

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205582Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Edvardas Kaminskas, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA #</b>	205582 submitted under 505(b)(2)
<b>Supplement #</b>	(b) (4)
<b>Applicant Name</b>	Sun Pharma Global FZE
<b>Date of Submission</b>	March 25, 2013
<b>PDUFA Goal Date</b>	January 27, 2014
<b>Proprietary Name / Established (USAN) Name</b>	Decitabine for Injection Decitabine
<b>Dosage Forms / Strength</b>	50 mg of decitabine (lyophilized powder) in a 20mL glass vial
<b>Proposed Indications</b>	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.
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Thomas M. Herndon, M.D./Albert Deisseroth, M.D., Ph.D.
Pharmacology Toxicology Review	Pedro L. Del Valle, Ph.D./Haleh Saber, Ph.D./John Leighton, Ph.D., DABT
ONDQA	William M. Adams, Ph.D./Ali al Hakim, Ph.D.
ONDQA Biopharmaceutics REview	Elsbeth Chikhale, Ph.D./Sandra Suarez-Sharp, Ph.D.
Microbiology Review	Neal J. Sweeney, Ph.D./Brian S. Riley, Ph.D.
Clinical Pharmacology Review	Young Jin Moon, Ph.D./Julie M. Bullock, Ph.D.
OPDP	Nisha Patel
CDTL Review	Albert Deisseroth, M.D., Ph.D.
OND/IO Regulatory Affairs Team	Mary Ann Holovac, R.Ph.

OND=Office of New Drugs  
 ONDQA=Office of New Drug Quality Assessment  
 OPDP=Office of Prescription Drug Promotion  
 CDTL=Cross-Discipline Team Leader

## Signatory Authority Review Template

### 1. Introduction

This is a 505(b)(2) application by Sun Pharmaceuticals Global FZE based on the Eisai's NDA 21790 for Dacogen®, Decitabine for Injection, 50 mg/vial. Sun Pharmaceuticals' Decitabine for Injection is a new formulation that differs from that of Dacogen.

“Dacogen is a sterile, lyophilized powder containing Decitabine and the ingredients of (b) (4) phosphate (b) (4) in a single-use glass vial which is to be reconstituted with sterile Water for Injection, USP to a concentration of 5 mg/mL Decitabine, then admixed with 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP; 5% Dextrose Injection, USP; or Lactated Ringer's Injection, USP to a concentration of 0.1-1.0 mg/mL for intravenous infusion.”

The proposed product is in two parts. The Drug Product is a lyophilized drug substance in a single-use glass vial. The Diluent is an aqueous (b) (4) solution in a single-use glass vial. The vials are presented together in a combi-pack cardboard carton with appropriate labels and labeling. The Drug Product is to be reconstituted with Diluent to obtain a 5 mg/mL solution of Decitabine which is then to be admixed for intravenous infusion as described for Dacogen above. Reconstituted solutions of the proposed product and Dacogen are shown to be qualitatively and quantitatively the same.” (Description as in CMC Review).

### 2. Background

There are three broad categories of available treatments for patients with myelodysplastic syndromes (MDS). These are supportive care, including transfusions, erythropoiesis-stimulating agents, and granulocyte colony-stimulating agents, chemotherapy (DNA demethylating agents azacitidine and decitabine, and immunomodulating agent lenalidomide), and stem cell transplant.

The applicant submitted this NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and as such relies on publically available information. Three sources of safety information were presented in the application: the approved label for Dacogen, published reports, and adverse events reported to the FDA post approval of Dacogen.

A pre-NDA meeting with the FDA was held on February 6, 2012. CMC, nonclinical and clinical issues were addressed at the meeting. During the meeting the FDA and the applicant agreed that no clinical studies of Decitabine for Injection were needed if a biowaiver was granted. A Biowaiver Request is included in this submission. The approved label for Dacogen

together with publications describing new safety information were to serve as the basis for Integrated Summary of Safety, and a summary of clinical efficacy was not needed for this submission.

### 3. CMC/Device

From CMC Review:

“Complete CMC on Drug Substance is provided in Sun Pharmaceutical Industries Ltd.’s type II DMF 26256. The application includes synopses of key CMC information on drug substance and on Drug Product and Diluent. The applicant’s claim for a categorical exclusion from the environmental assessment requirement for Drug Product and Diluent is acceptable. Acceptable labels and labeling are provided for Drug Product and Diluent.”

“A product development report addresses formulation, manufacturing operations, process parameters (including solution hold times), in-process controls, packaging components, container/closure integrity, and stability of the reconstituted solution and admixture solutions. Decitabine in solution is shown to be very sensitive to heat, light, acid hydrolysis, base hydrolysis, and oxidation.”

“The proposed release specification is adequate in that it addresses identity; assay, organic and inorganic impurities; (b) (4) water content; weight variation; and USP <1> requirements. Reference standards for specific organic impurities are addressed in DMF 26256. The Proposed acceptance criteria are justified by process capability; ICH Q3C safety limits; USP expectations; and safety studies on specified organic impurities. Batch analysis data from 3 exhibit batches is provided. Each batch meets the proposed specification...Data from primary studies and a forced degradation study using the 3 exhibit batches (b) (4) of 24 months with storage at USP controlled temperature in the proposed packaging system and combi-pack.”

From CMC Review:

#### **Description of How the Drug Product is Intended to be Used**

Decitabine for Injection is a cytotoxic drug which is intended to be reconstituted with Decitabine for Injection Diluent to a concentration of 5 mg/mL, then immediately admixed with 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; or Lactated Ringer’s Injection, USP to a concentration of 0.1-1.0%. This solution is to be administered by intravenous infusion. The admixture solution may be stored at room temperature for up to 15 minutes or at 2-8°C for up to 7 hours before administration.

#### **Basis for Approvability or Not-Approval Recommendation**

CMC information on Drug Substance provided in type II DMF 25256; and on Drug Product and Diluent provided in this application is complete and described in sufficient detail. All deficiencies have been addressed, and acceptable labels and labeling are provided.

*I concur with the conclusions reached by the CMC reviewer that there are no outstanding CMC issues that preclude approval.*

From ONDQA Product Quality Review:

**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**.

*I concur with the conclusions reached by the ONDQA Biopharmaceutics reviewer that there are no outstanding Product Quality- Biopharmaceutics issues that preclude approval.*

## 4. Nonclinical Pharmacology/Toxicology

From Pharmacology/Toxicology Review:

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.

*I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.*

## 5. Clinical Pharmacology/Biopharmaceutics

From Clinical Pharmacology/Biopharmaceutics Review:

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.

*I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.*

## 6. Clinical Microbiology

From Product Quality Microbiology Review:

“The drug product is (b) (4)  
Based upon information provided, no microbiology deficiencies were identified...Recommended for Approval.”

*I concur with the conclusions reached by the product quality microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.*

## 7. Clinical/Statistical-Efficacy

No new efficacy data was submitted with this application.

## 8. Safety

From Clinical Review:

The Safety Summary, which showed that decitabine is without significant new risks when administered to patients with MDS, included

- A review of the most recent Dacogen label (March 2010) which included information on one randomized trial and three single-arm studies and two schedules of drug administration,
- An updated review of the world literature since the most recent Dacogen label, which revealed no new safety signal, and

- A review of the AERS data from 2010 through August, 2012, which comprised 290 reports that identified Dacogen as suspect drug.

On the basis of the above data the Clinical Team recommends approval of this application.

*I concur with the conclusions reached by the Clinical reviewer that there are no outstanding safety issues that preclude approval.*

## **9. Advisory Committee Meeting**

This application was not presented to an Advisory Committee.

## **10. Pediatrics**

No pediatric information was included in this supplement.

## **11. Other Relevant Regulatory Issues**

This application was discussed by OND/IO Regulatory Affairs Team, and was cleared for action from a 505(b)(2) perspective.

OPDP reviewed the draft Package Insert and had no comments on the proposed PI.

*There are no other unresolved relevant regulatory issues.*

## **12. Labeling**

Changes in 2 Dosage and Administration, 11 Description, and 16 How Supplied/Storage and Handling are made to the new presentation of Decitabine for Injection.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

I recommend approval of NDA 205582 Decitabine for Injection, submitted by Sun Pharma Global FZE.

- Risk Benefit Assessment

The Risk Benefit assessment of Decitabine for Injection is the same as that of the approved innovator DACOGEN.

- Recommendation for Postmarketing Risk Management Activities

There are no Postmarketing Risk Management Activities for this application.

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- Recommendation for other Postmarketing Study Commitments

There are no other Postmarketing Study Commitments for this application.

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/s/  
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EDVARDAS KAMINSKAS

01/22/2014