CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 200-403
Supporting document/s:	SDN-1; -5; -11
Applicant's letter date:	April 29, 2010; Oct. 8, 2010; Dec. 23, 2010
CDER stamp date:	April 30, 2010; Oct. 18, 2010; Dec. 27, 2010
Product:	Hydromorphone Hydrochloride Injection, USP
Indication:	Management of pain in patients where an opioid analgesic is appropriate
Applicant:	Hospira, Inc. 275 North Filed Dr. Lake Forest, IL 60045
Review Division:	Division of Anesthesia and Analgesia Products
Reviewer:	BeLinda A. Hayes, Ph.D.
Supervisor/Team Leader:	R. Daniel Mellon, Ph.D.
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Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

This NDA application is recommended for approval from a nonclinical pharmacology and toxicology perspective with a post-marketing requirement as noted below.

1.1.2 Additional Non Clinical Recommendations

As of the date of this review, there is one outstanding issue with potential toxicological relevance. The issue is not deemed an approval issue, as noted below.

(b) (4)

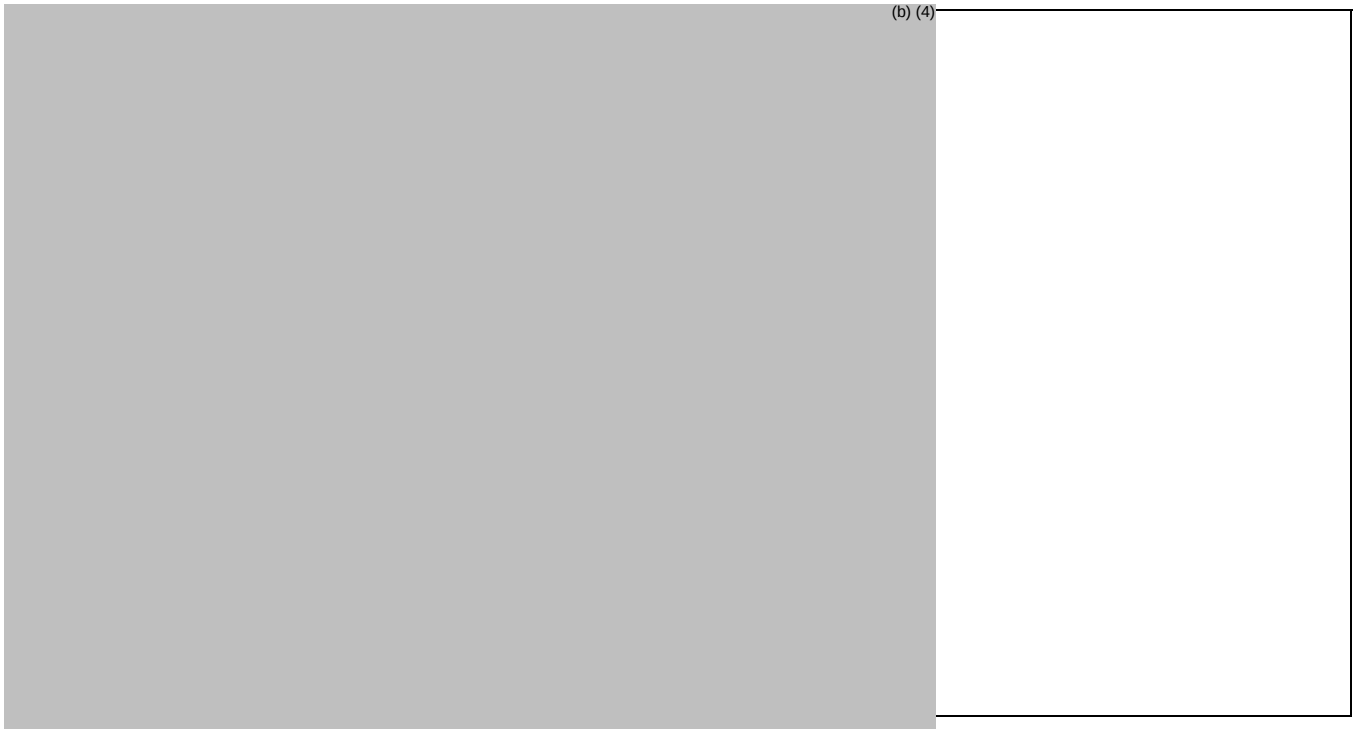
The Applicant must (b) (4) Safety qualification must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat dose toxicology study of 3 month duration to support the proposed specification of NMT (b) (4). As this drug substance DMF has been previously deemed adequate by the FDA for an approved generic drug, this concern may be addressed via a post-marketing requirement.

1.1.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes and the rationale for the proposed changes. The recommended changes from the proposed labeling are in red or strikeout font.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
8 USE IN SPECIFIC POPULATIONS		
(b) (4)		To be consistent with the Dilaudid Injection label.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



1.2 Brief Discussion of Nonclinical Findings

Hospira Inc. has submitted a New Drug Application (NDA) for Hydromorphone Hydrochloride Injection USP (1, 2 or 4 mg/mL hydromorphone hydrochloride) administered subcutaneously or intramuscularly every (b) (4) as necessary for the management of pain in patients where an opioid analgesic is appropriate. The NDA was submitted as a 505(b)(2) application with the referenced drug as Dilaudid (NDA 19-034). No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant is relying on the Agency's previous finding of safety for the Dilaudid NDA (owned by Purdue Pharma) and information from the literature.

The pharmacology and toxicology of hydromorphone are well characterized; hence there are no nonclinical safety issues unique to this hydromorphone product relevant to clinical use for NDA 200-403.

2 Drug Information

2.1 Drug

Hydromorphone Hydrochloride

2.1.1 CAS Registry Number (Optional)

№ 71-68-1

2.1.2 Generic Name

International Nonproprietary Name (INN): Hydromorphone Hydrochloride
European Pharmacopoeia Name (EPN): Hydromorphone Hydrochloride
United States Adopted Name (USAN): Hydromorphone Hydrochloride

2.1.3 Code Name

Hospira Drug Code/Computer №: 11438621

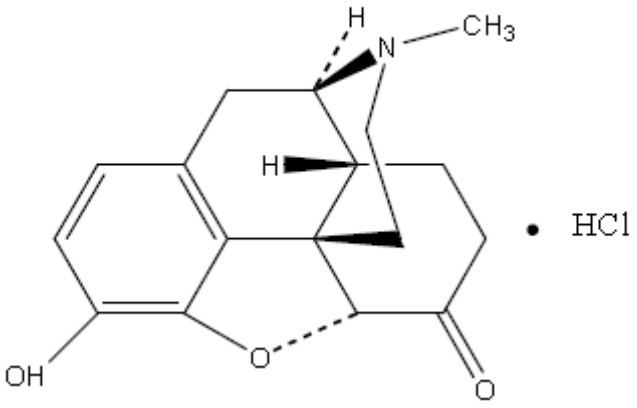
2.1.4 Chemical Name

IUPAC Name: 4,5 alpha-epoxy-3-hydroxy-17-methyl morphinan-6-one
Chemical Abstracts Service (CAS) Index Name: 4,5α-Epoxy-3-hydroxy-17-methyl morphinan-6-one hydrochloride

2.1.5 Molecular Formula/Molecular Weight

$C_{17}H_{19}NO_3$•HCl/321.80

2.1.6 Structure



2.1.7 Pharmacologic class

Opioid Agonist

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

DMFs №	Subject of DMF	Holder
(b) (4)		

2.3 Clinical Formulation

Hydromorphone Hydrochloride Injection, USP will be marketed as 1 mg/mL, 2 mg/mL and 4 mg/mL strengths for intravenous, subcutaneous or intramuscular administration. The recommended dosage is 10 to 20 mg every (b) (4) for both acute and chronic pain. The clinical formulation is an (b) (4), clear, colorless to nearly colorless solution which will be contained in four distinct closure systems. The pH of the drug product will be in the range of 3.5 – 5.5.

The four distinct closure systems and their components are described as follows:

1. **Single dose vial.** The single dose vial is a 2 mL (b) (4) vial closure system comprised of a (b) (4) glass which according to the Applicant meets the current USP <660> requirements. As depicted in table 1, the primary components of this container system are: a glass vial, (b) (4) rubber stopper and aluminum seal. Hospira has used this closure system in these approved products by the Agency: Enalapilat Injection USP (ANDA 75-458) and Hydromorphone Injection USP High Potency (ANDA 78-591). *See the Quality reviewer's review for detail review of the acceptability of this closure system.*

Table 1. Components of the (b) (4) vial closure system.

Primary Component	Description	Supplier
Container	Unprinted (b) (4) Vial, 2 mL, 13 mm (b) (4)	(b) (4)
Closure	Rubber Closure, 13 mm, (b) (4)	
Seal	Aluminum Seal, 13 mm	

2. **Ampul.** The glass ampul (1 ML) is a (b) (4) glass which according to the Applicant meets the current USP <660> requirements. *See the Quality reviewer's review for detail review of the acceptability of this closure system.*

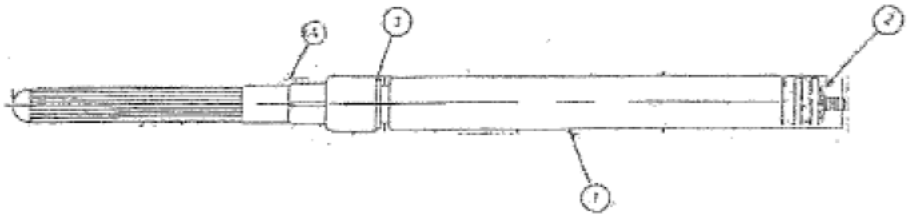
3. **iSecure™ Syringe.** The iSecure™ syringe is a ready-to-use "disposable" syringe holders; the configuration of the iSecure syringe is depicted in figure 1. As depicted in table 2, the primary components of this container system are: a cartridge, plunger, seal, and needle assembly. The cartridge is a (b) (4)

glass which according to the Applicant meets the current USP <660> requirements. Hospira has used this closure system in these approved products by the Agency: Odansetron Injection, USP (ANDA 77-880), Ketorolac Tromethamine Injection USP (ANDA 74-993) and Midazolam Hydrochloride Injection USP (ANDA 75-856). On December 11, 2006, the Agency's Center for Devices and Radiologic Health (CDRH) cleared Hospira's 510(k) for this iSecure Syringe Cartridge Holder (№ Ko63180). *See Quality reviewer's review for detail review of this closure system.*

Table 2. Components of the iSecure™ Syringe.

Primary Component	Description	Supplier
USP (b) (4) Cartridge	Cartridge, 1.5 mL, (b) (4)	(b) (4)
Plunger	Plunger, 0.290", (b) (4) Gray	
Seal	(b) (4) Cap, Grooved, (b) (4) (b) (4) Gray Liner	
Needle Assembly	Needle Assembly, 1.5 mL iSecure	

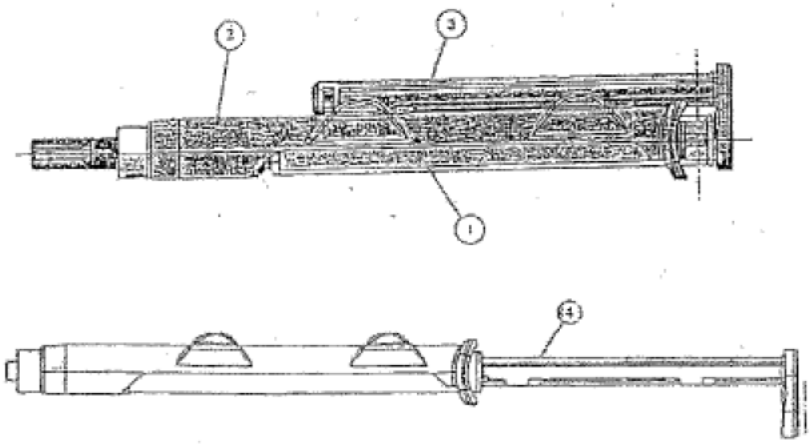
Prefilled Syringe



1 Glass Cartridge
2 Plunger
3 (b) (4) Seal
4 Needle Assembly

iSecure™ Syringe

(Prefilled Syringe with iSecure™ Ready-To-Use Disposable Holder Attached)



1 Prefilled Syringe (non-activated)
2 iSecure™ Holder body attachment
3 iSecure™ Holder rod attachment
4 iSecure™ Holder rod released from the body and inserted into plunger end of the syringe cartridge for activation

Note: The iSecure™ holder is packaged with each prefilled syringe for the convenience of the clinician.

Figure 1. Diagram of iSecure syringe closure system.

4. **Carpuject Syringes.** Carpuject syringe is a "reusable" syringe; the configuration of the Carpuject syringe is depicted in figure 2. As depicted in table 3, the primary components of this container system are: a cartridge, plunger, seal, and needle assembly. The cartridge is a (b) (4) glass which according to the Applicant meets the current USP <660> requirements. Hospira has used this closure system in the following approved products by the Agency: Ketorolac Tromethamine Injection USP (ANDA 74-993) and Midazolam Hydrochloride

Injection USP (ANDA 75-856). *See Quality reviewer's review for detail review of this closure system.*

Table 3. Components of the Carpuject syringe.

Primary Component	Description	Supplier
USP (b) (4) Cartridge	Cartridge, 2.5 mL, (b) (4)	(b) (4)
Plunger	Plunger, 0.290", (b) (4) Gray, Insert Plunger	
Seal	(b) (4) Cap, Grooved, (b) (4) Gray Liner	
Needle Assembly	Needle Assembly, 22 gauge, Luer Lock, Green	

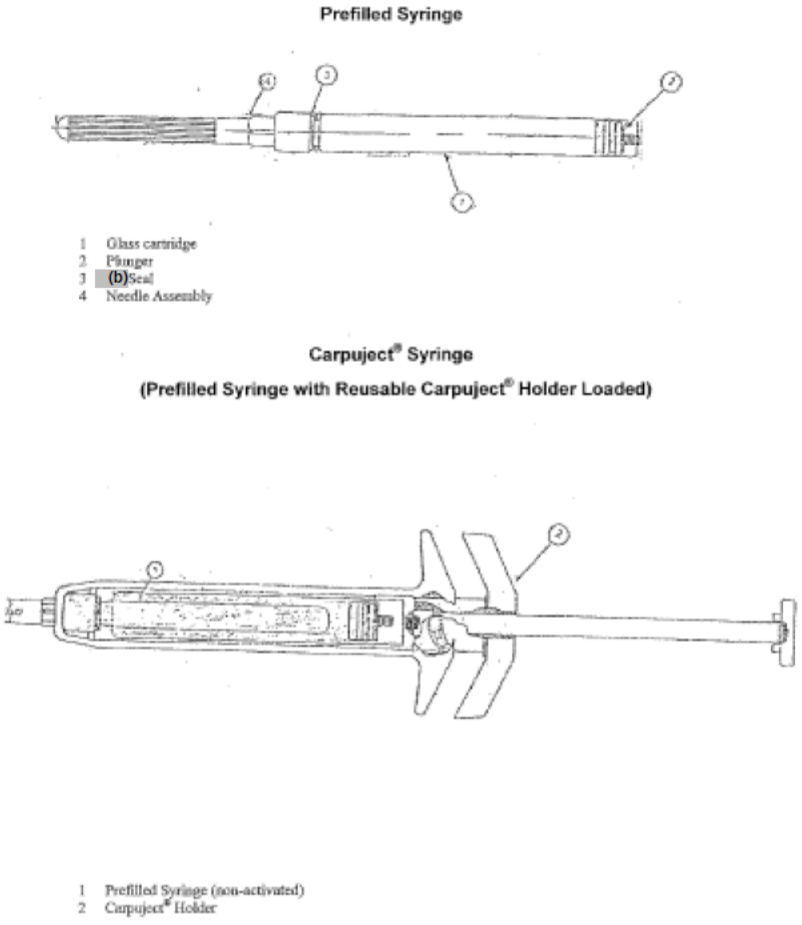


Figure 2. Diagram of the Carpuject Syringe.

2.3.1 Drug Formulation

The components, quantitative composition, and function of the ingredients for the dosage strengths are provided in the table below.

Component	Reference	Function	1 mg/mL	2 mg/mL	4 mg/mL
			Quantity per unit		
Hydromorphone HCl	USP	Active ingredient	1.0 mg	2.0 mg	4.0 mg
Sodium Lactate (b) (4)	USP	(b) (4			(b) (4)
(b) (4)	USP				
Sodium Chloride	USP, EP, BP				
(b) (4)	USP				
	NF, EP				
Lactic Acid	USP				
Sodium Hydroxide, (b) (4)	NF				
(b) (4)	NF				

q.s. = Quantity sufficient
A.R. = As required
1: (b) (4)
2: The final pH range of the finished drug product is 3.5 – 5.5.
3 (b) (4)

2.3.2 Comments on Novel Excipients

There are no novel excipients in the drug product. The excipients, sodium lactate (b) (4) USP; lactic acid USP; sodium chloride USP, EP, BP; sodium hydroxide, (b) (4), used in the formulation of hydromorphone hydrochloride injection, USP meet USP requirements and are found in approved parenteral drug products within approved ranges.

2.3.3 Comments on Impurities/Degradants of Concern

Impurities in the hydromorphone drug substance:

According to the ICH Q3A (R2) guidance, the qualification threshold for non-toxic drug substance impurities for a (b) (4) is (b) (4) intake, whichever is lower. As this hydromorphone product is intended for hospital or hospice use, the Applicant has proposed a maximum theoretical daily dose for hydromorphone injection (SC or IM) of (b) (4) for the treatment of chronic pain in individuals with moderate to severe pain.

Following the initial review of NDA 200-403, the pharmacology/toxicology review team conveyed the following potential review issues to the Applicant in the 74-day letter (July 9, 2010):

1. Your drug substance acceptance criteria for (b) (4) (b) (4) the ICH Q3A(R2) qualification threshold of NMT (b) (4) or (b) (4), whichever is lower. (b) (4) NMT (b) (4) or provide adequate safety qualification, which must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay

for DNA damage) and a repeat dose toxicology study of 1 month duration to support the proposed specifications.

2. The current standard for potentially genotoxic impurities is to reduce the exposure to these impurities NMT [redacted]. Provide your rationale, including discussions regarding technical feasibility, for the proposed specifications for [redacted]
3. Provide the structure and CAS number for [redacted] and indicate if it contains a structural alert for mutagenicity. If this [redacted] a structural alert, [redacted] the acceptance criteria to NMT [redacted] unless adequate justification is provided that this is not technically feasible. In addition provide the structure and CAS number for Impurities identified as [redacted]
4. Given that [redacted] has been reported to test positive in carcinogenicity studies, reduce this impurity to NMT [redacted] or submit justification for the safety of the levels you have proposed, including supporting references. Such a safety assessment must take into consideration the maximum theoretical daily dose (MTDD) of hydromorphone via use of this product. To establish a MTDD, submit actual clinical use data for this or comparable products for review by the Division. Note that, although [redacted] there is no minimum quantity of [redacted] required to produce the intended effect of analgesia. Therefore, further justification for levels of [redacted] as an impurity, in this hydromorphone product, that exceed [redacted] will be required.

Impurities in the hydromorphone drug substance are listed in table 1. The original proposed specifications were revised in the Applicant's submission dated October 8, 2010 (NOTE: This appears to be supporting document number 5 in DARRTs which incorrectly lists the letter date as October 18, 2010). Specific impurities of concern are discussed below.

Table 4. Drug substance impurities.

Impurity	Chemical Name	Origin	Proposed Specification
Impurities of concern: Exceed ICH Q3A(R2) and/or structural alerts			
[redacted]	[redacted]	[redacted]	[redacted]

Impurity	Chemical Name	Origin	Proposed Specification
	(b) (4)		
Impurities that meet ICH Q3A(R2)			
(b) (4)			

(b) (4)

Hydromorphone hydrochloride obtained from (b) (4) contains the impurity (b) (4). (b) (4) that is a structural alert for mutagenicity. (b) (4) specification for this impurity was originally limited to (b) (4) Because potentially genotoxic substances present a safety concern, it is the Agency policy that such substances should be evaluated for their genotoxic potential or reduced to acceptable levels. The potential genotoxic effects of (b) (4) were not described in the (b) (4) DMF (b) (4). Consistent with Agency precedent set in 2004, the specification of NMT (b) (4) is acceptable. The Agency has accepted specification of NMT (b) (4) However, (b) (4) to NMT (b) (4) which at a maximum daily dose of (b) (4) would result in exposure to (b) (4) which is below the threshold of toxicological concern and therefore acceptable.

(b) (4)

(b) (4) was identified as a (b) (4) (b) (4) degradation product in hydromorphone drug substance. The drug substance impurity (b) (4) exceed the ICH Q3A (R2) qualification threshold of NMT (b) (4) (b) (4) has not been qualified for its genotoxic potential. On October 8, 2009, the Applicant submitted a response to the Agency information request. The Applicant has agreed to lower the specification of (b) (4) of NMT (b) (4) to (b) (4) to meet ICH Q3A (R2). The newly proposed specification of NMT (b) (4) for (b) (4) by the Applicant for the drug substance is adequate.

(b) (4)

has been identified as a (b) (4) impurity in hydromorphone drug substance. The original proposed specification for (b) (4) was NMT (b) (4) which is the limit that is established for a potential genotoxic impurity with (b) (4) The Applicant did not provide any information for the reasoning for

establishing the specification of (b) (4) for a potential genotoxic impurity and not a non-genotoxic impurity.

In response to the Agency information request, the Applicant submitted the following response for (b) (4)

- The Applicant stated that (b) (4) is a (b) (4) structure (figure 3). A CAS number was not provided.

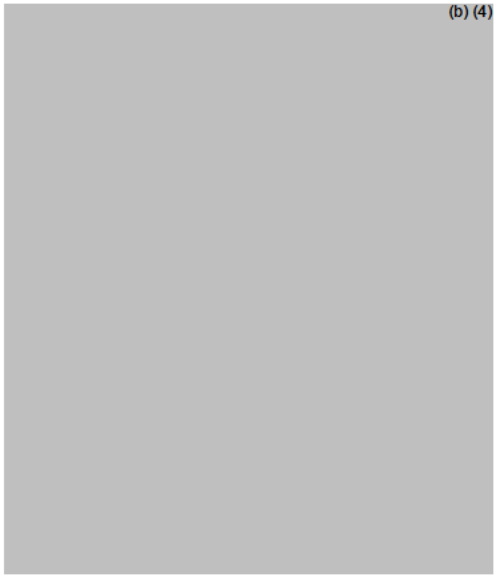


Figure 3. Structure of (b) (4)

- The Applicant has revised the specification of (b) (4) The original specification (NMT (b) (4)) of (b) (4) is being (b) (4) to NMT (b) (4) (NMT (b) (4)).
- Based on proposed Maximum Daily Dose (MDD) of (b) (4) for hydromorphone, the Applicant predicted the potential exposure to (b) (4) to be (b) (4) based on the following calculation:

(b) (4)

The reviewer concurs with the Applicant's proposed MDD of (b) (4) for hydromoporphone injection based on the premise that the drug product will be administered every (b) (4) in a hospital or hospice setting. Pain control can be controlled in most non-tolerant individual with (b) (4) of hydromorphone per day (b) (4)) following parenteral administration. However, opioid tolerant individuals may require higher doses for adequate pain relief. In these individuals, a high potency formulation of hydromorphone is recommended. Per DrugDex Evaluation, Dilaudid-HP injection is recommended for use in opioid tolerant patients. The newly proposed specification of NMT (b) (4) for (b) (4) by the Applicant for the drug substance is adequate.

(b) (4)

(b) (4) has been identified as (b) (4) impurity in hydromorphone drug substance. The original proposed specification for (b) (4) was NMT (b) (4); thus exceeding the ICH Q3A (R2) qualification threshold of NMT (b) (4). (b) (4) has not been qualified for its genotoxic potential. In response to the Agency information request, the following responses for (b) (4) were submitted:

- The Applicant stated that (b) (4) is (b) (4) structure (figure 4). A CAS number was not provided.

(b) (4)

Figure 4. Structure of (b) (4)

- The Applicant has agreed to (b) (4) original specification of (b) (4) from NMT (b) (4) to meet ICH Q3A (R2). The newly proposed specification of NMT (b) (4) for (b) (4) by the Applicant for the drug substance is adequate.

(b) (4)

has been identified as (b) (4) impurity in hydromorphone drug substance. The original proposed specification for (b) (4) was NMT (b) (4) thus exceeding the ICH Q3A (R2) qualification threshold of NMT (b) (4). (b) (4) has not been qualified for its genotoxic potential. In response to the Agency information request, the following responses for (b) (4) were submitted:

- The Applicant reconfirmed that (b) (4) is a (b) (4) impurity (b) (4)
- The identity of (b) (4) has not been fully elucidated. It was reported that (b) (4) (b) (4)

- LC/MS analysis indicated that the molecular weight of (b) (4) was approximately (b) (4).
- (b) (4)
- A CAS number for (b) (4) was not provided.
- (b) (4)
- The following structure (figure 5) is being proposed for (b) (4) The DMF holder (b) (4) is conducting additional studies to confirm this proposed structure. However, the identity has not been confirmed as of the date of this review.

(b) (4)

Figure 5. Proposed structure of (b) (4)

The reviewer does not concur with the Applicant to (b) (4). If the Applicant (b) (4) adequate qualification must be provided. As this DMF has been deemed acceptable for an FDA-approved generic drug product, this may be addressed in the post-marketing period.

(b) (4)

has been identified as (b) (4) impurity in hydromorphone drug substance. The original proposed specification for (b) (4) was NMT (b) (4).

(b) (4)

(b) (4) was considered positive for carcinogenicity. There was a positive trend in the incidence of renal tubular adenonma, mononuclear cell leukemia and histocytic sarcomas in rats; hepatocellular adenomas and histiocytic sarcomas were observed in mice. Because (b) (4) is a potential carcinogenic, (b) (4) In response to the Agency information request, the following responses for (b) (4) were submitted:

- The Applicant has revised the specification of impurity (b) (4) The original specification (NMT (b) (4)) of impurity (b) (4) NMT (b) (4) (NMT (b) (4)).
- The Applicant did not submit actual clinical use data to support the proposed MDD of (b) (4). Using a MDD of (b) (4) for hydromorphone, the Applicant predicted the potential exposure to impurity (b) (4) to be (b) (4) based on the following calculation:

  (b) (4)

The reviewer concurs with the Applicant's estimated potential exposure to impurity (b) (4) for the reasons stated above for (b) (4) Despite the structural alert for mutagenicity, the existing genetic toxicology data on (b) (4) actually suggests that the compound is not genotoxic; suggesting that there should be a threshold for carcinogenicity. No evidence of genetic toxicity by (b) (4) was found in the Ames test, in vivo mouse micronucleus assay and in vivo mouse lymphoma L5178Y/tfr cell test (b) (4) Although the existing rodent carcinogenicity data report equivocal evidence of carcinogenicity activity of (b) (4) in female F344/N rats, the studies suggest a NOEL for oral carcinogenicity at ~90 mg/m^2 in the rat and ~105 mg/m^2 in the mouse (female) based on body surface area. At the proposed human daily dose of NMT (b) (4) mg/m^2) a significant safety margin exists (>128,000x) for tumor development. Therefore, the proposed specification of NMT (b) (4) is acceptable.

Impurities in the hydromorphone drug product:

According to the ICH Q3B (R2), the qualification threshold for impurities (degradants) in the drug product for an MDD of the drug substance between 10 and 100 mg/per day is 0.5% or 200 mcg TDI, whichever is lower.

Impurities identified in the drug product are presented in table 2. Per ICH Q3B (R2), the current specification proposed by the Applicant for these impurities are adequate.

Table 5. Drug product impurities.

Impurities/Degradant	Proposed Specification	Acceptable?
(b) (4)	NMT (b) (4)	Yes
	NMT	Yes
	NMT	Yes
	NMT	Yes

Leachables:

The Applicant did not submit data to support the safety of their drug product in terms of potential leachables from the glass vials or Carpuject and iSyringe cartridges. However, the safety of these containers had been established by the Agency. The glass vials, Carpuject, iSyringe and (b) (4) rubber stopper of the vial are in other FDA-approved parenteral products.

While the non-clinical review team has no safety issues with the proposed packaging system for the hydromorphone drug product based on previous use of the container closure system in FDA approved drug products, the chemistry review team has requested a specific leachable assessment on the closure system. In the July 9, 2010 74-day letter, the chemistry review team pointed out that that the Applicant had provided an extractables assessment for the (b) (4) closures for injections, but no information on a leachables assessment in all of the proposed drug product packaging configurations. The chemistry review team requested that the Applicant provide an adequate justification (including supportive data) for the absence of leachables in all of your proposed packaging configurations. In response to the Agency request for the leachables assessment on all of the proposed drug product packaging, the Applicant informed the Agency on October 8, 2010 that a leachables study is ongoing. The leachables study is being conducted in accordance with the FDA Guidance document "Container Closure Systems for Packaging Human Drugs and Biologics", USP <661>.

On December 23, 2010, the Applicant submitted data from a stopper extractable/leachable study conducted on (b) (4) Gray stopper material. In this study, potential leachables were assessed. Results from the study identified several potential leachables with the following RRT values in the extractable sample. However, when these potential leachables were compared to the chromatograms from the 18-month stability study, these leachables were not detected in the hydromorphone solution. Furthermore, other observed unspecified impurities observed in the 18-month stability study were below the ICH Q3B(R2) threshold of 0.2% and 0.5% for identification and qualification thresholds, respectively. The daily exposure to these impurities will be less than (b) (4). For detail analysis of the 18-month stability data, see the Chemist review.

RRT values of potential leachables from (b) (4) Sampling Material (b) (4)

Additional leachables studies are ongoing; however, these data will be submitted to support a proposed extension of the 18 month expiry being proposed by the CMC review team. *When these data are submitted the pharmacology/toxicology reviewer will evaluate the data*. *A toxicological risk assessment will be performed if leachables are detected*. This can be reviewed as part of a CMC supplement to extent the expiry.

2.4 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is the same as the reference product Dilaudid. Hydromorphone Injection USP is intended for patients where an opioid analgesic is appropriate. Hydromorphone Hydrochloride Injection USP will be marketed in 3 strengths, 1 mg/mL, 2 mg/mL and 4 mg/mL for parenteral administration. The recommended dosage is 1 to 2 mg subcutaneously or intramuscularly every (b) (4) as needed for management of pain. It is recommended that the dose be adjusted according to the severity of the patient's pain. Although tolerance develops to opioids with repeated use, Dilaudid HP 10 mg/mL product should be used for opioid tolerant patients. Therefore, the proposed maximum daily dose of this product of (b) (4) is reasonable based on clinical use (as discussed with the medical officer).

2.5 Regulatory Background

Hydromorphone Hydrochloride Injection, USP (b) (4) In responses to the Agency's 2006 "unapproved drug" initiative, Hospira, Inc. sent a letter dated June 22, 2009 informing the Agency their intention to submit a New Drug Application (b) (4). On April 29, 2010, NDA 200-403 was submitted via the 505(b)(2) pathway with the referenced drug Dilaudid (NDA 19-034) held by Purdue Pharma Products.

3 Studies Submitted

The sponsor did **not** conduct any toxicology studies in support of this NDA.

3.1 Studies Reviewed

N/A

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

4.1 Primary Pharmacology

Primary pharmacodynamics: Hydromorphone is an opioid agonist with activity at the μ-opioid receptor. Activation of μ-opioid-receptors is associated with analgesia, respiratory depression, sedation, decreased gastrointestinal motility, euphoria and physical dependence.

Mechanism of action: The primary mechanism action of hydromorphone in the treatment of pain is due to mu-opioid receptor agonist effects.

4.2 Secondary Pharmacology

The Applicant did not conduct formal secondary pharmacodynamics studies. As with other opioid analgesics, hydromorphone secondary pharmacological effects include dysphoria, euphoria, sedation, respiratory depression, decreased gastrointestinal motility and physical dependence.

4.3 Safety Pharmacology

The Sponsor did not conduct formal safety pharmacology studies. However, due to its extensive marketing history, nonclinical safety pharmacology studies are not necessary.

Neurological effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential neurological safety concerns with hydromorphone administration. A review of the literature did not identify any animal studies that specifically addressed hydromorphone-related neurological effects. According to the adverse event profile from the referenced product labeling, CNS-related side effects associated with the use of hydromorphone includes dizziness, headache somnolence, and sedation. More serious CNS-related adverse events reported with the use of hydromorphone includes myoclonia and seizures in compromised patients with cancer or severe pain.

Cardiovascular effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential cardiovascular safety concerns with hydromorphone administration. A review of the literature did not identify any animal studies that specifically addressing hydromorphone-related cardiovascular effects. However, according to the adverse event profile from the referenced product labeling, cardiovascular adverse reactions have been associated with hydromorphone. These adverse reactions include sinus bradycardia, sinus tachycardia, palpitations, hypertension, orthostatic hypotension and syncope. Orthostatic hypotension, peripheral edema or generalized edema may be a secondary effect of peripheral vasodilation.

Pulmonary effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential respiratory safety concerns with hydromorphone administration. Respiratory depression is a well known clinically significant effect of all opioid full agonists, including hydromorphone. Hydromorphone produces dose-related respiratory depression. Like other opioids, hydromorphone acts directly on the brain stem respiratory center; decreasing the response of the brain stem respiratory centers to increased PCO_2 and depression of pontine and medullary centers via its action at mu opioid receptors.

Renal effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential renal safety concerns with hydromorphone administration. A review of the literature did not identify any animal studies that specifically addressed hydromorphone-related renal effects.

Gastrointestinal effects: The Applicant did not conduct formal safety pharmacology studies to evaluate potential gastrointestinal safety concerns with hydromorphone administration. The following discussion was obtained from a review of the published literature.

Practically all commonly used opioids produce gastrointestinal adverse effects by a combination of actions on opioid receptors within the central nervous system and opioid receptors located within the enteric nervous system. Inhibition of gastrointestinal motility (i.e., propulsive peristalsis) is a long-known classical effect of morphine and morphine-like opiates. In addition to this effect, opioid drugs exert a wide spectrum of other effects on the mammalian intestinal function. These effects include reduction in secretions (pancreatic, biliary, and electrolyte/fluid) and increases in intestinal fluid absorption.

Knoll and colleagues (1974) reported that hydromorphone elicited qualitatively similar gastrointestinal effects in mice and guinea pigs as morphine. The effects of hydromorphone, morphine and several other opioids on intestinal propulsions (i.e., GI transit time) were evaluated in male and female mice. Mice were administered single subcutaneous doses (doses evaluated were not described) of hydromorphone, codeine, morphine, oxymorphone, methadone and pethidine 1 to 3 hours prior to the oral administration of charcoal solution (10% charcoal in saline). The distance covered by charcoal in the intestine in the opioid treated mice was compared to control mice. As depicted in the table (extrapolated from the article) below, relative to morphine, hydromorphone was more potent than morphine.

Inhibition of propulsive contractions in mice		
Opioid	**ED_{50} (mg/kg)**	**ED_{50} morphine/ ED_{50} (opioid)**
Morphine	4.6×10^{-6}	1.0
Hydromorphone	2.4×10^{-7}	19.0
Codeine	6.2×10^{-7}	7.4
Oxymorphone	1.4×10^{-6}	3.30

Inhibition of propulsive contractions in mice		
Opioid	**ED_{50} (mg/kg)**	**ED_{50} morphine/ ED_{50} (opioid)**
Methadone	1.3×10^{-5}	0.35
Pethidine	1.8×10^{-5}	0.26

King et al. (1935) reported that hydromorphone elicited qualitatively similar effects as morphine on the intestinal muscular of a Thirty-Vella loop of canine ileum. Hydromorphone and morphine at a dose of 0.01 and 0.1 mg/kg, respectively, decreased the frequency of segmentation while increasing the amplitude.

Gruber and Brundage (1935) compared the effects of hydromorphone and morphine on the Thirty-Vella loop of the jejunum and ileum in dogs. The effects of dilaudid and morphine on intestinal tone, rhythmic contraction and peristaltic contraction were evaluated in female dogs. Dogs were administered a single intravenous dose of hydromorphone (0.00005 to 5 mg/kg). Hydromorphone was qualitatively similar to morphine in its effects on the intestinal musculature of the Thirty-Vella loop of the dog ileum and jejunum. Both hydromorphone and morphine had a biphasic effect on musculature tone. At low doses, they increased musculature tone and higher doses, they decreased musculature tone. Hydromorphone was 10 times more potent than morphine in its effects on the general musculature tonus; maximum increase in the degree and duration maximum changes in general musculature tone and amplitude of tone were noted at 0.1 mg/kg and 1.0 mg/kg of Dilaudid and morphine, respectively. Both morphine and hydromorphone decreased the jejunum of the rhythmic contraction of the amplitude.

Abuse liability: As with most opiates, hydromorphone is a highly additive substance; it has a high abuse and dependence potential and produces tolerance. Hydromorphone immediate release is a DEA Schedule II controlled substance. The incidence and rates of prescription opioid abuse have increased in the United States over the past several years (Compton and Volkow, 2006). In a recent study, Walsh and colleagues (2008) compared the abuse liability of hydromorphone to that of hydrocodone and oxycodone following oral administration in non-dependent sporadic prescription opioid abusers in a double-blind, randomized, within-in subject, placebo-controlled outpatient study. All three opioids produced the typical μ opioid agonist profile of subjective (i.e., increased ratings of liking, good effects, high and opiate symptoms). Results indicated that the abuse potential/liability of hydromorphone did not differ substantially from oxycodone and hydrocodone in ratings of measures related to euphoria-like responses (i.e., liking for the drug, good effects, high, and MBG scores) and sedation (i.e., PCAG scores, sleepy and nodding).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK/ADME studies were submitted by the Applicant.
The pharmacokinetic profile and ADME of hydromorphone hydrochloride are well known. The oral bioavailability of hydromorphone is approximately 60%. Following absorption, hydromorphone is widely distributed. In humans, hydromorphone is distributed into brain, intestinal tract, liver, lungs, kidneys, spleen and skeletal muscle. Hydromorphone crosses the placenta.

Hydromorphone is extensively metabolized by hepatic oxidation and conjugation. Major metabolites in humans include hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphine-3-glucoside and dihydromorphine-6-glucoside. Minor metabolites of hydromorphone include dihydro-iso-morphine and dihydromorphine.

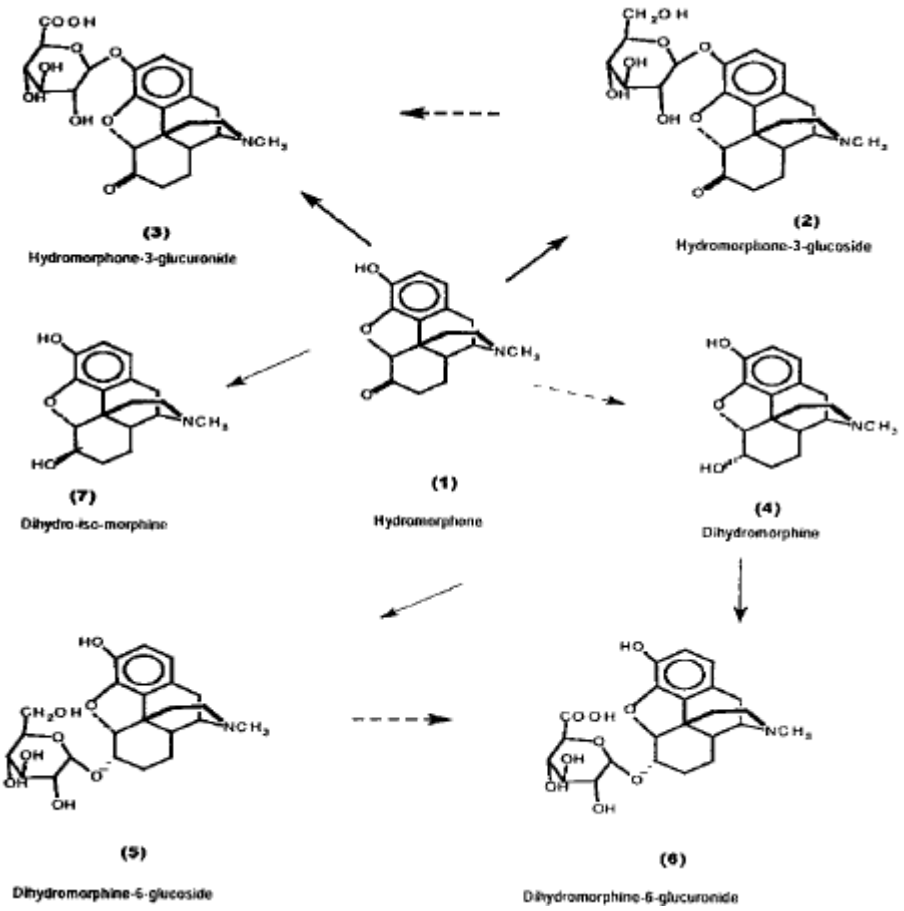


Figure 6. Proposed hydromorphone metabolic pathway.

5.2 Toxicokinetics

No toxicokinetics studies were submitted by the Applicant.

6 General Toxicology

No toxicology studies were submitted by the Applicant.

Special Evaluation

No new studies were submitted by the Applicant.

Stability and Homogeneity

Not applicable

7 Genetic Toxicology

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

No new studies were submitted by the Applicant.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

No new studies were submitted by the Applicant.

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

No new studies were submitted by the Applicant.

7.4 Other Genetic Toxicity Studies

No new studies were submitted by the Applicant.

8 Carcinogenicity

No carcinogenicity studies were submitted by the Applicant.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No fertility and early embryonic development studies were submitted by the Applicant.

9.2 Embryonic Fetal Development

No embryonic fetal development studies were submitted by the Applicant.

9.3 Prenatal and Postnatal Development

No prenatal and postnatal development studies were submitted by the Applicant.

10 Special Toxicology Studies

Not applicable

11 Integrated Summary and Safety Evaluation

Hydromorphone Hydrochloride Injection, USP [redacted] (b) (4). Because the pharmacology and toxicology of hydromorphone are well characterized, there are no safety issues/concerns from the nonclinical perspective with the hydromorphone component of this drug product.

There is one outstanding CMC related issues that have not been adequately addressed by the Applicant as of the date of this review. The Applicant has not yet definitively identified the chemical structure of the drug substance [redacted] (b) (4) which exceeds [redacted] (b) (4) the ICHQ3A [redacted] (b) (4) qualification threshold.

The Applicant submitted leachable data to support an [redacted] (b) (4) shelf life for the hydromorphone drug product. The Applicant has additional leachables studies ongoing; the results of the leachable study will have to be reviewed should leachables be identified. Toxicological risk assessment may be required at that time.

12 Appendix/Attachments

Reference:

Compton, S.D., Volkow, N.D. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug and Alcohol Dependence 81:103-107, 2006.

Grubber, C.M., Brundage, J.T. A comparative study of the actions of morphine and dilaudid (dihydromorphinone hydrochloride) on the intact small intestine of the dog. J. Pharmacol. Exp. Ther. 53:120-136, 1935.

[redacted] (b) (4)

[redacted] (b) (4)


(b) (4)

(b) (4)

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/s/

BELINDA A HAYES
01/24/2011

RICHARD D MELLON
01/24/2011
I concur with Dr. Hayes' recommendation regarding approval and with the requested PMR.

PHARMACOLOGY TOXICOLOGY REVIEW AND EVALUATION
Addendum to Primary Review (January 24, 2011)

APPLICATIONNUMBER:	200403
TYPE OF SUBMISSION:	Amendment
SUPPORTING DOCUMENT/S:	SDN-1;-21
APPLICANT'S LETTER DATE:	April 29, 2010; October 7, 2011
CDER STAMP DATE:	October 7, 2011
PRODUCT:	Hydromorphone Hydrochloride Injection, USP
FORMULATION:	Solution
INDICATION:	Management of pain in patients where an opioid analgesic is appropriate
SPONSOR:	Hospira, Inc. 275 North Field Drive Lake Forest, IL 60045.
PHARM/TOX REVIEWER:	BeLinda A. Hayes, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR:	Bob A. Rappaport, M.D.
PROJECT MANAGER:	Lisa Basham, M.S.

1 Recommendation

1.1 Approvability

This NDA application is recommended for approval from a nonclinical pharmacology and toxicology perspective with no post-marketing requirements; the deficiencies that triggered the recommendation for post-marketing requirements during the first review cycle have been adequately addressed by the Applicant and are no longer necessary.

1.2 Labeling

The pharmacology/toxicology review team has no new recommended changes to proposed labeling. The Applicant did not make any changes to the proposed labeling changes from the first review cycle.

2 Regulatory Background

Hydromorphone Hydrochloride Injection, USP (b) (4) In responses to the Agency's 2006 "unapproved drug" initiative, Hospira Inc. submitted NDA 200403 for Hydromorphone Hydrochloride Injection, USP (1, 2 and 4 mg/mL hydromorphone hydrochloride) on April 29,

2010 under 505(b)(2) regulations with the referenced drug Dilaudid (NDA 19034) held by Purdue Pharma Products. Hydromorphone Hydrochloride Injection USP is intended to be administered subcutaneously or intramuscularly every (b) (4) as necessary for the management of pain in patients where an opioid analgesic is appropriate. No pharmacology or toxicology studies were submitted in support of this NDA. The Applicant relied on the Agency's previous finding of safety for Dilaudid (NDA 19034) and information from the literature.

During the initial review of NDA 200403, the pharmacology/toxicology review team identified several impurities that were potential review issues. These potential review issues were conveyed to the Applicant in the 74-day letter dated July 9, 2010:

1. Your drug substance acceptance criteria for pseudohydromorphone, (b) (4) and (b) (4) exceed the ICH Q3A(R2) qualification threshold of (b) (4), whichever is lower. (b) (4) which must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat dose toxicology study of 1 month duration to support the proposed specifications.
2. The current standard for potentially genotoxic impurities is to reduce the exposure to these impurities NMT (b) (4). Provide your rationale, including discussions regarding technical feasibility, for the proposed specifications for morphinone and (b) (4)
3. Provide the structure and CAS number for (b) (4) and indicate if it contains a structural alert for mutagenicity. If this (b) (4) a structural alert, reduce the acceptance criteria to NMT (b) (4) unless adequate justification is provided that this is not technically feasible. In addition provide the structure and CAS number for Impurities identified as (b) (4).
4. Given that (b) (4) has been reported to test positive in carcinogenicity studies, (b) (4), including supporting references. Such a safety assessment must take into consideration the maximum theoretical daily dose (MTDD) of hydromorphone via use of this product. To establish a MTDD, submit actual clinical use data for this or comparable products for review by the Division. (b) (4) Therefore, further justification for levels of (b) (4) as an impurity, in this hydromorphone product, that exceed (b) (4) will be required.

On October 8, 2009, the Applicant submitted a response to the Agency information request in the 74-day letter. In response to the Agency request, the Applicant adequately addressed the Agency concerns for the following drug substance impurities: [redacted]. The Applicant [redacted] these impurities to meet ICH Q3A qualification threshold of NMT [redacted]. Also, the DMF holder [redacted] the specification for the [redacted]. [redacted] specification was [redacted] from NMT [redacted] to NMT [redacted]; [redacted]. On the other hand, the Applicant did not adequately address the review issues pertaining to drug substance [redacted] The Applicant [redacted] the specification of the drug substance [redacted] which exceeded [redacted] the qualification threshold, or provide adequate safety qualification; [redacted] Also, the Applicant did not identify the chemical structure of [redacted] only a tentative proposed structure was submitted.

During the first review cycle, the Agency deemed that the safety and efficacy of hydromorphone hydrochloride to be comparable to Dilaudid. However, on February 25, 2011; a tentative approval action was issued to Hospira Inc because of a pending law suit. At the time that NDA 200403 was submitted to the Agency, Purdue's patent (№ 6589960) for Dilaudid was effective until November 9, 2020; and subsequently, Hospira was being sued by Purdue for patent infringement.

At the time that the Agency's tentative approval letter dated February 25, 2011 was issued to Hospira Inc., the concerns/issues for [redacted] were still an outstanding issue with potential toxicological relevance. However, as noted in the Pharmacology/Toxicology review dated January 24, 2011, the issue was not deemed an approval issue; but must be addressed as a post-marketing requirement. The non-clinical recommendation noted in the review is copied below.

> "The Applicant has not adequately responded to the Agency request to [redacted] adequate safety qualification. The Applicant must provide definitive identification of the impurity structure [redacted] Safety qualification must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat dose toxicology study of 3 month duration to support the proposed specification of NMT [redacted] As this drug substance DMF has been previously deemed adequate by the FDA for an approved generic drug, this concern may be addressed via a post-marketing requirement."

3 Summary

On October 7, 2011, the Applicant submitted a minor amendment in response to the Agency's tentative approval of their NDA and a request for full approval. In this amendment, the Applicant did address the pending outstanding issue for (b) (4) The original proposed specification of (b) (4) was revised in their amendment to the NDA. The Applicant reduced the specification of (b) (4) to meet ICH Q3A(R2).

(b) (4)

During the first review cycle, (b) (4) was identified as a (b) (4) impurity in hydromorphone drug substance and had not been qualified for genotoxic potential. The original proposed specification for (b) (4) was NMT (b) (4) thus exceeding the ICH Q3A(R2) qualification threshold of NMT (b) (4) In response to the Agency initial information request during the first review cycle, the Applicant lowered the original specification of (b) (4) from NMT (b) (4) to (b) (4) to meet ICH Q3A(R2). The newly proposed specification of NMT (b) (4) for (b) (4) by the Applicant for the drug substance is adequate.

In addition to tightening the specification of (b) (4) the manufacturer of the drug substance conducted a QSAR analysis of (b) (4) Results from this analysis provided the following characterization of (b) (4)

(b) (4)

(b) (4)

- Using Derek (Nexus 2.0) quantitative structure-activity relationship analysis to characterize (b) (4) potential toxicity, the following information was provided

(b) (4)

4 CONCLUSION AND RECOMMENDATIONS

The Sponsor reduced the specification for (b) (4) to meet the ICH Q3A(R2) safety qualification threshold. In addition, information on the characterization of (b) (4) was submitted in the DMF. (b) (4), the manufacturer of the drug substance, confirmed the earlier proposed structure of (b) (4) and provided the molecular weight and molecular formula. Results from the Derek analysis suggested that there is no concern that (b) (4) is genotoxic or that (b) (4) poses any greater risk relative to the parent compound hydromorphone. No further studies are necessary.

Based on the information provided to date for NDA 200403, there are no safety issues/concerns from the nonclinical perspective with the hydromorphone component of this drug product, NDA 200403 may be approved without any post-marketing requirements.

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/s/

BELINDA A HAYES
11/09/2011

RICHARD D MELLON
11/09/2011
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200403 **Applicant: Hospira** **Stamp Date: 29-Apr-2010**

Drug Name: Hydromorphone HCl Injection **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing: NDA may be filed.

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A, no new nonclinical data provided, sponsor is relying upon the Agency's previous findings for NDA 19-034 (Dilaudid)
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A; see response to item 1 above There is no pharm/tox section in this NDA submission.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A; see response to item 1 above There is no pharm/tox section in this NDA submission.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		See response to item 1 above
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			This product contains (b) (4) rather than (b) (4) and uses sodium chloride to adjust tonicity. Justification provided is that this is used commonly in parenteral formulations.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A; see response to item 1 above
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A; see response to item 1 above
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A; there was no preNDA meeting.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Label is that of Dilauded.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		x	No, some DS specs exceed ICHQ3A(R2) and will require tightening or justification of safety.
11	Has the applicant addressed any abuse potential issues in the submission?		x	See response to item 1 above
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __yes_____

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

Although there are not yet adequate data to justify the proposed drug substance specifications, the specs may be tightened and therefore additional studies may not be needed to approve this application. As such, as per OND policy, this is not considered this a filing issue.

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

1. Your drug substance specifications for [redacted] exceed the ICH Q3A(R2) qualification threshold of NMT [redacted] whichever is lower. [redacted] which must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat dose toxicology study of 1 month duration to support the proposed specifications.
2. The current standard for potentially genotoxic impurities is to reduce the exposure to these impurities NMT [redacted]. Provide rationale, including discussions regarding technical feasibility, for the proposed specifications for morphinone and [redacted]
3. Provide the structure and CAS number for [redacted] and indicate if it contains a structural alert for mutagenicity. If this [redacted] a structural alert, it should also be reduced to NMT [redacted] unless adequate justification is provided that this is not technically feasible.
4. Given that [redacted] has been reported to test positive in carcinogenicity studies, this impurity [redacted] Such a safety assessment must take into consideration the maximum theoretical daily dose

(MTDD) of hydromorphone via use of this product taking into consideration the development of tolerance to opioids. To establish a MTDD, submit actual clinical use data for this or comparable products for review by the Division. Note that although (b) (4) is listed in the CFR as an acceptable direct flavoring agent, it is not clear what the allowable minimum quantity required to product the intended effects can be applied to your product; therefore, further justification will be required.

Reviewing Pharmacologist	Date
R. Daniel Mellon, Ph.D.	6/8/2010
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200403	ORIG-1	HOSPIRA INC	Hydromorphone Hydrochloride Injection 1,2,4 mg/mL

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/s/

RICHARD D MELLON
06/17/2010