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APPLICATION NUMBER:

205582Orig1s000

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: 205582
Supporting document/s: 0000
Applicant's letter date: March 25, 2013
CDER stamp date: March 27, 2013
Product: Decitabine for Injection
Indication: Treatment of patients with myelodysplastic syndromes (MDS)
Applicant: Sun Pharma Global FZE
Review Division: Division of Hematology Oncology Toxicology
Reviewer: Pedro L. Del Valle, PhD
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1 Executive Summary

1.1 Introduction

Dacogen® (decitabine) is a nucleoside metabolic inhibitor approved in 2006 (NDA 021,790) for the treatment of patients with myelodysplastic syndromes (MDS). Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis.

The listed drug (LD), Dacogen, is a lyophilized product approved for intravenous injection and supplied in a single-dose vial containing 50 mg of decitabine and monobasic potassium phosphate NF and sodium hydroxide (b) (4)

(b) (4) Upon reconstitution with 10 mL of Sterile Water for Injection, each mL of Dacogen contains approximately 5 mg of decitabine. The applicant, Sun Pharma Global FZE (thereafter referred to as Sun Pharma in this review), has submitted this 505(b)(2) NDA for an indication and dosing instructions identical to that of the LD. The to-be-marketed formulation proposed by Sun Pharma consist of two vials: a vial containing 50 mg of decitabine and a vial containing the diluent, a mixture of monobasic potassium phosphate NF, sodium hydroxide, NF and Water for Injection USP. Upon reconstitution with the diluent, the Sun Pharma's Decitabine for Injection is similar in composition to the LD.

The Applicant, Sun Pharma, included in this NDA a repeat-dose study in CD-1 mice to compare the toxicity profile of Sun Pharma's Decitabine for Injection and Dacogen and to qualify the safety of impurities at relative retention time ((b) (4) and (b) (4)). These two impurities have specifications above the qualification threshold at no more than (NMT) (b) (4) and (b) (4) respectively. Data provided evidence that Sun Pharma's Decitabine for Injection and Dacogen had similar toxicity profile; impurities at (b) (4) and (b) (4) were present in both drug products used in the animal study and their amount increased over time above the specifications.

1.2 Brief Discussion of Nonclinical Findings

Sun Pharma relies upon the Agency's previous findings of safety and effectiveness for Dacogen. The Applicant conducted a GLP repeat-dose toxicology study in CD-1 mice to compare the toxicity profile of Sun Pharma's Decitabine for Injection and Dacogen and to qualify impurities at (b) (4) and (b) (4), present above the qualification threshold.

The toxicology study included assessment of clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weight, gross pathology, histopathology, and dose formulation analysis quantifying impurities at (b) (4) and (b) (4) at the beginning and at the end of the dosing period.

The toxicology profile was comparable for the two drug products; target tissues affected were testis and epididymis in both Sun Pharma's Decitabine for Injection and Dacogen; impurities at (b) (4) and (b) (4) were present in both drug products and the amount of those impurities increased over time. The total amount of the 2 impurities in the drug products at the end of the study was higher than the proposed specification; the 2 impurities are considered qualified. There are no pharmacology/ toxicology concerns with this application.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, Decitabine for Injection may be approved for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

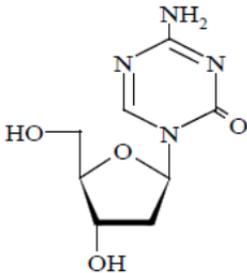
None

1.3.3 Labeling

The nonclinical sections of the label will be comparable to the label of the listed drug. Section 15 (References) of the label has been updated with the link. This revision will be made to the label of Dacogen at a later time.

2 Drug Information

2.1 Drug

CAS Registry Number	2353-33-5
Generic Name (also the INN and USAN)	Decitabine
Code Name	NA
Chemical Name	4-Amino-1-(2-deoxy-β-erythro-pentofuranosyl)-,3,5-triazin-2(1H)-one OR 1-(2-Deoxy-β-D-ribofuranosyl)-5-azacytosine
Molecular Formula	C ₈ H ₁₂ N ₄ O ₄
Molecular Weight	228.1
Structure or Biochemical Description	
Pharmacologic Class	Nucleic Acid Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA #021790 for Dacogen

2.3 Drug Formulation

Decitabine for Injection is presented in 2 vials; a vial containing 50 mg of decitabine and a vial containing a sterile diluent. The vial of decitabine contains a sterile, lyophilized, non-pyrogenic powder supplied in a single-dose glass vial containing 50 mg of decitabine. The vial of the diluent contains monobasic potassium phosphate NF, sodium hydroxide, NF and Water for Injection USP. The contents of the two vials are to be reconstituted and further diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection before administration by intravenous infusion.

Table 1 Composition of Reconstituted Drug Product

(Excerpted from Applicant's Submission)

Composition of Reconstituted Drug Product

<u>Components</u>	<u>mg/mL</u>	<u>% Composition (%w/v)</u>
Decitabine	5.00	0.5
Monobasic Potassium Phosphate, NF	6.8	0.68
Sodium Hydroxide, NF	1.16	0.116
Water for Injection, USP	q.s. 1.0 mL	

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Impurities at (b) (4) and (b) (4) present in the final reconstituted and diluted drug product are above the limits specified in ICH Q3B(R2). A GLP repeat-dose toxicology study in CD-1 mice was conducted to qualify their safety; dose formulation analysis conducted at the end of the study (Day 5 of cycle 2) showed that impurities at (b) (4) and (b) (4) were present in both drug products and their amount increased over time above the specifications. The toxicology profile was comparable for the two drug products.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indications and dosing instructions for Decitabine for Injection are identical to those of the Listed Drug Dacogen e.g. treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

2.7 Regulatory Background

A pre-NDA meeting was held under PIND [REDACTED] (b) (4) on February 6, 2012.

3 Studies Submitted

3.1 Studies Reviewed

	Study Report	Title
<i>Toxicology</i>		
1	BRT_12_081_TN	A 2-Dosing Cycle Intravenous Repeated Dose Toxicity Study in CD-1 Mice to Qualify the Impurities [REDACTED] (b) (4) and [REDACTED] (b) (4) Present in Decitabine Injection

3.2 Studies Not Reviewed

	Study Report	Title
<i>Toxicology</i>		
1	BRT_12_051_TN	A 2-Cycle Pilot Intravenous Toxicity Study of Decitabine Injection in CD-1 Mice

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No studies conducted

4.2 Secondary Pharmacology

No studies conducted

4.3 Safety Pharmacology

No studies conducted

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No studies conducted

5.2 Toxicokinetics

No studies conducted

6 General Toxicology

6.1 Single-Dose Toxicity

No studies conducted

6.2 Repeat-Dose Toxicity

Study title:

Study no.:	BRT_12_081_TN
Study report location:	eCTD 4.2.3.7.6.
Conducting laboratory and location:	Sun Pharma Advanced Research Company Limited Tandalja, Vadodara – 390 020, India
Date of study initiation:	October 13, 2012
GLP compliance:	OECD
QA statement:	YES
Drug, lot #, and % purity:	Decitabine for Injection, Lot # [REDACTED] (b) (4), Purity 102.6% Dacogen, Lot # JKK2449, Purity 96.4%

Key Study Findings

- Overall, toxicities were comparable between Sun Pharma's drug product and Dacogen.
- Mortality occurred in 1/10 females receiving Decitabine for Injection at 0.6 mg/kg/day.
- Hematology: dose-related decreases in red cell parameters, increases in WBC, neutrophils and monocytes, and increase/decrease in platelets occurred in Decitabine for Injection or Dacogen groups.
- Clinical Chemistry: dose-related decreases in alkaline phosphatase (ALP) and cholesterol occurred in Decitabine for Injection or Dacogen groups.
- Organ weight: target organs affected were testis and epididymis in both Decitabine for Injection and Dacogen groups with significant decreases in absolute and relative organ weight.
- Pathology: the findings above corresponded with oligospermia and spermatozoa degeneration in the testis and with oligospermia in the epididymis.

Methods

Doses:	Control: Diluent for Decitabine for Injection Decitabine for Injection: 0.2, 0.4, 0.6 mg/kg/day Dacogen 0.6 mg/kg/day
Frequency of dosing:	Once daily for 5 days in 2 cycles with 23 drug-free period between cycles
Route of administration:	Intravenous into a tail vein
Dose volume:	Range from 3.4 to 10 mL/kg
Formulation/Vehicle:	Diluent for Decitabine for Injection
Species/Strain:	CD-1 Mice breed in India
Number/Sex/Group:	10/sex/group
Age:	6-7 weeks at initiation of dosing
Weight:	Males: 33.86 to 36.34 g Females: 26.12 to 28.30 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None reported

Observations and Results**Mortality**

One female in the 0.6 mg/kg/day Decitabine for Injection group was found dead on Day 31 immediately after dosing, e.g. the 3rd day of dosing in cycle 2. There were no clinical signs reported for this animal; however, the body weight gain for this animal was only 27% compared to the group mean. There was no clinical pathology data reported because of early death and there were no gross abnormalities or histopathology findings that could be attributed to Decitabine for Injection administration. This early death may be related to Decitabine for Injection since it occurred immediately after dosing.

Clinical Signs

No clinical signs observed for females.

In males, clinical signs included the following:

- a mild wound in the ventral side from Day 12 through Day 57 for one male in the 0.4 mg/kg/day Decitabine for Injection group,
- a mild growth near the anal region from Day 12 through the end of the study for three males in the 0.6 mg/kg/day Decitabine for Injection group,
- a mild wound near the anal region reported from Day 12 through the end of the study for four males in the 0.6 mg/kg/day Decitabine for Injection group.

The study report did not describe any veterinary intervention to control these wounds.

Body Weight

Mean body weight was similar among the different groups throughout the study.

Food Consumption

Mean food consumption was similar among the different groups throughout the study.

Ophthalmoscopy

No conducted

ECG

No conducted

Hematology

Blood samples for hematology evaluations were taken at the end of the dosing phase on Day 57.

- Overall, changes in hematology parameters at 0.6 mg/kg/day dose were comparable for Sun Pharma's drug product and Dacogen.
- Decreases in red cell parameters (RBC, hemoglobin and hematocrit) occurred in males administered Decitabine for Injection or Dacogen.
- Increases in WBC, neutrophils, mean platelet volume (MPV) and monocytes occurred in both Decitabine for Injection and Dacogen groups except for males given Dacogen that presented no increase in neutrophils.
- Increases or decreases in platelets in animals given Decitabine for Injection were statistically significantly at 0.6 mg/kg/day; animals administered Dacogen presented significant decreases in platelets.
- Other changes in hematological values were of low magnitude

Table 2 Fold Change of Hematological Parameters compared to Control Group at the end of the 2-Dosing Cycle

Parameter	Sex	Decitabine for Injection (mg/kg/day)			Dacogen (mg/kg/day)
		0.2	0.4	0.6	0.6
WBC	M	2.25 ↑	1.46↑	1.90 ↑	1.65↑
	F	1.06	1.10	1.20↑	1.06
RBC	M	0.91↓	0.86 ↓	0.78 ↓	0.86 ↓
	F	1.00	1.00	0.97	0.99
Hemoglobin	M	0.93↓	0.87 ↓	0.82 ↓	0.88 ↓
	F	1.02	1.01	1.01	1.02
Hematocrit	M	0.92 ↓	0.88 ↓	0.85 ↓	0.88 ↓
	F	1.04	1.00	1.01	1.02
MPV	M	1.16↑	1.13↑	1.10	1.09
	F	1.06	1.13↑	1.09	1.08↑
Neutrophil	M	3.62 ↑	2.34 ↑	4.65 ↑	1.00
	F	1.21 ↑	1.73 ↑	2.23 ↑	1.83 ↑
Lymphocyte	M	1.55 ↑	1.00	0.75 ↓	1.68 ↑
	F	1.03	1.00	1.05	0.68 ↓
Monocytes	M	3.71 ↑	3.71 ↑	2.33 ↑	1.71 ↑
	F	2.47 ↑	1.33 ↑	2.47 ↑	1.60 ↑
Platelet	M	1.16↑	1.11↑	1.50 ↑	0.82 ↓
	F	0.87↓	0.90↓	0.86 ↓	0.75 ↓

Values in **bold** were significantly different from control

Clinical Chemistry

Blood samples for clinical pathology evaluations were taken at the end of the dosing phase on Day 57.

- Overall, changes in clinical chemistry parameters at 0.6 mg/kg/day dose were comparable for Sun Pharma's drug product and Dacogen.
- Decreases in ALP, cholesterol, total bilirubin, total protein and lower A/G ratios occurred in both Decitabine for Injection and Dacogen groups except for unchanged values for cholesterol in females dosed with Dacogen.
- Increases in urea values occurred in both Decitabine for Injection and Dacogen groups.
- Calcium values were significantly higher in animals given Dacogen.

Table 3 Fold Change of Clinical Chemistry Parameters compared to Control Group at the end of the 2-Dosing Cycle

Parameter	Sex	Decitabine for Injection (mg/kg/day)			Dacogen (mg/kg/day)
		0.2	0.4	0.6	0.6
ALP	M	1.01	0.68 ↓	0.47 ↓	0.60 ↓
	F	1.07	1.06	1.06	0.86 ↓
Cholesterol	M	0.97	0.88 ↓	0.74 ↓	0.80 ↓
	F	1.06	1.04	1.06	1.04
Urea	M	1.07	1.27 ↑	1.11↑	0.99
	F	1.15↑	0.98	1.05	1.13↑
Total Protein	M	0.97	0.96	0.91↓	0.97
	F	0.95 ↓	0.97	1.00	0.92 ↓
Calcium	M	0.99	0.97	1.00	1.06 ↑
	F	0.98	0.98	1.02	1.06 ↑
Total Bilirubin	M	0.75 ↓	0.75 ↓	0.67 ↓	0.64 ↓
	F	1.02	0.82↓	0.84↓	0.82↓
A/G ratio	M	0.98	0.93↓	0.90 ↓	0.89 ↓
	F	1.01	0.99	0.98	0.99

Values in **bold** were significantly different from control

Urinalysis

No conducted

Gross Pathology

No clear drug-related findings. Thymus was small in size in one male at 0.4 mg/kg/day and two males at 0.6 mg/kg/day, both in the Decitabine for Injection groups. However, organ weight data indicated that females in both Decitabine for Injection and Dacogen groups had significantly decreased weight of thymus.

Organ Weight

Absolute and organ-to-terminal body weight ratios were significantly decreased for testis and epididymis in both Decitabine for Injection and Dacogen groups. Decreased testis weight corresponded with oligospermia and spermatozoa degeneration; decreased

epididymis weight corresponded with oligospermia in the high-dose groups. Decitabine effects in testis were previously reported for Dacogen and are included in the label.

Significantly decreased weight of thymus occurred in females given Decitabine for Injection or Dacogen.

Table 4 Fold Change in Organ Weight compared to Control Group at the end of the 2-Dosing Cycle

Parameter	Sex	Decitabine for Injection (mg/kg/day)			Dacogen (mg/kg/day)
		0.2	0.4	0.6	0.6
Epididymis	M	0.97	0.84↓	0.85↓	0.81↓
Testes	M	0.65↓	0.46↓	0.45↓	0.45↓
Thymus	M	1.27↑	0.88↓	0.97↓	1.02
	F	0.75↓	0.70↓	0.67↓	0.80↓

Values in **bold** were significantly different from control

Histopathology

Adequate Battery: YES

Peer Review: YES

Histological Findings

According to the summary of microscopic findings, the severity of findings were graded as minimal<mild<moderate<severe.

Table 5 Histopathological Findings in mice at the end of the 2-Dosing Cycle

Dose (mg/kg/day)	Males					Females				
	0 Diluent	0.2	0.4	0.6	0.6 Dacogen	0 Diluent	0.2	0.4	0.6	0.6 Dacogen
Number of Animals in Group	10	10	10	10	10	10	10	10	10	10
SPLEEN										
- Megakaryocytes	4a	--	--	5	6	2	--	--	2	2
- Brown pigments	0	--	--	--	1	--	--	--	--	1
LIVER										
- FLI	7a	--	--	0	4a	8a	--	--	2a	3a
- Vacuolation	10a	--	--	9a	7a	10a	--	--	3a	7a
- Pyknotic nuclei	10a	--	--	7a	4a	10a	--	--	10a	8a
- Necrosis	0	--	--	1a	0	0	--	--	0	0
ADRENALS										
- Vacuolation	4a, 1b	--	--	1a	3a	4a,5b,1c	--	--	7a,1b	2a,5b,1c
- Hemorrhage in medulla	0	--	--	1a	1a	0	--	--	0	0
- Extracortical nodules	0	--	--	0	0	0	--	--	1a	0
BRAIN (Cerebrum)										
- Vacuolation	1a	--	--	1a	1a	0	--	--	1a	1a
- Glial nodules	7a,1b	--	--	7a	7a,3b	9a	--	--	6a,1b	4a,3b
- Hemorrhage	1a	--	--	0	0	0	--	--	0	0
- Congestion	1a	--	--	0	0	0	--	--	0	0
KIDNEYS										

- Congestion, cortex	0	--	--	0	1a	1a	--	--	1a	0
- Mineralization in tubules, cortex	0	--	--	0	1a	0	--	--	0	0
- FLI, cortex	8a	--	--	6a	3a	3a	--	--	1a	4a,1b
- Cyst, cortex	0	--	--	0	0	0	--	--	0	1a
- Chronic nephritis, cortex	0	--	--	0	0	0	--	--	0	1a
- Cyst, medulla	0	--	--	1a	0	0	--	--	1a	0
- FLI, medulla	0	--	--	0	0	0	--	--	1a	0
- Congestion, medulla	0	--	--	0	4a	0	--	--	0	0
EPIDIDYMES										
-Oligospermia	10a	0	0	10a	7a	--	--	--	--	--
TESTES										
- Oligospermia	0	0	6a	8a,2b	8a,2b	--	--	--	--	--
- Degenerated spermatozoa	1a	0	6a	10a	8a	--	--	--	--	--
- Vacuolation in seminiferous tubules	0	0	0	0	2a	--	--	--	--	--
BONE (Femur)										
- Lipocytes	5a,2b	--	--	3a	2a,2b,1c	5a,2b,1c	--	--	5a,3b	2a,6b
STERNUM										
- Lipocytes	5a,2b	--	--	3a	2a,2b,1c	5a,2b,1c	--	--	5a,3b	2a,6b

--: tissue not evaluated; FLI: foci of lymphocytic infiltration

a: minimal; b: mild; c: moderate; d: severe

Microscopic findings in males administered Decitabine for Injection or Dacogen included:

- Minimal to mild oligospermia and degeneration of spermatozoa in the testis.
- Vacuolation of seminiferous tubules; present only in Dacogen-treated mice.
- Oligospermia in the epididymis in both Decitabine for Injection and Dacogen groups (also seen in the control).

Microscopic findings in kidneys including foci of lymphocytic infiltration, cyst and/or congestion in the medulla occurred in animals administered Decitabine for Injection or Dacogen.

Special Evaluation

None

Toxicokinetics

No conducted

Dosing Solution Analysis

Drug products were analyzed for quantitation of impurities on Day 1 of cycle 1 and Day 5 of cycle 2, Table 6, 12 Appendix/Attachments. Decitabine for Injection presented a slightly higher fold-increase in impurities than Dacogen at the end of the dosing period. The impurities at (b) (4) and (b) (4) as well as the total impurities were above the proposed specifications on Day 5 of cycle 2.

Table 6 Amount of Impurities present in Decitabine for Injection and Dacogen at the beginning and at the end of dosing

Impurity		C	RRT (b) (4)	RRT (b) (4)	Highest Unknown	Total Impurities	Decitabine %
Specification NMT (%)		0.25	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Decitabine for Injection Lot # (b) (4)	Day 1-Cycle 1	0.036	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Day 5-Cycle 2	0.066	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
	Fold Change	1.8	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Within specification
Dacogen Lot # 11K03RA	Day 1-Cycle 1	0.052	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Day 5-Cycle 2	0.062	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
	Fold Change	1.2	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Within specification

Values in bold represent values above the set specification level

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/s/

PEDRO L DEL VALLE
10/16/2013

HALEH SABER
10/16/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 205582

Applicant: Sun Pharma

Stamp Date: March 27, 2013

Drug Name: Decitabine for Injection

NDA Type: 505(b)(2)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		The Applicant is relying on the label of the Listed Drug (Dacogen) and published literature for pharmacology and toxicology information. The Applicant conducted an in vivo study to evaluate two impurities present in the drug product.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
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)?	√		
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).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	√		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	√		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA**

	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?	√		The Applicant will follow the label of the listed drug
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		A GLP study was conducted to qualify two impurities present above the threshold in the drug product.
11	Has the applicant addressed any abuse potential issues in the submission?			NA
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?		√	

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

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

NA

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

None

Pedro L. Del Valle, PhD
Reviewing Pharmacologist

May 16, 2013
Date

Haleh Saber, PhD
Team Leader/Supervisor

May 16, 2013
Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PEDRO L DEL VALLE
05/17/2013

HALEH SABER
05/17/2013