrometra | N/A | N/A | N/A | N/A | 0 | 0 | 1 | 1 |
| Cystic formation | N/A | N/A | N/A | N/A | 0 | 0 | 0 | 1 |
| Tonsils Congestion | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Submandibular Lymph Nodes Pigmentation | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 |

There was an increased incidence of lymphoid aggregations in the gall bladder observed in the high dose females compared to control. There was an increased incidence of nephropathy observed in the high dose males compared to control. There was an increased incidence of lymphoid hyperplasia in the spleen observed in the high dose males compared to control. There was an increased incidence of congestion in

the tonsils observed in both the high dose males and females. These observations are dose-dependent and therefore considered treatment-related.

Granular hyperplasia and secretory activity of the mammary gland were observed in the female low-, mid-, and high-dose groups without a clear dose-dependency. As such, these observations can be dismissed.

Cranio-pharyngeal cysts of the pituitary were observed in the males in the mid- and high dose groups and in all female dose groups. Cystic formation in the uterus was also observed in the high dose female dose group. Cysts, in general, are water-filled sacs that resolve on their own over time and as such, can be dismissed.

Chronic inflammation of the skin was only observed in the mid- and high-dose males without a clear dose-dependency. As such, this observation can be dismissed.

Vascular degenerative changes in the urinary bladder was observed in the control males, as well as the mid- and high-dose males and the mid-dose females without a clear dose-dependency. As such, this observation can be dismissed.

Hydrometra of the uterus was observed in the mid- and high-dose females without a clear dose-dependency. As such, this observation can be dismissed.

Pigmentation of the submandibular lymph nodes were observed in the mid- and high-dose males as well as the mid-dose females without a clear dose-dependency. As such, this observation can be dismissed.

Histopathology was not performed in the recovery dogs.

There were no further treatment-related changes in histopathology.

Toxicokinetics

Toxicokinetics were not performed for this study.

Dosing Solution Analysis

Qualitative and quantitative analysis of (b) (4) was performed before the start of treatment and was repeated at the end of the study. The following tables illustrate the quantitative analysis of the samples of (b) (4) before treatment and at the end of the study (from the Applicant's submission):

Before the start of the study

| Pellets weighted | Amount found | | Mean | Standard deviation | Precision |
|------------------|------------------|-------|--------------|--------------------|-------------|
| W (g) | Net weight x (g) | C % | % | | CV % |
| 2.0027* | 0.4970 | 24.82 | 25.04 | 0.246 | 0.98 |
| 2.0029 | 0.5008 | 25.00 | | | |
| 2.0092 | 0.4984 | 24.81 | | | |
| 2.0006 | 0.5072 | 25.35 | | | |
| 2.0089 | 0.5070 | 25.24 | | | |

End of the study

| Pellets weighted | Amount found | | Mean | Standard deviation | Precision |
|------------------|------------------|-------|--------------|--------------------|-------------|
| W (g) | Net weight x (g) | C % | % | | CV % |
| 2.0033* | 0.4991 | 24.91 | 24.95 | 0.179 | 0.72 |
| 2.0055 | 0.4985 | 24.86 | | | |
| 2.0036 | 0.4975 | 24.83 | | | |
| 2.0003 | 0.4974 | 24.87 | | | |
| 2.0005 | 0.5053 | 25.26 | | | |

As shown in the tables above, the average amount of (b) (4) before the start of treatment is similar to the amount at the end of the study. Thus, similar amounts of (b) (4) were given throughout the study.

7 Genetic Toxicology

There were no new genetic toxicology studies with morphine submitted in this NDA.

The Applicant submitted several genetic toxicology studies using either (b) (4) and are reviewed below. These studies are also cross-referenced in MF (b) (4)

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Study title: Salmonella Typhimurium Reverse Mutation Assay with

(b) (4)

Study no.: B16-901500
Study report location: Module 4 of the Electronic Submission
Conducting laboratory and location: (b) (4)

Date of study initiation: July 26, 2005
GLP compliance: Yes. Signature provided on August 16, 2005
QA statement: Yes. Signature provided on August 16, 2005
Drug, lot #, and % purity: (b) (4), batch B050432001, described as a liquid dispersion with approximately 40% dry substance with no description of purity in the final report.

Key Study Findings

- *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were treated with 0, 33, 100, 333, 1000, 2500, and 5000 mcg/plate of (b) (4) in an Ames assay.
- This Ames assay is considered valid.
- (b) (4) was not mutagenic in the strains tested under the conditions of this study.
- No *E. coli* strains were used and as such, which evaluates gene mutations from AT base pair changes. However, *S. typhimurium* strain TA102 is used, which evaluates gene mutations from AT base pair changes.

Methods

| | |
|-------------------------------------|--|
| Strains: | <i>S. typhimurium</i> strains TA98, TA100, TA102, TA1535, and TA1537 |
| Concentrations in definitive study: | 33, 100, 333, 1000, 2500, and 5000 mcg/plate |
| Basis of concentration selection: | Nontoxicity to bacteria at the highest dose of 5000 mg/plate |
| Negative control: | DMSO |
| Positive control: | In the absence of S9 metabolic activation: 4-nitro-o-phenylene-diamine or 4-NOPD (TA98 and TA1537), sodium azide (TA100 and TA1535), and methyl methane sulfonate or MMS (TA102); In the presence of S9 metabolic activation: 2-aminoanthracene (TA98, TA100, TA102, TA1535, and TA1537) |
| Formulation/Vehicle: | DMSO. It is noted that a precipitate did form at 5000 mcg/plate. |
| Incubation & sampling time: | (b) (4) in vehicle (DMSO), vehicle alone (negative control), or positive control was pre-incubated with the bacteria with and without S9 mix in the top agar. The solution was mixed and overlaid onto a minimal bottom agar. After the overlay solidified, the plates were inverted and incubated at 37°C for 48 hrs. Afterwards, the plates were scored. All concentrations and controls (both positive and negative) in the initial toxicity-mutation assay and in the confirmatory mutagenicity assay were plated in triplicate. |

Study Validity

The study is considered valid for the following reasons: 1) the appropriate controls were used; 2) the appropriate strains were tested (however, no strains of *E. coli* were used; 3) the positive control substances produced reliable positive results; 4) the highest concentration of (b) (4) tested reached the maximum recommended concentration of 5000 mcg/plate; and 5) there was no evidence for a dose-dependent increase in revertants following drug treatment.

This study is appropriate to detect gene mutations from GC base pair changes or frameshifts due to the strains of *S. typhimurium* used. However, gene mutations from AT base pair changes that normally come from using *E. coli* strain were evaluated using the *S. typhimurium* strain TA102 (Kamber et al., 2009). Thus *S. typhimurium* stain TA102 can be used in lieu of *E. coli* strain WP2 uvrA to evaluate gene mutations from AT base pair changes.

Results

The following table illustrates the results of the confirmatory assay (from the Applicant's submission):

| Study Name: 901500 Experiment: 901500 HV2 Pre Assay Conditions: | | | Study Code: (b)(4) 901500 Date Plated: 08/08/2005 Date Counted: 11/08/2005 | | | | | |
|---|-----------------------------|-----------------------|--|----------------------|----------------------|-----------------------|------------------------|------------|
| Metabolic Activation | Test Group | Dose Level (µg/plate) | Revertant Colony Counts (Mean ±SD) | | | | | |
| | | | TA 1535 | TA 1537 | TA 98 | TA 100 | TA 102 | |
| Without Activation | DMSO | | 20 ± 8 | 10 ± 5 | 20 ± 2 | 101 ± 21 | 350 ± 13 | |
| | Untreated | | 20 ± 3 | 12 ± 2 | 23 ± 1 | 109 ± 13 | 352 ± 10 | |
| | (b)(4) | 33 µg | 17 ± 2 | 16 ± 7 | 14 ± 2 | 92 ± 10 | 354 ± 29 | |
| | | 100 µg | 12 ± 5 | 12 ± 2 | 22 ± 6 | 104 ± 2 | 393 ± 14 | |
| | | 333 µg | 13 ± 1 | 15 ± 6 | 19 ± 4 | 95 ± 5 | 371 ± 65 | |
| | | 1000 µg | 18 ± 3 | 13 ± 2 | 20 ± 4 | 98 ± 11 | 352 ± 22 | |
| | | 2500 µg | 16 ± 6 | 15 ± 6 | 15 ± 7 | 96 ± 25 | 366 ± 17 | |
| | | 5000 µg | 13 ± 3 ^{PM} | 12 ± 3 ^{PM} | 16 ± 2 ^{PM} | 98 ± 3 ^{PM} | 337 ± 15 ^{PM} | |
| | | NaN3 | 10 µg | 1310 ± 4 | | | 1976 ± 86 | |
| | | 4-NOPD | 10 µg | | | 337 ± 19 | | |
| | | 4-NOPD | 50 µg | | 128 ± 12 | | | |
| | | MMS | 4.0 µL | | | | | 1810 ± 37 |
| | With Activation | DMSO | | 18 ± 5 | 14 ± 3 | 31 ± 12 | 121 ± 13 | 494 ± 9 |
| | | Untreated | | 25 ± 5 | 22 ± 8 | 32 ± 8 | 138 ± 23 | 536 ± 14 |
| (b)(4) | | 33 µg | 21 ± 9 | 13 ± 2 | 36 ± 6 | 114 ± 12 | 468 ± 18 | |
| | | 100 µg | 25 ± 8 | 11 ± 4 | 23 ± 6 | 128 ± 18 | 527 ± 71 | |
| | | 333 µg | 22 ± 5 | 18 ± 5 | 29 ± 2 | 131 ± 13 | 478 ± 29 | |
| | | 1000 µg | 19 ± 8 | 20 ± 7 | 31 ± 9 | 119 ± 13 | 436 ± 13 | |
| | | 2500 µg | 20 ± 6 | 16 ± 4 | 31 ± 7 | 121 ± 9 | 468 ± 17 | |
| | | 5000 µg | 20 ± 3 ^{PM} | 12 ± 3 ^{PM} | 23 ± 2 ^{PM} | 112 ± 9 ^{PM} | 424 ± 16 ^{PM} | |
| | | 2-AA | 2.5 µg | 217 ± 22 | 104 ± 10 | 687 ± 43 | 1047 ± 117 | |
| | | 2-AA | 10.0 µg | | | | | 2028 ± 205 |
| Key to Positive Controls | | | Key to Plate Postfix Codes | | | | | |
| NaN3 | sodium azide | | P | Precipitate | | | | |
| 2-AA | 2-aminoanthracene | | M | Manual count | | | | |
| MMS | methyl methane sulfonate | | | | | | | |
| 4-NOPD | 4-nitro-o-phenylene-diamine | | | | | | | |

As shown in the table above, the number of revertant colonies that resulted from all the concentrations tested in all strains tested did not increase significantly from the vehicle and untreated controls. Furthermore, the number of revertant colonies in all strains treated with the test compound was less than the historical control (see the Historical Control table below, from the Applicant's submission):

| Strain | | without S9 mix | | | | with S9 mix | | | |
|---------|------------------|----------------|------|------|------|-------------|------|-----|------|
| | | Mean | SD | Min | Max | Mean | SD | Min | Max |
| TA 1535 | Solvent control | 19 | 6 | 9 | 35 | 21 | 7 | 7 | 41 |
| | Negative control | 18 | 5 | 10 | 30 | 21 | 6 | 9 | 38 |
| | Positive control | 1681 | 789 | 1003 | 4900 | 387 | 126 | 172 | 695 |
| TA1537 | Solvent control | 12 | 3 | 4 | 29 | 18 | 6 | 6 | 36 |
| | Negative control | 11 | 3 | 5 | 29 | 19 | 6 | 8 | 33 |
| | Positive control | 87 | 18 | 52 | 191 | 337 | 191 | 94 | 746 |
| TA 98 | Solvent control | 26 | 6 | 14 | 58 | 39 | 9 | 21 | 57 |
| | Negative control | 26 | 6 | 15 | 60 | 41 | 9 | 17 | 64 |
| | Positive control | 361 | 204 | 176 | 1818 | 2386 | 1195 | 296 | 4854 |
| TA 100 | Solvent control | 131 | 24 | 91 | 198 | 147 | 25 | 109 | 281 |
| | Negative control | 140 | 21 | 101 | 189 | 154 | 23 | 103 | 254 |
| | Positive control | 2030 | 340 | 1178 | 2872 | 2629 | 1326 | 546 | 5230 |
| TA 102 | Solvent control | 351 | 61 | 242 | 455 | 461 | 91 | 332 | 607 |
| | Negative control | 364 | 60 | 242 | 458 | 465 | 97 | 280 | 614 |
| | Positive control | 3352 | 1541 | 1220 | 5904 | 2104 | 752 | 872 | 3052 |

Mean = mean value of revertants/plate

SD = standard deviation

Min = minimal value/Max = maximal value

Thus, (b) (4) was not mutagenic under the conditions of this assay to evaluate gene mutations arising from GC and AT base pair changes.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells with (b) (4)

Study no.: B14-855500
 Study report location: Module 4 of the Electronic Submission
 Conducting laboratory and location: (b) (4)

Date of study initiation: October 7, 2004
 GLP compliance: Yes. Signature provided on January 28, 2005
 QA statement: Yes. Signature provided on January 28, 2005

Drug, lot #, and % purity: (b) (4); batch # B031032002; Supplied as an aqueous dispersion containing 40.7% dry substance in content with no description of the purity in the final report.

Key Study Findings

- Mouse Lymphoma L5178Y cells were treated with 0, 195.3, 390.6, 781.3, 1562.5, 3125, and 6250 mcg/mL of [REDACTED]^{(b) (4)} in the cell mutation assay at the thymidine kinase locus.
- This assay is considered valid.
- [REDACTED]^{(b) (4)} is not considered mutagenic under the conditions of this study.

Methods

| | |
|-------------------------------------|---|
| Cell line: | Mouse Lymphoma L5178Y cells |
| Concentrations in definitive study: | 195.3, 390.6, 781.3, 1562.5, 3125, and 6250 mcg/mL |
| Basis of concentration selection: | Maximum tolerated dose in the pre-test |
| Negative control: | Deionized water |
| Positive control: | Methyl methane sulfonate (MMS) for the without metabolic activation condition; Cyclophosphamide (CPA) for the with metabolic activation condition |
| Formulation/Vehicle: | Deionized water |
| Incubation & sampling time: | L5178Y cells were exposed to the test compound for 4 hours with and without metabolic activation at 37°C in the first experiment and for 24 hours without metabolic activation at 37°C in the second experiment. Each experiment used duplicate cultures. |

Study Validity

The study was deemed valid for the following reasons: 1) vehicle control cultures exhibited a mean cloning efficiency of 50% or greater; 2) vehicle control cultures gave a mean mutant frequency less than 150×10^{-6} and at least 12×10^{-6} ; 3) positive controls exhibited appropriate responses; 4) concentrations were appropriate in that either a positive mutant frequency response or an 80% reduction in RTG or a persistent precipitate was achieved; and 5) the ability to recover small colonies was demonstrated by sizing of the positive control.

Results

The following table illustrates the number of mutant colonies after treatment with [REDACTED]^{(b) (4)} with and without metabolic activation in Experiment 1 and without metabolic activation in Experiment 2 (from the Applicant's submission):

| | conc. µg | S9 | relative | relative | mutant | | relative | relative | mutant | |
|----------------------------|----------|-----|------------------|--|-----------------------|-----------|-------------------|--|-----------------------|-----------|
| | per mL | mix | cloning | total | colonies/ | induction | cloning | total | colonies/ | induction |
| | | | efficiency 1 | growth | 10 ⁶ cells | factor | efficiency 1 | growth | 10 ⁶ cells | factor |
| Column | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Experiment I | | | culture I | | | | culture II | | | |
| Neg. control with medium | | - | 100.0 | 100.0 | 130 | | 100.0 | 100.0 | 81 | |
| Solvent control with water | | - | 100.0 | 100.0 | 175 | 1.0 | 100.0 | 100.0 | 65 | 1.0 |
| Pos. Control with MMS | 13.0 | - | 96.2 | 39.2 | 432 | 3.3 | 106.0 | 35.6 | 262 | 3.2 |
| Test item | 195.3 | - | 107.4 | culture was not continued [#] | | | 88.8 | culture was not continued [#] | | |
| Test item | 390.6 | - | 77.5 | 92.2 | 162 | 0.9 | 103.7 | 92.1 | 74 | 1.1 |
| Test item | 781.3 | - | 88.1 | 118.9 | 146 | 0.8 | 105.6 | 138.4 | 64 | 1.0 |
| Test item | 1562.5 | - | 88.1 | 97.7 | 179 | 1.0 | 118.8 | 119.9 | 71 | 1.1 |
| Test item | 3125 (p) | - | 97.8 | 139.1 | 127 | 0.7 | 124.0 | 105.4 | 63 | 1.0 |
| Test item | 6250 (p) | - | 102.3 | 108.1 | 209 | 1.2 | 109.6 | 146.3 | 48 | 0.7 |
| | | | | | | | | | | |
| Neg. control with medium | | + | 100.0 | 100.0 | 92 | | 100.0 | 100.0 | 73 | |
| Solvent control with water | | + | 100.0 | 100.0 | 52 | 1.0 | 100.0 | 100.0 | 61 | 1.0 |
| Pos. control with CPA | 3.0 | + | 32.7 | 10.4 | 334 | 3.6 | 27.2 | 16.8 | 369 | 5.1 |
| Test item | 195.3 | + | 97.1 | culture was not continued [#] | | | 96.9 | culture was not continued [#] | | |
| Test item | 390.6 | + | 143.6 | 80.4 | 67 | 1.3 | 120.2 | 53.1 | 95 | 1.5 |
| Test item | 781.3 | + | 97.1 | 46.4 | 80 | 1.5 | 94.0 | 60.3 | 85 | 1.4 |
| Test item | 1562.5 | + | 135.9 | 65.0 | 87 | 1.7 | 91.2 | 94.9 | 103 | 1.7 |
| Test item | 3125 (p) | + | 109.6 | 76.5 | 65 | 1.3 | 85.9 | 89.5 | 97 | 1.6 |
| Test item | 6250 (p) | + | 72.8 | 51.4 | 51 | 1.0 | 129.5 | 94.9 | 110 | 1.8 |
| Experiment II | | | culture I | | | | culture II | | | |
| Neg. control with medium | | - | 100.0 | 100.0 | 71 | | 100.0 | 100.0 | 75 | |
| Solvent control with water | | - | 100.0 | 100.0 | 65 | 1.0 | 100.0 | 100.0 | 47 | 1.0 |
| Solv. control with MMS | 13.0 | - | 36.1 | 22.5 | 456 | 6.4 | 11.9 | 11.5 | 681 | 9.1 |
| Test item | 195.3 | - | 135.1 | culture was not continued [#] | | | 84.2 | culture was not continued [#] | | |
| Test item | 390.6 | - | 101.7 | 105.5 | 83 | 1.3 | 71.0 | 86.2 | 71 | 1.5 |
| Test item | 781.3 | - | 141.4 | 119.6 | 52 | 0.8 | 107.6 | 72.0 | 73 | 1.5 |
| Test item | 1562.5 | - | 100.0 | 125.3 | 67 | 1.0 | 106.0 | 100.8 | 53 | 1.1 |
| Test item | 3125 (p) | - | 112.9 | 151.7 | 46 | 0.7 | 215.4 | 121.8 | 58 | 1.2 |
| Test item | 6250 (p) | - | 98.4 | 128.7 | 59 | 0.9 | 38.3 | 82.7 | 47 | 1.0 |

- # culture was not continued since a minimum of four concentrations is required by the guidelines
- p heavy precipitation, visible by the naked eye

As shown in the table above, the number of mutant colonies/10⁶ cells in L5718Y cells treated with increasing concentrations of (b) (4) was no different than the controls as well as the historical control ranges (see the Historical Data below, from the Applicant's submission):

These values represent the historical control data from 2000 – 2003 (data with CPA since 2003).

| Number of mutant colonies per 10 ⁶ cells | | | | | | | | |
|---|------------------|-------------|----------------------|-------------|-----------------|-------------|-----------------|-------------|
| 4 h treatment | | | | | | | | |
| | Negative control | | Positive control | | | | Solvent control | |
| | without S9 mix | with S9 mix | without S9 mix | with S9 mix | with S9 mix | with S9 mix | without S9 mix | with S9 mix |
| | | | MMS | 3-MC | DMNA | CPA | | |
| range: | 41 – 193 | 41 – 197 | 292 – 3321 | 176 – 2705 | 183 – 847 | 287 – 1098 | 44 – 224 | 44 – 217 |
| Mean value: | 105 | 111 | 557 | 387 | 366 | 584 | 106 | 112 |
| Standard deviation: | 33 | 34 | 315 | 197 | 168 | 265 | 36 | 32 |
| 24 h treatment | | | | | | | | |
| | Negative control | | Positive control | | Solvent control | | | |
| | without S9 mix | | without S9 mix (MMS) | | without S9 mix | | | |
| range: | 40 – 207 | | 268 – 2431 | | 33 – 192 | | | |
| Mean value: | 102 | | 962 | | 105 | | | |
| Standard deviation: | 35 | | 472 | | 34 | | | |

Thus, (b) (4) did not induce mutations in L5178Y cells in the mouse lymphoma thymidine kinase locus assay in the presence and absence of metabolic activation, under the conditions of this study.

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

Study title: (b) (4) **Micronucleus Test in Mice**

Study no: B18-54000
 Study report location: Module 4 of the Electronic Submission
 Conducting laboratory and location: (b) (4)

Date of study initiation: July 4, 2006
 GLP compliance: Yes. Signature provided on February 16, 2007
 QA statement: Yes. Signature provided on February 16, 2007
 Drug, lot #, and % purity: (b) (4); batch # B050432001; Supplied as an aqueous dispersion containing 40% dry substance with no description of the purity in the final report.

Key Study Findings

- CD-1 mice were treated with 0, 500, 1000, and 2000 mg/kg of (b) (4) in a single dose administration via oral gavage.
- Mice were sacrificed at the 24 and 48 hour sampling time points and bone marrow was collected from the femur of each mouse.
- This study is considered valid.
- There were no treatment-related changes in body weight.
- (b) (4) did not induce the formation of micronuclei in mouse polychromatic erythrocytes under the conditions of this study.

Methods

| | |
|----------------------------|---|
| Doses in definitive study: | 0, 500, 1000, and 2000 mg/kg |
| Frequency of dosing: | One time administration |
| Route of administration: | Oral gavage |
| Dose volume: | 10 mL/kg |
| Formulation/Vehicle: | Sterile distilled water of injectable grade |
| Species/Strain: | Mice/Hsd:ICR (CD-1) |
| Number/Sex/Group: | 5/sex/group. These animals were sacrificed at the 24 hour sampling time. |
| Satellite groups: | Additional 5/sex/group in the control and high dose groups. These animals were sacrificed at the 48 hour sampling time. |
| Basis of dose selection: | The high dose of 2000 mg/kg is considered the limit dose in a previously conducted toxicity test. |
| Negative control: | Sterile distilled water of injectable grade |
| Positive control: | Mitomycin-C (3.0 mg/kg) |

The following table illustrates the treatment groups and sampling times (from the Applicant's submission):

| Group Colour code | Treatment (mg/kg active ingredient) M/F | Animal numbers | | Sampling time |
|----------------------|--|-------------------------------|-------------------------------|-------------------------------|
| | | Males | Females | |
| 1 White | Vehicle 0.0 | 2 - 10 52 - 60 | 1 - 9 51 - 59 | 24 hrs 48 hrs |
| 2 Yellow | Test item 500 1250 as supplied | 12 - 20 | 11 - 19 | 24 hrs |
| 3 Blue | Test item 1000 2500 as supplied | 22 - 30 | 21 - 29 | 24 hrs |
| 4 Pink | Test item 2000 5000 as supplied | 32 - 40 62 - 70 72 - 80 | 31 - 39 61 - 69 71 - 79 | 24 hrs 48 hrs 24-48 hrs |
| 5 Red | Mitomycin-C 3.0 | 42 - 50 | 41 - 49 | 24 hrs |

At each of the 24 and 48 hour sampling time points, the femurs were removed from each mouse and bone marrow cells were collected from the excised femurs. Bone marrow smears were then prepared and examined.

Study Validity

The study is deemed valid for the following reasons: 1) dosing appeared to be adequate based upon the results of the dose-ranging study; 2) preparation and administration of the test substance was acceptable; 3) administration of the test compound by oral gavage was used to obtain exposure to the test compound; 4) the species and number of animals/sex/group were acceptable; 5) tissue sampling and analysis was acceptable; and 6) positive controls exhibited appropriate responses; and 7) the proportion of immature erythrocytes among total erythrocytes was less than 20% of the control value.

Results

There were no treatment-related changes in body weights.

The following summary table illustrates the formulation of micronucleated polychromatic erythrocytes (PCEs) following treatment with (b) (4) (from the Applicant's submission):

(b) (4) : MICRONUCLEUS TEST

TABLE 7 - Summary table

STUDY NO.: 54000

VEHICLE: STERILE DISTILLED WATER

| Treatment | Dose-level (mg/kg) | Incidence of micronucleated PCE's | | | PCE/(PCE+NCE) % over the mean negative control value | | |
|----------------------------|-----------------------|--------------------------------------|--------|-----|---|-------|-----|
| | | M/F | Mean | SE | | Range | |
| <u>24 hr sampling time</u> | | | | | | | |
| Vehicle | 10 ml/kg | | 0.1 | 0.1 | 0.0 | 0.5 | 100 |
| Test item | 500 | | 0.4 | 0.2 | 0.0 | 2.5 | 102 |
| Test item | 1000 | | 0.6* | 0.1 | 0.0 | 1.0 | 99 |
| Test item | 2000 | | 0.4* | 0.1 | 0.0 | 1.5 | 103 |
| Mitomycin-C | 3.00 | | 9.4*** | 2.8 | 0.0 | 27.5 | 102 |
| <u>48 hr sampling time</u> | | | | | | | |
| Vehicle | 10 ml/kg | | 0.9 | 0.2 | 0.0 | 2.0 | 100 |
| Test item | 2000 | | 0.9 | 0.2 | 0.0 | 2.0 | 110 |

Key:

PCE : Polychromatic erythrocytes

NCE : Normochromatic erythrocytes

* : Incidence significantly greater than control value at $p < 0.05$ ** : Incidence significantly greater than control value at $p < 0.01$ *** : Incidence significantly greater than control value at $p < 0.001$

As shown in the table above, there was a statically significant increase in the incidence of micronucleated PCEs in the 1000 and 2000 mg/kg dose groups compare to control at the 24 hour sampling while there was no difference between the control and 2000 mg/kg dose group at the 48 hour sampling. However, the incidence of micronucleated PCEs in the 1000 and 2000 mg/kg dose groups is within the range of micronucleated PCEs in the historical control at the 24 hour sampling (see table below, from the Applicant's submission):

**HISTORICAL CONTROL DATA
FOR INCIDENCES OF MICRONUCLEATED PCEs**

(1991 – 2006)

| | <i>24 hour Negative Control</i> | | | <i>48 hour Negative Control</i> | | |
|-----------------------|---------------------------------|------|-------|---------------------------------|------|-------|
| | M | F | M + F | M | F | M + F |
| Mean | 1.0 | 1.0 | 1.0 | 0.9 | 1.0 | 1.0 |
| SD (σ_{n-1}) | 0.47 | 0.46 | 0.40 | 0.53 | 0.47 | 0.43 |
| n | 94 | 94 | 94 | 91 | 91 | 91 |
| Maximum | 2.6 | 2.0 | 2.2 | 3.4 | 2.2 | 2.5 |
| Minimum | 0.0 | 0.1 | 0.1 | 0.0 | 0.0 | 0.2 |

SD = standard deviation

n = number of experiments

Thus, (b) (4) administered by oral gavage at doses up to 2000 mg/kg, does not induce micronuclei in polychromatic erythrocytes under the conditions of this study.

8 Carcinogenicity

There were no carcinogenicity studies with morphine submitted in this NDA nor are they required for this 505(b)(2) application as per OND policy. There are no carcinogenicity studies for the (b) (4) copolymers.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with morphine submitted in this NDA nor are they required for this 505(b)(2) application.

Embryonic fetal development studies in rats and rabbits with (b) (4) were submitted in this NDA are reviewed below. These studies are cross-referenced in MF (b) (4). It is noted that (b) (4) is confirmed to be (b) (4).

9.2 Embryonic Fetal Development

Study title: Investigation of the Effect of 2837 D Administered in the Food on the Pregnant Rat and the Foetus (2837 D = (b) (4))

Study no.: B03-101325
 Study report location: Module 4 of the Electronic Submission
 Conducting laboratory and location: (b) (4)
 Date of study initiation: This study was done from September 1973 to February 1974 prior to GLP (the final report was dated March 29, 1974).
 GLP compliance: See GLP compliance evaluation below
 QA statement: None
 Drug, lot #, and % purity: The drug 2937 D is (b) (4) which has been confirmed to be (b) (4). As this study was pre GLPs, the study report does not contain any drug lot numbers or purity information.

Key Study Findings

- Female Sprague-Dawley rats were dosed with 0, 500, and 2000 mg/kg of (b) (4) orally via the diet on a daily basis from the 6th to the 15th day of pregnancy.
- The rats were sacrificed on Day 19 of pregnancy and the fetuses were removed for examination.
- All rats survived to the scheduled necropsy.
- There were no treatment-related changes in behavior, external appearance, nature of feces, body weight, and food consumption in the maternal rats. However, there was an increased urinary excretion during the treatment period in the 2000 mg/kg dose group compared to control that returned to control levels once treatment with (b) (4) ceased. Increased urinary excretion is not deleterious to health and is dismissed.
- In the dams, there was a slight dose-dependent increase in the corpora lutea (total and per dam), implantations (total and per dam), and fetuses (total and per dam) in the 500 and 2000 mg/kg dose groups compared to control; however, the magnitude of the changes is not clinically significant as the values are within the normal range for this species.
- In the fetuses, there were no treatment-related changes in macroscopic observations, fetal weight or in the number of resorptions (left, right, total, per dam, early, and late), dead fetuses, runts, deformities, variations (number of animals with variations/nature of variations, appraisal of internal organs, and the variations rate), delayed ossifications (phalanges, sternbrae, skull, and

hypoplasia of the 12th/13th pair of ribs), and the % pre- and post-implantation losses or displacement of testes.

- These data suggest that both the maternal and fetal NOAEL is 2000 mg/kg.
- At the MTDD of 2 g/day of morphine, which results in (b) (4) of the (b) (4) (b) (4), the exposure margin for this level of (b) (4) based on the maternal and fetal NOAEL is 671.
- This is in concurrence with the Applicant's maternal and fetal NOAELs, which are both 2000 mg/kg.
- As there is no apparent systemic absorption of the copolymer backbone, the reproductive and developmental toxicology studies with (b) (4) are relevant to confirm lack of absorption of smaller molecular weight impurities, if present. In addition, this study is also relevant as part of the safety justification for the (b) (4).

Methods

Doses: 0, 500, and 2000 mg/kg
 Frequency of dosing: Once daily from the 6th to the 15th day of pregnancy
 Dose volume: Unknown (rats ate feed containing (b) (4) (b) (4) until they were satiated)
 Route of administration: Oral via diet
 Formulation/Vehicle: The test compound is in the feed. See below for the contents of the food given to each rat.
 Species/Strain: Rats/Sprague-Dawley
 Number/Sex/Group: 20/sex/group (females only); male rats were used for mating purposes only
 Satellite groups: No toxicokinetics group
 Study design: See the table below
 Deviation from study protocol: Amendments to results were incorporated into this review. This Final Study Report did not include a protocol deviation section.

The following table illustrates the study design (from the Applicant's submission):

| Group | 2837 D dosage in mg/kg body wt/day in the feedstuff | Treated feedstuff in g/kg body wt/day | No. of female animals |
|-------|---|---------------------------------------|-----------------------|
| (I) | 500 | 5 | 20 |
| (II) | 2000 | 20 | 20 |
| (III) | Controls | 20 (Blank preparation) | 20 |

It is important to note that in modern GLP-complaint studies, the dosing period is Day 7 of gestation to Day 17 of gestation with Caesarean-sectioning on Day 21 of gestation.

The following table illustrates the contents of the food for each rat without (b) (4)
(b) (4) (from the Applicant's submission):

Standardised maintenance diet for rats and mice

(b)(4)

(Company: [REDACTED])Crude nutrients
(% in the diet - mean)

| | |
|---------------|------|
| Crude protein | 19.0 |
| Crude fat | 4.2 |
| Crude fibre | 6.0 |
| Ash | 7.0 |
| Water | 12.5 |

Convertible energy
(Kcal/g)

2.8

Amino acids
(% in crude protein - mean)

| | |
|----------------------------|-----|
| Lysine | 6.8 |
| Lysine available therefrom | 3.2 |
| Methionine + cysteine | 4.4 |
| Phenylalanine + tyrosine | 9.0 |
| Arginine | 6.5 |
| Histidine | 2.9 |
| Tryptophan | 1.4 |
| Threonine | 4.3 |
| Isoleucine | 6.6 |
| Leucine | 9.0 |
| Valine | 5.3 |

Minerals
(% in the diet - mean)

| | |
|------------|------|
| Calcium | 0.95 |
| Phosphorus | 0.8 |
| Magnesium | 0.2 |
| Sodium | 0.25 |
| Potassium | 0.6 |
| Chlorine | 0.7 |

Trace elements
(mg in 1000 g of diet - mean)

| | |
|-----------|-----|
| Manganese | 100 |
| Iron | 180 |
| Copper | 15 |
| Zinc | 55 |
| Iodine | 1.5 |
| Fluorine | 0.4 |

Vitamins

(Supplements in 1000 g of diet)

| | |
|-------------------------|------------|
| Vitamin A | 15000 I.U. |
| Vitamin D ₃ | 1600 I.U. |
| Vitamin E | 75 mg |
| Vitamin K ₃ | 3 mg |
| Vitamin B ₁ | 18 mg |
| Vitamin B ₂ | 12 mg |
| Vitamin B ₆ | 9 mg |
| Vitamin B ₁₂ | 24 µg |
| Nicotinic acid | 36 mg |
| Pantothenic acid | 21 mg |
| Folic acid | 2 mg |
| Biotin | 60 µg |
| Choline | 600 mg |
| Vitamin C | 36 mg |

The test compound, (b) (4) was sprayed onto the food (at a ratio of 1:10) and allowed to dry prior to feeding to the rats. The food was sprayed with water and dried prior to feeding the control rats.

The initial weights of the female rats were between 202 to 258 g and the initial age was 101 ± 3 days.

Fertile male rats weighing between 300 and 400 g were used as the mating partners.

Successful mating (conception) was confirmed via a vaginal smear sperm test, which is designated as Day 0.

GLP compliance evaluation report was performed by the Applicant. The report notes that there were multiple deficiencies from a GLP standpoint but points out 2 deficiencies. The study was deficient in the characterization and analysis of the test article and the study was deficient in the archival of records. However, the report notes that the study was conducted according to FDA and WHO guidelines at the time.

Observations and Results

Mortality

Mortality checks were performed daily. There were no unscheduled deaths in this study.

Clinical Signs

Behavioral, external appearance, and nature of the feces were monitored daily. There were no treatment-related changes in behavior, external appearance, and nature of feces. Urinary excretion increased during the treatment period in the 2000 mg/kg dose group. However, this finding was no longer observed once treatment with the test compound was discontinued during Days 16 to 19. Increased urinary excretion is not deleterious to health and is dismissed.

Body Weight

Body weight gains are examined in this study as it is in modern GLP-compliant studies. Body weight was measured and recorded daily. The following table illustrates the body weight during the treatment period (data from the Applicant's submission):

| Day of Pregnancy | 0 mg/kg | 500 mg/kg | 2000 mg/kg |
|------------------|------------------|------------------|------------------|
| 0 | 227.6 \pm 16.3 | 227.4 \pm 16.4 | 230.0 \pm 17.4 |
| 6 | 236.6 \pm 14.6 | 240.0 \pm 14.6 | 243.6 \pm 17.0 |
| 15 | 253.8 \pm 14.9 | 254.9 \pm 15.5 | 261.1 \pm 15.4 |
| 19 | 325.1 \pm 21.5 | 325.3 \pm 24.4 | 326.1 \pm 22.2 |

There were no treatment-related changes in body weight as the body weights were within 10% between the dose groups for the same day of pregnancy.

Food Consumption

Food consumption was measured and recorded daily. There were no treatment-related changes in food consumption between the dose groups.

Toxicokinetics

Toxicokinetics were not performed in this study.

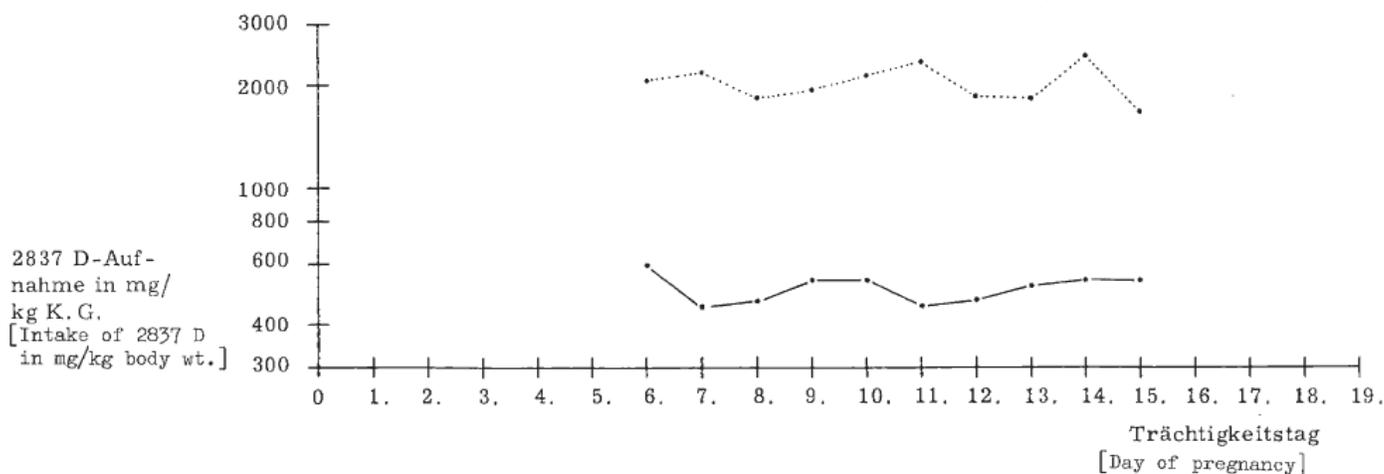
Dosing Solution Analysis

There was no dosing solution analysis performed. However, the substance intake was measured and illustrated in the following figure (from the Applicant's submission):

ABBILDUNG 2 [Figure 2]

Teratogenversuch [Teratogenicity study]
 Substanzaufnahme von weiblichen Sprague-Dawley-Ratten [Substance intake by female Sprague-Dawley rats]
 Mittelwerte von je 20 Tieren [Mean values of each group of 20 animals]

| | | |
|-------|---------------|--|
| —•— | Gruppe (I) | 500 mg 2837 D/kg K.G. im Futter |
| | [Group (I)] | [500 mg of 2837 D/kg body wt. in the feedstuff] |
| - - - | Gruppe (II) | 2000 mg 2837 D/kg K.G. im Futter |
| | [Group (II)] | [2000 mg of 2837 D/kg body wt. in the feedstuff] |
| · · · | Gruppe (III) | Kontrolle |
| | [Group (III)] | [Controls] |



As shown in the figure above, the 500 mg/kg dose group received approximately 500 mg/kg of the test compound and the 2000 mg/kg dose group received approximately

2000 mg/kg of the test compound during the treatment period. Thus, each rat received the proper dose of the test compound.

Necropsy

On the 19th day of pregnancy, the rats were sacrificed and the uterus was removed and prepared. The fetuses were removed and the following tests were performed (from the Applicant's submission):

- (a) Counting of the foetuses.
- (b) Determination of the sex and viability of the foetuses (spontaneous respiration, autokinesis).
- (c) Determination of the number and size of resorption sites.
- (d) Determination of corpora lutea and situation of the foetuses in the uterus.
- (e) Determination of the weights of the foetuses. Those animals whose weights are lower than 70 per cent of the average for the litter are designated as runts.
- (f) External inspection of the foetuses for any damage, particularly deformities.
- (g) Determination of the number and type of any variations (retardations).
- (h) Autopsy of the foetuses:
 - 1) Opening up the abdominal and thoracic cavities (without damaging ribs and sternum): determination of the site, size and condition of the internal organs.
 - 2) Staining the skeleton with alizarin and examining the skeletal system by DAWSON'S method.

It is noted that retardations are delays in more modern studies. The skeleton was stained with alizarin and was examined. As such, fetal soft tissue alterations, fetal skeletal alterations, and fetal ossifications were considered.

There were no treatment-related changes in the macroscopic observations of the internal organs (gross pathology).

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The Cesarean section data collected in this study are comparable to modern GLP-compliant studies. The following table illustrates more parameters that were examined in terms of Cesarean section and offspring data (from the Applicant's submission):

Corpora lutea per dam

Implantations per dam

Foetuses per dam

Resorptions per dam

early resorptions: < 2 mm

late resorptions: > 2 mm

$$\text{resorptions rate} = \frac{\text{resorptions}}{\text{implantations}} \times 100$$

Dead foetuses per dam

Runts per dam

Deformed foetuses per dam

$$\text{deformities rate} = \frac{\text{deformities}}{\text{foetuses}} \times 100$$

Variations (including retardations)

$$\text{variations rate} = \frac{\text{variations}}{\text{foetuses}} \times 100$$

$$\text{Pre-implantation loss} = \frac{\text{corpora lutea} - \text{implantations}}{\text{corpora lutea}} \times 100$$

$$\text{Postimplantation loss} = \frac{\text{implantations} - \text{living foetuses}}{\text{implantations}} \times 100$$

Statistical analysis: Student's t test $P \leq 0.01$

The following table illustrates the fertility results (data from the Applicant's submission):

| | Control | 500 mg/kg | 2000 mg/kg |
|----------------------|------------|------------|------------|
| No. of rats used | 24 | 25 | 23 |
| No. of pregnant rats | 20 | 20 | 20 |
| Corpora Lutea | | | |
| Left (%) | 138 (52%) | 145 (53%) | 139 (50%) |
| Right (%) | 132 (48%) | 129 (47%) | 139 (50%) |
| Total | 270 | 274 | 278 |
| Per Dam | 13.5 ± 1.6 | 13.7 ± 1.5 | 13.9 ± 1.6 |
| Implantations | | | |
| Left (%) | 135 (51%) | 144 (53%) | 137 (50%) |
| Right (%) | 129 (49%) | 126 (47%) | 136 (50%) |

| | | | |
|----------------------------|-------------------|-------------------|-------------------|
| Total Per Dam | 264 13.2 ± 1.8 | 270 13.5 ± 1.7 | 273 13.7 ± 1.6 |
| Fetuses | | | |
| Left (%) | 116 (50%) | 127 (53%) | 118 (48%) |
| Right (%) | 118 (50%) | 110 (47%) | 129 (52%) |
| Total | 234 | 237 | 247 |
| Per Dam | 11.7 ± 2.8 | 11.9 ± 2.9 | 12.4 ± 2.5 |
| Male (%) | 123 (53%) | 123 (52%) | 123 (50%) |
| Female (%) | 111 (47%) | 114 (48%) | 124 (50%) |
| Fetal Weight (g) | 3.52 ± 0.25 | 3.53 ± 0.26 | 3.50 ± 0.24 |
| Resorptions | | | |
| Left | 19 | 18 | 19 |
| Right | 11 | 15 | 7 |
| Total | 30 | 33 | 26 |
| Per Dam | 1.5 ± 1.6 | 1.7 ± 1.6 | 1.3 ± 1.7 |
| Early | 27 | 30 | 23 |
| Late | 3 | 3 | 3 |
| Resorption rate (%) | 11.4% | 12.2% | 9.5% |
| Dead Fetuses | 0 | 0 | 0 |
| Runts | | | |
| Total | 1 | 0 | 2 |
| Per Dam | 0.1 ± 0.2 | | 0.1 ± 0.3 |
| Pre-implantation Loss (%) | 2.2% | 1.5% | 1.8% |
| Post-implantation Loss (%) | 11.4% | 12.2% | 9.5% |

As shown in the table above, there was a slight dose-dependent increase in the number of corpora lutea, implantations, and fetuses (both total number and per dam). There was no dose-dependency in the number of resorptions (both total number and per dam), runts (both total number and per dam), % pre-implantation loss, and % post-implantation loss. The Applicant did not provide historical control data to determine whether the changes in the number of corpora lutea, implantations, and fetuses (both total number and per dam) are significant; however, the magnitude of the changes is not clinically significant as the values are within the normal range for this species.

Offspring (Malformations, Variations, etc.)

The offspring data collected in this study has a number of deficiencies in comparison to modern GLP-compliant studies. Fetal soft tissue alterations, fetal skeletal alterations, and fetal ossification sites were not examined. The following table illustrates the malformations and variations (data from the Applicant's submission):

| | Control | 500 mg/kg | 2000 mg/kg |
|---|---------|-----------|------------|
| Deformities | 0 | 0 | 0 |
| Variations | | | |
| No. of animals with variations/nature of variations | 27 | 36 | 33 |

| | | | |
|--|-------|-------|-------|
| Appraisal of internal organs (number of animals with variations) | 0 | 0 | 0 |
| Variations rate (%) | 11.5% | 15.2% | 13.4% |
| Delayed Ossifications | | | |
| Phalanges | 1 | 3 | 1 |
| Sternebrae | 26 | 30 | 28 |
| Skull | 2 | 4 | 3 |
| Hypoplasia of the 12/13 th pair of ribs | 6 | 5 | 6 |
| Displacement of Testes | 0 | 0 | 0 |
| No. of variations | 36 | 42 | 38 |
| No. of animals affected | 27 | 36 | 33 |

As shown in the table above, there was no dose-dependency in the variation, the variations rate, and delayed ossifications (phalanges, sternebrea, skull, and hypoplasia of the 12/13th pair of ribs). There were no deformities and displacement of testes in any of the dose groups. Thus, there were no treatment-related changes in the offspring parameters such as malformations and variations.

Study title: Examination on the Influence of 2837 E on the Pregnant Rabbit and the Foetus by Administration in the Diet (2837 E = [REDACTED] (b) (4))

Study no.: B04-101326
 Study report location: Module 4 of the Electronic Submission
 Conducting laboratory and location: [REDACTED] (b) (4)

Date of study initiation: The study was done between September 1973 and February 1974 prior to GLP (the final report was dated April 1, 1974).

GLP compliance: See GLP compliance evaluation below
 QA statement: None

Drug, lot #, and % purity: The drug 2937 E is [REDACTED] (b) (4) which has been confirmed to be [REDACTED] (b) (4). As this study was pre GLPs, the study report does not contain any drug lot numbers or purity information.

Key Study Findings

- Female New Zealand White rabbits were dosed with 0, 500, and 2000 mg/kg of [REDACTED] (b) (4) orally via the diet on a daily basis from the 6th to the 18th day of pregnancy.

- The rabbits were sacrificed on Day 29 of pregnancy and the fetuses were removed for examination.
- All rabbits survived up the scheduled necropsy.
- There were no treatment-related changes in behavior, external appearance, nature of feces, body weight, and food consumption in the maternal rabbits.
- In the fetuses, there were no treatment-related changes in macroscopic observations, the number of corpora leutea, implantations, fetuses, resorptions, dead fetuses, runts, and deformities as well as the % pre- and post-implantation losses and the appraisal of the internal organs.
- There was a decrease in the variations (number of animals with variations/nature of variations) as well as the variations rate in the 2000 mg/kg dose group.
- Delayed ossifications (phalanges, sternebrae, skull, and hypoplasia of the 12/13th pair of ribs) were not examined in this study.
- These data demonstrate that both the maternal and fetal NOAEL is considered 2000 mg/kg.
- This is in concurrence with the Applicant's maternal and fetal NOAELs, which are both 2000 mg/kg.
- At the MTDD of 2 g/day of morphine, which results in (b) (4) of (b) (4) the exposure margin for this level of (b) (4) based on both the maternal and fetal NOAEL is 1342.
- Although there is no apparent systemic absorption of the copolymer backbone, the reproductive and developmental toxicology studies with (b) (4) are relevant to confirm that there is no systemic absorption of the polymer and characterize the impact of any low molecular weight impurities, if present. This study is also relevant as part of the safety justification for the (b) (4), (b) (4).

Methods

| | |
|--------------------------------|---|
| Doses: | 0, 500, and 2000 mg/kg |
| Frequency of dosing: | Once daily from the 6 th to the 18 th day of pregnancy |
| Dose volume: | Unknown (rabbits ate feed containing (b) (4) (b) (4) until they were satiated) |
| Route of administration: | Oral via diet |
| Formulation/Vehicle: | The test compound is in the feed. See below for the contents of the food given to each rabbit. |
| Species/Strain: | Rabbit/New Zealand White |
| Number/Sex/Group: | 10/sex/group (females only); male rabbits were used for mating purposes only |
| Satellite groups: | No toxicokinetics group |
| Study design: | See the table below |
| Deviation from study protocol: | Amendments to results were incorporated into this review. This Final Study Report did not include a protocol deviation section. |

The following table illustrates the study design (from the Applicant's submission):

| Group | 2837 E dosage in mg/kg body wt/day in the feedstuff | Treated feedstuff in g/kg body wt/day | No. of female animals |
|-------|---|---------------------------------------|-----------------------|
| (I) | 500 | 5 | 10 |
| (II) | 2000 | 20 | 10 |
| (III) | Controls | 20 (Blank preparation) | 10 |

The following table illustrates the contents of the food for each rabbit without (b) (4)
(b) (4) (from the Applicant's submission):

Standardised maintenance diet for rabbits

(b) (4)

(Company: [REDACTED])

| Crude nutrients (% in the diet - mean) | | Amino acids (% in crude protein - mean) | |
|---|-------------------------|---|------|
| Crude protein | 18.0 | Lysine | 6.5 |
| Crude fat | 4.0 | Lysine available therefrom | 4.0 |
| Crude fibre | 12.5 | Methionine + cysteine | 4.2 |
| Ash | 9.0 | Phenylalanine + tyrosine | 8.2 |
| Water | 12.0 | Arginine | 6.4 |
| | | Histidine | 2.4 |
| | | Tryptophan | 1.5 |
| Convertible energy | | Threonine | 4.0 |
| (Kcal/g) | 2.7 | Isoleucine | 5.7 |
| | | Leucine | 7.7 |
| | | Valine | 5.4 |
| Minerals (% in the diet - mean) | | Trace elements (mg in 1000 g of diet - mean) | |
| Calcium | 1.0 | Manganese | 100 |
| Phosphorus | 0.8 | Iron | 220 |
| Magnesium | 0.25 | Copper | 17 |
| Sodium | 0.3 | Zinc | 85 |
| Potassium | 1.45 | Iodine | 1.5 |
| Chlorine | 0.4 | Fluorine | 0.4 |
| Vitamins (Supplements in 1000 g of diet) | | | |
| | Vitamin A | 15000 | I.U. |
| | Vitamin D ₃ | 1600 | I.U. |
| | Vitamin E | 75 | mg |
| | Vitamin K ₃ | 3 | mg |
| | Vitamin B ₁ | 18 | mg |
| | Vitamin B ₂ | 12 | mg |
| | Vitamin B ₆ | 9 | mg |
| | Vitamin B ₁₂ | 24 | µg |
| | Nicotinic acid | 36 | mg |
| | Pantothenic acid | 21 | mg |
| | Folic acid | 2 | mg |
| | Biotin | 60 | µg |
| | Choline | 600 | mg |
| | Vitamin C | 36 | mg |

The test compound, [REDACTED] (b) (4) is sprayed onto the food stuffs (at a ratio of 1:10) and allowed to dry prior to feeding to the rabbits. The food stuffs were sprayed with water and dried prior to feeding the control rabbits.

The initial ages of the female rabbits were between 8 and 9 months. The initial weights were between 3.6 to 4.4 kg.

Fertile male rabbits were used as mating partners in 3-day intervals.

Successful mating was established by observation and recorded as Day 0.

GLP compliance evaluation report was performed by the Applicant. The report notes that there were multiple deficiencies from a GLP standpoint but points out 2 deficiencies. The study was deficient in the characterization and analysis of the test article and the study was deficient in the archival of records. However, the report notes that the study was conducted according to FDA and WHO guidelines at the time.

Observations and Results

Mortality

Mortality checks were performed daily. All rabbits survived to the scheduled necropsy.

Clinical Signs

Behavioral, external appearance, and nature of the feces were monitored daily. There were no treatment-related changes in behavior, external appearance, and nature of feces.

Body Weight

Body weight gains are examined in this study as it is in modern GLP-compliant studies. Body weight was measured and recorded daily. Body weight was measured and recorded daily. The following table illustrates the body weight during the treatment period (data from the Applicant's submission):

| Day of Pregnancy | 0 mg/kg | 500 mg/kg | 2000 mg/kg |
|-------------------------|----------------|------------------|-------------------|
| 0 | 4.0 ± 0.2 | 4.0 ± 0.2 | 4.0 ± 0.2 |
| 6 | 4.1 ± 0.2 | 4.1 ± 0.2 | 4.1 ± 0.2 |
| 18 | 4.2 ± 0.2 | 4.2 ± 0.2 | 4.3 ± 0.2 |
| 29 | 4.4 ± 0.2 | 4.4 ± 0.2 | 4.4 ± 0.2 |

There were no treatment-related changes in body weight as the body weights were within 10% between the dose groups for the same day of pregnancy.

Food Consumption

Food consumption was measured and recorded daily. There were no treatment-related changes in food consumption.

Toxicokinetics

Toxicokinetics were not measured in this study.

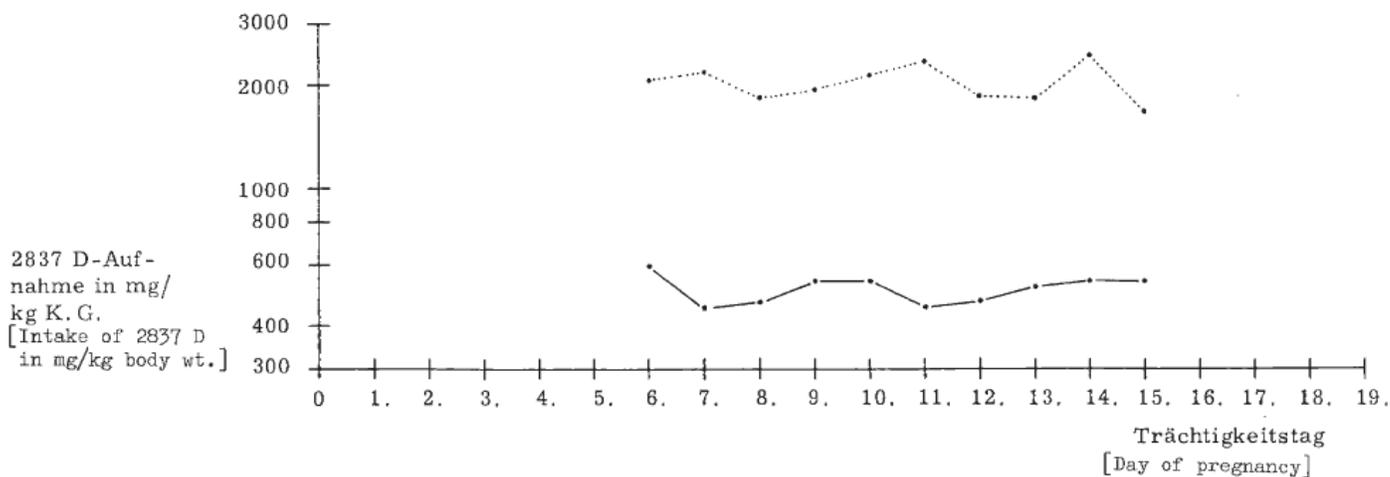
Dosing Solution Analysis

Dosing solution analysis was not performed in this study. However, the substance intake was measured and illustrated in the following figure (from the Applicant's submission):

ABBILDUNG 2 [Figure 2]

Teratogenversuch [Teratogenicity study]
 Substanzaufnahme von weiblichen Sprague-Dawley-Ratten [Substance intake by female Sprague-Dawley rats]
 Mittelwerte von je 20 Tieren [Mean values of each group of 20 animals]

| | | |
|-------|-------------------------------|--|
| —•— | Gruppe (I) [Group (I)] | 500 mg 2837 D/kg K.G. im Futter [500 mg of 2837 D/kg body wt. in the feedstuff] |
| - - - | Gruppe (II) [Group (II)] | 2000 mg 2837 D/kg K.G. im Futter [2000 mg of 2837 D/kg body wt. in the feedstuff] |
| · · · | Gruppe (III) [Group (III)] | Kontrolle [Controls] |



As shown in the figure above, the rabbits in the 500 mg/kg dose group received approximately 500 mg/kg of the test compound and the rabbits in the 2000 mg/kg dose group received approximately 2000 mg/kg of the test compound. Thus, each rabbit received the proper dose of the test compound.

Necropsy

On the 29th day of pregnancy, rabbits were sacrificed and the uterus was removed and prepared. The fetuses were removed and the following tests were performed (from the Applicant's submission):

- (a) Counting of the fetuses.
- (b) Determination of the sex and viability of the fetuses. They were considered to be viable if the animals were found to be alive after being in an incubator for 6 and 24 hours at 37°C (Criteria: spontaneous respiration, autokinesis).
- (c) Determination of the number and size of resorptions.
- (d) Determination of corpora lutea and situation of the fetuses in the uterus.
- (e) Determination of the weights of the fetuses. Those animals whose weights are lower than 70 per cent of the average for the litter are designated as runts.
- (f) External inspection of the fetuses for any damage, particularly deformities.
- (g) Determination of the number and type of any variations (retardations).
- (h) Autopsy of the fetuses:
 - 1) Opening up the abdominal and thoracic cavities (without damaging ribs and sternum): determination of the site, size and condition of the internal organs.
 - 2) Staining the skeleton with alizarin and examining the skeletal system by DAWSON'S method.

It is noted that retardations are delays in more modern studies. The skeleton was stained with alizarin and was examined. As such, fetal soft tissue alterations, fetal skeletal alterations, and fetal ossifications were considered.

There were no treatment-related changes in macroscopic observations (gross pathology).

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The Cesarean section data collected in this study is comparable to more modern GLP-compliant studies. The following parameters were determined in terms of Cesarean section and offspring data (from the Applicant's submission):

Corpora lutea per dam

Implantations per dam

Foetuses per dam

Resorptions per dam

early resorptions: < 2 g

late resorptions: > 2 g

$$\text{Resorptions rate} = \frac{\text{resorptions}}{\text{implantations}} \times 100$$

Dead foetuses per dam

Runts per dam

Deformed foetuses per dam

$$\text{deformities rate} = \frac{\text{deformities}}{\text{foetuses}} \times 100$$

Variations (including retardations)

$$\text{variations rate} = \frac{\text{variations}}{\text{foetuses}} \times 100$$

$$\text{Pre-implantation loss} = \frac{\text{corpora lutea} - \text{implantations}}{\text{corpora lutea}} \times 100$$

$$\text{Postimplantation loss} = \frac{\text{implantations} - \text{living foetuses}}{\text{implantations}} \times 100$$

Statistical analysis: Student's t test $P \leq 0.01$.

The following table illustrates the fertility results (data from the Applicant's submission):

| | Control | 500 mg/kg | 2000 mg/kg |
|-------------------------|------------|------------|------------|
| No. of rabbits used | 13 | 14 | 12 |
| No. of pregnant rabbits | 10 | 10 | 10 |
| Corpora Lutea | | | |
| Left (%) | 50 (49%) | 50 (47%) | 57 (54%) |
| Right (%) | 52 (51%) | 56 (53%) | 49 (46%) |
| Total | 102 | 106 | 106 |
| Per Dam | 10.2 ± 1.1 | 10.6 ± 1.2 | 10.6 ± 1.0 |
| Implantations | | | |
| Left (%) | 49 (50%) | 50 (49%) | 54 (53%) |
| Right (%) | 49 (50%) | 52 (51%) | 48 (47%) |
| Total | 98 | 102 | 102 |
| Per Dam | 9.8 ± 1.2 | 10.2 ± 1.1 | 10.2 ± 1.3 |
| Fetuses | | | |

| | | | |
|----------------------------|------------|------------|------------|
| Left (%) | 37 (45%) | 42 (47%) | 44 (51%) |
| Right (%) | 46 (55%) | 47 (53%) | 43 (49%) |
| Total | 83 | 89 | 87 |
| Per Dam | 8.3 ± 2.2 | 8.9 ± 2.5 | 8.7 ± 2.1 |
| Male (%) | 43 (52%) | 45 (51%) | 44 (51%) |
| Female (%) | 40 (48%) | 44 (49%) | 43 (49%) |
| Fetal Weight (g) | 35.2 ± 2.3 | 35.5 ± 2.2 | 34.8 ± 2.5 |
| Resorptions | | | |
| Left | 12 | 8 | 10 |
| Right | 3 | 5 | 5 |
| Total | 15 | 13 | 15 |
| Per Dam | 1.5 ± 1.4 | 1.3 ± 1.6 | 1.5 ± 1.4 |
| Early | 13 | 9 | 13 |
| Late | 2 | 4 | 2 |
| Resorption rate (%) | 15.3% | 12.7% | 14.7% |
| Dead Fetuses | | | |
| Total | 4 | 1 | 3 |
| Per Dam | 0.4 ± 0.8 | 0.1 ± 0.3 | 0.3 ± 0.9 |
| Runts | 0 | 0 | 0 |
| Pre-implantation Loss (%) | 3.9% | 3.8% | 3.8% |
| Post-implantation Loss (%) | 18.0% | 13.7% | 17.7% |

The parameters shown in the table above either did not demonstrate any dose dependency or were within the historical control range (as shown in the table below). Thus, it appears that there were no treatment-related changes in the number of corpora lutea, implantations, fetuses, resorptions, dead fetuses, and runts as well as the % pre- and post-implantation losses.

Offspring (Malformations, Variations, etc.)

The offspring data collected in this study has a number of deficiencies in comparison to modern GLP-compliant studies. Fetal soft tissue alterations, fetal skeletal alterations, and fetal ossification sites were not examined. The following table illustrates the malformations and variations (data from the Applicant's submission):

| | Control | 500 mg/kg | 2000 mg/kg |
|--|---------|-----------|------------|
| Deformities | 0 | 0 | 0 |
| Variations | | | |
| No. of animals with variations/nature of variations | 16 | 18 | 11 |
| Appraisal of internal organs (number of animals with variations) | 0 | 0 | 0 |
| Variations rate (%) | 19.3% | 20.2% | 12.6% |

As shown in the table above, there were no deformities and appraisal of the internal organs in any of the dose groups. There was a decrease in the variations (number of

animals with variations/nature of variations) and the variations rate at the 2000 mg/kg dose group compared to control. A decrease in the variations and variations rates is not considered adverse as fewer fetuses were observed with structural variations.

The following table illustrates the historical control experience with New Zealand White rabbits in the Applicant's laboratory from 1963 to 1970 (from the Applicant's submission):

A P P E N D I X

Experiences with NZW rabbits from
1963 to 1970 in our own laboratories [1]

| | Control animals [2] | Animals experiencing no significant effects from the substance [2] | Studies with a standard dose of thalidomide [3] |
|--------------------------------|------------------------|--|---|
| No. of pregnant animals | 844 | 4260 | 42 |
| No. of live and dead fetuses | 6410 | 31950 | 264 |
| Pregnancy rate [4] | 83 % | 86 % | - |
| Abortion rate [4] | 0.4 % | 0.5 % | 0.7 % |
| Live fetuses per dam [5] | 7.6 ± 0.9 | 7.5 ± 0.9 | 5.8 |
| Dead fetuses per dam [5] | 0.2 ± 0.3 | 0.3 ± 0.2 | 0.5 |
| Resorptions per dam [5] | 0.8 ± 0.4 | 0.9 ± 0.6 | 2.5 |
| Corpora lutea [4] per dam | 9.9 | 10.1 | 9.8 |
| Deformities | 0.41 % | 0.49 % [6] | 7.3 % [6] |
| Mean wt. of live fetuses in g. | 37.1 ± 3.0 | 36.8 ± 2.6 | -3.5 % |
| Mean wt. of placentas in g | 6.9 ± 0.6 | 6.9 ± 0.6 | -4.6 % |
| Pre-implantation losses [4] | 13.1 % | 13.9 % | 10.2 % |
| Postimplantation losses [4] | 11.6 % | 13.8 % | 34.1 % |

[1] All the figures have been calculated from the results of test groups. Standard deviations thus relate to the deviation of the individual group from the combined mean value of all groups.

[2] 102 test groups in all.

[3] 180 mg of thalidomide/kg body weight/day in the feedstuff; 4 test groups.

[4] From 1966 to 1970.

[5] With standard deviation.

[6] According to the type, the majority of the deformities lay within the domain of spontaneity.

10 Special Toxicology Studies

There were no special toxicology studies with morphine submitted in this NDA.

11 Integrated Summary and Safety Evaluation

There were no nonclinical studies submitted with morphine sulfate for primary and secondary pharmacology, safety pharmacology, ADME, toxicokinetics, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology, and special toxicology. There were no nonclinical safety concerns with the drug substance and drug product specifications as well as the container closure system as the proposed drug product is formulated as solid oral tablets. With the exception of (b) (4), all excipients in the composition of the proposed drug formulation are qualified for safety up to the maximum theoretical daily dose (MTDD) of 2 g/day of morphine.

Several nonclinical studies were submitted to the NDA to justify the levels of (b) (4) at the MTDD of 2 g/day of morphine sulfate, which are (b) (4) respectively. These studies were also cross-referenced in MF (b) (4) are similar ethyl acrylate and methyl methacrylate copolymers (2:1) with unique (b) (4) (b) (4) respectively) and with molecular weights of 750,000 and 600,000, respectively. The nonclinical studies with (b) (4) (an ethyl acrylate and methyl methacrylate copolymer (2:1) with (b) (4) and MW of 750,000) included an excretion and tissue distribution study evaluating radiolabelled (b) (4), embryofetal developmental toxicology in rat and rabbit with (b) (4), 6-month general toxicology with (b) (4) in the rat and with (b) (4) in the dog, mutagenicity (Ames) with (b) (4) as well as mutagenicity (Ames), micronucleus induction and mutation at the thymidine kinase locus in mouse lymphoma cells with (b) (4)

In the excretion and tissue distribution study, rats were administered a single oral dose (55 to 75 mg) of ¹⁴C-(b) (4). Approximately 97% of radioactivity was accounted for in the feces and 0.0092% of radioactivity was in the urine. Radioactivity in the various tissues, including the liver, spleen, mesenteric lymph nodes, small and large intestine, and blood, was not significantly different from background with no significant increasing trend of radioactivity in various tissues. (b) (4) does not appear to be absorbed systemically and is excreted in feces. Due to the lack of apparent systemic absorption, additional reproductive and developmental toxicology studies with the (b) (4) backbone do not appear to be necessary.

To characterize general toxicity, Sprague-Dawley rats were given 0, 500, and 2000 mg of (b) (4) via the diet for 6 months. Although conducted prior to GLP, a GLP evaluation was performed to determine GLP deficiencies, where it was concluded that this study can be used to support the safety of the test article up to 2000 mg/kg in rats because the study appears to be well-controlled and includes detailed tables and figures of the individual animal data results. All rats survived to the scheduled necropsy. There were no treatment-related changes in clinical signs (including behavioral changes), body weights, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, gross pathology, and organ weights. Microscopically, the observations of slight fatty degeneration in the liver and trace microliths in the kidney at the 2000 mg/kg dose group do not appear to be detrimental to health and may be dismissed. However, histopathology was not performed in the control, 500 mg/kg dose groups, and recovery groups in this study, making interpretation of the histopathology findings difficult. Assuming the changes in the liver and kidney are real, the NOAEL could be estimated to be 500 mg/kg; however, no histopathology was performed in the control, 500 mg/kg dose groups, or recovery groups. The human equivalent dose is 4864.9 mg of (b) (4) in an average human weighing 60 kg based on a body surface area comparison. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) and an exposure margin of 2.5 for the excipient and there is (b) (4) of (b) (4) and an exposure margin of 8.8 to the copolymeric backbone. Although the study does appear to be limited in terms of its utility, considering the apparent lack of systemic absorption of the radiolabeled material in the distribution study, if the kidney and liver findings are real they would have to either be due to low molecular weight impurities or the (b) (4)

Beagle dogs were administered 0, 200, 500, and 1000 mg/kg of (b) (4) once daily via an oral pellet for 7 days/week for a total of 26 weeks. It is noted that the actual doses given were 0, 50, 125, and 250 mg/kg since each pellet contains approximately 22.7% (b) (4). All dogs survived to the scheduled necropsy. There were no treatment-related changes in clinical signs and observations, food consumption, ophthalmoscopic examination, ECG, hematology, clinical chemistry, urinalysis, and fecal occult blood. No toxicokinetics were performed in this study. There was an approximately 10% decrease in the body weights of the high dose male dogs during the treatment phase as well as a 11.7% decrease in the high dose recovery female dogs. Macroscopically, abnormal size, content, area, and color were noted in general. These changes in the gall bladder, lymph nodes (female), mammary area (female), thyroid (female), urinary bladder (female), and uterus (female) occurred in the high dose dogs during the treatment period. In the recovery dogs, changes in gall bladder, mammary (female) and lymph nodes (females) were still observed in the high dose dogs. Delayed observations include the colon, lungs, prostate, and thymus in the high dose recovery males, as well as the gall bladder, ovaries, stomach, urinary bladder, and uterus in the high dose recovery females. The absolute organ weight changes include the right adrenal in the high dose males during the treatment period as well as the epididymis and prostate in the high dose recovery males and the pituitary in the high dose recovery females. The organ-to-body-weight ratio changes include the

prostate and right testis in the high dose recovery males as well as the heart the right thyroid in the high dose recovery females. Histopathological findings include the gall bladder (lymphoid aggregations) in the high dose females, kidneys (nephropathy) and spleen (lymphoid hyperplasia) in the high dose males, and tonsils (congestion) in both the high dose males and females. No histopathology was performed in the recovery dogs. The NOAEL is 500 (or 125) mg/kg due to the body weight, macroscopic, organ weight, organ-to-body-weight ratio, and histopathological changes at the high dose groups. The human equivalent dose of the NOAEL is 4054 mg of (b) (4) in an average human weighing 60 kg based on a body surface area comparison. At the MTDD of 2 g/day of morphine, there is (b) (4) of (b) (4) and an exposure margin of 2.1 for the excipient and there is (b) (4) of (b) (4) and an exposure margin of 7.37 for the copolymeric backbone.

(b) (4)

S. typhimurium strains TA98, TA100, TA102, TA1535, and TA1537 were treated with 0, 33, 100, 333, 1000, 2500, and 5000 mcg/plate of (b) (4) in an Ames assay. This Ames assay is considered valid. (b) (4) was not mutagenic in the strains tested under the conditions of this study. However, no *E. coli* strains were used and as such, no gene mutations from AT base pair changes could be evaluated.

Mouse Lymphoma L5178Y cells were treated with 0, 195.3, 390.6, 781.3, 1562.5, 3125, and 6250 mcg/mL of (b) (4) in the cell mutation assay at the thymidine kinase locus. This assay is considered valid. (b) (4) is not considered mutagenic under the conditions of this study.

CD-1 mice were treated with 0, 500, 1000, and 2000 mg/kg of (b) (4) in a single dose administration via oral gavage. Mice were sacrificed at the 24 and 48 hour sampling time points and bone marrow was collected from the femur of each mouse. This study is considered valid. There were no treatment-related changes in body weight. (b) (4) did not induce the formation of micronuclei in mouse polychromatic erythrocytes under the conditions of this study.

As discussed above, several genetic toxicology studies were conducted with (b) (4) and the weight of evidence suggests that these (b) (4) copolymers do not have mutagenic or clastogenic potential. A carcinogenic assessment was not conducted with any (b) (4) excipient. However, based on the negative genetic toxicology data, limited systemic exposure, lack of accumulation potential, negative histopathology data from chronic toxicology studies and knowledge

of other excipients that are high molecular weight copolymers, a carcinogenicity assessment of (b) (4) is not deemed necessary.

Moreover, due to the apparent lack of systemic absorption of (b) (4), the reproductive and developmental toxicology studies with the copolymeric backbone contained in (b) (4) are not necessary. However, the embryofetal studies in the rat and rabbit using (b) (4) were used to support the safety of the (b) (4) (see below).

Although the safety of the copolymeric backbone of (b) (4) have been addressed, the safety of the (b) (4) has not been adequately addressed. At the MTDD of 2 g/day of morphine, there are (b) (4) of the (b) (4). Both (b) (4) are considered novel for the oral route of administration and appear to be systemically absorbed. There are no reproductive and developmental studies with (b) (4) alone and only embryo-fetal development studies conducted in rats and rabbits with (b) (4) containing (b) (4).

Female Sprague-Dawley rats were dosed with 0, 500, and 2000 mg/kg of (b) (4) orally via the diet on a daily basis from the 6th to the 15th day of pregnancy in the rat embryofetal study. The rats were sacrificed on Day 19 of pregnancy and the fetuses were removed for examination. All rats survived to the scheduled necropsy. There were no treatment-related changes in behavior, external appearance, nature of feces, body weight, and food consumption in the maternal rats. Moreover, there was a dose-dependent increase in the corpora lutea (total and per dam), implantations (total and per dam), and fetuses (total and per dam) in the 500 and 2000 mg/kg dose groups compared to control; however, the magnitude of the changes is not clinically significant as the values are within the normal range for this species. In the dams, there was an increased urinary excretion during the treatment period in the 2000 mg/kg dose group compared to control that returned to control levels once treatment with (b) (4) ceased. The increased urinary excretion did not appear to result in any deleterious effects to health and therefore is not believed to have clinical significance. In the fetuses, there were no treatment-related changes in macroscopic observations, and fetal weight as well as in the number of resorptions (left, right, total, per dam, early, and late), dead fetuses, runts, deformities, variations (number of animals with variations/nature of variations, appraisal of internal organs, and the variations rate), delayed ossifications (phalanges, sternbrae, skull, and hypoplasia of the 12th/13th pair of ribs), and the % pre- and post-implantation losses and displacement of testes. These data suggest that both the maternal and fetal NOAELs are 2000 mg/kg. At the MTDD of 2 g/day of morphine, which results in (b) (4) of (b) (4), the exposure margin for this level of (b) (4) based on the maternal and fetal NOAEL is 671.

Female New Zealand White rabbits were dosed with 0, 500, and 2000 mg/kg of (b) (4) orally via the diet on a daily basis from the 6th to the 18th day of pregnancy in the rabbit embryofetal study. The rabbits were sacrificed on Day 29 of pregnancy and the fetuses were removed for examination. All rabbits survived up the

scheduled necropsy. There were no treatment-related changes in behavior, external appearance, nature of feces, body weight, and food consumption in the maternal rabbits. In the fetuses, there were no treatment-related changes in macroscopic observations, the number of corpora lutea, implantations, fetuses, resorptions, dead fetuses, runts, and deformities as well as the % pre- and post-implantation losses and the appraisal of the internal organs. There was a decrease in the variations (number of animals with variations/nature of variations) as well as the variations rate in the 2000 mg/kg dose group, which are not considered adverse. These data demonstrate that both the maternal and fetal NOELs are 2000 mg/kg. At the MTDD of 2 g/day of morphine, which results in (b) (4) of (b) (4), the exposure margin for this level of (b) (4) based on the maternal and fetal NOEL is 1342.

It is important to note that there were no other reproductive and developmental toxicology studies with (b) (4) such as the fertility and early embryonic development study as well as the pre- and postnatal development study. However, there are studies with an analogous compound, (b) (4) in the published literature regarding the fertility and pre- and postnatal development in rats that appear adequate and supportive. There are also 3-month feed studies with various analogous (b) (4) compounds such as (b) (4) in rats and dogs, -20 in dogs, and -40 in rats. Myocardial degeneration and necrosis was observed in the dog study with (b) (4) (b) (4) and hepatic necrosis was observed in the rat study with (b) (4) but at doses much greater than the level on (b) (4) present in Morphine ARER even at the MTDD for this drug product. Taken together, the data suggests minimal risks with these various length (b) (4) compounds. There are no genotoxicity studies or a carcinogenicity assessment with (b) (4); however, there is a mouse carcinogenicity assessment of the analogous compound (b) (4) in the published literature. The doses tested in the carcinogenicity assessment of (b) (4) showed that the test compound was noncarcinogenic. The 6-month rat and dog studies with (b) (4) may be used to justify the levels of the (b) (4). The rat NOEL of 2000 mg/kg yields an exposure margin of 671-fold, based on a body surface area comparison. The dog NOEL of 125 mg/kg yields an exposure margin of 140-fold, based on a body surface area comparison. In addition, the carcinogenicity assessment of (b) (4) is deemed not necessary after applying a weight-of-evidence approach as outlined in the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

(b) (4)

(b) (4)

From a nonclinical pharmacology toxicology perspective, the recommendation for the Morphine ARER drug product is a Complete Response. (b) (4)

Regarding (b) (4), the following studies are required as per ICH M3 and the excipients guidance:

1. Chronic toxicology studies with (b) (4) (6-month rodent and 9-month nonrodent) are required for a chronic indication.
2. Reproductive and developmental toxicology battery with (b) (4) (fertility and early embryonic development, embryofetal development, and pre- and postnatal development studies).
3. A carcinogenicity assessment of (b) (4) in rats and mice. As per the Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>, you may submit a justification to waive the carcinogenicity assessment.

12 Appendix/Attachments

(b) (4)

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(b) (4)

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(b) (4)

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See secondary review for additional discussion and recommendations.