

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205582Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Memorandum

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<b>NDA</b>	205582 SDN 1
<b>Submission Date:</b>	27 Mar 2013
<b>Drug Name:</b>	Decitabine for Injection
<b>Sponsor:</b>	Sun Pharma
<b>OCP Reviewers:</b>	Young Jin Moon, Ph.D.
<b>OCP Team Leader:</b>	Julie M. Bullock, Pharm.D.

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This 505(b)(2) application relies on the FDA's finding of safety and effectiveness for the listed drug, Dacogen<sup>®</sup> (decitabine) for Injection marketed by Eisai Inc. under the approved NDA 21790. Decitabine, an analogue of the natural nucleoside 2'-deoxycytidine, is approved for treatment of patients with myelodysplastic syndrome (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, intermediate2, and high-risk International Prognostic Scoring System groups. There are two regimens for Dacogen administration.

- Option 1: Administer Dacogen at a dose of 15 mg/m<sup>2</sup> by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks.
- Option 2: Administer Dacogen at a dose of 20 mg/m<sup>2</sup> by continuous intravenous infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks.

The proposed indications and dosing regimens for the Sun Pharma decitabine for Injection (proposed product) are same as those of the currently approved reference product. Both the proposed and the reference products are lyophilized powders containing 50 mg of decitabine in a 20-mL glass vial. For the proposed product a separate vial of diluent is included in the packaging, which upon reconstitution, result in a solution that is identical in composition to the reference product. The two products differ in whether the (b)(4) monobasic potassium phosphate and sodium hydroxide) are included in the lyophilized powder or in the diluent. For Dacogen<sup>®</sup>, these are included in the lyophilized powder; 10 mL Water for Injection, USP used for reconstitution. For the proposed decitabine for Injection drug product, these are included in the diluent.

The ONDQA-Biopharmaceutics reviewer concluded (DARRTS Communication date: 5/16/13) that given the identical composition of the reconstituted proposed product and reference drug product solutions, having the same pH and osmolarity, and the fact that they are intended solely for intravenous administration with the same instructions for further dilution and use, the requested Biowaiver can be granted.

This submission contains no new clinical pharmacology information for review. NDA 205582 is recommended for approval from the standpoint of clinical pharmacology.

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/s/  
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YOUNG J MOON  
08/08/2013

JULIE M BULLOCK  
08/14/2013

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING AND FINAL REVIEW

<b>NDA Number</b>	205582
<b>Submission Date</b>	3/27/13
<b>Product name, generic name of the active</b>	Decitabine for Injection
<b>Dosage form and strength</b>	Lyophilized powder for Injection – 50 mg/vial
<b>Route of Administration</b>	IV infusion
<b>Applicant</b>	Sun Pharma Global FZE
<b>Clinical Division</b>	Division of Hematology Products
<b>Type of Submission</b>	Original NDA – 505(b)(2)
<b>Biopharmaceutics Reviewer</b>	Elsbeth Chikhale, Ph.D.
<b>Acting Biopharmaceutics Team Leader</b>	Sandra Suarez-Sharp, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?	x		A BA/BE waiver request is included in the submission.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?	x		Immediately after reconstitution (50 mg in 10 mL), the solution should be further diluted with 0.9% NaCl, 5% dextrose, or Lactated Ringer's Injection to a final concentration of 0.1 – 1.0 mg/mL.

**PRODUCT QUALITY - BIOPHARMACEUTICS  
FILING AND FINAL REVIEW**

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
9.	Is there any <i>in vivo</i> BA or BE information in the submission?		x	A BA/BE waiver request is included in the submission.
10.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
12.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

**SUMMARY:**

This 505(b)(2) application relies on the FDA's finding of safety and effectiveness for the listed drug, Dacogen® (decitabine) for Injection marketed by Eisai Inc. under the approved NDA 21790. Decitabine, an analogue of the natural nucleoside 2'-deoxycytidine, is approved for treatment of patients with myelodysplastic syndrome (MDS). Decitabine for Injection, like Dacogen®, is intended for administration by injection as an intravenous infusion over either 1 or 3 hours. The proposed indications and dosing instructions for the proposed decitabine for Injection are identical to those of the currently approved reference product.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING AND FINAL REVIEW

### BIOPHARMACEUTICS INITIAL ASSESSMENT

#### **BIOPHARMACEUTICS INFORMATION:**

Both the proposed and the reference products are lyophilized powders containing 50 mg of decitabine in a 20-mL glass vial. For the proposed product a separate vial of diluent is included in the packaging, which upon reconstitution, result in a solution that is identical in composition to the reference product. The two products differ in whether the (b) (4) (monobasic potassium phosphate and sodium hydroxide) are included in the lyophilized powder or in the diluent. For Dacogen®, these are included in the lyophilized powder; 10 mL Water for Injection, USP is used for reconstitution. For the proposed decitabine for Injection drug product, these are included in the diluent.

**Table 1: Comparative Presentations/Compositions: Dacogen® versus Sun's Product**

	<b>Dacogen® (decitabine for injection) RLD (NDA 021790)</b>	<b>Decitabine for Injection (Sun)</b>
<b>Lyophilized Drug Vial (20-mL Glass):</b>		
Decitabine	50 mg	50 mg
Monobasic potassium phosphate, NF	68 mg	--
Sodium hydroxide, NF	11.6 mg	--
<b>Diluent (for Sun product, 10-mL Glass Vial):</b>		
Water for injection, USP	Not supplied; 10 mL of Water for Injection, USP	10 mL
Monobasic potassium phosphate, NF		68 mg
Sodium hydroxide, NF		11.6 mg
<b>Drug + Diluent (Initial Reconstitution<sup>1</sup>):</b>		
Decitabine	50 mg	50 mg
Monobasic potassium phosphate, NF	68 mg	68 mg
Sodium hydroxide, NF	11.6 mg	11.6 mg
Sterile Water for Injection	10 mL	10 mL

<sup>1</sup> After initial reconstitution, both Decitabine for Injection and Dacogen® preparations are to be further diluted in intravenous solutions before administration to a patient.

The Applicant is submitting a request for a Biowaiver of the need to perform an *in vivo* bioequivalence study on the basis of the similarity of its proposed product and the reference product. Specifically, based on 21 CFR 320.22(b)(1) such a waiver can be granted if the drug product:

"i) Is a parenteral solution intended solely for administration by injection or an ophthalmic or otic solution, and

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING AND FINAL REVIEW

ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.”

### **CONCLUSION:**

The proposed decitabine for injection product, when reconstituted, contains the same active and inactive ingredients in the same concentrations as the reconstituted reference product, Dacogen®. Given the identical composition of the reconstituted proposed product and reference drug product solutions, having the same pH and osmolarity, and the fact that they are intended solely for intravenous administration with the same instructions for further dilution and use, the requested Biowaiver can be granted.

### **RECOMMENDATION FOR FILING AND FINAL RECOMMENDATION:**

From the ONDQA-Biopharmaceutics perspective, NDA 205582 is fileable and the Biowaiver can be granted. There are no other pending Biopharmaceutics issues. Therefore, from the Biopharmaceutics perspective, NDA 205582 for Decitabine for Injection (50 mg/vial) is recommended for **APPROVAL**.

*{See appended electronic signature page}*

*5/16/13*

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

*5/16/13*

Sandra Suarez-Sharp, Ph.D.

Acting Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

Date

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/s/  
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ELSBETH G CHIKHALE  
05/16/2013

SANDRA SUAREZ  
05/16/2013