CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-790

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CERTIFICATION REGARDING SERVICES OF DEBARRED PERSONS

1. CERTIFICATION REQUIREMENT

SuperGen, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 subsections (a) or (b) of the Federal Food, Drug, and Cosmetic Act in connection with this NDA.

2. ADDITIONAL INFORMATION REQUIREMENT FOR NDA

No persons who work for SuperGen, Inc. or are affiliated with SuperGen, Inc. and were responsible for the development or submission of this application were convicted of offenses described in Section 306 Subsection (a) or (b) within the 5 years preceding the date of this application.

Signed

Audrey F Jakubowski 5/27/04

Audrey F. Jakubowski, Ph.D. Date

SuperGen, Inc.

4140 Dublin Blvd., Suite 200

Dublin, CA 94568

"Patents"

Patent Certifications

SuperGen claims no patents for Dacogen™ (decitabine) for injection. Please refer to the completed Form FDA 3542a.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-790

NAME OF APPLICANT / NDA HOLDER
SuperGen, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
DACOGEN (Decitabine)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Decitabine also known as 5-aza-2'-deoxycytidine	50 mg/vial

DOSAGE FORM
Lyophilized powder

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☑ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	28/Oct/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name SuperGen, Inc.	
Address 4140 Dublin Boulevard, Suite 200	City/State Dublin
ZIP Code 94568	Telephone Number (925) 560-0100
FAX Number *(if available)* (925) 560-0101	E-Mail Address *(if available)*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(925) 560-0100

3. PRODUCT NAME

Dacogen(TM) (decitabine) for injection

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-790

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(to be submitted by 9/30/04)
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Audrey F Jakubowski	Sr. VP, Regulatory Affairs and Quality	05/27/2004

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

file "Exclusivity"

SuperGen, Inc.
NDA: 21-790 Dacogen™ (decitabine) for Injection
Module 1 – Administrative and Prescribing Information

Statements of Claimed Exclusivity and Associated Certifications

Decitabine (5-aza-2'deoxycytidine) received Orphan Drug Designation (application #98-1222) on February 22, 1999 for the treatment of myelodysplastic syndromes. This was issued to Pharmachemie and was transferred to SuperGen, Inc. on November 20, 2000. Please refer to copies of these letters.

Upon approval of NDA 21-790 for Dacogen™ (decitabine) for injection, SuperGen, Inc. is entitled to a sever-year exclusivity period as per § 21 CFR 316.31(a).

User Fee

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: SuperGen, Inc.	DATE OF SUBMISSION: 10/29/2004
TELEPHONE NO. *(Include Area Code)*: 925-560-0100	FACSIMILE (FAX) Number *(Include Area Code)*: 925-551-6472
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 4140 Dublin Blvd., Suite 200 Dublin, CA 94568	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 21-790

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: decitabine

PROPRIETARY NAME *(trade name)* IF ANY: Dacogen(TM)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: See attachment

CODE NAME *(If any)*:

DOSAGE FORM: Lyophilized powder

STRENGTHS: 50 mg/vial

ROUTE OF ADMINISTRATION: intravenous

(PROPOSED) INDICATION(S) FOR USE:
myelodysplastic syndrome

RECEIVED
NOV 0 1 2004
CDR / CDER

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
- [x] NEW DRUG APPLICATION (NDA, 21 CFR 314.50)
- [ ] ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
- [ ] BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- [ ] 505 (b)(1)
- [ ] 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug:
Holder of Approved Application:

TYPE OF SUBMISSION *(check one)*
- [x] ORIGINAL APPLICATION
- [ ] AMENDMENT TO A PENDING APPLICATION
- [ ] RESUBMISSION
- [ ] PRESUBMISSION
- [ ] ANNUAL REPORT
- [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT
- [ ] EFFICACY SUPPLEMENT
- [ ] LABELING SUPPLEMENT
- [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- [ ] OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: 04/21/2004

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY
- [ ] CBE
- [ ] CBE-30
- [ ] Prior Approval (PA)

REASON FOR SUBMISSION:

PROPOSED MARKETING STATUS *(check one)*
- [x] PRESCRIPTION PRODUCT (Rx)
- [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED:

THIS APPLICATION IS
- [ ] PAPER
- [ ] PAPER AND ELECTRONIC
- [x] ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See attachment

This application contains the following items: *(Check all that apply)*	
☑	1. Index
☑	2. Labeling *(check one)* ☑ Draft Labeling ☐ Final Printed Labeling
☑	3. Summary (21 CFR 314.50 (c))
☑	4. Chemistry section
	☑ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	☐ B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☑	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☑	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☑	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☑	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☑	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☑	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☑	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☑	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☑	15. Establishment description (21 CFR Part 600, if applicable)
☑	16. Debarment certification (FD&C Act 306 (k)(1))
☑	17. Field copy certification (21 CFR 314.50 (l)(3))
☑	18. User Fee Cover Sheet (Form FDA 3397)
☑	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sign	Audrey F. Jakubowski, PhD, Chief Regulatory & Quality Officer	10/29/2004

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
4140 Dublin Blvd., Suite 200, Dublin, CA 94568	925-560-0100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-790 SUPPL # HFD # 150

Trade Name Dacogen Injection

Generic Name decitabine for injection

Applicant Name MGI PHARMA, Inc

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Brenda J. Atkins
Title: Consumer Safety Officer
Date: April 20, 2006

Name of Office/Division Director signing form:
Division of Drug Oncology Products/Robert L. Justice, M.D.
Title: Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Robert Justice
4/21/2006 01:25:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Azra Raza, M.D.
c/o Stephanie Gregory, M.D.
1725 W Harrison Street
Suite 834
Chicago, IL 60612-3861

Dear ~~Dr. Raza~~:

Between February 8-22, 2006 Mr. Kujtim Sadiku representing the Food and Drug Administration (FDA), conducted an investigation and met with current Rush University Medical Center staff, to review your conduct of a clinical investigation protocol D-0007, entitled "A Randomized, Open-Label, Phase III Trial of Decitabine (5-aza-2'-deoxycytidine) Versus Supportive Care in Adults With Advanced-Stage Myelodysplastic Syndromes (MDS)." The study of the investigational drug Dacogen™ (decitabine) Injection was performed for MGI Pharma, the current sponsor.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We are aware that at the conclusion of the inspection, Mr. Sadiku presented and discussed with Dr. Stephanie Gregory Form FDA 483, Inspectional Observations. We are also aware that you, Dr. Azra Raza, were responsible for study D-0007 at this site from December 18, 2001 through August 8, 2004, and that Dr. Stephanie Gregory accepted responsibility for study D-0007 on August 9, 2004. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

   a. According to Protocol D-0007 instructions, Serious Adverse Events (SAEs) must be reported within 24 hours to the sponsor. Our investigation found that some SAEs were not reported within the required timeframes. For example;

Subject	SAE	Event Date	Date Sponsor Notified
1046-5068 [redacted]	diverticulitis	[redacted]	4/15/2003
1046-5072 [redacted]	Supraventricular tachycardia	[redacted]	7/23/2002
1046-5088 [redacted]	Nightsweats, fever	[redacted]	9/12/2002

1046-5102 [redacted]	Pneumonia	[redacted]	4/15/2003
1046-5124 [redacted]	hypotension	[redacted]	3/24/2003
1046-5136 [redacted]	Pneumonia	[redacted]	7/25/2003
	Pneumonia	[redacted]	7/25/2003

b. Our investigation found that some subjects missed protocol required periodic assessments, including those that were necessary to monitoring efficacy endpoint achievement. For example;

Subject	Missing Assessment	Study Visit
1046-5056 [redacted]	Quality of Life Questionnaire	Cycle #1
1046-5062 [redacted]	Physical Exam	Cycle #1
	Clinical Lab Assessment	Cycle #1
	Clinical Lab Assessment	Cycle #1
	Quality of Life Questionnaire	Post Treatment
	Bone Marrow Evaluation	Post Treatment
1046-5068 [redacted]	Bone Marrow Evaluation	Pre-study
	Quality of Life Questionnaire	Baseline
	Schedule of Events	Cycle #1
	Physical Exam	Cycle #1
	Schedule of Events	Cycle #2
1046-5078 [redacted]	Quality of Life Questionnaire	Baseline
1046-5088 [redacted]	Physical Exam	Cycle #1
	Serum Chemistry	Cycle #1
	Quality of Life Questionnaire	Cycle #1
	Bone Marrow Evaluation	Post Treatment
	Quality of Life Questionnaire	Post Treatment
1046-5095 [redacted]	Quality of Life Questionnaire	Baseline
	Physical Exam	Cycle #1
	Bone Marrow Evaluation	Cycle #3
	Quality of Life Questionnaire	Cycle #3
	Physical Exam	Post Treatment
	Bone Marrow Evaluation	Post Treatment
	Quality of Life Questionnaire	Post Treatment
1046-5144 [redacted]	Physical Exam	Baseline
	Quality of Life Questionnaire	Baseline
	Hematology/Serum Chemistry Tests	Baseline
	Schedule of Events	Cycle #1
	Quality of Life Questionnaire	Cycle #1
	Hematology/Serum Chemistry Tests	Post Treatment
	Quality of Life Questionnaire	Post Treatment
	Physical Exam	Post Treatment
	Bone Marrow Evaluation	Post Treatment

c. You failed to follow protocol instructions for Inclusion/Exclusion Criteria. Specifically, total bilirubin >1.5 mg/dL prior to enrollment was an Exclusion Criteria as defined in Protocol Section 2.1(f). Subject 1046-5144 was enrolled despite having a total bilirubin of 1.7 mg/dL on 1/14/2003.

2. You failed maintain adequate and accurate records [21 CFR 312.62]. For example,

   a. Source documentation to support 11 blood transfusion recorded events for 3 subjects enrolled in study D-0007 were not available onsite for review.

   b. Transfused product documented on 11/12/02 in the Case Report Form Transfusion Log, random donor platelets, was not consistent with the transfused product recorded in the source documents, single donor platelets, for subject 1046-5088.

   c. Date of Death recorded in the Case Report Form, [redacted], was not consistent with the date of death recorded in the source documents, [redacted] for subject 1046-5124.

3. You failed to obtain adequate subject informed consent [21 CFR 50.20]. For example, subjects 1046-5088 and 1046-5095 did not sign the updated informed consent document (version dated 8/21/02) which contained updated adverse event information.

As the clinical investigator, you are responsible for ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for protecting the rights, safety and welfare of study subjects.

We request that you inform this office in writing of the actions that you have taken or plan to take to bring your procedures into compliance with FDA regulations. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Mr. Kujtim Sadiku during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Leslie Ball
5/11/2006 02:53:17 PM

Office of Drug Safety

MEMO

To: Robert Justice, MD
Acting Director, Division of Drug Oncology Products, HFD-150

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, WO22, Mailstop 4447

Through: Nora Roselle, PharmD, Acting Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support (DMETS), WO22, Mailstop 4447

Date: January 11, 2006

Re: ODS Consult 05-0002-1; Dacogen (Decitabine for Injection) 50 mg vial; NDA 21-790

This memorandum is in response to a December 22, 2005 request from your Division for a re-review of the proprietary name, Dacogen™. The proposed proprietary name, Dacogen™, was found acceptable by DMETS in the initial review dated June 23, 2005 (ODS Consult 05-0002). Labels and labeling were also reviewed in the initial consult. Revised container labels and carton labeling have not been submitted and therefore will not be reviewed at this time.

Since we conducted our previous review, the Expert Panel has identified one proprietary name, AtroPen®, and one established name, Baclofen, as having sound-alike similarities to Dacogen™. However, upon final review by DMETS, AtroPen® will not be discussed further due to the lack of convincing phonetic similarities and differences in product characteristics (strength, frequency of administration, availability, dose, route of administration, and setting of use). These will minimize confusion between the name pair.

Baclofen may sound similar to Dacogen™ when spoken. Baclofen is indicated for the treatment of reversible and intractable spasticity. Baclofen is the generic name or established name for Lioresal® and Kemstro™. Lioresal is available as oral tablets and as a solution for injection. Kemstro™ is available as orally disintegrating tablets. Baclofen and Dacogen™ are phonetically similar because they contain three syllables and each syllable of both names may sound similar [(DĂ- vs. BĂ-), (-CŌ vs. -CLŌ), and (-GEN vs. -FEN)]. Despite the phonetic similarities between the names, there are product characteristics which may help differentiate one drug from the other (see Table 1, page 2). Dacogen™ and Baclofen differ with respect to the route of administration, dosage form, strength, dosing regimen, class of agent (chemotherapeutic agent vs. non-chemotherapeutic agent), and indication for use.

Table 1. Product Comparisons

Proprietary name	Dacogen (proposed)	Lioresal®	Lioresal® Intrathecal	Kemstro™
Established Name	Decitabine for Injection	Baclofen	Baclofen	Baclofen
Strength(s)	50 mg vial	10 mg 20 mg	0.05 mg/mL 10 mg/5 mL 10 mg/20 mL	10 mg 20 mg
Indication(s) for use	Myelodysplastic Syndrome	Reversible spasticity	Intractable spasticity	Reversible spasticity
Route(s) of administration	Intravenous	Oral	Intrathecal	Oral
Dosage form(s)	Lyophilized powder for injection	Oral tablet	Solution for injection	Oral disintegrating tablet
Usual dosage	First treatment cycle: 15 mg/m^2 administered by continuous intravenous infusion over 3 hours, repeated every 8 hours for 3 days. Subsequent cycles: Repeat the above cycle every 6 weeks. A minimum of four cycles is recommended, however a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit.	5 mg three times per day, may increase 5 mg per dose every 3 days to a maximum of 80 mg/day.	Test dose: 50 mcg to 100 mcg Maintenance intrathecal infusion via intrathecal pump (after a positive response to test dose): Initially, infuse at a 24-hourly rate dosed at twice the test dose.	5 mg three times per day, may increase 5 mg per dose every 3 days to a maximum of 80 mg/day.

From the chart above, Dacogen, unlike Baclofen, is dosed based on a patient's body surface area (BSA). For example, a prescription written for Dacogen™ would likely specify the (mg/m^2) dose to be given as well as the actual (calculated) dose that the patient is to receive based on the patient's BSA (e.g. A patient with a BSA of 2: "Dacogen 15 mg/m^2 = 30 mg dose"). Since it is a chemotherapeutic agent, the patient's height, weight, and BSA would likely be specified on an order (or the information readily available) so that that the dose can be double checked. Also, Dacogen™ will likely be prepared and administered by healthcare professionals specially trained in how to prepare and administer chemotherapeutic agents. It requires special preparation and handling, such that administration must be initiated no later than seven hours after preparation. Therefore, it is likely that the preparation and administration of the drug would be closely coordinated. Because of the different product characteristics, DMETS feels that the potential to confuse the two names is minimal.

We remind you of our container label and labeling comments contained in our initial consult dated June 23, 2005. In addition to those comments, we have the following comment which might minimize potential user error.

INSERT LABELING

In summary, DMETS has no objections to the use of the proprietary name, Dacogen™. Additionally, DDMAC finds the proprietary name, Dacogen™, acceptable from a promotional perpective. DMETS recommends implementation of the labeling recommendations outlined in our previous review as well as the insert comment included in this review. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days fron the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact the project manager, Diane Smith, at 301-796-0538.

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/s/

Loretta Holmes
2/7/2006 03:25:35 PM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
2/7/2006 03:38:39 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/7/2006 03:47:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/7/2006 04:51:07 PM
DRUG SAFETY OFFICE REVIEWER

SuperGen®

November 18, 2005

Robert Justice, M.D.
Acting Director, Office of Oncology Drug Products
Food and Drug Administration
Central Document Room
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: NDA #21-790
Dacogen™ (decitabine) for Injection
Approvable Letter Safety Update (Amendment No. 0005)

Dear Dr. Justice:

In response to the Approvable Letter dated September 1, 2005, and as stated in Sponsor's Amendment No. 0004 cover letter, this Safety Update (Amendment No. 0005) is provided.

If you have any questions regarding this submission, please contact the undersigned.

Sincerely,

Sherry L. Chandler for

Audrey F. Jakubowski, Ph.D.
Senior Vice President, Regulatory Affairs and Quality Assurance
Chief Regulatory and Quality Officer
SuperGen, Inc.
4140 Dublin Blvd., Suite 200
Office: (925) 560-0100
Fax: (925) 551-6472
Cell: (925) 719-2116
Email: ajakubowski@supergen.com

FDA Note:
See Clinical and Statistical Review dated 4-5-2006.

cc: Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd
Beltsville, MD 20705-1266

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Audrey Jakubowski, PhD, SuperGen
Fax: 925-551-6472

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 8-11-05

COMMENTS: Re: your pending NDA 21-790 for Dacogen (decitabine), as discussed in our telecon, below are the comments from the DSI report:

The following are bullets from the DSI Inspection Report for the University of Washington:

Transfusion records were inadequate or inaccurate for three subjects:

- Source documents indicate that subject [redacted] 5113 received two units of packed red blood cells (PRBCs) on [redacted]

[redacted] However, these six transfusions are not recorded on the CRF and are not included in the sponsor's data listing.

- Source documents indicate that subject [redacted] 5135 received PRBC transfusions about every two to three weeks from [redacted] However, the CRF and sponsor's data listing indicates transfusions started [redacted]

- Source documents could not be located for subject [redacted] 5157 for 17 of 28 platelet and PRBC transfusions shown in the sponsor's data listing.

The following are bullets from the DSI Inspection Report for the Moffitt Cancer Center:

transfusion records were inadequate or inaccurate for six subjects:

Subject (treatment)	Date	Source Doc. # units	CRF # units	Data Listings # units
[redacted] 5042 (SC)		0	1 platelet	2 platelets
[redacted] 5028 (D)		0	2 PRBC	PRBC
		0	unknown platelets	unknown platelets
		0	2 PRBC	2 PRBC
[redacted] 5009 (SC)		0	2 PRBC	2 PRBC
		0	2 PRBC	2 PRBC
		0	2 platelet	2 platelet
[redacted] 5012 (SC)		0	2 PRBC	2 PRBC
		0	2 PRBC	2 PRBC
		0	2 PRBC	2 PRBC
[redacted] 5094 (D)		2 PRBC	1 PRBC	1 PRBC
		2 PRBC	0 PRBC	0 PRBC
[redacted] 5100 (D)		2 PRBC	1 PRBC	1 PRBC
		2 PRBC	0	0
		1 Platelet	0	0
		1 PRBC	2 PRBC	2 PRBC
		2 PRBC	0	0
		0 platelet	1 platelet	1 Platelet
		1 PRBC	2 PRBC	3 PRBC
		PRBC	1 PRBC	2 PRBC
		3 PRBC	3 PRBC	6 PRBC

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/s/

Dotti Pease
8/11/05 07:10:44 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5750 FAX: (301) 594-0499

TO: Audrey Jakubowski, PhD, SuperGen
Fax: 925-551-6472

FROM: Nicholette Y. Hemingway, Project Manager
Phone: (301) 594-5750

Total number of pages, including cover sheet 2

Date: 7-13-05

COMMENTS: Re: your NDA 21-790 for Dacogen (decitabine) for the treatment of myelodysplastic syndrome (MDS), we have the following request from our clinical review team. Please address this comment as soon as possible.

Please provide the following information:

1. Revise Table 7 in the Dacogen Package insert to include Common Adverse Events in =>5% of Dacogen patients (instead of =>10%).

Please call me at the above number if you have any questions.

Nicholette

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/s/

Nicholette Hemingway
7/13/05 03:53:23 PM
CSO

NDA REGULATORY FILING REVIEW

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA #: 21-790, Dacogen (Decitabine) Injection for the treatment of myelodysplastic sysdromes.

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☒

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). n/a no listed product

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☒

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.) ** *This application contained no patent certification.* **

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☒ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☒ NO ☐

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/s/

Dotti Pease
6/2/05 11:02:10 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5750 FAX: (301) 594-0499

TO: Audrey Jakubowski, PhD, SuperGen
Fax: 925-551-6472

FROM: Nicholette Y. Hemingway, Project Manager
Phone: (301) 594-5750

Total number of pages, including cover sheet 2

Date: 3-11-05

COMMENTS: Re: your NDA 21-790 for Dacogen (decitabine) for the treatment of myelodysplastic syndrome (MDS), we have the following request from our statistics review team. Please address these comments by COB March 21, 2005.

Comments –

- Are dataset "analysis" (submitted to the Agency) and "analysis_file" (used in the sponsor's SAS program) the same datasets? The statistical reviewer is not sure because variables used in the sponsor's program, say last_lab_date, withdrawal_date, last_followup_date are not in the "analysis" dataset which has last_lab, withdraw, and

last_fol. Please submit the correct SAS programs, and other necessary programs if any, such as init.sas, used in the program.

- In the submitted file "define.pdf", the reviewer used "site", "center", and "investigator" to search "define.pdf" but found no variables named above in the datasets. Please indicate which variable is for site and submit the SAS code for producing table in section 16.1.9.2.

Please send these responses by email to HemingwayN@cder.fda.gov

Please call me at the above number if you have any questions.

Nicholette

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/s/

Nicholette Hemingway
3/11/05 02:16:22 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Division of Oncology Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: January 27, 2005

TO: Audrey F. Jakubowski, Ph.D.
Vice President, Regulatory Affairs
Phone (925) 560-0100 x352
Fax (925) 551-6472

FROM: Brenda J. Atkins, Regulatory Project Manager
Ph: (301) 594-5767/Fx: (301) 594-0498

NDA/DRUG: NDA 21-790/Dacogen™ (decitabine) for injection

SUBJECT: **Clinical Reviewer's Requests**

Please respond to the following requests:

1. Has decitabine been licensed in any other country? If so, please provide a copy of the package insert.

2. Have any licensing applications been submitted in other countries and for what indications?

3. The Listing of Transfusions (Appendix 16.2.6.26) is extremely difficult to maneuver through. Please construct

   Tables of Efficacy Parameters of Response for Subjects Whose Best Response was CR, PR, or HI for each subject with these responses.

   - In those tables list in columns the following information:

- Best Response (CR, PR, HI), Treatment (Baseline, then Decitabine or Supportive care), Cycle #, Study Day, Date, Hematology Results (Hgb, Platelets, WBC, ANC, % bone marrow blasts), Transfusions (Platelets, PRBC, # of units).

You do not have to construct this information for non-responders.

This will allow us to confirm the best response and the duration of response. This is the key element of Clinical Benefit of the Drug.

At this time, we have no questions or special requests regarding your 120-day safety update report. Please refer to 21 CFR 314.50(d)(5)(vi)(b) for guidance on its contents.

Your responses should be submitted to your NDA in the usual manner, i.e. via the Electronic Document Room (EDR).

Please respond as soon as possible.

Sincerely,

_____

Brenda J. Atkins, Regulatory Project Manager
Division of Oncology Drug Products

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/s/

Brenda Atkins
1/27/05 10:45:14 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-790 Supplement # [SE1] SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Dacogen™
Generic Name: decitabine for injection
Strengths: 50 mg/vial Dosage form: Lyophized powder

Applicant: SuperGen, Inc.

Date of Application: 10-29-04
Date of Receipt: 11-01-04
Date clock started after UN: N/A
Date of Filing Meeting: 11-01-04
Filing Date: 01-14-05
Action Goal Date (optional): 09-01-05(S) User Fee Goal Date: 09-01-05

Indication(s) requested: Myelodysplastic Syndrome (MDS)

Type of Original NDA: (b)(1) ___√___ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

____ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S ___√___ P _____
Resubmission after withdrawal? ___No___ Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) ___1___
Other (orphan, OTC, etc.) ___Orphan Drug Status 03-08-99 (Pharmachemie USA, Inc) 11-20-00 (SuperGen, Inc.)___

Form 3397 (User Fee Cover Sheet) submitted: [YES] NO

User Fee Status: Paid _____ Exempt (orphan, government) ___√___
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES [NO]

  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? [YES] NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES [NO]

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? [N/A] YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO

- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? [YES] NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? [ALL]

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO

- Is it an electronic CTD? N/A YES [NO]
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? [YES] NO

- Exclusivity requested? [YES] 7 years NO
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? [YES] NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? [YES] NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name [(Yes)]/Applicant name correct in COMIS [(YES)] ? If not, have the Document Room make the corrections.

- List referenced IND numbers: 33,929

- End-of-Phase 2 Meeting(s)? Date(s) 8-5-98, 6-14-99, 1-31-01, 8-15-03
  [Yes]
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 4-25-03, 2-6-04
  [Yes]
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES [NO]

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

[N/A] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

[N/A] YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES] NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES [NO]

- Establishment Evaluation Request (EER) submitted to DMPQ? [YES] NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? [YES] NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 20, 2004

BACKGROUND:

"Decitabine (5-aza-2"-deoxycytidine; NSC 127716) was first synthesized in Czechoslovakia in 1964 (Pliml and Sorm). Anti-leukemic activity was first demonstrated in mice in 1968 (Sorm and Vesely) and confirmed in mice by a second group in 1978 (Momparler and Gonzales). Anti-leukemia activity was demonstrated in children with chemotherapy-resistant acute leukemia in 1981 (Rivard et al.). Further interest was stimulated in this compound when it was demonstrated to be more potent than cytosine arabinoside and to induce cell differentiation (Chabot and Momparler, 1990). This offered a potential two- pronged attack in hematological malignancies: cytotoxicity at high doses and cell differentiation to a non- neoplastic cell line at lower doses.

"Early studies with decitabine were conducted in many tumor types, but few responses were noted in solid tumors. In a Phase I study (n = 21), (van Groeningen et al. 1986) and seven Phase II studies (n = 153) in solid tumors conducted by the European Organization for Research and Treatment of Cancer (EORTC) up to February 1989, one response was seen in a patient with an ethmoid sinus tumor and one partial response in a patient with malignant melanoma (Dodion et al., 1990). Studies in hematological malignancies showed more responses, but myelotoxicity was notable with the dose schedules used."

Decitabine was licensed by SuperGen, Inc. (SGI) from Pharmachemie B.V. in 1998. The sponsorship of IND 33,929 was transferred by Pharmachemie to SuperGen on November 5, 1999. Dacogen was granted Orphan Drug Status for use in patients with MDS in the US on November 22, 2000 and in the EU on February 14, 2003. The sponsor's meeting request of June 23, 2003 stated that 'The drug substance and drug product manufacturers have remained the same for the duration of SGI's clinical development program. SGI has worked closely with Pharmachemie to insure that all appropriate controls and test methods are in place for both the clinical trial material and future commercial production.

"Based on the results of two Phase II clinical trials (PCH 95- 11 and PCH 97- 19) of low-dose Dacogen in myelodysplastic syndromes (MDS) and several publications, SuperGen, Inc. prepared a Phase III protocol (D-0007)." This protocol was discussed with FDA at an End of Phase II meeting on January 31, 2001, where FDA requested and the sponsor agreed upon a composite endpoint, time to progression to AML or death.
Three clinical trials are provided in support of the use of Dacogen in the treatment of all subtypes of MDS:

• D- 007: A randomized, open- label, Phase III trial of decitabine versus supportive care in adults with advanced- stage myelodysplastic syndrome (n = 170) • PCH 95- 11: A Phase II open- label study of decitabine in patients with advanced MDS (n = 66) • PCH 97- 19: A Phase II compassionate- use study of decitabine in patients with advanced MDS (n = 98) At the time these protocols were designed, there was no approved treatment for MDS in either the EU or US. In both the US and EU, supportive medical care was generally considered the standard of care for most of these patients. Vidaza (5- azacytidine) was approved in the US in May 2004 for treatment of advanced MDS, based on a retrospective analysis of a CALGB Phase III protocol and supportive Phase II studies. No agent is currently approved in the EU for the treatment of MDS. Dacogen and Vidaza are unique molecules with different mechanisms of action and clinical activity.

The Agency has requested foreign marketing history on decitabine from the sponsor as of January 27, 2005.

ATTENDEES: Grant Williams, M.D. (Deputy Director); Ann Farrell, M.D. (Clinical Team Leader); Edvardas Kaminskas, M.D., (Clinical Reviewer); Raji Sridhara, Ph.D. (Biometrics Team Leader); John Leighton, Ph.D. (Pharmacology/Toxicology Team Leader); Brian Booth, Ph.D., (Biopharm Team Leader); Roshni Ramchandani, Ph.D. (Biopharm Reviewer)

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Edvardas Kaminskas, M.D.
Secondary Medical:	Ann Farrell, M.D.
Statistical:	Kun He/Raji Sridhara
Pharmacology:	Anwar Goheer/John Leighton
Statistical Pharmacology:	
Chemistry:	Josephine Jee/N. Chidambaram
Environmental Assessment (if needed):	
Biopharmaceutical:	Roshni Ramchandani/Brian Booth
Microbiology, sterility:	David Hussong
Microbiology, clinical (for antimicrobial products only):	
DSI:	David Gan/Leslie Ball
Regulatory Project Management:	Nicholette Hemingway
Other Consults:	

Per reviewers, are all parts in English or English translation? [YES] NO
If no, explain:

CLINICAL FILE __√__ REFUSE TO FILE _____

- Clinical site inspection needed: [YES] NO
  Two largest sites should be inspected
- Advisory Committee Meeting needed? YES, date if known _____ [NO]

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

[N/A] YES NO

CLINICAL MICROBIOLOGY [NA] _____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE __√__ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __√__ REFUSE TO FILE _____

- Biopharm. inspection needed: YES [NO]

PHARMACOLOGY NA _____ FILE __√__ REFUSE TO FILE _____

- GLP inspection needed: YES [NO]

CHEMISTRY FILE __√__ REFUSE TO FILE _____

- Establishment(s) ready for inspection? [YES] NO
- Microbiology [YES] NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__√__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__√__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. No filing issues - conveyed to applicant by Day 74 (letter sent on 01-05-05).
2. ODAC consults [Yes] No Patient consults [Yes] No

   Division Director specified on 1-03-05 use of two(2) ODAC consultants and one(1) patient consultant.
3. DSI inspections [Yes] No

_____
Regulatory Project Manager, HFD-150

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Brenda Atkins
1/28/05 05:09:59 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

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 October 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dacogen™ (decitabine) for injection, 50 mg/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 31, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Brenda Atkins, Regulatory Project Manager, at (301) 594-5767.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Richard Pazdur
1/5/05 11:23:56 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Division of Oncology Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: December 28, 2004

TO: Audrey F. Jakubowski, Ph.D.
Vice President, Regulatory Affairs
Phone (925) 560-0100 x352
Fax (925) 551-6472

FROM: Brenda J. Atkins, Regulatory Project Manager
Ph: (301) 594-5767/Fx: (301) 594-0498

NDA/DRUG: NDA 21-790/Dacogen™ (decitabine) for injection

SUBJECT: **Biometrics Reviewer's Request**

The Biometrics Reviewer of your NDA requests the following:

Please submit SAS codes for the following:

(a) SAS programs that produced all efficacy results in Section 11 Efficacy Evaluation (Study report page 57 to page 93);

(b) all raw as well as derived variables in .xpt format;

(c) SAS programs by which the derived variables were produced from the raw variables; and

(d) SAS programs for interim analysis based on 45 first events.

Your response should be submitted to your NDA in the usual manner, i.e. via the Electronic Document Room (EDR).

Please respond as soon as possible.

Sincerely,

_____

Brenda J. Atkins, Regulatory Project Manager
Division of Oncology Drug Products

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/s/

Brenda Atkins
12/28/04 06:09:15 PM
CSO

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:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Dacogen™ (decitabine) for injection, 50 mg/vial

Review Priority Classification: Standard (S)

Date of Application: October 29, 2004

Date of Receipt: November 1, 2004

Our Reference Number: NDA 21-790

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 31, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 1, 2005

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products HFD-150
Attention: Division Document Room, Room 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Brenda Atkins, Regulatory Project Manager, at (301) 594-5767.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Brenda Atkins
12/29/04 02:38:22 PM
Signing for Dotti Pease, CPMS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22 RM3437 ATTN: Quynh Nguyen 301-796-0510	Brenda Atkins, Project Manager Office of Oncology Drug Products/Division of Drug Oncology Products Phone: 301-796-1324/Fax: 301-796-9845

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 22, 2005		21-790	Resubmission of NDA (Class 2)	November 14, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Dacogen™ (decitabine for injection)	S		DDOP Goal Date=03-31-~~05~~ 06 PDUFA Goal Date=05-16-~~05~~ 06

NAME OF FIRM: SuperGen, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the following tradename: Dacogen. (DMETS review previously issued 6-23-05 on the original NDA submission of 10-29-04)

This NDA is due on May 15, 2006 (PDUFA Date) and DDOP's internal goal date is March 31, 2005 (tentative). We ask for a completion date of March 20, 2005 (negotiable), so there is adequate time to insert the tradename into all appropriate correspondence and labeling prior to taking an action.

PDUFA DATE: * May 15, 2006

***Please Note: DDOP Management and the review team are planning to take action on the NDA resubmission within a 3-4 month timeframe).**

Medical Officer is Edvardas Kaminskas

All review materials can be found in the Electronic Document Room. Consult entered into DFS on 12-22-05.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
See electronic signature in DFS.	☐ MAIL ☑ DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Brenda Atkins
12/22/2005 05:37:33 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: January 6, 2005 **DOCUMENT DATE:** October 29, 2004	**DESIRED COMPLETION DATE:** August 11, 2005 **PDUFA DATE:** September 1, 2005	**ODS CONSULT #:** 05-0002

TO: Richard Pazdur, MD
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Nicholette Hemingway
Project Manager, Division of Oncology Drug Products
HFD-150

PRODUCT NAME: **Dacogen™** Decitabine for Injection 50 mg per vial NDA#: 21-790	**NDA SPONSOR:** SuperGen, Inc

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Dacogen™. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review, in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Dacogen™ acceptable from a promotional perspective.

Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 11, 2005

NDA# 21-790

NAME OF DRUG: **Dacogen™** (Decitabine for Injection)
50 mg per vial

NDA HOLDER: SuperGen, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150) for an assessment of the proprietary name Dacogen in regard to potential name confusion with other proprietary and/or established drug names. Container labels as well as carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Dacogen (Decitabine) for Injection is indicated for the treatment of Myelodysplastic Syndrome. Recommended dosing is 15 mg/m^2 via intravenous infusion over three hours, which is repeated every eight hours for three days. This cycle is repeated every six weeks for a minimum of four cycles. However, for a complete or partial response, the patient may require more than four cycles. Dosing may be delayed or adjusted in accordance with the patient's hematologic recovery. Dacogen will be supplied as a sterile lyophilized white to almost white powder. This will be a single-dose vial containing 50 mg of decitabine, which will be reconstituted with 10 mL of sterile water for injection. Subsequent to reconstitution, each milliliter will contain 5 mg of decitabine that should be further diluted with intravenous fluids, such as 0.9% sodium chloride, 5% dextrose or lactated ringer's solution, to a final concentration of 0.1 to 1 mg per milliliter. If the reconstituted solution is not used within 15 minutes, the dilution must occur with cold infusion fluids and stored between two and eight degrees Celsius for a maximum of seven hours prior to administration.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Dacogen to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Dacogen. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Dacogen acceptable from a promotional perspective.

2. Six proprietary names (Adagen, Daraprim, Decadron, Depogen, Desogen and Macugen) were identified by Expert Panel and two by independent review (Depacon and Doxepin) that were thought to have the potential for confusion with Dacogen. These products with the available dosage forms and usual dosage are listed in Table 1 (see page 3, 4 and 5).

Table 1: Potential Sound-Alike/Look-Alike Names for DACOGEN Identified by DMETS Expert Panel and Independent Review

Product Name	Established name, Dosage Form(s) Strength(s)	Usual adult dose*	Other**
Dacogen	Decitabine for Injection 50 mg	15 mg/m² over three hours to be repeated every eight hours for three days. This cycle is repeated every six weeks for a minimum of four cycles	
Adagen®	Pegademase Bovine, 250 units/mL; 1.5 mL Vial	Administer every 7 days by Intramuscular injection as follows: first dose-10 U/kg; second dose-15 U/kg; third dose-20 U/kg with maintenance dose, of 20 U/kg/week. The dose may be increased weekly by increments of 5 U/week, with a maximum of 30 U/week.	SA
Depacon®	Valproate Sodium Injection, 500 mg/5 mL	For IV use only. Administer as a 60-minute infusion (but not more than 20mg/min) with the same frequency as the oral products. Dosing ranges from 10-15 mg/kg/day, which may be increased by 5-10 mg /kg/day until optimal clinical response (up to 60 mg/kg/day).	LA
Depogen®	Estradiol Cypionate 5 mg/5 mL, 10 mL vial	1 to 5 mg intramuscularly every three to four weeks	SA/LA
Desogen®	Desogestreland Ethinylestradiol Tablets 150 mcg/300 mcg	One tablet daily for 21 days. Last seven tablets are inactive.	LA/SA
Macugen®	Pegaptanib Sodium Injection, Prefilled Syringe with 0.3 mg in 90 mcL	0.3 mg every 6 weeks by intravitreous injection.	SA
Doxepin	Doxepin Capsules: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg Oral Solution: 10 mg/mL	Mild-to-moderate illness: Individualize dosage. Initially, 75 mg/day. Usual optimum dosage is 75 to 150 mg/day. Alternatively, the total daily dosage, up to	LA

Table 1: Potential Sound-Alike/Look-Alike Names for DACOGEN Identified by DMETS Expert Panel and Independent Review			
Product Name	Established name(s) and Strength	[illegible] dose	Other**
Dacogen	Decitabine for Injection 50 mg	[illegible] over three hours to be repeated every eight hours for three days. This cycle is repeated every six weeks for a minimum of four cycles.	
		150 mg, may be given at bedtime. Maximum dose is 150 mg/day. Mild symptomatology or emotional symptoms accompanying organic disease: 25 to 50 mg/day is often effective. More severe anxiety or depression: Higher doses (eg, 50 mg 3 times/day) may be required; if necessary, gradually increase to 300 mg/day.	
Decadron®	Dexamethasone Tablets: 0.5 mg, 0.75 mg Previously Decadron-branded products now only available in generic:: Solution for Injection: 4mg/mL and 24 mg/mL Elixir 0.5 mg/5 mL Tablets: 0.25 mg, 1.5 mg, 6 mg Otic Solution: 0.1% Dexamethasone Sodium Phosphate Ophthalmic Solution: 0.1% Dexamethasone Sodium Phosphate Ophthalmic Ointment: 0.05% Dexamethasone phosphate Other brands: Hexadrol (Dexamethasone Tablets) 4 mg Hexadrol (Dexamethasone Oral Solution) 0.5 mg/5 mL Generic products: Oral Concentrate: 1 mg/mL Tablets: 1 mg, 2 mg Dexamethazone Sodium Phosphate solution for injection: 10 mg/mL (1 mL and 10 mL) and 20 mg/mL (5 mL)	Doses are variable. Initial dose: 0.75-9 mg/day. Maintenance dosage: Decrease initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response. Intra-articular, Intramuscular, Intravenous: Usual doses range from 1/3 to ½ of oral doses given every 12 hours. Cerebral edema: 4 mg every 6 hours Shock: 1 to 6 mg/kg as a single injection (up to 40 mg) Intra-acrticular: Large joints: 2 -4 mg Small joints: 0.8 to 1 mg Bursae: 2 to 3 mg Tendon sheaths: 0.4- 1 mg Soft tissue infiltration: 2 to 6 mg Ganglia: 1 to 2 mg Ophthalmic: 1-2 drops every hour during the day and every 2 hours during the night. May reduce dosage to 1 drop every 4 hours, down to 3 or 4 times daily Otic: Thin coating 3 to 4 times a day, may reduce to twice daily or daily	SA
Daraprim®	Pyrimethamine Tablets, 25 mg	Prophylaxis for malaria: Adults and children (older than 10 years of age): 25 mg once weekly. Children (4 to 10 years of age): 12.5 mg once weekly. Infants and children (younger than 4 years of age): 6.25 mg once weekly. Treatment of acute malaria: 25 mg daily for 2 days, with a sulfonamide. If used alone: Adults and children (older than 10 years of age): 50 mg daily for 2 days. Children (4 to 10 years of age): 25 mg daily for 2 days.	LA/SA

Table 1: Potential Sound-Alike/Look-Alike Names for DACOGEN Identified by DMETS Expert Panel and Independent Review			
Product Name	Established name (Proposed Strength)	Usual adult dose	Other**
Dacogen	Decitabine for injection 50 mg	[illegible] over three hours to be repeated every eight hours for three days. This cycle is repeated every six weeks for a minimum of four cycles.	
		Toxoplasmosis: The dosage required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalaria dosage. Adults: Initial dose is 50 to 75 mg daily with 1 to 4 g of a sulfonamide of the sulfapyrimidine type (e.g., sulfadoxine). Continue for 1 to 3 weeks, depending on response and tolerance. Dosage for each drug may then be reduced by one half and continued for an additional 4 or 5 weeks. Children: Dosage is 1 mg/kg/day divided into 2 equal daily doses; after 2 to 4 days, reduce to one half and continue for approximately 1 month.	
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists that operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Dacogen were captured by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Dacogen with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Dacogen (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Dacogen 50mg as dir in clinic today #1	Dacogen 50 mg as directed in clinic today dispense number one
Inpatient RX: Dacogen 30 mg IV infusion after current IV is finished	

2. Results:

One voice respondent interpreted the proposed name as Macugen. Macugen is a currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

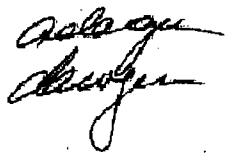
1. Look-alike and Sound-alike Names

In reviewing the proprietary name Dacogen, the primary concerns related to look-alike and sound-alike confusion with Adagen, Daraprim, Decadron, Depacon, Depogen, Desogen, Doxepin, and Macugen. DMETS would like to acknowledge that a search of Micromedex[6] (Martindale's Complete Drug Reference component) found the look-alike and sound-alike medication, Dicogen that is marketed in Taiwan. Although the look-alike and sound-alike characteristics are obvious, DMETS believes the actual possibility for confusion with Dicogen is minimal due to areas of marketing.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Dacogen could be confused with Macugen as one respondent misinterpreted the proposed name as this, a currently marketed ophthalmic product. The remaining misinterpretations were misspelled/phonetic variations of the proposed name.

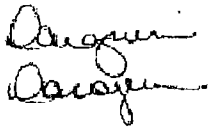
a. Adagen may look and sound similar to Dacogen when scripted and spoken. Adagen contains bovine pegademase, which is used to treat ADA-deficient severe combined immunodeficiency disease (SCID). The product is dosed every seven days as an intramuscular injection. The first dose is 10 units per kilogram, the second dose is 15 units per kilogram and the third dose is 20 units per kilogram. The maintenance dose is 20 units per kilogram, which may be increased by 5 units per kilogram if necessary. The maximum single dose is 30 units per kilogram. Adagen should not be diluted or mixed with any other drug prior to administration and should be stored under refrigeration. The orthographic similarities stem from the identical ending of "gen" and the likeness of the preceding "a" and "o" when scripted. In addition, a reader could transpose the leading "A" and "D" (especially when written in lower case), which may result in transcription error or misinterpretation of the name when hurried.

[6] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.



The auditory similarities stem from the shared ending of "gen", central "ă" sound and three syllable count. However, verbally, the leading "D" of Dacogen should serve as a distinguishing characteristic in speech. The products share a similar dosage form (injection). The products differ in the following characteristics: dosage regimen (every 7 days compared with every 8 hours, then every six weeks), indication of use (ADA-deficient severe combined immunodeficiency disease compared with myelodysplastic syndrome), storage (refrigeration compared to room temperature), and strength (250 units/mL compared with 50 mg). Although both drug products require calculation for dosing, Adagen is based on units per kilogram and Dacogen based on milligram per m^2 and the actual doses will differ significantly with Adagen dosed over one-hundred units (typically dosed in the 100's of units) compared with less than 50 milligrams for Dacogen. In addition, due to their context and specificity of use, the likelihood for verbal or ambiguously written prescriptions is minimal, which should help to alleviate auditory or scripted confusion. Due to the differences in product characteristics, DMETS believe the chance of error to be minimal.

b. Daraprim may look and sound similar to Dacogen when scripted and spoken. Daraprim contains pyrimethamine for the prevention of malaria and treatment of malaria and toxoplasmosis. The orthographic similarities stem from the shared leading "D", central placement of a downstroke and the likeness of "r" and "c" with the concluding "m" and "n" upon scripting. The auditory similarities stem from the shared leading "D", three syllable count and likeness of the concluding "m" and "n" in speech. However, the concluding letter combinations of "prim" and "gen" should serve as a distinguishing characteristic in speech.



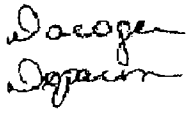
In addition, the products differ in route of administration (oral compared with intravenous infusion), strength (25 mg tablets compared with 50 mg vial), dosage regimen (6.5 to 25 mg weekly or 6.25 mg to 75 mg daily compared with 15 mg/m^2 over three hours every 8 hours for three days every six weeks), dosage form (tablet compared with injectable), and primary context of use (tablets used at home/traveling compared with infusion in a physician's office, hospital, hospice or clinic). However, there is the possibility for a numerical dose overlap at 25 mg (for Dacogen, 135 pound patient at 64 inches). In addition, since pediatric dosing is weight dependent there could be dosing overlaps. The likelihood for confusing Dacogen for Daraprim is greater, since the Daraprim name has a higher verbal/visual association due to length of time on the market (approved in 1953). Due to the context of use, frequency of administration and the necessity for preparation (reconstitution and dilution) for Dacogen, the administration will most likely occur in the hospital or in an outpatient clinic associated with the hospital. According to JCAHO requirements, medication orders must document all the elements required to accurately complete the order, such as frequency and route of administration. The inclusion of these data on an order would serve to differentiate the two drug products. The dosing regimens differ at daily/weekly for Daraprim compared to the 3 hour infusion every 8 hours for three days and Daraprim is an orally administered compared to the intravenous administration of Dacogen. In addition, the context of use would help to alleviate confusion, as Dacogen will be used primarily utilized by oncologist or hematologist with Daraprim (inpatient use) used by infectious disease specialist. Due to these different characteristics, DMETS believes the possibility for confusion to be minimal.

c. Decadron may sound similar to Dacogen when spoken. Decadron contains dexamethasone for the treatment of various conditions that include allergic conditions, cerebral edema, collagen diseases, dermatologic conditions, edematous states, endocrine disorders, gastrointestinal diseases, hematologic disorders, neoplastic diseases, ophthalmic diseases, respiratory disease, and rheumatic disorders. In addition, dexamethasone is used for diagnostic testing for adrenocortical hyperfunction. Dosing is varied, but initial doses range from 0.75 mg to 9 mg per day. It is preferred that maintenance dosing consists of the lowest possible dose for clinical effect. Verbally, the leading two syllables of "deco" and "daco" may sound similar. However, the concluding "dron" and "gen" should serve to distinguish the two names in speech. This was confirmed by the verbal studies conducted by DMETS that found all participants identified the "gen" of Dacogen, although spellings varied. As Decadron is a well recognized proprietary name (approved 1958), the generic products marketed today may be written using this proprietary name. Thus, DMETS will consider all dexamethasone products for comparison. The route of administration may serve as a distinct characteristic for differentiation. For the oral preparations of dexamethasone, the products differ in the following product characteristics: strength (0.5 mg, 0.75 mg, 1 mg, 2 mg, 4 mg, 6 mg, 0.5 mg/5mL, and 1 mg/mL compared to 50 mg vial), dose (0.75 to 9 mg per day compared to 15 mg/m^2), and frequency (every 6 to 12 hours compared to a single, 30 minute infusion to be repeated every 8 hours for three days). For the otic and ophthalmic formulations, the products do not share any product characteristics as shown by the following: strength (0.1% compared to 50 mg vial), dose (1 to 2 drops/thin layer compared to 15 mg/m^2), and frequency (every hour/three to four times daily compared to 15 mg/m^2 every 8 hours for three days). In addition, because the product is available for both otic and ophthalmic use, prescriptions will typically indicate the route of administration for proper order completion. For the injection preparation of Decadron, the drug products share the route of administration of intravenous injection. However, dexamethasone may also be administered intramuscularly and intra-articularly. Intra-articular administration will likely be distinguishable by the need to denote where (joint, tissue) to be administered. The products differ in strength (4 mg/mL, 10 mg/mL, 20 mg/mL, 24 mg/mL compared to a single 50 mg vial) and frequency of dosing (every 6 to 12 hours compared to a single 30 minute infusion, repeated every 8 hours for three days). However, intra-articular dosing is a single administration to be repeated every 3 to 5 days or every 2 to 4 weeks, which differs from Dacogen frequency of dosing. Overall, drug names are less likely to be confused because of the need for additional product characteristic descriptions. The abbreviations for the route of administration (PO= oral compared with INJ= injectable) could potentially be confused, despite different preparations. However, dosing for Dacogen is usually higher than those seen for Decadron. Thus, the continuously higher doses may alert practitioners to the differences. All this, in addition to difference in the endings of the name should lead to product differentiation; thus DMETS believes the possibility for confusion to be minimal.

d. Depacon may look similar to Dacogen when scripted. Depacon contains valproate sodium for the treatment of seizures by serving as an intravenous alternative for patients whom oral administration is temporarily not feasible. Depacon is administered as a 60-minute infusion (but not more than 20 mg/min) with the same frequency as the oral products. Dosing ranges from 10-15 mg/kg/day, which may be increased by 5-10 mg/kg/day until optimal clinical response (up to 60 mg/kg/day). The orthographic similarities stem from the shared leading "D" and concluding "n". The common, although transposed, downstroke and shared "c" may still be identified as the opposite position. Research, such as the article by Grainger and Whitney[7] has found that letters may be conversely positioned and the reader still identify the word correctly; this could be

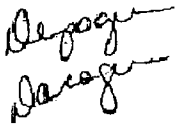
[7] Grainger and Whitney. Does the huamn mnid raed wrods as a wlohe? Trends in Cognitive Sciences. 8 (4) 58-59. http://www.cs.umd.edu/~shankar/cwhitney/Papers/TICS.pdf

extrapolated to conclude that the reader may misidentify a word if there is enough similarity to another well recognized name or word.



The drug products share a route of administration (intravenous infusion) and dose (up to 15 mg/kg compared with 15 mg/m^2). However, it is common for practitioners to order by the required dose for the patient. Thus, a 130 pound, 64 inch patient would be dosed with 886 mg of Depacon per day compared with 24.45 mg of Dacogen. Since this dose is so significantly different (i.e., dose of Depacon will be significantly higher than those of Dacogen) and Dacogen has such a narrow index of use, the confusion should be minimized. As valproate is a familiar drug product, many practitioners are aware that this product is dosed as milligram per kilogram, not "m^2"; thus, the "m^2" serves as a distinguishing characteristic. Furthermore, practitioners may be prescribing valproate using the established name in lieu of the proprietary name, Depacon. In addition, per the Saegis[8] database, the sales volume for Depacon is low. The products also differ in strength (100 mg compared with 50 mg vial), infusion times (over 60 minutes compared with over three hours), and context of use (short-term therapy for seizure activity in patients where oral therapy is not feasible compared with 24-week therapy). Due to differing characteristics, DMETS believes the possibility for error to be minimal.

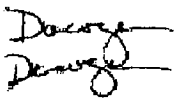
e. Depogen may look and sound similar to Dacogen when written and spoken. Depogen contains estradiol cypionate (in oil for injection) for the treatment of moderate to severe vasomotor symptoms associated with menopause or hypoestrogenism caused by hypogonadism. Recommended dosing is 1 mg to 5 mg intramuscularly every three to four weeks for moderate to severe vasomotor symptoms associated with menopause. For female hypogonadism, the dosing is 1.5 to 2 mg intramuscularly at monthly intervals. The product is available as 5 mg/mL in a 10 mL vial. Orthographically, the names share the same ending of "ogen" with the identical leading "D."



The auditory similarities stem from the shared leading "D", central "o" and concluding "gen." The products may be differentiated by the strength (5 mg/mL compared with 50 mg vial), dose (1.5 mg to 2 mg compared with 15 mg/m^2), and dosing frequency (monthly compared with every 8 hours for three days every six weeks). In addition, both products have specialized use, with Depogen primary administered by a gynecologist and Dacogen by an immunologist or oncologist. Furthermore, the Saegis[9] database notes the sales volume for Depogen to be low. Due to the apparent low usage compounded by the differences in dose and frequency, DMETS believes the possibility for error to be minimal.

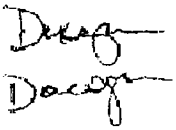
f. Desogen may look or sound similar to Dacogen when scripted and spoken. Desogen contains 150 micrograms of Desogestrel and 30 micrograms of ethinyl estradiol in each of the 21 active tablets. Desogen is indicated for the prevention of pregnancy. The patient is to take one tablet daily for twenty-one days. The auditory and orthographic similarities result from the shared leading "D" and ending of "ogen" (see below).

[8] The Saegis[8] Pharma-In-Use database was searched for drug names with potential for confusion.
[9] The Saegis[9] Pharma-In-Use database was searched for drug names with potential for confusion.



The auditory similarities are also compounded by the three syllable count and orthographically by the shared seven letter count. However, they differ in product characteristics including the following: route of administration (oral compared with intravenous infusion), strength (150 mcg/30mcg compared with 50 mg), dosage form (tablet compared with injection), dispensing amount (one pack/28 tablets compared with one vial or bottle), indication of use (oral contraception compared with myelodysplastic syndrome), dose (one tablet compared with 15 mg/m^2), and frequency of dosing (daily compared with a single 30 minute infusion, repeated every 8 hours for three days, every 6 weeks). Although the look-alike and sound-alike properties are strong, the differing product characteristics minimize the likelihood for name confusion.

g. Doxepin may look like Dacogen when scripted. Doxepin is used for the treatment of depression/anxiety. Recommended initial dosing for mild to moderate illness is 75 mg per day, with usual optimum dosing at 75 to 150 mg per day. Patients with more severe anxiety or depression may be increased to 300 mg per day; where patients with mild symptomatology or emotional symptoms accompanying organic disease are dosed at 25 to 50 mg per day. The orthographic similarities stem from the shared leading "D", downstroke of "p" and "g", and concluding "n." Furthermore, "o", "a", "i" and "e" may all have a likeness when encompassed in a name (see below).



The products share an available strength of 50 mg and the dose may overlap (25 mg). However, the products differ in characteristics such as route of administration (oral compared with intravenous infusion), frequency of dosing (daily compared with three hour infusion every 8 hours for three days every 6 weeks), and duration of therapy (maintenance therapy compared with four six-week cycles). Due to the context of use, frequency of administration and the necessity for preparation (reconstitution and dilution) for Dacogen, the administration will most likely occur in the hospital or in an outpatient clinic associated with the hospital. According to JCAHO requirements, medication orders must document all the elements required to accurately complete the order, such as frequency and route of administration. The inclusion of these data on an order would serve to differentiate the two drug products. The dosing regimens differ at daily for doxepin compared to the 3 hour infusion every 8 hours for three days for Dacogen and doxepin is an orally administered compared to the intravenous administration of Dacogen. Thus due to the differences in dosage form, dose and dosing frequency, DMETS believes the possibility for error to be minimal.

h. Macugen may sound similar to Dacogen, which was confirmed by a participant of the verbal study conducted by DMETS. Macugen contains pegaptanib that is an intravitreal injection for the neovascular age-related macular degeneration. The recommended dose is 0.3 mg once every six weeks via intravitreous injection. The drug product should be stored under refrigeration and is available as a single-use glass syringe that delivers 0.3 mg in 90 microliters. The drug product is packaged in two pouches; one containing the glass syringe of drug product and the second containing the plunger rod and flange. The auditory similarities stem from the shared ending of "gen", three syllable count and likeness of the central "cu" and "co" in speech. However, the leading "M" and "D" should help to differentiate the product names. In addition, the drug products differ in route of administration (intravitreous compared with intravenous infusion), available strength

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Dacogen. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name Dacogen acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Kim Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Dacogen)

Inpatient	Outpatient	Voice
Dacogen	Dacogen	macugen
Dacogen	Dacogen	Dacogen
Dacogen	Dacogen	Darogen
Dacogen	Daiogen	Dapogen
Dacogen	Dacogen	Dacogen
Dacogen	Dacogen	Dacagen
Dacogen	Dacogen	Dacagen
Dacogen	Dacogen	Dacojen
Dacogen	Daiogen	Bacogen
Dacogen	Dacosyn	Bacogen
Dacogen	Dacogen	Dacogen
Dacogen	Dacogen	Dacogen
Dacaron	Docagen	Dacagen
Dacogen	Dacogen	
	Dacogen	
	Daesgen	
	Doeogen	

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

/s/

Kimberly Culley
6/22/05 09:31:27 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/22/05 06:21:56 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/23/05 06:32:08 AM
DRUG SAFETY OFFICE REVIEWER

SuperGen®

October 29, 2004

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products (HFD 150)
Document Control Room 2061
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1448

RE: New Drug Application # 21-790
Dacogen™ (decitabine) for injection
Clinical portion of a rolling submission
Request for Priority Review

Dear Dr. Pazdur,

In accordance with Section 505(b) of the Federal Food, Drug and Cosmetic Act and 21CFR 314.50, this submission provides the Clinical section of NDA #21-790. Decitabine, the active ingredient in Dacogen has been granted Orphan Drug Status (February 22, 1999) and Fast Track designation on May 9, 2003. It has also been the subject of an EOP2 meeting with the Agency on January 31, 2001, April 25, 2003 and August 15, 2003 (CMC) and a pre-NDA meeting on February 6, 2004. The proposal for a rolling NDA was submitted March 26, 2004 and accepted April 21, 2004.

In accordance with the Guidance to Industry, "Fast Track Drug Development Programs – Designation, Development, and Application Review" (July 2004), SuperGen requests priority review of this NDA. After completion of two phase II trials in Europe, SuperGen conducted a phase III study in myelodysplastic syndrome (MDS).

During the time of the development program, there were no approved therapies for MDS; supportive care (transfusion, antibiotics, hematopoietic growth factors) had been the standard of care. Outcome on supportive care, however, is unsatisfactory because patients continue to be exposed to the inherent complications of worsening cytopenias and leukemic transformation. Additionally, patients are exposed to complications of transfusions, which include transfusion reactions, antibody development to blood components, iron overload, and cost.

In the Phase III study, overall Response Rate (CR+PR) in the Dacogen arm was 17% (15/89) vs. 0% in Supportive Care ($p<0.001$). More than half (53%) of the responders (8/15 CR and 7/15 PR) had a CR. Median time to response onset for Dacogen was 89

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days and the median duration of response to Dacogen was 266 days (131-346). Dacogen patients had increased transfusion requirement early on treatment but more frequently became transfusion independent during continued therapy. Dacogen patients also had significantly better global health status, greater physical functioning ability and less fatigue and dyspnea by Quality of Life measures.

The 17% Overall Response Rate (CR+PR) and the 29% Improvement Rate (CR+PR+HI) in the Phase III study were consistent with the results of the two supportive Phase II studies. In the Phase II studies, the Overall Response Rates were 24 and 26%, and the Improvement Rates were 38% and 41%. Responses were durable and observed across IPSS, FAB, gender, age, previous treatment, and type of MDS (*de novo* or secondary) in all three studies. Clinical benefits in Dacogen responders included independence from RBC and platelet transfusions, improved quality of life, longer survival and prolonged time to AML or death.

On May 19, 2004, one agent was approved for the treatment of MDS, but was not available as a positive control therapy during the Dacogen development program. The Dacogen Phase III study was run to current clinical standards and used newer and stricter criteria to evaluate response. For all the above reasons, the Sponsor requests priority review of this NDA.

This submission is provided in the format of the Common Technical Document (CTD), in electronic format, following the relevant Guidances to Industry and ICH documents. The submission is provided on DLT tape and has been sent to the Electronic Document Room in Beltsville, MD. As a convenience to the Reviewer, this submission includes the entire NDA submission, including the Chemistry, Manufacturing and Controls portion (submitted May 27, 2004) and the Nonclinical portion (submitted August 21, 2004).

As a guide to the Reviewer:

Module 1 includes the basic information required for a filing to the FDA, including product labeling.

Module 2 includes the CTD table of contents and the summary documents.

Module 3 includes the information on the drug substance (decitabine) and the drug product (Dacogen), including all of the attachments, executed batch records and references mentioned in the text.

Module 4 includes the nonclinical study reports and references cited in the nonclinical summaries in Module 2.4 and Module 2.6.

Module 5 includes all the study reports and case report forms from the clinical trials that support this NDA. SuperGen has conducted a phase III study in MDS, which, along with two large phase II studies, support this indication. Additional safety information from phase I and II studies are also submitted.

If you have any questions regarding this submission or require any additional information, please contact the undersigned at the numbers provided.

Sincerely,

for

Audrey F. Jakubowski, Ph.D.
Sr. Vice President, Regulatory Affairs and Quality
Chief Regulatory and Quality Officer

Office: 925-560-0100 x352
Home Office: 410-827-9450
Email: ajakubowski@supergen.com

cc: Food and Drug Administration
Center for Drug Evaluation Research
Central Document Room
5901-B Ammendale Rd
Beltsville, MD 20705-1266

MEETING MINUTES

MEETING DATE: April 25, 2003 **TIME:** 2:30 **LOCATION:** G

IND: 33,929 **Meeting Request Submission Date:** March 24, 2003
FDA Response Date: March 26, 2003
Briefing Document Submission Date: April 11, 2003

DRUG: Decitabine **INDICATION:** myelodysplastic syndrome

SPONSOR: SuperGen **TYPE of MEETING:** pre-NDA

FDA PARTICIPANTS: Robert Temple, M.D., Dir., ODEI
Bruce Cheson, M.D., ODAC Consultant (pre-mtg review)
Richard Pazdur, M.D. Dir., DODP
Grant Williams, M.D., Dep. Dir., DODP
Ann Farrell, M.D., Acting Medical Team Leader, DODP
Ramzi Dagher, M.D., Medical Officer, DODP
Anwar Goheer, Ph.D., Pharmacologist, DODP
Atik Rahman, Ph.D., Clin. Phar./Biopharm. TL, DODP (pre-mtg)
Sophia Abraham, Ph.D., Clin. Pharm. Rev., DODP (pre-mtg)
Peiling Yang, Ph.D., Statistician, DODP
John McCormick, M.D., Orphan Products Development
Dotti Pease, Project Manager, DODP
Maitreyee Hazarika, M.D., Medical Officer, DODP
Robert Kane, M.D., Medical Officer, DODP

SPONSOR: Emil Bayar, M.D., Dir., Hematology/Oncology, Medical Monitor
Gil Fine, Ph.D., Sen. Dir., Biometrics and Data Management
Audrey Jakubowski, Ph.D., V.P., Regulatory Affairs
John Lyons, Ph.D., Sen. Dir., Scientific Development
Michael McCullar, Ph.D., Exec. Dir., Strategic Project Management
Craig Rosenfeld, M.D., Chief Scientific Officer, Sen. V.P.

MEETING OBJECTIVES: Discuss sponsor's proposal to submit an NDA for myelodysplastic syndrome (MDS) based on interim data and to answer their specific questions.

BACKGROUND: An EOP2 meeting had been held August 5, 1998 (with Pharmachemie, the previous sponsor) to discuss the MDS clinical development plan. At this meeting, sponsor proposed doing two well-controlled phase 2 trials – FDA strongly recommended at least one adequately sized and controlled Phase 3 study with a supportive phase 2 study and stated that for

high-risk MDS patients a complete response (CR) might be a potential surrogate endpoint for accelerated approval.

Another EOP2 meeting was held on January 31, 2001, this time with SuperGen, the new sponsor. The sponsor proposed a single randomized open label phase 3 study of decitabine vs. supportive care with CR and partial response (PR) as the primary endpoints and survival and others as the secondary endpoints. It was agreed during discussion that the primary endpoint should be time to acute myeloid leukemia (AML) and that a sample size of 80 patients per arm was acceptable - FDA recommended against an interim analysis for efficacy because of this small sample size.

The current meeting was scheduled to discuss a proposal to submit an NDA based on the interim analysis of time-to-progression to AML or death for accelerated approval and use the completed study as the confirmatory trial.

After the pre-meeting on April 17, 2003, FDA responses were faxed to the sponsor (below). (Of note, the sponsor subsequently inquired about the possibility of using response rate for the purposes of accelerated approval. This issue was further addressed at the meeting.) Sponsor chose to still have the face-to-face meeting, and the discussion is indicated in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the Agency agree that the data presented are sufficient to grant Fast Track status to decitabine (DAC) in the treatment of Myelodysplastic Syndromes (MDS)?

   FDA – The clinical database you describe includes the elements which would need to be considered for fast-track designation. Please submit a specific request for our review.

2. The DAC development program falls under SubPart E, since MDS is a serious, life-threatening disease with no FDA approved therapies. The data presented in this document show that patients treated with DAC have a significantly longer time to progression to AML or death than those given standard of care.

   FDA : Fast-Track designation and accelerated approval under subpart H are two separate and independent processes.

   a. SuperGen plans to submit an NDA containing the interim analysis of the Phase III DAC-0007 data and the phase II data to support the use of DAC in Advanced-Stage adult MDS patients. Does the Agency consider this clinical package acceptable for Accelerated Approval?

      FDA – No. With respect to the interim findings presented in the meeting package, it is noteworthy that the claimed effect is not statistically persuasive (p = .049 instead of planned p = .0052). Furthermore, the data suggests that benefit in higher-risk

populations may be more substantial, although it is too early to make definitive judgements about this issue. Should you fail to demonstrate ultimate benefit in the overall intent-to-treat population, any subgroup analyses would be considered exploratory. Interpretation of these issues will be somewhat hampered by the fact that intermediate-1 patients were added to the eligible population on 10/26/01.

For the purposes of accelerated approval under subpart H, a surrogate endpoint reasonably likely to predict clinical benefit would usually be examined. Study DAC-0007 has a primary endpoint of time to AML or death, which could qualify it as one supportive trial for the purpose of full approval if a statistically significant finding in a prespecified final analysis of the intent to treat population was demonstrated. As all patients have been enrolled, a final analysis can be contemplated in a reasonable timeline, after a specific number of events have occurred.

Finally, it may be difficult to complete DAC-0007 in a post-approval environment, thus abrogating the possibility of confirming clinical benefit in this patient population.

Sponsor – From the data presented on the objective response rate from the Phase III study as well as the supporting data from the multicenter Phase II study, SuperGen requests clarification regarding whether these data for a surrogate endpoint would qualify for accelerated approval.

FDA – At this time, we do not consider response rate (RR) an acceptable surrogate endpoint in this clinical setting. You should submit a new proposal with a rationale/justification for RR as a surrogate endpoint in MDS and showing that the magnitude of this RR is significant.

b. In the spirit of the March 12-13, 2003 ODAC meeting, SuperGen proposes that the final analysis of the randomized Phase III study (DAC-0007) be identified as the confirmatory study for full approval. Does the Agency accept this proposal?

FDA – No. See a above.

c. SuperGen is evaluating more convenient dose schedules or alternate routes of administration of DAC. Would a study of this type also be useful as a confirmatory trial?

FDA – No. See a above. Accelerated approval is not an option at this point; hence, discussion of a confirmatory trial is irrelevant. However, in general, we would be interested in more detailed proposals regarding evaluation of alternative schedules or routes of administration, which could be used in the design of other supportive trials.

3. Patients in the control arm of D-0007are not eligible to receive DAC until they progress to ANIL and qualify for the companion protocol DAC-0 11. SuperGen seeks Agency guidance

regarding the most appropriate way to manage the completion of the D-0007 study without placing any patients at risk.

a. SuperGen plans to share the results of the interim analysis of DAC-0007 with Investigators. Does the Agency agree that this is appropriate?

FDA – see 2 a. No. The results of an interim analysis should be confidential and released only if there are ethical considerations.

b. Can the Agency offer any guidance on how to insure that patients in the Supportive Care arm complete the study in the same manner as before the interim analysis?

FDA – see 2 a.

4. Sample size for the D-0007 study was calculated assuming a 6-month accrual and 24 month duration to complete. Actual accrual took 20 months (July 2001 to March 2003). If study duration is not extended to collect information on additional events beyond the protocol-specified 24 months, the effective statistical power will be <70%, based on the assumptions made in the original power calculation. SuperGen proposes extending the study an additional 7 months for the confirmation of interim results. This allows the data to mature and simultaneously retain 80% power for the study. Does the Agency accept this proposal?

FDA - Since the primary analysis is unstratified logrank test, the timing for the final analysis should be based on reaching a certain number of events, not on calendar time. The nominal significance level for the final analysis should be determined accordingly. If there is a possibility for increasing the event size during the study, an adaptive statistical testing procedure needs to be pre-specified in the protocol to preserve potential inflation of the false positive error rate.

FDA – The sponsor subsequently proposed that the final analysis would be performed when 92 patients had reached the study endpoint. This is acceptable.

5. SuperGen intends to present data from the Interim Analysis of 45 patients at the Annual Meeting of the American Society of Hematology Meeting in December 2003. The abstract deadline is in August. Would this have any adverse impact on the approval process for DAC, since the NDA could be under review at that time?

FDA – Publication of interim analysis results may jeopardize the completion of the trial and ultimate demonstration of efficacy. Hence, we strongly discourage release of the results of the interim analysis.

ADDITIONAL FDA COMMENTS:

Clinical Pharmacology and Biopharmaceutics:

We recommend that you submit your clinical pharmacology/ biopharmaceutics development plan for the use of decitabine in patients with MDS. We also recommend that you request a meeting to discuss any issue regarding this plan.

OTHER FDA COMMENTS: see attachments – included in fax but not discussed.

ACTION ITEMS:

Sponsor will consider our comments further and may submit another proposal for accelerated approval.

After the meeting, FDA further indicated that we would consider a proposal for a confirmatory study using a related patient population. Whether a CML population could be found that would be considered a related population would depend on the sponsor's proposal and FDA consideration of this proposal.

_____ **Concurrence Chair:** _____

Dotti Pease
Chief, Project Management Staff

Ramzi Dagher, M.D.
Medical Officer

ATTACHMENTS: SuperGen's April 21, 2003 E-Mail responses to FDA's responses
FDA Standard pre-NDA bullets

Inquiry 1: Stratification by IPSS Classification

SuperGen wishes to clarify the use of IPSS classification as a stratification criterion. In response to SuperGen's Question 2a, the Agency stated "Interpretation of these issues will be somewhat hampered by the fact that intermediate-1 patients were added to the eligible patient population on 10/26/01 and **randomization strata were modified to include IPSS classification on 4/24/02**" (emphasis added). SuperGen wishes to clarify that randomization is stratified by IPSS classification and prior treatment for MDS (yes/no) and that these stratification factors have been used since the initiation of the study.

Does this clarification resolve the Agency's concern stated in their response to question 2a?

Inquiry 2: Use of Surrogate Endpoints for Accelerated Approval

SuperGen understands that under the provisions of Subpart H, a surrogate endpoint reasonably likely to predict clinical benefit could be acceptable for Accelerated Approval. As described in the published literature and from Agency decisions on other NDAs, objective response rates have been used as surrogate endpoints in clinical trials of drugs to treat both solid tumor and hematological malignancies. In the recent case of oxaliplatin, objective response rate (complete response + partial response) from an interim analysis was used for this purpose. In an additional example, gemtuzumab was granted accelerated approval in elderly patients with CD33+ acute myelocytic leukemia (AML). AML in the elderly has similarities to patients eligible for D-0007. Gemtuzumab received accelerated approval based on response rates (complete remission + complete remission with delayed platelet recovery) from a single pivotal Phase II study in 37 patients, supported by two small single-arm Phase II studies.

The data shown here as Table 1 were presented in SuperGen's briefing document as Table 7 (page 22). We limited the information in Table 1 to include only the number of PRs and CRs, as these are surrogate endpoints that have been accepted as predictive of clinical benefit. Data presented in the briefing document regarding our interim analysis indicated that patients randomized to Decitabine achieved a statistically superior response rate ($p = 0.0106$) compared to patients randomized to the control arm. These results are very similar to data generated by the original Sponsor in multicenter Phase II studies that were also presented in the briefing document. The Phase II results are presented here as Table 2.

Table 1. Best Response on Study Based on Investigator's Assessment

	Decitabine (N=29)	Supportive Care (N=27)	p-value[1]
Best Response on Study			0.0106
CR (Complete Response)	2 (7%)	0	
PR (Partial Response)	5 (17%)	0	

[1]from 2-sided Fisher's Exact Test for equal overall response rate (CR+PR)

Table 2. Best Response on Study Based on Investigator's Assessment in Study 95-11

Best Response on Study (N=66)	
CR	13 (20%)
PR	3 (5%)

At the time the briefing document was assembled, SuperGen did not have in-house the results of an independent review of patient responses but this review was mentioned on page 13 of the briefing document. Data from this independent review became available too late to present in the briefing document but are presented here as Table 3. They independently confirm that patients receiving Decitabine in study D-0007 had a statistically superior response rate over the supportive care arm. Table 4 provides a summary of response rates for the two trials, including the independent review of D-0007.

Table 3. Best Response Based on Blinded Independent Review of Evaluable Patients

	Decitabine (N=46)	Supportive Care (N=42)	p-value[1]
Best Response on Study			0.0079
CR	5 (11 %)	0	
PR	7 (15 %)	2 (5%)	

Table 4. Summary of Response Data in Decitabine Trials for MDS

	PCH 95-11	D-0007 Investigator's Assessment (N=56)		D-0007 Blinded, Independent Review (N=88)	
		Control	Decitabine	Control	Decitabine
CR	20%	0%	7%	0%	11%
PR	5%	0%	17%	5%	15%
Significance		P = 0.0106		P= 0.0079	

The Briefing Document focused discussion on the use of the interim analysis of the primary endpoint (time to AML or death) as a basis for accelerated approval. The agency commented that this endpoint was not a surrogate and was not appropriate for accelerated approval. SuperGen accepts this clarification but is compelled to inquire about the data presented on an accepted surrogate endpoint, namely, response rate. SuperGen requests clarification on the following concerns:

a) From the data presented on the objective response rate from the Phase III study as well as the supporting data from the multicenter Phase II study, SuperGen requests clarification regarding whether these data for a surrogate endpoint would qualify for accelerated approval?

b) The dataset for the interim analysis consisted of all patients randomized on the date of the 45th event. At the time of the interim analysis, only the data shown in the briefing document were available. Since that time, more Case Report Forms have come in-house and SuperGen would like to update the data on secondary endpoints. Would the Agency consider such an update as an additional interim analysis?

Inquiry 3: SubPart E: Serious or Life-Threatening

Does the Agency agree that myelodysplastic syndromes qualify as a serious or life-threatening disease under SubPart E??

Inquiry 4: Proposed Final Analysis

SuperGen requests clarification of the Agency's response to question 4. The original study protocol incorporated a time dimension in the power calculation and SuperGen's proposal in question 4 was based on those criteria.

Sample size for study D-0007 assumed a 6-month accrual and a 24-month duration to complete. Actual accrual took 21 months (July 2001 to April 2003). If the study is not extended to allow for the collection of information on additional events beyond the protocol-specified 24 months (ending July 2003), the effective statistical power will be 68%. This is clearly unacceptable.

Using the assumptions in the original power calculation (median times to AML or death of 12 and 22 months in the supportive care and decitabine treatment arms, respectively) and the actual 21-month accrual period, the expected number of patients that will reach a study endpoint by February 2004 (31-month study duration) is 92. The statistical power of a log rank test at the two-sided 5% level of significance for this scenario is 80%. SuperGen proposes stopping the study and performing the final analysis when 92 patients (58% of all patients) have reached study endpoint.

Does the Agency accept this proposal?

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. Pediatric Final Rule

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the

third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

4. Pediatric Exclusivity

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.-≤ 2Year		>2-≤12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	

Other

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/s/

Ramzi Dagher
5/15/03 08:22:35 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 33,929

SuperGen, Inc.
Attention: Audrey Jakubowski, Ph.D.
Vice President, Regulatory Affairs
4140 Dublin Boulevard, Suite 200
Dublin, CA 94568

Dear Dr. Jakubowski:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DACOGEN™ (decitabine) for injection.

We also refer to your March 5, 2004, request, serial number 164, for a special clinical protocol assessment, received March 8, 2004. The protocol is entitled "Intergroup Study (EORTC protocol 06011), Intravenous low-dose decitabine versus supportive care in elderly patients with primary Myelodysplastic Syndrome (MDS) (>10% blasts or high-risk cytogenetics), secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy: an EORTC-German MDS Study Group randomized phase III study".

We have completed our review of your submission and, based on the information submitted, have the following comments.

1. If this study is well-conducted, and after FDA review, demonstrates statistically significant survival advantage over supportive care, it will support an NDA for treatment of MDS.

2. Please confirm that the primary analysis for the primary endpoint, overall survival, will be the unstratified logrank test and that the final analysis will be performed when 185 deaths have been reported.

3. In estimating the sample size, you may want to consider the number of patients who will drop out of the study and those who will receive a nonrandomized therapy after patients go off protocol therapy.

4. Please clarify how many centers are participating in this trial and provide the detailed minimization technique for random treatment allocation. Since there are so many strata, with only 220 patients in the trial, the minimization technique may still allow for a considerable amount of imbalance.

5. With regard to quality of life measurements, you proposed a significance test to compare the compliance rates. Please note that failure to reject the null hypothesis does not imply that the compliance rates are equivalent between treatment arms.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Brenda Atkins, Consumer Safety Officer, at 301-594-5767.

Sincerely,

{See appended electronic signature page}

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

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/s/

Richard Pazdur
4/26/04 05:14:15 PM

MEETING MINUTES

MEETING DATE: February 6, 2004 **TIME:** 1:00 PM **LOCATION:** CR G

IND: 33,929 **Meeting Request Submission Date:** December 23, 2003(SN160)
FDA Response Date: December 30, 2003
Briefing Document Submission Date: January 12, 2004(SN161)

DRUG: Dacogen™ (decitabine) for injection

INDICATION: Myelodysplastic syndrome

SPONSOR: SuperGen, Inc.

TYPE of MEETING: Pre-NDA Type B Meeting

FDA PARTICIPANTS, TITLES AND OFFICES (attendees bolded):
Richard Pazdur, M.D., Director, Division of Oncology Drug Products (DODP)
Grant Williams, M.D., Deputy Director, DODP
Bruce Cheson, M.D., ODAC consultant (Pre-meeting only)
Lilia Talarico, M.D., Associate Director, DODP
Ramzi Dagher, M.D., Clinical Team Leader, DODP
Qin Ryan, M.D., Ph.D., Medical Officer, DODP
Atiqur Rahman, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, DODP
Sophia Abraham, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DODP
Raji Sridhara, Ph.D., Acting Biometrics Team Leader, DODP
Tan Nguyen, M.D., Office of Orphan Products Development (teleconference)
Brenda Atkins, Project Manager, DODP

INDUSTRY PARTICIPANTS AND TITLES:
Karl Mettinger, M.D., Ph.D., Senior Vice President, Chief Medical Officer
Michael McCullar, Ph.D., Senior Director, Strategic Operations and Registration Programs
Craig Rosenfeld, M.D., Senior Vice President and Chief Scientific Officer
Gil Fine, Ph.D., Senior Director, Biometrics and Statistics
Audrey Jakubowski, Ph.D., Vice President, Regulatory Affairs
Jocelyn Rojas, R.N. M.S.
Sheldon Mullins, Director, Regulatory Affairs

MEETING OBJECTIVES:

To discuss the content and format of the planned NDA for Dacogen™ (decitabine) for injection.

BACKGROUND:

Significant Regulatory history

August 5, 1998- FDA met with Pharmachemie, the original IND 33,929 holder, and discussed development of DAC in the treatment of MDS. The Agency indicated that a single phase 3 study supported by a single phase 2 study could be sufficient for an NDA in high risk patients. The Agency also commented that hematologic response (CR, PR) could be acceptable as a potential surrogate endpoint in high risk MDS patients and a randomized phase 3 trial might assess a composite endpoint.

1999 - SuperGen acquired DAC from Pharmachemie.

January 31, 2001 – FDA met with SuperGen about D-0007 phase 3 trial design. A composite endpoint, time to progression to AML or death was agreed upon.

April 25, 2003 – The sponsor's NDA proposal for AA was not accepted by FDA, since time to AML progression or death would be endpoints used for regular approval. Using RR as a surrogate endpoint was discussed and FDA requested information supporting the use of RR as a surrogate endpoint in MDS. FDA indicated that regular approval would be considered if D-0007 resulted in a statistically significant finding in a pre-specified final analysis of the ITT population.

NDA application goal:

1. Regular approval

2. AA by RR with EORTC study as phase 4 commitment.

3. Intent to request for pilot 1 program immediately after this meeting.

Information on RR in relation to survival based on sponsor literature search: Appendix 3, page 3 of meeting package.

Summary of Supportive Studies in MDS

	[redacted]	[redacted]	**Intergroup**[4]	[redacted]	[redacted]	**Decitabine**[1]
Type of Study	Retrospective	Phase 2	Phase 3	Retrospective	Retrospective	Phase 2
No. of Pts.	394	22	141	20	63	66
Eligibility	RAEB, RAEB-t/ Int-1, Int-2, High	RAEB, RAEB-t	Severe cytopenia or transfusions	RAEB, CMML	RAEB, RAEB-T, CMML	All FAB
Age (median)	~60	64	70	68	-	68
CR	58%	55%	11%	15%	44%	20%
PR		18%	21%	-	16%	5%
Failure		27%	-	85%	19%	
Induction Death	5-21% depending on chemotherapy regimen	9%	2%	-	20%	8%
Overall median survival		18 months	7 months	Not stated	See text	15 months
Survival for CR	19 months (median)[a]	24 months (median)[b]	-	31, 35+, 37+	See text	19 months (median)
Survival for non-CR	9 months (median)[a]	12 months (median)[b]	-	1 month (median)		Not stated
Survival for responders[c]	-	-	13.6 months (median)[d]			
Survival for non-responders			5.8 months (median)[d]			

[a] From landmark time of 6 weeks $p < 0.01$

[a] $p < 0.05$ by two sided log rank test

[c] Response was defined as $\geq 50\%$ reduction in marrow cellularity

[d] $p = 0.0517$ by log rank test

NDA proposal:

The decitabine (DAC) NDA proposal consists of data from one phase 3 trial (85 patients) and two phase 2 trials (164 patients), with the support of 6 other phase 1-2 trials (133 Patients) and 3 phase 1-2 pediatric trials (55 patients), as detailed in Table 1, page 9 of IND33929/SN161. The phase 3 trial, D-0007 is summarized as follows:

Study design		Open label, 1:1 randomization, multicenter, DAC 15 mg/m2 IV q 8hr on days 1-3 every 6-8 weeks versus supportive care in MDS patients.	
Amendment	1	3/13/2001	Changed primary endpoint to time to AML or death, accepted by FDA
	2	2/5/2002	Eliminated crossover and expanded the inclusion criteria from IPSS High risk and Intermediate-2 to also include Intermediate-1 MDS patients
	3	7/18-2002	Retrospective review of bone marrow by an outside expert.
End points		Primary	Time to death or progression to AML (TDA)
		Secondary	Hematologic response rate, survival, quality of life, transfusion requirements, incidence of febrile neutropenic episodes, duration of response and toxicity.
Sample		170 patients, enrollment started 7/2001 and completed on 4/7/2003	
Statistics		Two sided log-rank test and generalized Wilcoxon test for primary end points.	
Unplanned analysis		Cytogenetic response rate	
Efficacy		Interim analysis based on 45 patients indicated a 105 days versus 92 days median time to TDA ($p = 0.033$, Table 5, page 19). The difference is most significant in the High risk patient group (19 pts), 101 versus 51 days, $p = 0.012$. Also see figure 1-4. There were 3/21 CRs (14%), and 0 PRs (table 9, page 24). Survival is not reported at this time.	
Endpoint definition		Time to AML or death is the number of days from randomization (day 1) to death from any cause or progression to AML (30% or more blasts determined by the site or off site pathologist from on-study or off-study follow up bone marrow aspiration or biopsy).	
Censoring		• Date the patient was last known to be alive for lost to follow up • Date the patient first received decitabine for crossover from supportive care • Date the patient first received therapy for MDS out side randomized treatment arm (transfusion or epo) • Date the patient withdrew consent	

Supportive studies:

Protocol	Design	MDS pts (HR & Int2 %)	CR(%)	PR(%)	HR(%)	Other
PCH 95-11	European P2 single arm	66 (70%)	11 (17)	8 (12)	7 (11)	Median survival = 1.24 years. safety
PCH 97-19	Compassionate use	98 (52%)	17 (20)	10 (12)	17 (20)	Median duration of CR and PR = 107 days. safety
88-01	P1-2, AML and MDS	8/38	n/a	n/a	n/a	Safety
91-01	P2	21				Safety
91-02	P1	46				Safety
95-04	P1	8				Safety
95-05	P1	14				Safety
97-06	P2	6				Safety
79-01	P1 pediatric Leukemia	17/27				PK/PD, Safety
79-02	P1 pediatric Leukemia	25				PK/PD, Safety
90-01	P2 pediatric Leukemia	3				Terminated due to slow enrollment

EORTC 06011

Study Design	EORTC-German study, open label, randomized, multicenter, DAC 15 mg/m2 IV q 8hr on days 1-3 every 6 weeks versus supportive care in MDS (age > 60, high risk or >10% blasts).	
End points	Primary	Overall survival (intend to change to time to death and AML)
	Secondary	RR, PFS, QoL, safety, hospitalization days, number of transfusions
Sample	220	
Analysis	K-M, two sided log-rank test for primary analysis. The interim analysis will be performed at the end of accrual or 93 deaths, which ever comes first.	
Estimated completion date	Oct 2006	

FDA responses (**bolded**) were faxed to the sponsor on February 5, 2004. The sponsor chose to still have the face-to-face meeting, and the discussion is indicated in ***italics*** **(bolded)**.

QUESTIONS

1. The composite primary endpoint of 'time to AML or death' was agreed to by the Agency in the EOP2 meeting (January 31, 2001). A treatment that provides significant prolongation of time to AML or death provides direct clinical benefit to a patient and should qualify for 'regular' approval. Does the Agency agree?

FDA Response:

If the final analysis of the intent to treat population demonstrates a statistically significant finding, regular approval can be considered. Patients with Intermediate-1 risk who are randomized to the study should be considered part of the ITT population. Any subgroup analysis may only be considered exploratory.

2. The original eligibility for the Phase III study (D-0007) was limited to patients with Intermediate-2 and High Risk MDS.

a. If Study D-0007 shows a significant benefit for Dacogen treatment in the original target population (Int-2 and High Risk) and the Sponsor submitted the NDA as outlined in this Briefing Document, would this NDA be considered for regular approval?

FDA Response:

See answer to question 1.

b. If Study D-0007 shows a highly significant benefit in High Risk patients only and the Sponsor submitted the NDA as outlined in this Briefing Document, would this NDA be considered for regular approval?

FDA Response:

No. See answer to question 1. If a primary analysis has failed to meet its primary objective any subgroup analysis will be considered exploratory. In addition, the number of High Risk patients presented in your package is too small to be the basis of a conclusion that decitabine has efficacy.

Furthermore, the FDA considers you have conducted multiple interim analyses with multiple comparisons. In this context, the p-values presented in the meeting package are not interpretable.

Discussion:

The sponsor does not agree that they have conducted multiple analyses. Any subgroup analysis and adjustment for type 1 error for multiple analyses and comparisons will be a review issue.

3. Hematologic response (CR + PR + HI) as defined in the D-0007 protocol incorporates durable (minimum 2 months) improvement in peripheral blood counts that are transfusion and growth factor independent in addition to bone marrow normalization. (Cheson, 2000) This response definition, as used in this protocol, is accepted in the medical community as a surrogate for clinical benefit in MDS patients. Does the Agency accept the definition of hematologic response as a surrogate endpoint in MDS?

FDA Response:

No. HI is inconsistent from patient to patient since it is used to indicate variable levels of increase in one hematologic lineage or multilineage improvement in others. In Cheson's paper, the use of HI as an endpoint was noted to be most relevant to the lower risk MDS patients, whereas CR and prolongation of survival were considered more relevant to the higher risk patients.

4. Phase II studies demonstrated hematologic responses to decitabine treatment. The Phase III study (D-0007) includes a stricter definition of hematologic response (Cheson, 2000) as a secondary endpoint in this study. Would this NDA be considered for accelerated approval if Study D-0007 shows significantly higher hematologic responses to Dacogen compared to the standard of care treatment?

FDA Response:

No. Refer to our response to question 1. The meaning of hematologic responses (PR, CR, and HI) can be variable in this population. However, durable CRs would be of interest.

Discussion:

A review of CRs and PRs would be entertained by the Agency. The acceptability of this endpoint would depend on the magnitude of difference between the two arms and duration of response and relative number of CRs and PRs.

5. In a previous meeting, the Agency suggested that SuperGen consider performing a study in Europe. SuperGen is currently supporting an EORTC clinical trial of Dacogen vs. Best Supportive Care with eligibility criteria similar to D-0007. The EORTC study has already accrued >40 patients from a planned accrual of 220. The study design and size are very similar to Study D-0007 and SuperGen is working with the EORTC to modify the primary endpoint from survival to 'time to AML or death' in order to expedite completion of the study. An outline of the protocol is provided in Appendix 2. If this NDA were approved under the provisions for Accelerated Approval, would this study be considered an adequate confirmatory trial to secure regular approval?

FDA Response:

We are not considering this data in the briefing package for accelerated approval. We suggest that the EORTC study maintain a primary endpoint of overall survival. Please submit the EORTC protocol for a Special Protocol Assessment (SPA). This study, which may have regulatory impact in the U.S., should be submitted under an IND.

6. SuperGen provided detailed analysis plans in this Briefing Document.
a. Does the Agency accept the approach outlined in the document for
    1. Data censoring,
    2. Using peripheral blood blast counts where bone marrows do not exist,
    3. Proposed landmark analysis?

FDA Response (Question 6.a.1):

This is not acceptable. Data should be censored only for patients who are lost to follow up, or withdraw consent, or have not reached the specified event (AML or death).

Discussion:

The protocol specified definition of censoring for patients receiving alternative MDS therapy will not be used in the final analyses.

FDA Response (Question 6.a.2):

Discussion:

The FDA agreed that patients may be deemed as progressing based on peripheral blast counts alone if no marrow is available.

FDA Response (Question 6.a.3):

The proposed landmark analysis is not acceptable as a primary efficacy analysis.

b. Are there additional analyses the Agency would expect to see in the NDA?

FDA Response:

No

7. Regarding the format and content of the clinical module for this NDA, does the Agency accept SuperGen's proposals for

a. Studies that will be provided as Abbreviated reports or Synopses?

FDA Response:

See above.

Discussion:

The review team will re-evaluate and get back to the sponsor.

b. The content of the planned Clinical Pharmacology/Pharmacokinetics section?

FDA Response:

The content of your planned Clinical Pharmacology/Human Pharmacokinetic section of your anticipated NDA submission is not adequate:

1. **You should provide information on the metabolic pathways for decitabine and cytochrome P450 enzyme(s) involved (if any) in drug metabolism. The activity of the major circulating metabolite(s) should be also addressed.**

2. **You should provide information on the single- and multiple-dose pharmacokinetics (PK) in an adequate number of MDS patients at the proposed dosing regimen following a 1-hour infusion every 8 hour at a daily dose of 45 mg/m^2 on Days 1-3 in the first cycle. Time-dependent pharmacokinetics (change in PK from cycle to cycle) should be also addressed.**

3. **You should provide information on the effects of demographics such as age, gender, and ethnicity on the PK of decitabine.**

4. **How are you planning to address the use of decitabine in patients with hepatic or renal impairment in the package insert for Dacogen™?**

5. **You should examine in *in vitro* microsomal studies the potential for decitabine to inhibit and/or induce cytochrome P450 enzymes to predict the potential for drug-drug interactions *in vivo*.**

6. **You should provide information on the possible drug-drug interactions between decitabine and most commonly co-administered drugs in MDS patients.**

7. **You should provide the rationale for the selection of dose and dosing schedule in your pivotal Phase 3 study and whether this selection was based on identified biomarkers and in their relationships to safety, efficacy, and drug exposure.**

Discussion:

The sponsor acknowledges the FDA comments. Please submit any proposed study protocol(s) related to your clinical pharmacology plan.

c. Narratives on patients who died?

FDA Response:

Please clarify your plan for submission of narratives. Do you plan to submit narratives for patients who progressed to AML?

Discussion:

The sponsor does not plan to submit narratives for patients who progressed to AML.

d. The overall content of the clinical module for this NDA?

FDA Response:

See above. No further comment.

Final discussion items:

None

OTHER FDA COMMENTS:

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

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Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

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Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.- ≤ 2Year		>2-≤12	
	12-16		17-64		• 65	
Race:	White		Black		Asian	
	Other					

ACTION ITEMS:

1. **The sponsor should submit the EORTC protocol to the Agency as a request for a Special Protocol Assessment (SPA) to the IND.**
2. **The Agency will re-evaluate the sponsor's proposal to submit abbreviated reports or synopses in their NDA.**
3. **In response to the Clinical Pharmacology and Biopharmaceutics comments, the sponsor should submit any proposed study protocols related to the clinical pharmacology plan for the NDA.**

/s/ 2-20-04 (paper version)
Brenda Atkins
Project Manager

Concurrence Chair: (see electronic signature)
Ramzi Dagher, M.D.
Clinical Team Leader

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/s/

Ramzi Dagher
3/5/04 08:11:56 AM

MEETING MINUTES

MEETING DATE: August 15, 2003 **TIME:** 1:00 **LOCATION:** CR B

IND: 33,929/SN152/SN156 **Meeting Request Submission Date:** June 23, 2003
FDA Response Date: July 4, 2003
Briefing Document Submission Date: July 23, 2003

DRUG: Dacogen™ (decitabine) for injection **INDICATION:** Myelodysplastic syndrome

SPONSOR: SuperGen, Inc.

TYPE of MEETING: CMC – End of Phase 2 Type B Meeting

FDA PARTICIPANTS:

Richard Lostritto, Chemist Team Leader, Division of Oncology Drug Products (DODP)
Josephine Jee, Chemistry Reviewer, DODP (pre-meeting only)
Brenda Atkins, Project Manager, DODP

SPONSOR/APPLICANT: SuperGen, Inc. (SGI)

Sanjeev Redkar, Ph.D., Senior Director, Pharmaceutical Development
Rajashree Joshi, Ph.D., Director, Formulation Development
Fred Grab, Ph.D., Vice President, Compliance and Regulatory Affairs, CMC Submissions
Sheldon Mullins, Manager, Regulatory Submissions – CMC Submissions
SanJeev Redkar, Ph.D., Senior Manager, Process Development
Mike McCullar, Ph.D., Executive Director, Strategic Project Management
Craig Rosenfeld, M.D., Senior VP and Chief Scientific Officer
Sam Boddapati, Ph.D., Senior Director, Regulatory Affairs

MEETING OBJECTIVES: To discuss the elements of the Chemistry, Manufacturing and Controls information generated to support a planned NDA filing for Dacogen™ (decitabine) for injection.

BACKGROUND:

A pre-NDA meeting was held with the sponsor on April 25, 2003. FDA meeting minutes of August 5, 1998 with Pharmachemie, B.V. stated that it was "highly recommended that you request a CMC EOP 2 meeting as soon as possible." Decitabine was licensed by SuperGen, Inc. from Pharmachemie B.V. in 1998. The sponsorship of IND 33,929 was transferred by Pharmachemie to SuperGen in November 1999. FDA responses (below) were faxed to the sponsor on August 14, 2003. The sponsor chose to still have the face-to-face meeting, and the discussion is indicated in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Drug Substance

1. [redacted]), the first isolated intermediate, meets the requirements for starting material as per ICH Q7A guidance as described below:
   - incorporated as a significant structural fragment into the structure of the decitabine drug substance,
   - commercially available,
   - can be well characterized, and
   - [redacted] final decitabine drug substance.

   SuperGen plans to designate [redacted] as the starting material for the manufacture of decitabine drug substance.

   Would the Agency accept [redacted] as the starting material for the decitabine drug substance manufacturing process?

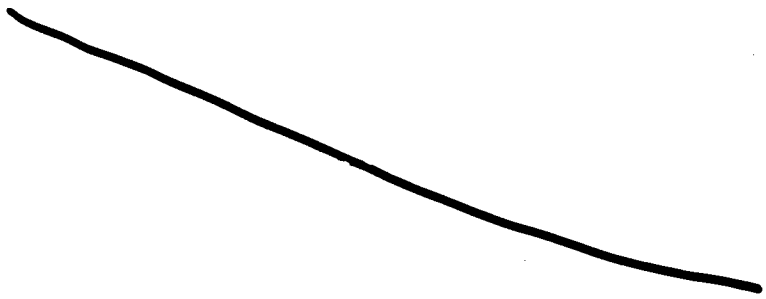
   FDA Response:

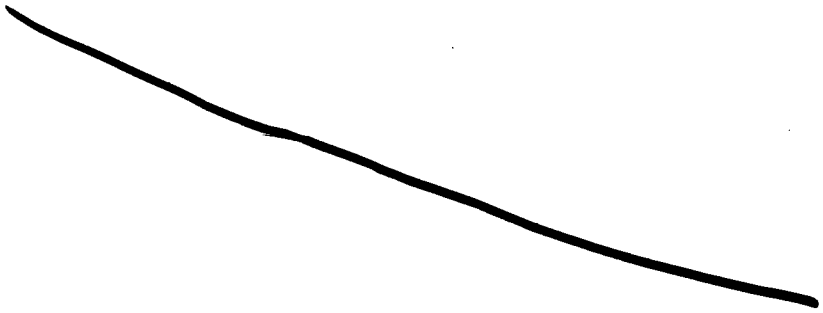
   Your approach seems reasonable to support filing of the NDA. However, the value of your approach in support of the NDA is a review issue. The scheme of decitabine synthetic route and the description of each synthetic step should be provided.

   [redacted] is manufactured by [redacted] as stated in this submission. Is this material made specifically for SuperGen?

   Discussion: ***SGI will provide information regarding change control, vendor qualifications, and multiple batches of data to support their proposal to use [redacted] as their starting material.***

   Points to consider:





FDA Response:

Your approach seems reasonable to support filing of the NDA. However, the value of your approach in support of the NDA is a review issue. You should submit appropriate comparative data demonstrating that the lots used for the preparation of your Phase 3 clinical trial meet the same specifications of the last [redacted] lots.

3. The assay for drug substance for release testing is performed using a USP [redacted] and related substances are quantified using a validated, stability indicating HPLC method. For stability testing, a validated, stability-indicating HPLC method is used for assay and related substances. These methods for release and stability testing have been used for all past lots of decitabine drug substance, including the [redacted] proposed NDA qualifying lots. We plan to retain the non-stability indicating [redacted] assay for the release of drug substance during the commercial phase. We are aware that the ICH guidance document allows sponsors to use a non- stability indicating method for release assay in combination with an appropriate method for quantifying impurities including degradation products.

   Would the Agency accept the non- stability indicating USP [redacted] method for drug substance assay during release testing?

   If a decitabine-specific [redacted] method for release assay is required for commercial phase, would the release assay values generated using the [redacted] assay in the past for the [redacted] proposed NDA qualifying lots, be acceptable?

FDA Response:

Please provide a validation study demonstrating that the two methods are equivalent for assay and provide comparability data demonstrating that the [redacted] and HPLC methods are equivalent.

The answer to the second question above depends upon the results of comparative data.

Discussion: SGI will provide the required information.

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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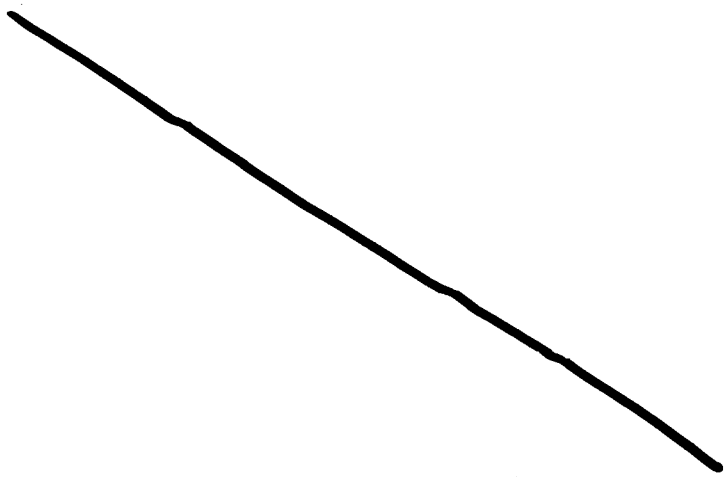
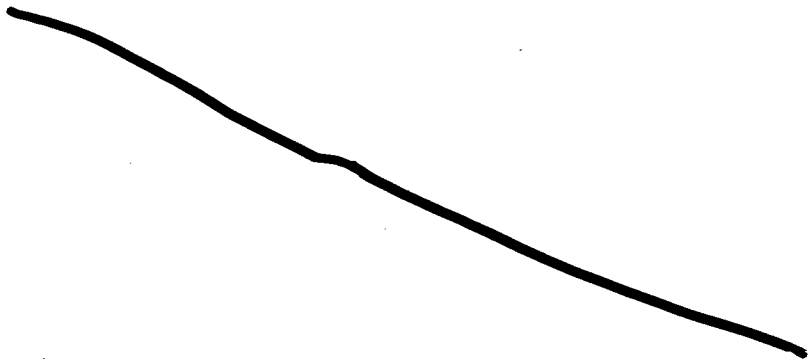


ACTION ITEMS:

1. SGI will provide information regarding change control, vendor qualifications, and multiple batches of data to support their proposal to use [redacted] as their starting material. (See question 1 under drug substance.)

2. SGI will provide a validation study demonstrating that the [redacted] methods are equivalent for assay and provide comparability data demonstrating that the [redacted] and [redacted] methods are equivalent. (See question 3 under drug substance.)

3. [redacted]



4. [redacted]

5. SGI agreed to submit appropriate toxicological data prior to the NDA filing. (See question 8 under drug product.)

/s/ 8-27-03
Brenda Atkins
Project Manager

Concurrence Chair: /s/ 8-28-03
Richard Lostritto, Ph.D.
Chemistry Team Leader

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/s/

Richard Lostritto
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 33,929

SuperGen
4140 Dublin Blvd., Suite 200
Dublin, CA 94568

Attention: Audrey F. Jakubowski, Ph.D.
Vice President Regulatory Affairs

Dear Dr. Jakubowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Decitabine.

We also refer to your April 18, 2003, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Decitabine for myelodysplastic syndrome as a fast track product.

We are granting fast track designation for the following reasons:

1. Myelodysplastic syndrome is a serious, life-threatening disease that is fatal in many patients and for which there is no approved therapy.

2. Decitabine is currently being evaluated in this population in a phase 3 study of Decitabine + Best Supportive Care (BSC) vs. BSC.

If you pursue a clinical development program that does not support use of Decitabine for myelodysplastic syndrome, we will not review the application under the fast track development program.

If you have any questions, call Dotti Pease, Chief, Project Management Staff, at (301) 594-5742.

Sincerely,

{See appended electronic signature page}

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

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/s/

Richard Pazdur
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