CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205582Orig1s000

MEDICAL REVIEW(S)

Secondary (Team Leader) Review

Date	December 30, 2013
From	Albert Deisseroth, MD, PhD
Subject	Secondary Review
NDA Number	NDA 205582
Applicant	Sun Pharma Global FZE
Date of Submission	March 25, 2013
PDUFA Goal Date	January 27, 2014
Established Name	Decitabine for Injection
Dosage forms/Strength	Lyophilized powder containing 50 mg of decitabine in a 20 mL glass vial
Applicant's Proposed Indication	Treatment of patients with myelodysplastic syndromes (MDS)
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Thomas Herndon, MD
Pharmacology/Toxicology	Pedro L. Del Valle, PhD
CMC	William M. Adams, PhD
Regulatory Program Manager	Lara Akinsanya

TABLE OF CONTENTS

1. INTRODUCTION (This section was excerpted in part from the review of Dr. Tom Herndon):

On December March 25, 2013, Sun Pharmaceuticals Global FZE submitted a NDA under the 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.

The proposed indication is the same as that for Dacogen: Treatment of patients with myelodysplastic syndrome (MDS).

Decitabine for Injection is a new formulation that differs from that of Dacogen. The drug product is the same (lyophilized powder containing 50 mg of decitabine in a 20 mL glass vial). However, in contrast to Dacogen, in which the drug product contains monobasic potassium phosphate and sodium hydroxide (b) (4) in the glass vial which contains the drug product, Decitabine for Injection provides the drug product without the monobasic potassium phosphate and sodium hydroxide, which is provided in a separate diluent vial containing 10 mL of Water for Injection. Dacogen is reconstituted in 10 mL of USP water, while Decitabine for Injection is reconstituted in the diluent containing potassium phosphate and sodium hydroxide. Once reconstituted, both Dacogen and Decitabine for Injection result in a solution of the same composition.

Benefit Risk Discussion (This section is excerpted in part from the clinical review of Dr. Tom Herndon):

Efficacy: There are no new efficacy data provided with the application.

CMC: There were two impurities found in Decitabine for Injection: (b) (4) Sun proposed limits of (b) (4) as release criteria respectively for these two impurities.

Non-Clinical: The applicant performed a GLP repeat-dose toxicity study in CD-1 mice to compare the toxicity profile of Decitabine for Injection with that of Dacogen. These studies showed that the adverse event profiles of Decitibine for Injection and Dacogen were identical.

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

a. A review of the most recent label (March 2010) which included information on one randomized trial and three open-label single arm studies; two schedules of administration were reviewed: the first regimen which consisted of 15 mg/m^2 infused over 3 hours every 8 hours for 3 days for one cycle, repeated every 6 weeks, and a second regimen consisting of 20 mg/m^2 infused over a 1 hour period on Days 1-5 of Week 1 every 4 weeks (one cycle);

b. An updated review of the worldwide literature since the most recent version of the Dacogen label (March 2010) which revealed no new safety signal;
c. A review of the AERS data from 2010 through August 2012 which detected no new safety signal.

Recommendation for Regulatory Action: On the basis of the above, this reviewer recommends approval.

2. BACKGROUND

2.a. Regulatory History (This section was excerpted from the review of Dr. Tom Herndon):

A pre-NDA Meeting was held on February 6, 2012. At the meeting, the Division of Hematology Products (DHP) expressed concern regarding the presence of levels of an impurity in the drug product, designated by its relative retention time, (b) (4), which exceeded ICH qualification standard limits. The impurity was identified as (b) (4). The applicant proposed one single specification for this impurity, (b) (4). Since the meeting, the applicant identified another impurity, (b) (4), in the drug product that also exceeds ICH qualification thresholds. The impurity was identified as (b) (4) The applicant proposed a limit of (b) (4) for the release and stability specifications.

The applicant performed a good laboratory practice (GLP) repeat-dose toxicity study in CD-1 mice to compare the toxicity profile of Decitabine for Injection with that of Dacogen to qualify the two impurities, (b) (4) and (b) (4). The results showed that, when dosed at 0.6 mg/kg/day, the toxicity profiles of both products were comparable.

During the pre-NDA meeting, the applicant and FDA agreed that no clinical studies of Decitabine for Injection were needed to be conducted if a biowaiver was granted. The applicant is requesting a waiver of the need to conduct in vivo bioequivalence studies, as outlined in 21 CFR 320.22(b)(1). A Biowaiver Request is included in this submission in Module 1.

The approved label for Dacogen (March 2010), together with publications describing new safety information identified in search of the literature since the most recent revision, serves as the basis for the Integrated Summary of Safety in this NDA. The applicant and FDA agreed that a summary of clinical efficacy is not needed for this submission.

2.b. MDS (This section was excerpted from the review of Dr. Tom Herndon):

There are three broad categories of available treatments for patients with MDS. These are supportive care, chemotherapy, and stem cell transplant. Commonly used supportive care treatments for patients with MDS include transfusions to treat anemia and thrombocytopenia, the use of erythropoiesis-stimulating agents (ESAs) such as epoetin alfa (Epogen®, Procrit®) and

darbepoetin alfa (Aranesp®) and granulocyte colony-stimulating factors such as filgrastim. Antibiotics may be given for infection(s).

The commonly used chemotherapy agents for the treatment of patients with MDS are azacitidine, decitabine, and lenalidomide. Both azacitidine and decitabine are approved by the FDA to treat all types of MDS, although they are used most often for patients with higher IPSS scores. Lenalidomide is approved for patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. These three agents are summarized in Table 1.

Table 1: Commonly used chemotherapy agents for the treatment of patients with MDS

Drug	Class	Approval Date
Azacitidine (Vidaza)	Nucleoside analog	19 MAY 2004
Decitabine (Dacogen)	Nucleoside analog	02 MAY 2006
Lenalidomide (Revlimid)	IMiD*	27 DEC 2005

*Immunomodulatory drug (IMiD)

Some patients with MDS receive immunosuppressive therapy with anti-thymocyte globulin (ATG) which may decrease the need for red blood cell transfusions.

Patients with high-risk subtypes of MDS with an increased risk of developing acute myelogenous leukemia (AML) may receive chemotherapy used to treat AML, such as cytarabine, idarubicin or daunorubicin.

High-dose chemotherapy with stem cell transplantation (please clarify and specify allograft (myeloablative), allograft (reduced intensity) and auto is the only current treatment that can produce a long-term remission. However, transplantation may not be suitable for many patients with MDS.

3. CMC: Please see above Benefit-Risk discussion and CMC Review of Dr. William Adams for details. Dr. Adams recommended approval.

4.NON-CLINICAL: Please see above Benefit-Risk discussion and the Pharmcology/Toxicology Review of Dr. Pedro L. Del Valle for details. Dr. Del Valle recommended approval.

5. EFFICACY: No new efficacy data was submitted with the application.

6. SAFETY (This section is excerpted from the review of Dr. Tom Herndon): A search of the published literature was conducted on January 16, 2013. A summary of the AERS Database covering 2006 to 2012. No new safety information was found that should be added to the label. Dr. Herndon recommends approval.

7. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

8. OTHER RELEVANT REGULATORY ISSUES: None

9. LABELING: The labeling is currently under negotiation.

10. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT: This reviewer recommends approval.

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

/s/

ALBERT B DEISSEROTH
12/30/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205582
Priority or Standard	Standard
Submit Date(s)	25 MAR 2013
Received Date(s)	27 MAR 2013
PDUFA Goal Date	26 JAN 2014
Division / Office	DHP / OHOP
Reviewer Name(s)	Thomas M. Herndon
Review Completion Date	11 OCT 2013
Established Name	Decitabine for Injection
(Proposed) Trade Name	
Therapeutic Class	Nucleoside analog
Applicant	Sun Pharma Global FZE
Formulation(s)	Lyophilized powder containing 50 mg of decitabine in a 20 ml glass vial
Dosing Regimen	There are two regimens for administration. With either regimen it is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. <u>Treatment Regimen – Option 1</u> Administer at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks. <u>Treatment Regimen – Option 2</u> Administer at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks.
Indication(s)	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.
Intended Population(s)	Patients with 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.

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

Error! No table of figures entries found.

Abbreviation	Definition
AERS	Adverse Event Reporting System
AML	acute myelogenous leukemia
ATG	antithymocyte globulin
ESA	erythropoiesis-stimulating agents
FAB	French-American-British
IMiD	immunomodulatory drug
IPSS	International Prognostic Scoring System
MDS	myelodysplastic syndrome

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action from Clinical is approval.

1.2 Risk Benefit Assessment

The benefit and risk of Decitabine for Injection is expected to be the same as the approved product, Dacogen®.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of evidence**: MDS is a serious condition for which the innovator product, Dacogen, has been shown to have a favorable risk benefit.	**Conclusions (implications for decision):** The candidate drug product, which is identical to Dacogen is expected to beneficial to patients with MDS.
Unmet Medical Need	**Summary of evidence**: There is no unmet medical need.	**Conclusions (implications for decision):** None
Clinical Benefit	**Summary of evidence**: There is no new efficacy data in this submission.	**Conclusions (implications for decision):** None
Risk	**Summary of evidence**: The safety data contained in this submission does not change the safety profile of Dacogen.	**Conclusions (implications for decision):** The candidate drug and Dacogen are expected to have the same risk profile.
Risk Management	**Summary of evidence**: Benefit risk is favorable for this drug for which the drug product is identical to the approved product, Dacogen after reconsituton.	**Conclusions (implications for decision):** Approval recommended.
Benefit-Risk Summary and Assessment The benefit and risk of Decitabine for Injection is expected to be the same as the approved product, Dacogen.		

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

Decitabine for Injection is a new formulation and presentation of the approved product, Dacogen®. The proposed indications and dosing instructions for Decitabine for Injection are identical to those of the currently approved product.

Decitabine drug substance is manufactured by Sun Pharmaceutical Industries Limited, Ahmednagar. The drug product is a lyophilized powder containing 50 mg of decitabine in a 20 mL glass vial, the same presentation as Dacogen. Decitabine for Injection comes with a diluent that contains monobasic potassium phosphate and sodium hydroxide, while Dacogen contains monobasic potassium phosphate and sodium hydroxide (b) (4) in the vial containing the drug product. Upon reconstitution with 10 ml Water for Injection, USP (in the case of Dacogen) or the diluent (in the case of Decitabine for Injection) both result in a solution of the same composition.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are three broad categories of available treatments for patients with MDS. These are supportive care, chemotherapy, and stem cell transplant. Commonly used supportive care treatments for patients with MDS include transfusions to treat anemia and thrombocytopenia, the use of erythropoiesis-stimulating agents (ESAs) such as epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®) and granulocyte colony-stimulating factors such as filgrastim. Antibiotics may be given for infection(s).

The commonly used chemotherapy agents for the treatment of patients with MDS are azacitidine, decitabine, and lenalidomide. Both azacitidine and decitabine are approved by the FDA to treat all types of MDS, although they are used most often for patients with higher IPSS scores. Lenalidomide is approved for patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. These three agents are summarized in Table 1.

Table 1: Commonly used chemotherapy agents for the treatment of patients with MDS

Drug	Class	Approval Date
Azacitidine (Vidaza)	Nucleoside analog	19 MAY 2004
Decitabine (Dacogen)	Nucleoside analog	02 MAY 2006

Drug	Class	Approval Date
Lenalidomide (Revlimid)	IMiD*	27 DEC 2005

*Immunomodulatory drug (IMiD)

Some patients with MDS receive immunosuppressive therapy with anti-thymocyte globulin (ATG) which may decrease the need for red blood cell transfusions.

Patients with high-risk subtypes of MDS with an increased risk of developing acute myelogenous leukemia (AML) may receive chemotherapy used to treat AML, such as cytarabine, idarubicin or daunorubicin.

High-dose chemotherapy with stem cell transplantation by allograft (myeloablative or reduced intensity) is the only current treatment that can produce a long-term remission. However, transplantation may not be suitable for many patients with MDS.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, decitabine, has been marketed in the United States as Dacogen since May 2006 and administered at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days which is repeated every 6 weeks (Option 1). In March 2010, a second treatment regimen (20 mg/m^2 by continuous IV infusion over 1 hour repeated daily for 5 days every 4 weeks) was approved and included in the prescribing information (Option 2).

According to the current prescribing information for Dacogen, the most commonly occurring adverse reactions associated with decitabine are neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia. The most common adverse reactions leading to discontinuation are thrombocytopenia, neutropenia, pneumonia, *Mycobacterium avium* complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, and abnormal liver function tests. The most common adverse reactions leading to dose delays are neutropenia, pulmonary edema, atrial fibrillation, central line infection, and febrile neutropenia. The most common adverse reactions leading to dose reduction are neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, and pharyngitis.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety profile of the related drug, Vidaza® (azacitidine), is similar to Dacogen. According to the current prescribing information for azacitidine, the most common adverse reactions to azacitidine were thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. Most common adverse reactions of azacitidine when administered by the IV route also included petechiae, rigors, weakness and hypokalemia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA Meeting was held on 6 FEB 2012. At the meeting, the Division of Hematology Products (DHP) expressed concern regarding the presence of levels of an impurity in the drug product, designated by its relative retention time, (b) (4), which exceeded ICH qualification standard limits. The impurity was identified as (b) (4). The applicant proposed one single specification for this impurity, (b) (4). Since the meeting, the applicant identified another impurity, (b) (4), in the drug product that also exceeds ICH qualification thresholds. The impurity was identified as (b) (4). The applicant proposed a limit of (b) (4) for the release and stability specifications.

The applicant performed a good laboratory practice (GLP) repeat-dose toxicity study in CD-1 mice to compare the toxicity profile of Decitabine for Injection with that of Dacogen to qualify the two impurities, (b) (4) and (b) (4). The results showed that, when dosed at 0.6 mg/kg/day, the toxicity profiles of both products were comparable.

During the pre-NDA meeting, the applicant and FDA agreed that no clinical studies of Decitabine for Injection were needed to be conducted if a biowaiver was granted. The applicant is requesting a waiver of the need to conduct in vivo bioequivalence studies, as outlined in 21 CFR 320.22(b)(1). A Biowaiver Request is included in this submission in Module 1.

The approved label for Dacogen (March 2010), together with publications describing new safety information identified in search of the literature since the most recent revision, serves as the basis for the Integrated Summary of Safety in this NDA. The applicant and FDA agreed that a summary of clinical efficacy is not needed for this submission.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and it was easy to find the necessary information. The clinical portion of the submission was complete and no additional requests for data from the applicant were required.

3.2 Compliance with Good Clinical Practices

Not applicable. No clinical studies submitted.

3.3 Financial Disclosures

Not applicable. No clinical studies submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See CMC review

4.2 Clinical Microbiology

See Clinical Microbiology review

4.3 Preclinical Pharmacology/Toxicology

See Non-clinical review

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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. See Clinical Pharmacology review for details.

4.4.2 Pharmacodynamics

See Clinical Pharmacology review

4.4.3 Pharmacokinetics

See Clinical Pharmacology review

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This section is not applicable. No clinical studies submitted.

5.2 Review Strategy

The application is submitted under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and, as such, reliance is primarily on publicly available information. There is no new efficacy data submitted as part of this application as the application relies on the efficacy data for Dacogen.

There are three sources of publically available information addressing the safety of decitabine. These are the approved labeling for Dacogen, published reports, and adverse events reported to the FDA during post-marketing of Dacogen. These are included in an Integrated Summary of Safety which will be the focus of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable. No clinical studies submitted.

6 Review of Efficacy

Efficacy Summary

This section is not applicable.

6.1 Indication

This section is not applicable.

6.1.1 Methods

This section is not applicable.

6.1.2 Demographics

This section is not applicable.

6.1.3 Subject Disposition

This section is not applicable.

6.1.4 Analysis of Primary Endpoint(s)

This section is not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

This section is not applicable.

6.1.6 Other Endpoints

This section is not applicable.

6.1.7 Subpopulations

This section is not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section is not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This section is not applicable.

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable.

7 Review of Safety

Safety Summary

The Applicant submitted labeled safety information for Dacogen updated by a review of the worldwide literature published since the most recent version of the Dacogen label (most recently revised March 2010). The intent of the literature review and review of other publically available information was to identify any new safety information that warrants addition to the labeling. The literature search performed to identify any new safety information that warrants addition to the labeling also identified two recent publications that report safety with use of decitabine in patients with renal insufficiency and hemodialysis, respectively.

The literature search, including the search performed as part of the 120-day safety update, conducted to supplement the labeled information, did not identify any new

information relevant to potential drug interactions with decitabine. The literature search did not identify additional information about overdose or abuse.

No safety signal was apparent in the adverse event terms from Adverse Event Reporting System (AERS) data from 2010 through August 2012, comprising 290 reports that identify decitabine as a suspect drug.

Based on this review, decitabine is found to be without significant new risks when administered to patients with MDS at the approved dosages.

7.1 Methods

The Applicant submitted labeled safety information for Dacogen, which was updated by a review of the worldwide literature published since the most recent version of the Dacogen label (most recently revised March 2010) (see Section 8). The intent of the literature review and review of other publically available information was to identify any new safety information that warrants addition to the labeling.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The most recent version of the Dacogen labeling is March 2010. This label indicates that decitabine has been studied in four clinical trials in patients with MDS: a single randomized, open-label study comparing decitabine with supportive care to supportive care alone and three open-label, single-arm studies.

The randomized, open-label study was a Phase 3 open-label, multicenter study in the United States, part of the original NDA submission, which evaluated decitabine for treatment of adults with MDS meeting French-American-British (FAB) classification criteria and International Prognostic Scoring System (IPSS) High-Risk, Intermediate-2 and Intermediate-1 prognostic scores. Patients were randomized on a 1:1 basis to receive decitabine plus supportive care or supportive care alone. Decitabine was administered intravenously at a dose of 15 mg/m^2 infused over a 3-hour period every 8 hours for 3 days—this constituted one cycle, which was repeated every 6 weeks depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. The World Health Organization criteria were used to grade the intensity of adverse events.

Three open-label, single-arm, multicenter studies were conducted to evaluate the safety and efficacy of decitabine in MDS patients with any of the FAB subtypes. As described in the Summary Basis of Approval, two of these trials were European studies included in the original NDA. The dose of decitabine was the same as for the Phase 3 study (Option 1), except that it was administered over 4 hours instead of 3 hours. The National Cancer Institute Common Toxicity Criteria were used to grade the severity of

adverse events. These trials were supportive of the safety and efficacy of Option 1 dosing.

The third single-arm study was subsequently submitted to the NDA in support of an alternative, convenient dosing schedule that allows for shorter infusion time and once daily dosing (Option 2). This study was conducted in North America in patients with IPSS Intermediate-1, Intermediate-2, or high risk prognostic scores. Decitabine was administered intravenously at a dose of 20 mg/m^2 infused over a 1-hour period on Days 1-5 of Week 1 every 4 weeks (one cycle). This treatment regimen was not repeated (patients received only one cycle). Ninety-nine patients received decitabine at this dosage.

7.1.2 Categorization of Adverse Events

The category of adverse events is included in the current Decitabine label.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2.2 Explorations for Dose Response

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2.3 Special Animal and/or In Vitro Testing

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2.4 Routine Clinical Testing

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.3 Major Safety Results

7.3.1 Deaths

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.3.2 Nonfatal Serious Adverse Events

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.3.3 Dropouts and/or Discontinuations

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.3.4 Significant Adverse Events

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.3.5 Submission Specific Primary Safety Concerns

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4.2 Laboratory Findings

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4.3 Vital Signs

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4.4 Electrocardiograms (ECGs)

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4.5 Special Safety Studies/Clinical Trials

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.4.6 Immunogenicity

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.5.2 Time Dependency for Adverse Events

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.5.3 Drug-Demographic Interactions

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.5.4 Drug-Disease Interactions

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.5.5 Drug-Drug Interactions

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.6.2 Human Reproduction and Pregnancy Data

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This section is not applicable as there is no new clinical trial data submitted in this NDA.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

A search of the published literature was conducted on 16 January 2013 to identify safety information for Dacogen published since March 2010 (the most recent revision date of the Dacogen package insert). Four publications providing new safety information are included in the Integrated Summary of Safety. Two publications pertain to case reports of unlabeled adverse events of acute lung injury and neutrophilic eccrine hidradenitis, respectively. The two remaining articles report safety with use of Dacogen in patients with renal insufficiency.

The literature search conducted for the 120-day Safety Update identified one case report of chronic myelomonocytic leukemia with normal cytogenetics at diagnosis treated with Dacogen in which the patient evolved to acute myeloid leukemia with i(17q) shortly after suspending treatment.

A summary of the marketing experience with decitabine was obtained from the FDA's Adverse Event Reporting System (AERS Database), covering data from marketing (2006) through 27 August 2012, the extent of information publicly available as of 25 January 2013 (the date the AERS data was requested). The data were obtained from FOI Services, Inc., who purchases the databases supplied by the government. Overall, there are an estimated 1307 MedWatch reports in AERS that identify Dacogen as a primary or secondary suspect drug (the total number of individual safety reports may include duplicate reports; this tally excludes cases with no outcome). These data were then further sorted for those with an event date of 1 January 2010 or later, resulting in 290 reports. The results are shown in Table 2.

Table 2: Adverse events from post-maketing data

MedDRA Preferred Term	Number of Reports
Febrile neutropenia	86
Pyrexia	42
Anemia	30
Neutropenia	29
White blood cell count decreased	28
Dyspnea	27
Fatigue	26

MedDRA Preferred Term	Number of Reports
Asthenia	23
Platelet count decreased	23
Fall	22
Pneumonia	21
Dizziness	20
Hemoglobin decreased	20
Thrombocytopenia	20
Diarrhea	17
Infection	17
Neutrophil count decreased	17
Sepsis	16
Chills	14
Cough	14
Hypotension	14
Loss of consciousness	14
Edema peripheral	14
Lung infection	13
Abdominal pain	12
Confusional state	12
Hypoxia	12
Respiratory failure	12
Myelodysplastic syndrome	11
Pleural effusion	11
Vomiting	11
Cellulitis	10
Decreased appetite	10
Fluid overload	10
General physical health deterioration	10
Pain	10
Staphylococcal infection	10

Reviewer's Comment: The literature search performed to identify any new safety information that warrants addition to the labeling found two recent case reports of acute fibrinous and organizing pneumonia and neutrophilic eccrine hidradentitis, respectively, temporally related to use of Dacogen that resolved with discontinuation of Dacogen and corticosteroid treatment. Neutrophilic eccrine hidradentitis reoccurred with a subsequent decitabine exposure. The clinical significance of this report, given the various possible etiologies of acute fibrinous and organizing pneumonia, is unclear. Neutrophilic eccrine hidradenitis is not labeled; related skin disorders listed in the label include rash and skin lesions during clinical studies and Sweet's Syndrome (acute febrile neutrophilic dermatosis) in postmarketing experience. There is no direct MedDRA preferred term for this disorder. The clinical significance of this published report is unclear.

The literature search conducted in support of the 120-Day Safety Update identified one case report of chronic myelomonocytic leukemia with normal cytogenics at diagnosis treated with Dacogen that evolved to acute myeloid leukemia with isochromosome 17q shortly after suspending treatment. The clinical significance of this published report is unclear.

No safety signal was apparent in the adverse event terms from AERS data from 2010 through August 2012, comprising 290 reports that identify Dacogen as a suspect drug.

9 Appendices

None

9.1 Literature Review/References

Batty GN, Kantarjian H, Issa JP, et al. Feasibility of therapy with hypomethylating agents in patients with renal insufficiency. Clin Lymphoma, Myeloma Leuk 2010; 10:205-210.

Dacogen® Prescribing Information, Revised March 2010.

Kourelis TV, Moustakakis MN, Silk R, Boruchov A, Bilgrami SF. Decitabine for acute myeloid leukemia in a patient undergoing hemodialysis. Eur. J. Inflamm 2011;9:289-292.

Marwaha M and Bahrain H. Decitabine-induced acute lung injury. Commun Oncol 2012; 9:106-107.

Ng ES, Aw DC, Tan KB, et al. Neutrophilic eccrine hidradenitis associated with decitabine. Leuk Res 2010; 34(5): 130-132.

Sousa JC, Germano RT, Castro CCM, et al. Case report of isochromosome 17q in acute myeloid leukemia with myelodysplasia-related changes after treatment with a hypomethylating agent. Genet Mol Res 2012;11: 2045-2050.

9.2 Labeling Recommendations

No new labeling recommendations from Clinical

9.3 Advisory Committee Meeting

None

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

/s/

THOMAS M HERNDON
10/17/2013

ALBERT B DEISSEROTH
10/17/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205882 **Applicant:** Sun Pharma **Stamp Date:** 27-MAR-2013

Drug Name: Decitabine for Injection **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	505(b)(2)
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		No formal analysis, but references to Dacogen
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Dacogen
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	NDA relies on and references efficacy data for Dacogen

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	NDA relies on and references efficacy data for Dacogen
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		The ISS does not have bookmarks and is difficult to navigate.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	NDA relies on and references safety data for Dacogen
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_X_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

The application is fileable from the clinical perspective.

There are no filing issues to be conveyed.

Clinical requests that the Applicant provide an ISS document with Bookmarks for ease of review.

Thomas M. Hendar — 2013 May 22

Reviewing Medical Officer — Date

[signature] — 2013 May 22

Clinical Team Leader — Date

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

/s/

THOMAS M HERNDON
05/22/2013

ALBERT B DEISSEROTH
05/22/2013