CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-790

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-790

MGI PHARMA, INC.
5775 West Old Shakopee Road, #100
Bloomington, MN 55437

Attention: Timothy K. Ressler, MS, MT, (ASCP)
Vice President Regulatory Affairs

Dear Mr. Ressler:

Please refer to your new drug application (NDA) dated November 14, 2005, received November 15, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dacogen™ (decitabine) for Injection 50 mg/vial.

We acknowledge receipt of your submissions dated November 18, 2005, February 21, 2006; and March 20, March 23, and March 31, 2006; and April 11,2006. The November 14, 2005 submission constituted a complete response to our August 31, 2005 action letter.

This new drug application provides for the use of Dacogen™ (decitabine) for Injection 50 mg/vial for myelodysplastic syndrome (MDS).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and the immediate container and carton labels (submitted March 23, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-790**." Approval of this submission by FDA is not required before the labeling is used.

Although not considered post-marketing commitments, we have the following recommendations.

1. Please provide the results of the following study when complete: EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

2. We recommend that you conduct *in vitro* studies in human hepatic microsomes to evaluate if decitabine inhibits CYP2C8.

Updates to the above recommendations and the Clinical Pharmacology and Biopharmaceutic's recommendations listed in your November 14, 2005 letter should be included in your annual reports to the NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Drug Oncology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Brenda Atkins, Regulatory Project Manager at (301) 796-1324.

Sincerely,
{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures – Approved Labeling, Immediate Container and Carton labels

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/s/

Richard Pazdur
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APPLICATION NUMBER:

21-790

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-790

SuperGen, Inc.
4140 Dublin Boulevard, Suite 200
Dublin, CA 94568

Attention: Audrey Jakubowski, Ph.D.
Chief Regulatory & Quality Officer

Dear Dr. Jakubowski:

Please refer to your new drug application (NDA) dated October 29, 2004, received November 1, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dacogen™ (decitabine) for Injection, 50 mg/vial.

We acknowledge receipt of your submissions dated May 24, 2004; August 21, 2004; January 5, 2005; February 14 and 28, 2005; March 21, 2005; June 1, 13, and 24, 2005; July 19 and 21, 2005; and August 4, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to correct the following deficiencies:

Clinical

The Division of Scientific Investigations (DSI) audited the two sites that accrued the most patients to the major trial (D-0007). These sites were the H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL and the Washington University School of Medicine in St. Louis, MO. When the inspectors compared the source documentation with the case report forms (CRFs) and data listings, they uncovered multiple instances where patients' data were inconsistent. At the Moffitt Cancer Center, 34 patients were enrolled in the study. Of these 34 patients, 12 patient records were inspected. Of these 12 patient records, 6 (50%) had inconsistent data where the source document recorded that the patient had a transfusion and the CRF or data listings did not or the source document did not record a transfusion but the CRF and data listing did. At the Washington University site, similar observations were found, although the frequency appeared to be less. Since the primary endpoint encompassed data on transfusions and the demonstration of decitabine's proposed clinical benefit was the elimination of transfusions, the transfusion data appear too unreliable to be used for an approval decision.

Our recommendations are:

1. Verify all transfusion data with the source documentation and, based on that data verification, submit an amendment to the NDA revising the study report, CRFs, data listings, and data sets as necessary. Following the resubmission, DSI would inspect these and other study sites; or

2. Submit the results from study EORTC 06011: Phase 3 randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

In addition, we have the following recommendations and comments which you should address in your response to this letter:

Chemistry

Comments pertaining to the Drug Substance:

We recommend that [redacted]

Clinical Pharmacology and Biopharmaceutics

1. We recommend that you conduct a mass balance study to assess renal and non-renal pathways of elimination of decitabine and we recommend that you screen any major metabolites *in vitro* for pharmacological activity to determine if there is any need for any organ impairment studies.

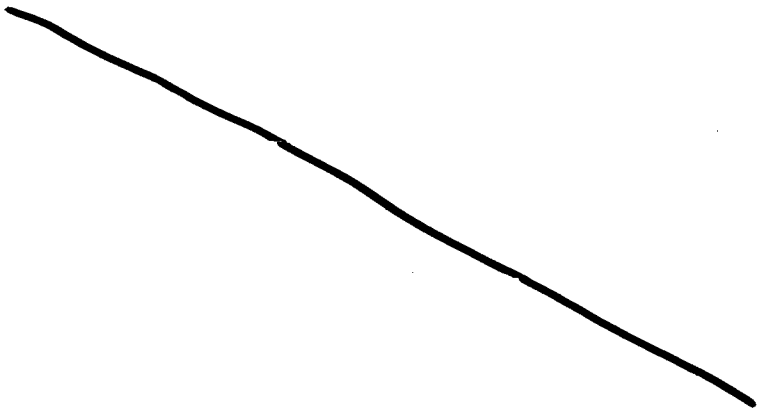
   Rationale: Very limited data are available on the pharmacokinetics of decitabine. The exact metabolic fate and pathways of elimination of decitabine are unknown. This information is critical in determining if decitabine can be used in patients with renal and/or hepatic impairment and if dosing adjustments would be needed for the safe use of decitabine in these patients.

2. We recommend that you conduct exposure-response analyses for measures of toxicity and effectiveness in ongoing and future clinical studies. You should consider assessing intracellular levels of drug and active metabolites as measures of exposure in the exposure-response analysis. These analyses may help enable the determination of optimal dosing regimens for MDS as well as for other indications.

   Rationale: The optimal dosing regimen for decitabine in MDS is not known. Only one dosing regimen of decitabine was evaluated in the current submission. The exposure-response relationship for decitabine has not been elaborated. Characterization of the exposure-response relationship for decitabine can help in optimization of dosing regimens for MDS as well as for other future indications.

3. We suggest that you plan to evaluate *ex vivo* DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and determine whether DNMT inhibition is correlated with exposure and with response rates in ongoing and future studies.

   Rationale: In vitro data indicate that decitabine inhibits DNMT, and studies have shown that hypomethylation of DNA restores expression of tumor suppressor genes and induces cell differentiation. Examination of ex vivo DNMT inhibition in ongoing and future clinical studies of decitabine would be important in improving the understanding of the PK-PD relationship for decitabine. Further, understanding the correlation of exposure of decitabine and/or its active metabolites to DNMT inhibition and how that links to clinical response rates would be important in predicting exposures associated with optimal clinical response rates and might help to identify responders and non-responders to treatment.

4. 

5. We recommend that you conduct *in vitro* studies to determine the CYP450 inhibition and induction potential of decitabine. Depending on the results, drug-drug interaction studies may be necessary. We also recommend that you conduct *in vitro* studies to evaluate if decitabine is a substrate of p-glycoproteins and its inhibition potential for p-glycoproteins.

In addition, we will review the labeling portion of your NDA and provide comments when you submit a complete response to the above issues.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division, the Division of Drug Oncology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Nicholette Hemingway, Regulatory Project Manager, at (301) 594-5750.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Karen Weiss
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