CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Administrative Documents

PATENT CERTIFICATION

Mytozytrex™

As per 21 CFR § 314.53 (3), the applicant certifies that there are no relevant patents for which claim the drug or the drug product or which claim a method of using the drug product.

SuperGen, Inc

S. Boddapati

Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 50-763 SUPPL # _____

Trade Name MITOExtra™ Generic Name Mitomycin for Injection

Applicant Name SuperGen, Inc. HFD-150

Approval Date November 14, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)? _____

   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 / X /

      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.

      Product contains an unapproved inactive ingredient which may affect bioavailability/bioequivalence.

      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 /_X_/

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

_____

_____

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 50-450 Drug Name Mutamycin (Mitomycin for Injection, USP

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ 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: _____

_____

_____

/S/

Signature of Preparer

Title: Project Manager

12-Nov-02

Date

/S/ -MD

Signature of Office or Division Director

Acting Director, DODP

11/14/02

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 50-763 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: May 14, 2002 Action Date: November 14, 2002

HFD-150 Trade and generic names/dosage form: Mitozytrex ™ (mitomycin for injection), 5 mg

Applicant: SuperGen, Inc. Therapeutic Class: 3-S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):_____

Indication #1: Disseminated adenocarcinoma of the pancreas

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☑ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, pleas e see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Disseminated adenocarcinoma of the stomach

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☑ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, pleas e see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 9-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301-594-7337

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
11/18/02 01:25:11 PM

CERTIFICATION REGARDING SERVICES OF DEBARRED PERSONS

Mytozytrex™

1. CERTIFICATION REQUIREMENT

SuperGen, Inc certifies that the services of any person debarred under Section 306 Subsections (a) or (b) has not and will not be used in any capacity in connection with this NDA.

2. ADDITIONAL INFORMATION REQUIREMENT FOR NDA

Furthermore, a list of all convictions, described in Section 306 Subsections (a) or (b) that occurred within the previous 5 years before the date of this application, of the applicant and affiliated persons responsible for the development or the applicant and affiliated persons responsible for the development or submission of this application, includes no persons. No person is on this list, because neither the applicant nor any affiliated person responsible for the development or submission of the application has been convicted of any of the charges described in Section 306 Subsection (a) or (b) within 5 years before the date of this application.

SuperGen, Inc

S. Boddapati

Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs

Medical Team Leader Review

NDA # 50-763
Mitozytrex TM (mitomycin for injection)
Applicant: **SuperGen, Inc**
Date of Original Submission: **December 12, 1997**
Date of Resubmission: **March 20, 2002**
Date Review Complete: **November 14, 2002**

The FDA review team recommends approval of this NDA for Mitozytrex. An overview of the salient review issues examined by each review discipline and the regulatory issues associated with this 505 (b)(2) application have been summarized in this Medical Team Leader Review.

Regulatory Overview
The NDA for Mitozytrex was filed as a 505(b)(2) application in December of 1997. Although the active ingredient is mitomycin, the same active ingredient as the approved drug product Mutamycin, Mitozytrex was not accepted as an ANDA in Generic Drugs because Mitozytrex substitutes the excipient hydroxypropyl β cyclodextrin (HPβCD) for mannitol, the solubilizing agent in Mutamcyin. In this 505(b)(2) application, the applicant relies on the previous investigations that established the effectiveness and supported the labeling of the innovator product Mutamycin. Applicants of a 505(b)(2) NDA can rely on reference to approved labeling of an innovator product to establish safety and effectiveness, as long as the applicant can "build a bridge" between their product and the approved product, usually through a bioavailability study. In this case the applicant is relying on the FDA's previous findings of safety and efficacy in the review of the Mutamycin NDA. The only additional data necessary (beyond the bioequivalence bridge) are those to support changes made to the product.

The original 505(b)(2) application for Mitozytrex was not approved (letter dated December 11, 1998) because the applicant failed to demonstrate bioequivalence between Mutamycin and Mitozytrex. Although the nonapproval letter's list of deficiencies was limited to bioequivalence issues, the letter requested that a resubmission of the application address not only the inadequate bioequivalence analysis through:

"reanalysis of study ME001....using statistical procedures described in the Agency's guidance document ....Patients considered outliers on statistical grounds should be further explored from a physiologic standpoint to provide justification for their exclusion from the re-analysis of this study. Alternatively, a new study demonstrating bioequivalence of Mitozytrex and Mutamcyin should be performed."

But also address repeat dosing:

"The pharmacokinetics of Mitozytrex should be studied in consecutive cycles of therapy as proposed in study ME2....., you are encouraged to obtain blood samples for the pharmacokinetic evaluation of Mitozytrex in the second and/or third cycles of treatment. Alternatively, a repeat cycle toxicology study in animals to confirm that Mitozytrex does not pose a worse safety profile relative to Mutamycin could be performed. This study should incorporate toxicokinetics."

The Medical Team Leader review from the December 1997 application, written by Dr. Julie Beitz, MD, clarifies that the request for repeat dose data reflected concerns regarding the lack of safety data for repeated doses of Mitozytrex. Dr. Beitz pointed out in her FDA Review Team Summary that shortly after the December 1997 filing the FDA had informed the applicant that prior to full marketing approval the FDA would require a clinical study of multiple doses "to confirm that Mitozytrex does not pose any unique safety risks." The applicant was informed of this February 11, 1998 and the applicant subsequently (July 7, 1998) proposed that this study (ME02), which was to begin accrual in August 1998, should be conducted as a post-approval commitment, and that in the meantime the label restrict use to two cycles of Mitozytrex. This proposal was not accepted by the FDA.

The review issues key to evaluation of the resubmission of this 505(b)(2) application for Mitozytrex are listed below and will be briefly discussed in the following section, **FDA Review Team Issues**:

1. Clinical Pharmacology and Biopharmaceutics:
   A. Was bioequivalence of Mutamycin and Mitozytrex established?
   B. Did the pharmacokinetics of Mitozytrex change with repeat dosing?
2. Clinical Safety
   A. Was there evidence of "unique safety risks" with multiple doses of Mitozytrex, i.e. with repeated administration of hydroxypropyl β cyclodextrin (HPβCD) in combination with mitomycin?
   B. Was there adequate evidence of improved safety in terms of decreased extravasation injury associated with Mitozytrex to support any such claims that the applicant might make in the label?
   C. Are there unique safety concerns associated with this product, given its hydroxypropyl β cyclodextrin (HPβCD) component and the off-label uses of mitomycin?
3. Pharmacology/Toxicology
   A. Are there unique safety concerns associated with this product, given its hydroxypropyl β cyclodextrin (HPβCD) component and the preclinical safety data associated with this excipient?
   B. Does preclinical evidence of improved safety exist, particularly for decreased extravasation injury, to support any potential labeling claims for Mitozytrex?
   C. Is there additional preclinical mitomycin safety information that warrants update of the label, i.e. usage in pregnancy and impact on fertility?
4. Chemistry
   A. Are the advantages described by the applicant of the substitution of hydroxypropyl β cyclodextrin (HPβCD) for mannitol in the formulation of mitomycin, enhanced solubility and stability, supported by the data submitted?
5. Regulatory Issues
   A. Labeling limitations on 505(b)(2) applications that reference the data presented in the approved label of the innovator product.
   B. Requirement to determine that the innovator product's NDA had not been withdrawn for reasons of safety or efficacy.
   C. Acceptability of the product name

FDA Review Team Issues

Clinical Pharmacology and Biopharmaceutics In the review of the original NDA submission (December 1997) the applicant did not use acceptable statistical methodology to test bioequivalence, and when the appropriate statistical procedure was applied by the FDA's Biopharmaceutics reviewer (two one-sided t-test procedure) for analysis of AUC, AUC_∞, and C_{max}, bioequivalence of Mitozytrex and Mutamycin was not demonstrated. Considerable variability in the pharmacokinetic parameters of Mitozytrex compared to Mutamycin was observed - the coefficients of variation for Mitozytrex were approximately twice that of Mutamycin.

In this NDA submission the applicant used the statistical procedures described in the FDA guidance to reanalyze the bioequivalence study of Mitozytrex and Mutamycin, and to evaluate the pharmacokinetics of sequential dosing in the new repeat dose Mitozytrex pharmacokinetic/safety study. Exclusion of an outlier patient from the reanalysis of the bioequivalance study yielded adequate evidence of bioequivalence with Mutmycin, and the variability associated with Mitozytrex decreased (coefficients of variation, CV%, for AUCt, AUCinf, and Cmax were similar to those associated with Mutamycin). The reasons given by the applicant to support exclusion of the "outlier"patient, which were considered valid by the Biopharmaceutics review team, included an argument that the patient's metabolic profile could have differed from other patients based on her liver metastases from primary liver cancer and history of left hepatic lobectomy (mitomycin is metabolized by the liver). In addition, the patient had evidence of clinical deterioration between the initial dose of Mutamycin and the subsequent administration of Mitozytrex that could have contributed to observed changes. Three days prior to the Mitozytrex administration the patient had to be admitted to the hospital for nausea/vomiting and evidence of intravascular contraction – elevation of creatinine from 0.8 to 1.5 mg/dL, hypercalcemia (10.3 mg/dL) and hyperkalemia (6.4 mmol/L). (This patient had ascites treated with spironolactone.) Mitomycin levels (Tmax and AUC) after Mutamycin were in fact 1.5-2 times the expected values, and subsequent to her clinical deterioration and Mitozytrex administration were 4-5 times the expected values.

In the pharmacokinetic/safety study designed to assess consecutive administration of Mitozytrex (ME02), 23 patients had pharmacokinetic evaluation at Cycles 1 and 2, and 10 at Cycles 1 and 3. (More patients completed 2 and 3 cycles for collection of safety data. See ***Clinical Safety*** section below.) Equivalence between Cycles 1 and 2 was demonstrated, and although not equivalent, the pharmacokinetics of Cycles 1 and 3 were considered sufficiently similar by the FDA Biopharmaceutics reviewer.

Clinical Safety Dr. Julie Beitz, MD concluded in her review of the bioequivalence study ME01 (in the initial submission of NDA50-763) that the adverse events associated with Mitozytrex were consistent with those mentioned in product labeling for mitomycin. She noted no significant difference in hematological and non-hematological adverse events, including elevation of hepatic transaminases, bilirubin or alkaline phosphatase, between Mutamycin and Mitozytrex. Severity grading was not provided for the non-laboratory adverse events.

Dr. Nancy Scher, MD conducted the clinical review of the repeat dose study, ME02, included in this resubmission of NDA 50-763. Safety evaluations were available for 39 patients who were treated with two cycles of Mitozytrex, 22 additional patients treated to a total of 3 cycles, and 8 who were treated with a total of 4 cycles. Investigators were allowed to select a dose of Mitozytrex in the range of 15-20 mg/m^2 every 6 weeks, but nearly all patients were treated at a dose of 15 mg /m^2. Only 4 of the 116 patients enrolled in the study were treated at a dose of 20 mg/m^2, and all but one received a single cycle. Dr. Scher also found no evidence that the safety

profile of Mitozytrex was significantly different from mitomycin. (In fact, one patient did experience tissue necrosis at the injection site.) She specifically examined the safety data for any urologic/nephrologic toxicity that might have been attributable to the hydroxypropyl β cyclodextrin component of Mitozytrex, in light of preclinical evidence that hydroxypropyl β cyclodextrin parenteral administration to rodents and nonrodents is associated with nephrotoxicity and bladder toxicity(see ***Pharmacology/Toxicology*** section below) and found no safety signal.

In the review team's consideration of the safety implications of the hydroxypropyl β cyclodextrin excipient of Mitozytrex (see ***Pharmacology/Toxicology*** section below), off label uses of mitomycin were examined. Currently the labeled indication for mitomycin is disseminated adenocarcinoma of the stomach or pancreas. Patients with disseminated stomach or pancreatic cancer have a poor prognosis and limited survival. The carcinogenicity signal associated with hydroxypropyl β cyclodextrin observed in rats, pancreatic carcinoma (and a trend for increased colon and mammary adenocarcinoma), is not a substantial concern in those patients for whom mitomycin is labeled. However, mitomycin is used off-label in combination with 5-fluorouracil and radiotherapy for the treatment of anal carcinoma. Patients with anal carcinoma are potentially curable and have a prolonged survival relative to patients with disseminated pancreatic or gastric carcinoma. The FDA review team did not believe the potential risks of off label administration of a hydroxypropyl β cyclodextrin-containing mitomycin formulation to patients with anal carcinoma were of a magnitude that justified denying product approval. The degree of hydroxypropyl β cyclodextrin exposure during a course of mitomycin treatment for anal carcinoma would be limited, as mitomycin treatment in this disease generally involves a maximum of two doses, each usually less than 15 mg/m^2.

A source of greater concern to the review team was the potential for off label intravesical administration of Mitozytrex for treatment of bladder carcinoma. Literature review revealed that mitomycin's off label use for this disease involves weekly intravesical administration of 40 mg prepared in 20cc water. The current mitomycin label includes in its Precautions section a reference to this off label route of administration and its association with bladder fibrosis/contraction, in rare cases requiring cystectomy. Given that a 40 mg intravesical dose of Mitozytrex would involve concomitant administration of 16 grams of hydroxypropyl β cyclodextrin in a total volume of 20 cc of water, the review team had safety concerns regarding this unstudied route of administration. There were no pre-clinical intravesical administration data for hydroxypropyl β cyclodextrin, but the FDA Pharmacology/Toxicology reviewer Dr. Margaret Brower, Ph. D. pointed out that parenteral administration of hydroxypropyl β cyclodextrin (at doses of approximately 1/60 and 1/20 of the amount of hydroxypropyl β cyclodextrin administered per recommended human intravenous dose of Mitozytrex on a mg/m^2 basis) resulted in bladder changes in rodents and dogs, including edema, inflammation, cellular inclusions, bladder stones and metaplasia. In addition, neither the degree of systemic absorption of hydroxypropyl β cyclodextrin in weekly intravesical administration, nor the impact of the hydroxypropyl β cyclodextrin on systemic absorption of mitomycin from intravesical administration of Mitozytrex has been studied.

The FDA review team agreed that although the potential for unstudied off label intravesical use of Mitozytrex did not justify nonapproval, the product label should clearly state the safety concerns regarding intravesical administration of hydroxypropyl β cyclodextrin raised by the preclinical data. Inclusion of safety warnings for off-label use in the Mytozytrex label was facilitated by the presence in the current Mutamycin label's Precautions and Adverse Reactions sections of references to risk associated with off label intravesical administration of mitomycin. These references were augmented by the FDA in the Mitozytrex label with information about

bladder changes associated with hydroxypropyl β cyclodextrin and a statement that "the safety of intravesical administration of Mitozytrex and its hydroxypropyl β cyclodextrin excipient have not been studied". The FDA also moved these data from the Precautions section to the Warnings section, in the interest of risk management.

Pharmacology/Toxicology There are unique safety concerns associated with Mitozytrex, given the preclinical safety data for its hydroxypropyl β cyclodextrin (HPβCD) component. These preclinical data include development of pancreatic, colon, and mammary adenocarcinomas in rats, nephrotoxicity (irreversible renal necrosis) attributed to accumulation and recrystallization of hydroxypropyl β cyclodextrin in proximal tubules in rodents and nonrodents, and bladder edema, inflammation, metaplasia and stones after parenteral administration to rodents and dogs. The clinical relevance of these signals in light of mitomycin's labeled indication and off label uses was discussed in the ***Clinical Safety*** section above. The off-label discussion was limited to those uses that involve patients with relatively good prognoses. Mitomycin's other off label uses include its incorporation in combination chemotherapy regimens for treatment of advanced breast cancer and lung cancer, usually as "salvage" therapy in patient populations with a poor prognosis.

Preclinical animal toxicology studies provided to support a claim of decreased extravasation injury were not consistent and persuasive. The chemical association of mitomycin with the hydroxypropyl β cyclodextrin (HPβCD), the mechanism purported to decrease extravasation injury risk, was refuted by data presented by the FDA Chemistry reviewer, Dr. Yung-Ao Hsieh, Ph. D. (See ***Chemistry*** section below.) In addition, an extravasation injury occurred in the repeat dose clinical study ME02.

Dr. Margaret Brower reviewed the literature for information on the pregnancy/reproductive toxicology of hydroxypropyl β cyclodextrin (HPβCD) and incorporated this information in the label. Also included was updated pregnancy/reproductive toxicity data on mitomycin. The latter will be sent to the sponsor of the innovator for appropriately updating the Mutamycin label. Both mitomycin and hydroxypropyl β cyclodextrin are fetotoxic. Mitomycin causes exencephaly, club foot, cleft palate, hydronephrosis and retarded development of reproductive organs in rodents. Hydroxypropyl β cyclodextrin causes incomplete ossification and depressed fetal body weight in rats. Mitomycin decreases sperm production, count and motility, resulting in reduced pregnancy rates and increased frequency of malformations in mice. It also inhibits fertilization and implantation when administered to female mice.

Chemistry The applicant claimed that hydroxypropyl β cyclodextrin enhanced solubility and stability of mitomycin, and proposed that complexes formed between the hydroxypropyl β cyclodextrin and mitomycin in the administration solution could decrease local tissue injury in extravasations. The practical impact of any increased solubility is not apparent. The instructions for reconstitution of the Mitozytrex and Mutamycin products are identical in terms of steps required and time necessary for dissolution. The only difference is that Mitozytrex calls for slightly less sterile water, 8.5cc vs. 10cc. With regard to stability, storage conditions for unreconstituted Mitozytrex and Mutamycin are identical. The applicant reported that duration of stability of the reconstituted product (8.5cc water added to the vial for Mitozytrex or 10cc water added to vial for Mutamycin) was longer under refrigeration for Mitozytrex:

Stability Claim for Reconstituted Product

Reconstituted Product	Refrigerated Period of Stability	Room Temperature Period of Stability

Mutamycin (0.5 mg/cc)	14 days	7 days
Mitozytrex (0.5 mg/cc)	3 months	7 days

Although the reconstituted Mitozytrex product appears to have longer refrigerated stability, the FDA Chemistry review team was unwilling to include these stability data for the reconstituted product in the label because microbiology data were not provided to support the lack of bacterial growth in the vial during the 3 months of refrigeration, or for the 7 days unrefrigerated.

Stability of the final diluted product in various diluents is provided in the current Mutamycin label and is compared to that reported for the Mitozytrex product in the summary table below.

Stability Claim for Final Diluted Product at Room Temperature

Diluted Product	Mutamycin Period of Stability	Mitozytrex Period of Stability
5% Dextrose in Water	3 hours	No more than 4 hours
Normal Saline	12 hours	No more than 48 hours
Lactated Ringer Solution	24 hours	No more than 24 hours

The Mitozytrex solutions are stable for a slightly longer period of time in D5W solutions than Mutamycin, and of similar stability duration for solutions of lactated ringer's. Duration of stability was only notably longer for normal saline solutions. Saline solutions of Mutamycin that contain heparin 1000-10,000 units have longer stability than listed in the table above, 48 hours at room temperature, but the Mitozytrex product also has longer stability with the addition of heparin - 72 hours.

Data were presented on the percentage of mitomycin that is complexed to hydroxypropyl β cyclodextrin when mixed in varying concentrations with sterile water and normal saline. When Mitozytrex is reconstituted in its vial with sterile water, the final concentration of mitomycin is 0.5 mg/cc. Phase stability analysis reveals that at this concentration there is minimal complexing of mitomycin with hydroxypropyl β cyclodextrin, and any existent complexing would further decrease with the final dilution for administration. Mitomycin is only loosely bound to the surface of hydroxypropyl β cyclodextrin, and the complex dissociates with first dilution. These complexing data led the FDA Chemistry reviewer, Dr. Yung-Ao Hsieh, Ph. D. to conclude that the applicant's theory that an active complex between mitomycin and hydroxypropyl β cyclodextrin would result in less extravasation injury is unlikely to be a reality.

Regulatory Issues A 505(b)(2) application may reference the efficacy data presented in the approved label of the innovator product. The applicant has created a bridge with Mutamycin via a bioequivalence study, has presented repeat dose safety and pharmacokinetic data for the Mitozytrex product, and has referenced the efficacy of mitomycin presented in the Mutamycin product label. Unlike contemporary labels for other chemotherapeutic agents, the Mutamycin (approved in 1974) product label does not include a clinical studies section or any specific efficacy data. The only reference to efficacy is found in its Indication section:

"Mutamycin is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven

combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mutamycin is not recommended to replace appropriate surgery and/or radiotherapy."

Although modern levels of evidence required to support these claims of effectiveness are not presented in the referenced label, it was clear [redacted] that the review division was bound by 505(b)(2) regulations to retain the innovator label unchanged, but for information relevant to the unique aspects of the Mitozytrex product, i.e. chemistry, pharmacokinetics, toxicology and safety.

From a safety and toxicology standpoint, the label could be individualized to address issues relevant to the hydroxypropyl β cyclodextrin excipient and to include important safety information obtained from the literature on mitomycin. These issues have been discussed in the ***Clinical Safety*** and ***Pharmacology/Toxicology*** sections above. FDA concerns about off label use could be addressed in light of the cautionary safety statements regarding off label intravesical use already present in the current Mutamycin label. A change in the recommended Mitozytrex dose from the dose of mitomycin recommended in the Mutamycin label was justified on safety grounds because the lower Mitozytrex dose was the only dose studied in the two clinical studies submitted, ME001 and ME02. (See further discussion in ***Conclusions*** section below.)

From a technical standpoint, if a product references the label of an approved product, that product must appear in the *Orange Book*, and if the NDA has been withdrawn, the FDA must establish that the product was not withdrawn because of issues with safety or lack of efficacy. The innovator product's (Mutamycin) NDA was withdrawn and it is currently marketed (and appears in the *Orange Book*) as Mutamycin, under an ANDA. The Office of Generic Drugs was contacted and the Division of Oncology Drug Product's Division file on the original Mutamycin NDA was reviewed to clarify the circumstances under which the Mutamycin NDA was withdrawn. Correspondence indicates that the original NDA was withdrawn and resubmitted as an ANDA for a change of site of manufacture, not for issues of safety or efficacy.

The applicant's proposed name for the mitomycin product developed under NDA 50-763, MITOExtra, was rejected by the FDA review division because the name implied added benefit over mitomycin. The Mitozytrex product merely represents a different formulation of mitomycin, and no safety or efficacy benefit associated with this formulation was shown in the data submitted in this NDA resubmission. The applicant's final proposed name for the product, Mitozytrex, was approved.

The Division of Scientific Investigations inspected two sites that accrued the largest number of patients in the repeat dose study ME02. Multiple protocol violations were found at both sites, most of which could have been avoided by merely amending the protocol eligibility criteria. However, the violations at one site were of significant enough concern to the DSI reviewer that he recommended that the data from that site not be viewed as reliable support for the NDA.

Conclusions

The FDA review team recommends approval of Mitozytrex. Bioequivalence with Mutamycin was demonstrated, and there was no evidence of increased or unique toxicity observed in the Mitozytrex sequential dose trial, ME02, relative to historical mitomycin safety data.

As discussed in this review summary, the FDA review team was bound to the existing content of the innovator Mutamycin label under 505(b)(2) regulations. Although the indication in the Mutamycin label is not supported within that label by data that would meet modern standards of evidence of effectiveness (Mutamycin was approved in 1974), the referenced innovator label's indication could not be significantly altered given the 505(b)(2) regulations. Although the FDA would only allow a lower dose of Mitozytrex than that recommended in the Mutamycin label (15 mg/m^2 vs. 20 mg/m^2) in the Dosage and Administration section of the Mitozytrex label, this could be justified in light of the 505(b)(2) regulations because the safety of Mitozytrex had only been studied at this lower dose. Tumor responses were observed in the sequential dose study (in a heterogeneous solid tumor population) at this lower dose, and review of the literature revealed that the 20 mg/m^2 intravenous dose recommended in the Mutamycin label is not commonly used (for intravenous administration). The usual doses reported in the literature were in the range of 10-15 mg/m^2. The FDA could and did require that the applicant revise the Mitozytrex label to strengthen the preclinical safety information regarding the hydroxypropyl β cyclodextrin excipient in the Warnings and Precautions sections. The FDA also strengthened cautionary statements regarding the unknown safety of off label intravesical administration of this hydroxypropyl β cyclodextrin formulation, and included these statements in the Warnings section of the label. Hydroxypropyl β cyclodextrin and mitomycin pregnancy and reproductive toxicology data found in a literature review were also incorporated. The latter information (for mitomycin) will be sent to the owner of the innovator product, Mutamycin, with a request to appropriately update that label.

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

/s/

Donna Griebel
11/14/02 04:57:00 PM
MEDICAL OFFICER

Grant Williams
11/14/02 05:15:20 PM
MEDICAL OFFICER

Atkins, Brenda J

From: Holovac, Mary Ann
Sent: Monday, December 02, 2002 3:00 PM
To: Atkins, Brenda J
Subject: Mitozytrex patents

Hi,
I just received a copy of a patent submission from SuperGen for NDA 50763 which references a telephone request from you for patent information.
Just wanted to let you know that applications approved under the former section 507 (the 50-000 antibiotics) are not requred to submit patent information to the agency.
Thanks.
Mary Ann

Mary Ann Holovac, R.Ph.
US Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
(301)827-0492(phone)
(301)827-5911(fax)
holovacm@cder.fda.gov

Atkins, Brenda J

From: Pease, Dorothy W
Sent: Tuesday, December 03, 2002 11:15 AM
To: Atkins, Brenda J
Subject: RE: Mitozytrex patents

You also don't need to do an exclusivity checklist for antibiotics as they don't get exclusivity either.

Dotti

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Catherine Miller, MT(ASCP)
Joseph A. Grillo, Regulatory Review Officer
Division of Drug Marketing, Advertisement, and Communication
Professional Review Group II/Team 3

FROM: Brenda Atkins, CSO, DODP, HFD-150/4-5767
Nancy Scher, Medical Officer, DODP, HFD-150/4-5745

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06-18-02		50-763	Class 2 Resubmission of NDA	3-20-02 (BZ) and 5-13-02 (AZ)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Mitomycin for Injection			Within 3-6 weeks prior to UF Date which is 11-14-02

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)*: Labeling Review

II. BIOMETRICS

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

This paper NDA application is a Class 2 resubmission of an application that was originally dated December 10, 1997. The resubmission, dated March 20, 2002 comprised a total of 9 volumes with tabs numbered 1-43. Each tab represented the sponsor's response to the 43 FDA comments and requests for additional information listed in the December 11, 1998 not approvable (NA) letter. Please see attachments listed below that should assist you in your review of the labeling. Please call at 594-5767 should you have any questions or need any additional documentation.

Attachments: **Draft Package Insert, Container and Carton Labels (submitted paper copy 3-20-02/MS Word version submitted 5-13-02 with major amendment)**
December 11, 1998 Not Approvable (NA) Letter

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND ☐ DFS 6-18-02
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

14 pages redacted from this section of the approval package consisted of draft labeling

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
6/18/02 02:24:27 PM
Process as outgoing consult. Paper copy with attachments were mailed 6-18-02.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: SAM BODDAPATI	**From:** BRENDA ATKINS
Fax: (925) 551-6472	**Fax:** (301) 594-0498
Phone: (925) 560-0100	**Phone:** (301) 594-5767
Pages, including cover sheet: 16 pages	**Date:** NOVEMBER 8, 2002
Re: LABELING REVISIONS	

COMMENTS:

Dear Sam:

Please see the attached labeling as submitted via e-mail on today at 6:08 PM (EST). Please note that the last page of this fax are the revised vial and Carton labels

Thanks

/S/

MESSAGE CONFIRMATION

11/08/02 18:46

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/0Ξ	05'55"	9259041921	CALLING	16	OK	0000

11/08/02 18:38 NO.009 001

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: SAM BOODAPATI **From:** BRENDA ATKINS

Fax: (925) 551-6472 **Fax:** (301) 594-0498

Phone: (925) 560-0100 **Phone:** (301) 594-5767

Pages, including cover sheet: 16 pages **Date:** NOVEMBER 8, 2002

Re: LABELING REVISIONS

Atkins, Brenda J

From: Atkins, Brenda J
Sent: Friday, November 08, 2002 6:08 PM
To: 'samb@supergen.com'
Subject: MITOExtra/MITOZytrex Labeling

Importance: High

Dr. Boddapati:

Our revisions to your proposed labeling received May 13, 2002 are attached.

PI Revisions 11-08-02 to spons...

This e-mail also serves as confirmation of our Tuesday, November 12, 2002 1:00 pm meeting. We will be assembled in our Conference Room B. The telephone number that you can reach us on is (301) 827-4220, or if you prefer setting up a conference call with the telephone company, please let me know the number and password prior to our teleconference.

It would make for a more productive meeting if you can submit your proposals in advance of our teleconference so that we can all be on the same page. We'll all have to move quickly on this as our **Goal Date on your application is November 14, 2002.**

I am also faxing you a copy of this attachment and a copy of the revised vial and carton labels.

Have a good week-end.

Sincerely,

Brenda Atkins, Project Manager
Division of Oncology Drug Products Division
Center for Drug Evaluation and Research

13 pages redacted from this section of the approval package consisted of draft labeling

SUPERGEN, INC.
4140 Dublin Blvd., Suite 200, Dublin, CA 94568

Fax

To:	Brenda Atkins	**From:**	Sam Boddapati
Company:	FDA, CDER, Div. Oncology	**Company:**	SuperGen, Inc.
Fax:	301-594-0498	**Fax:**	(925) 551-6472
		Phone:	(925) 550-0100
Date:	November 11, 2002	**Pages:**	~~10~~ 15
Re:	**NDA 50-763 Mitozytrex™ (MITOExtra™), labeling**		
CC:			

Brenda,

Attached is a red-lined version of our proposed package insert for Mitozytrex™. This is the same version that was also sent to you via e-mail. (In the e-mail version, please note the electronic comments inserted into the document.)

We will be calling you in Conference Room B at 1:00 p.m. EST.

Sincerely,

V. Boddapati

Sam Boddapati, PhD

16 pages redacted from this section of the approval package consisted of draft labeling

Atkins, Brenda J

From: Boddapati, Sam [samb@supergen.com]
Sent: Monday, November 11, 2002 11:09 PM
To: 'Atkins, Brenda J'
Subject: RE: MITOExtra/MITOZytrex Labeling

Supergen PI Revisions to FDA v...

Dear Ms. Atkins,

We reviewed your draft label in the context of the current approved labeling for Mutamycin(R) (mitomycin for injection, USP), the innovator product for Mitozytrex(TM), and Sporonox(R) (itraconazole) injection, an approved injectable product containing HPBCD as a solubilizing agent. Janssen, the holder of the Sporonox NDA, has given SuperGen the rights to use HPBCD in oncology products and to cross-reference their DMF in our filings. We do not have direct access to Janssen data on HPBCD.

Our proposed revisions are provided along with electronic comments for clarification. We also faxed a hard copy to your attention.

We will call you tomorrow, Tuesday, November 12, at 1:00 p.m. EST to discuss the Mitozytrex labeling.

Sincerely,

Sam Boddapati, PhD

14 pages redacted from this section of the approval package consisted of draft labeling

Atkins, Brenda J

From: Atkins, Brenda J
Sent: Thursday, May 23, 2002 12:17 PM
To: Hsieh, Yung Ao; Schmidt, Wendelyn J; Rahman, Nam Atiqur; Duan, Zongyi J; Rothmann, Mark D; Scher, Nancy
Subject: NDA 50-763 - Mitomycin Package Insert

Package Insert for mitomycin:

Attached is a copy of the March 2002 PI for mitomycin to be used for markup as needed.

Please save onto your hard drive for future reference.

Brenda--PM

NDA 50-763
MITCExtra PI 3-02.d...

13 pages redacted from this section of the approval package consisted of draft labeling

SuperGen
THE KEY TO LIFE
4140 Dublin Boulevard, Suite 200, Dublin, CA 94568

Fax

To: Ms. Brenda Atkins	**From:** Sam Boddapati
Company: Division of Oncology; FDA	**Company:** SuperGen, Inc.
Fax: 1-301-594-0498	**Fax:** (925) 551-6472
Phone: 1-301-594-5767	**Phone:** (925) 560-0100 x 351
Date: May 13, 2002	**Pages:**
Re: NDA 50-763; MITOExtra (Mitomycin for Injection)	
CC:	

☐ PLEASE REPLY ☐ URGENT ☐ HARD COPY TO FOLLOW

Ref: NDA 50-763
MITOExtra (Mitomycin for Injection)
Labeling Response to Telephone Inquiry dated May 10, 2002

Dear Ms. Atkins:

Reference is made to above NDA for MITOExtra submitted on December 10, 1997 and to the telephone conversation of May 10, 2002 between Ms. Brenda Atkins, Project Manager, Division of Oncology and Dr. Sam Boddapati, SuperGen, Inc regarding the current container and carton labeling.

Draft container and carton labeling were provided on pages 1022 and 1030 of our original submission dated December 10, 1997. No changes had been made to these labeling pieces since the Division had not requested that we make any revisions to this labeling. Hence, the labeling provided previously is still current.

Should you require any additional information, please contact the undersigned at 925-560-0100.

Sincerely,

S. Boddapati

Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs

5-14-02
Requested immediate Container and carton labels electronically. Currently unavailable but sponsor will submit the week of 5/20 as there IT persons are attending class the week

/S/

SuperGen®, Inc.
NDA: 50-763 MITOExtra™ (Mitomycin for Injection)

General

Item 3. A revised package insert should be submitted that describes the results of bioequivalence and other clinical studies performed with MITOExtra™.

We have revised the package insert to include the results of bioequivalence and other clinical studies performed with MITOExtra™. Please see **Attachment 3** for the revised package insert.

Please also see our response to item 4.

ATTACHMENT 3

MITOExtra™ Package Insert (draft)

13 pages redacted from this section of the approval package consisted of draft labeling

CONSULTATION RESPONSE

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

DATE RECEIVED: September 30, 2002	**DUE DATE:** October 30, 2002	**ODS CONSULT #:** 02-0127-1

TO: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Brenda Atkins
Project Manager
HFD-150

PRODUCT NAME:	**NDA SPONSOR:**
Mitozytrex (Mitomycin Injection) 5 mg **NDA:** 50-763	SuperGen

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Oncology Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Mitozytrex" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS has no objections to the use of the proprietary name Mitozytrex.
2. DMETS recommends that the packaging for Mitozytrex be clearly differentiated from SuperGen's other marketed Mitomycin product and that during the launch practitioners are educated on the differences between these two products.
3. Please submit container labels and carton labeling for review upon receipt.

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 and established names from this date forward.

/S/

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

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 12, 2002

NDA # 50-763

NAME OF DRUG: Mitozytrex 5 mg
(Mitomycin Injection)

NDA HOLDER: SuperGen

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products, to review the proprietary name Mitozytrex, regarding potential name confusion with other proprietary/established drug names. The package insert labeling was reviewed for possible interventions to minimize medication errors. The container label and carton labeling were not submitted for review.

PRODUCT INFORMATION

Mitozytrex (mitomycin injection) is an antibiotic isolated from the broth of *Stretomyces caespitosus* which, has been shown to have anti-tumor activity. The proposed product Mitozytrex (mitomycin) and the currently available product Mitomycin for Injection (ANDA 64-144) will both be marketed by SuperGen. Mitozytrex contains hydroxypropyl β cyclodextrin (glucopyranose polymers used as a solubilizing agent) as an inactive ingredient. Mitomycin for Injection contains mannitol as an inactive ingredient and does not contain hydroxypropyl β cyclodextrin. The Division of Oncologic Drug Products indicated that this application is being reviewed in the Office of New Drugs instead of the Office of Generic Drugs because the product contains hydroxypropyl β cyclodextrin in lieu of mannitol.

Mitozytrex, in combination with other chemotherapeutic agents, is indicated for the treatment of disseminated adenocarcinoma of the stomach or pancreas. Mitozytrex may also be used as palliative treatment when other treatment modalities have failed. Use of Mitozytrex in primary therapy, as a single agent is not recommended. The recommended dose is 20 mg/m^2 given as a single intravenous dose through a functioning intravenous catheter. The dosing may be reduced based on the patient's prior response to therapy. Dosing may also be adjusted based on concomitant therapy with other myelosuppressive agents. Repeat doses should not be administered until the patients' leukocyte and platelet counts have returned to 4000/mm^2 and 100,000/mm^2 respectively. The drug should be stopped after two courses of therapy if disease progression continues because expected response with continued treatment is minimal. The most common adverse reactions involve bone marrow suppression, peripheral neuropathy, gastrointestinal events, alopecia, hepatic enzyme elevations, and injection site reactions. Mitozytrex will be marketed in 5 mg vials. When reconstituted with 8.5 mL of Sterile Water for Injection, the final concentration will be 0.5 mg per mL.

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 "Mitozytrex" to a degree where potential confusion between drug names could occur under the 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 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

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Mitozytrex." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified Mitoxantrone, [redacted] and Mycelex as having the potential for confusion with "Mitozytrex." These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

2. The Expert Panel also noted that Mitozytrex sounds and looks similar to Zyrtec if the first part of the name is misinterpreted or not noted.

3. DDMAC did not have concerns about the name Mitozytrex with regard to promotional claims.

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	Dosage form(s), Established name	Usual adult dose	Other**
Mitozytrex	Mitoxantrone Injection 2 mg/mL Vial	12 mg/m² daily by intravenous infusion on Day 1 to 3 (in combination with other chemotherapeutic agents)	N/A
Novantrone	Mitoxantrone Hydrochloride Injection 2 mg Vial	12 mg/m² daily by intravenous infusion on Day 1 to 3 (in combination with other chemotherapeutic agents)	SA/LA
—			
Mycelex	Clotrimazole • 100 mg, 200 mg, 500 mg Vaginal Tablets • 1% Topical Cream, Lotion, and Solution • 10 mg Oral Lozenges	One vaginal tablet at bedtime for 7-14 days Apply 2 times a day for 1-4 weeks Dissolve 1 lozenge 5 times a day for 14 days	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Mitozytrex with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 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 Mitozytrex (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

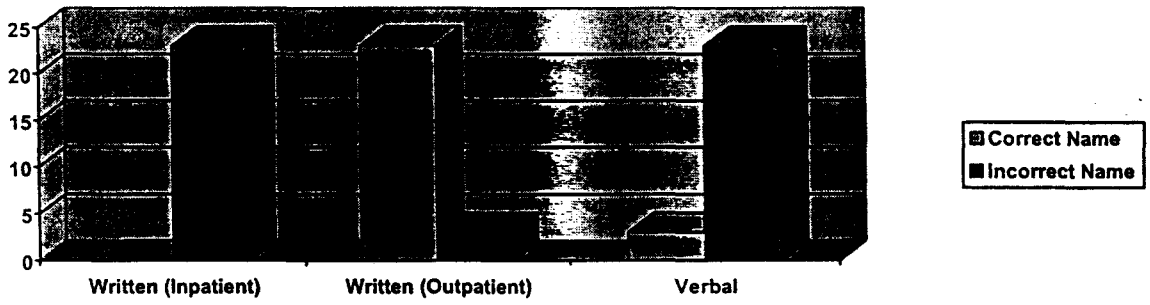
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Mitozytrex To be used in clinic as dir #3	...the last prescription is Mitozytrex to be used in the clinic as directed
Inpatient RX: Mitozytrex 1 Stat IV X 1	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	32	23 (72%)	0 (0%)	23 (100%)
Written Outpatient	39	26 (67%)	23 (88%)	3 (12%)
Verbal	37	26 (70%)	3 (12%)	23 (88%)
Total	108	75 (69%)	26 (35%)	49 (65%)



In the verbal study 23 of 26 (88%) participants interpreted "Mitozytrex" incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Mitozytrex." These include Midozitrex (4), Midozytrex (3), Mytozytrex (2), Mitozydex (2), Mydocytrex (1), Midozidrex (1), Miterzitrex (1), Mitocytrex (1), Mitoxitrex (1), Mitozidrix (1), Mitozitrec (1), Mitozytrax (1), and Mytozydrix (1). The remaining three misinterpretations were Mitre Zitrex, Mitre-Zytrex, and Midozydrox. None of the misinterpreted names were similar to an approved product.

Among the two written studies, 26 of 49 (53%) participants interpreted the name incorrectly. These misinterpretations included Mitozytrox (16), Mitozytox (2), Mitozytrax (2), Mitizytrox (1), Mitozynox (1), Motozytrex (1), Mifozytrex (1), Mitozytinex (1), and MitoZyterex (1). None of the misinterpreted names were similar to an approved product.

3. SAFETY EVALUATOR RISK ASSESSMENT

A. Look- and Sound-Alike Similarities

In reviewing the proprietary name Mitozytrex, the primary concerns raised were related to three sound and/or look-alike names: Mitoxantrone, — and Mycelex. Zyrtec was also identified as a potential sound and look-alike if the

first part of the proposed proprietary name 'Mito' was omitted, misinterpreted, or not noted. However, the differences in the route of administration, dosage formulation, dosing interval and indication of use minimizes the potential for name confusion between Mitozytrex and Zyrtec.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Mitozytrex can be confused with Mitoxantrone, or Mycelex. The majority of interpretations from the verbal prescription studies were phonetic interpretations of the drug name Mitozytrex. The majority of the misinterpretations from the written prescription studies were misspelled variations of the drug name Mitozytrex.

The established name for Novantrone is mitoxantrone hydrochloride. Mitoxantrone is an antineoplastic agent indicated for the treatment of acute nonlymphocytic leukemia or pain related to advanced hormone-refractory prostate cancer. Mitoxantrone and Mitozytrex may look alike depending upon how they are written. Both names begin with the letters 'Mito' and share common letters in the last syllable 'tr.' When scripted Mitozytrex requires two downstrokes (zy) in the third syllable whereas mitoxantrone does not require any downstrokes. The similar beginnings of each name contribute to the sound-alike characteristics. Additionally, the 'x' and 'z' sounds that begin the third syllable may sound similar when pronounced. Overall 'Xan' and 'Zy' sound phonetically different (z-an vs. z-eye) and are distinct when pronounced. The last part of each name is also distinct (trone vs. trex). There are some similarities between Mitoxantrone and Mitozytrex that may increase the potential for name confusion. Both drugs are chemotherapeutic agents, may be stored next to each other (when stored alphabetically by established name), and are ordered based on body surface area (i.e., milligrams per meter^2). Differences between the two products include Mitoxantrone is supplied as an injectable solution which can be further diluted. Mitozytrex is a powder that must be first reconstituted, then further diluted. Mitoxantrone is available as a 20 mg/10 mL vial, a 25 mg/12.5 mL vial and a 30 mg/15 mL vial whereas Mitozytrex will only be available as a 5 mg vial. The dosing intervals are also different, Mitoxantrone is given daily for three days while Mitozytrex is given once every 6 to 8 weeks. Although Mitoxantrone and Mitozytrex look and sound similar, the differences in the two products should decrease the potential for medication errors due to name confusion.

Since mitoxantrone and mitomycin (the established name of Mitozytrex) are currently marketed, DMETS conducted an Adverse Event Reporting System (AERS) search to determine if any reports of medication errors between the two products have been submitted. The MEDDRA Preferred Term (PT) 'Medication Error' and the terms 'Mitoxantrone,' 'Mitox%,' 'Novantrone,' 'Novan%,' 'Mitomycin,' 'Mitom%,' 'Mutamycin,' and 'Mutam%' were used as search criteria. The search identified thirty-three reports but none of the reports involved name confusion between Mitoxantrone and mitomycin or Mutamycin (Bristol-Myers-Squibb proprietary name).

Mycelex is an antifungal agent that is indicated for the treatment of tinea infections (e.g., pedis, and cruris), cutaneous candidiasis, vulvovaginal candidiasis, and oropharyngeal candidiasis. Mycelex and Mitozytrex both begin and end with the same letters ('M' and 'ex') which contributes to the sound-alike similarities. The first syllable ('Mi' vs. 'My') of each name sounds similar. However, there are differences that help to distinguish the two names. Mycelex has three syllables whereas Mitozytrex has four syllables. The middle two syllables of Mitozytrex (TOE ZY) are phonetically distinct when spoken and helps to distinguish the two names. Additionally, the products have different formulations (cream, oral tablet, vaginal tablet vs. solution for injection), dosing intervals (BID, 5 times a day, HS vs. one time single dose), and routes of administration (topically, oral, vaginal vs. injectable). Mitozytrex will only be available via a prescription while most of the Mycelex products are available over-the-counter (OTC). The differences between Mycelex and Mitozytrex will help to decrease the potential for name confusion between the two products.

2. Mitozytrex and Mitomycin Substitution Issues

DMETS is concerned that potential medication errors may occur between the currently marketed ANDA product, Mitomycin for Injection, and the proposed product Mitozytrex. Although these products contain the same active ingredient and are both indicated to treat disseminated adenocarcinoma of the stomach or pancreas and as palliative treatment when other treatment modalities fail, they do not contain the same inactive ingredients and will not be bioequivalent. Therefore, Mitomycin for Injection and Mitozytrex cannot be substituted for each other. Additionally, the stability profiles of reconstituted and diluted Mitomycin for Injection and Mitozytrex are different. However, practitioners may not realize these differences and may use the products interchangeably especially since they are both marketed by SuperGen. DMETS did not receive container label and carton labeling and thus cannot determine if the packaging presentation of Mitozytrex will be different than that of Mitomycin for Injection. Even though the packaging configuration may be clearly differentiated, these differences may not be evident to the practitioner. Thus the potential exists that a patient may receive Mitomycin for Injection (ANDA) instead of Mitozytrex or vice versa. Based on the data reviewed, DMETS cannot evaluate the potential adverse effects of a medication error where Mitozytrex is given in lieu of Mitomycin for Injection (or vice versa). Practitioners should be clearly educated on the differences between the two products and any potential consequences if the products are substituted for each other. DMETs recommends that SuperGen provide information pertaining to these differences during the initial launch of Mitozytrex.

III. RECOMMENDATIONS:

A. DMETS has no objection to the use of the proprietary name Mitozytrex.

B. DMETS recommends that the packaging for Mitozytrex be clearly differentiated from SuperGen's other marketed Mitomycin product and that during the launch practitioners be educated on the differences between these two products.

C. Please submit container labels and carton labeling for review upon receipt.

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 and established names from this date forward.

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 Sammie Beam, project manager, at 301-827-3242.

/S/

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
11/12/02 03:16:46 PM
PHARMACIST

Jerry Phillips
11/12/02 03:25:35 PM
DIRECTOR

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*
Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400 (Rm. 15B-03, PKLN Bldg.)

FROM: Brenda Atkins, CSO, DODP, HFD-150/4-5767

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 30, 2002		50-763	Sponsor Proposed Trade Name(s)	September 12, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
MITOExtra™ (Mitomycin for Injection)			Prior to NDA User Fee Date of 11-14-02

NAME OF FIRM: SuperGen

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: Our May 30, 2002 request for trade name (proprietary name) review to you was withdrawn on 6-13-02 because the DODP review team did not approve of the proposed name " MITOExtra™". On September 20, the sponsor proposed the following names: First Choice: Mitozytrex; Second Choice: [redacted] and Third Choice: [redacted]. Please review the proposed name(s) for acceptability. Please call should you have any questions at 594-5767.

ATTACHMENTS: Draft Package Insert, Container and Carton Labels
September 20, 2002 sponsor letter

PDUFA DATE: November 14, 2002

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL & DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Brenda Atkins
9/30/02 09:20:03 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: 13 June 2002

TO: Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs
Phone (925) 560-0100
Fax (925) 551-6472

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

NDA/DRUG: 50-763/MitoExtra™ (Mitomycin for Injection)

SUBJECT: **Request for Alternative Trade Name(s)**

Please refer to our December 11, 1998 letter (item #4) stating "The Agency's Labeling and Nomenclature Committee will review the proposed name, MITOExtra™, for appropriateness. The use of the suffix "Extra" might convey clinical benefits that are not or cannot be substantiated by data, or may be considered inappropriate."

Please submit alternative names for consideration as soon as possible. The consensus of the FDA review team of this NDA is that the proprietary name "MitoExtra" is not appropriate.

Please submit your response officially to the NDA. Please feel free to contact me on (301) 594-5767 if you have any questions regarding the contents of this transmission.

/S/

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

filed in DFS 6-13-02
Dr. Boddapati acknowledged receipt of the doc. on 6-14-02 and stated that they are working on this request.
/S/ CSO

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
6/13/02 02:38:05 PM
CSO

This document cancels the "May 30, 2002 Request for Tradename (proprietary name) Review" to the Division of Medication Errors and Technical Support, Office of Pharmacoepidemiology and Statistical Science.

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Division of Medication Errors and Technical Support
Office of Drug Safety, Office of Pharmacoepidemiology and Statistical Science, HFD-400
(Rm 15B-03, PKLN Bldg.)

FROM: Brenda Atkins, CSO, DODP, HFD-150/4-5767

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
05-30-02		50-763	Resubmission of NDA	3-20-02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
MITOExtra™ (Mitomycin for Injection)			09-6-02

NAME OF FIRM: SuperGen Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ PRE-NDA MEETING
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- ☐ RESUBMISSION
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- ☐ 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
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IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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- ☐ 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/SPECIAL INSTRUCTIONS:

This application is a Class 2 resubmission of an application dated December 10, 1997. The December 11, 1998 "Not Approvable (NA) letter, stated under "General" comments (Item #4 that the "The Agency's Labeling and Nomenclature Committee will review the proposed name, MITOExtra™, for appropriateness. The use of the suffix "Extra" might convey clinical benefits that are not or cannot be substantiated by data, or may be considered inappropriate." Page 1783 of the March 20, 2002 resubmission addresses this comment. Please review the proposed name for acceptability. Please call should you have any questions at 594-5767.

Attachments: **Draft Package Insert, Container and Carton Labels (submitted paper copy 3-20-02/MS Word version submitted 5-13-02 with major amendment)**
December 11, 1998 Not Approvable (NA) Letter
Page 1783 of March 20, 2002 resubmission

SI	5-30-02	METHOD OF DELIVERY (Check one)	
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		SIGNATURE OF DELIVERER	

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/s/

Brenda Atkins
5/30/02 06:30:56 PM
Process as outgoing consult. Paper versions of attachments were mailed 5-30-02.

To Do

Atkins, Brenda J

From: Scher, Nancy
Sent: Wednesday, October 30, 2002 2:56 PM
To: Atkins, Brenda J
Cc: Scher, Nancy; Griebel, Donna J
Subject: MitoExtra

done 10-30-02 @ 5:30 pm

Hi,
It's me again. Please FAX today:

We need yet another piece of information from SuperGen. We need to know the site locations of the patients who had PK data submitted to study ME2. We also need the number of patients per each site who had PK and patient initials and patient identifier number for any patients who had PK if they were from site 8.

Thanks.

Nancy S. Scher, MD, FACP
Division of Oncology Drug Products
HFD-150
1451 Rockville Pike
Rockville, MD 20852

Atkins, Brenda J

From: Scher, Nancy
Sent: Tuesday, October 29, 2002 7:13 PM
To: Atkins, Brenda J
Cc: Griebel, Donna J; Scher, Nancy
Subject: NDA Mito

Brenda,
Please do the following:

1. Send annotated, highlighted copies of the label (what we have so far) to the team. Remind them we have a meeting Thursday and would like them to look at the label so we can discuss.

2. Please send a Fax Wed AM to applicant, requesting information ASAP:

   a. Please state if you do or do not have a plan for pediatric development for this drug.

   b. For study ME2 we do not have your "120-Day Safety Update" analysis. In your discussion of safety, you do not specify the date of data cut-off or how mature was the follow-up. Please clarify and provide additional data as necessary.

Thanks.

Nancy S. Scher, MD, FACP
Division of Oncology Drug Products
HFD-150
1451 Rockville Pike
Rockville, MD 20852

Do 1st thing

Atkins, Brenda J

From: Hsieh, Yung Ao
Sent: Monday, October 28, 2002 2:22 PM
To: Atkins, Brenda J
Cc: Wood, Rebecca H
Subject: Re: NDA 50-763 Mitozytrex Labeling

Brenda,

Please communicate the attached comments/requests for drug product labeling to the applicant. Thanks.

Y. A. Hsieh

DPLabeling.doc

10-21-02 submission

1. **Uniform Storage Statement for Carton and Vial Labels and Package Insert:**
For a drug product which is demonstrated to be stable at 25°C/60% RH or 30°C/60% RH and intended to be stored at Controlled Room Temperature, the recommended labeling statement is :

DRAFT

2. **Package Insert**
The IV fluid stability table under statement 3 (under Stability in the DOSAGE AND ADMINISTRATION section):

The table should be revised to read:

IV Fluid	Stability
5% Dextrose Injection	no more than 4 hours
0.9% Sodium Chloride Injection	no more than 48 hours
Sodium Lactate Injection	no more than 24 hours

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

06/13/02 13:00

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
06/13	00'31"	9259041921	CALLING	01	OK	0000

06/13/02 12:59 NO.129 D01

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: 13 June 2002

TO: Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs
Phone (925) 560-0100
Fax (925) 551-6472

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

NDA/DRUG: 50-763/MitoExtra™ (Mitomycin for Injection)

SUBJECT: **Request for Alternative Trade Name(s)**

Please refer to our December 11, 1998 letter (item #4) stating "The Agency's Labeling and Nomenclature Committee will review the proposed name, MITOExtra™, for appropriateness. The use of the suffix "Extra" might

1 pages redacted from this section of the approval package consisted of draft labeling