CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40333

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #1
November 30, 1999

A. 1. **ANDA** 40-333

APPLICANT: Gensia Laboratories, Ltd.
17 Hughes
Irvine, CA 92618

2. PRODUCT NAME: Fluorouracil Injection, USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg/mL (10mL/vial, 500mg/vial), for intravenous injection

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: August 31,1998
Subject of this Review (Received September 1, 1998)

2. ASSIGNED FOR REVIEW: November 23, 1999

3. RELATED DOCUMENTS:
DMF
DMF

C. REMARKS: The application is recommended for approval by all other review disciplines. The application is pending approval upon an acceptable sterility assurance review.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the process are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

/S/ 11/30/99
Lynne A Ensor, Ph. D.

cc: Original **ANDA** 40-333
Duplicate ANDA
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Field Copy

MT. 12/7/99

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Micro Review #1

Microbiology Comments to be Provided to the Applicant

ANDA: 40-333 APPLICANT: Gensia Laboratories, Ltd.

DRUG PRODUCT: Fluorouracil Injection, USP, 50 mg/mL

A. Microbiology Deficiencies:

1. Regarding the batch record specification for the filters used to sterilize the bulk drug solution, pages 100151 and 100221 (v.1.1) of your batch records provide pre- and post- filtration bubble point specifications for filters. In your application, you specify that only filters are used in the production of the drug. Your batch records should be corrected to indicate specifications only for the filters used to produce Fluorouracil Injection.

2. Growth promotion results for media used to fill vials during your fills were not provided. Please provide growth promotion test results for the used during the fills, presented in your application to ensure that the is capable of supporting microbial growth.

3. validation test results are not complete. The minimum accumulated F_o achieved during individual cycles, control results, and thermocouple/ Biological Indicator (BI) placement maps are not provided for any of the BI challenge runs used to validate the for vial, stopper and production equipment sterilization. Please provide complete validation test results for the sterilization of vials, stopper and production equipment in the Be sure to include the minimum accumulated F_o achieved during individual cycles, control results, and thermocouple/Biological Indicator (BI) placement maps used during the BI challenges in your validation studies.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You do not provide a commitment for revalidation of the cycle used to sterilize the machine, surge tank and associated fixtures. Please provide a commitment for routine revalidation of the cycle used for line sterilization.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

/S/

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
HFD-620
Microbiology Review #2
January 12, 2000

A. 1. **ANDA** 40-333

APPLICANT: Gensia Laboratories, Ltd.
17 Hughes
Irvine, CA 92618

2. PRODUCT NAME: Fluorouracil Injection, USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg/mL (10mL/vial, 500mg/vial), for intravenous injection

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: August 31,1998
(Received September 1, 1998)

2. DATE OF AMENDMENT: December 21,1999
Subject of this Review **(Received December 23, 1999)**

3. ASSIGNED FOR REVIEW: January 11, 2000

4. RELATED DOCUMENTS: N/A

C. REMARKS: The subject amendment provides responses to the microbiology deficiencies provided to the applicant in the December 10, 1999 facsimile.

D. CONCLUSIONS: The submission **is recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes".

/S/ 1/12/00
Lynne A Ensor, Ph. D.

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Micro. Review #2