

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40333

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-333

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluorouracil

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

August 31, 1998

Original Submission

September 16, 1998

New Correspondence (revised first page of
form 356h submission)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF

DMF

DMF

DMF

13. DOSAGE FORM

Injectable

14. POTENCY

50 mg/mL

15. CHEMICAL NAME AND STRUCTURE

2,4(1H,3H)-Pyrimidinedione, 5-fluoro-

For structure, see USP 23, page 678.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

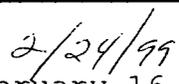
18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is not approvable. Inform the applicant of deficiencies.

19. REVIEWER:

DATE COMPLETED:

 Shirley S. Brown


February 16, 1999

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Chem Review #1

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-333

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluorouracil

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

August 31, 1998

Original Submission

September 16, 1998

New Correspondence (revised first page of form 356h submission)

*March 31, 1999

Amendment (responding to deficiencies per Chem Review #1)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF

DMF

DMF

DMF

13. DOSAGE FORM

Injectable

14. POTENCY

50 mg/mL, 10 mL SDV

15. CHEMICAL NAME AND STRUCTURE

2,4(1H,3H)-Pyrimidinedione, 5-fluoro-

For structure, see USP 23, page 678.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

As requested:

The applicant noted and acknowledged the following:

1. Since the subject product is an official article in the United States Pharmacopeia (USP), the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.
2. The microbiologist's review of the submission for sterility assurance is pending.

The response addressed the labeling deficiencies.

Additional stability data are provided.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is not approvable. Inform the applicant of deficiencies.

19. REVIEWER:

Shirley S. Brown

DATE COMPLETED:

September 10, 1999

September 17, 1999 (revised)

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Chem Review #2

Chemistry Closed

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-333

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluorouracil

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

August 31, 1998

Original Submission

September 16, 1998

New Correspondence (revised first page of form 356h submission)

March 31, 1999

Amendment (responding to deficiencies per Chem Review #1)

*October 25, 1999

Amendment (responding to deficiencies per Chem Review #2)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See review #1.

13. DOSAGE FORM

Injectable

14. POTENCY

50 mg/mL, 10 mL SDV

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

As requested:

- (1) The applicant noted and acknowledged that the microbiologist's review of the submission for sterility assurance is pending.
- (2) The response addressed the labeling deficiencies.
- (3) Additional stability data are provided.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry issues are closed.

19. REVIEWER:

/S/

Shirley S. Brown

DATE COMPLETED:

11/8/99

November 2, 1999

/S/

11/10/99

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Chem Review #3

ADDENDUM TO CHEMISTRY REVIEW #3 FOR ANDA 40-333

Correspondence dated November 12, 1999 amending the October 25, 1999 Amendment provides:

- (1) 18-month stability data. Per the 18-month trend, the proposed expiring dating period for the drug product is changed from 24-months to 18-months. **At the 18-month test station, the assay has declined MT % with the detection of very low level of impurities %)*.**

- (2) Assay release specification for the in-process bulk has been narrowed from %.
- (3) Assay release specification for the finished drug product has been narrowed from %.

Revised In-process tests/specifications are:

*The applicant should:

(1) Provide assay data for the RLD obtained from the market place showing similar low assay prior to the expiration date.

or

(2) Reduce the proposed expiration dating period to 12-months.

or

(3) Elucidate the degradation pathway and show the RLD has similar levels of degradants.

and

Commit to extend the expiration dating period only by prior approval supplement unless the degradation pathway has been elucidated and appropriate limits have been approved.

Note: The EER FUR is now acceptable dated 11/10/99.

REVIEWER:

DATE COMPLETED:

/S/

12/8/99

Shirley S. Brown

December 1, 1999

Chemistry Closed

CHEMISTRY REVIEW NO. 4

2. ANDA # 40-333

3. NAME AND ADDRESS OF APPLICANT

Gensia Sicor Pharmaceuticals, Inc.
17 Hughes
Irvine, CA 92618

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluorouracil

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

August 31, 1998

Original Submission

September 16, 1998

New Correspondence (revised first page of form 356h submission)

March 31, 1999

Amendment (responding to deficiencies per Chem Review #1)

October 25, 1999

Amendment (responding to deficiencies per Chem Review #2)

*December 21, 1999

Amendment (responding to deficiencies per Chem Review #3)

*January 7, 2000

Telephone Amendment

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See review #1.

13. DOSAGE FORM

Injectable

14. POTENCY

50 mg/mL, 10 mL SDV

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The applicant has received the microbiology review (deficiencies) and included the response with this submission.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry issues are closed. The ANDA is approvable pending micro review.

19. REVIEWER:

IS

Shirley S. Brown

DATE COMPLETED:

January 4, 2000

Micro review acceptable
per J. Ensor on 1/12/00.
ANDA is approvable.
IS
1/14/00

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Chem. Review #4

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-333 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL

The deficiencies presented below represents FAX deficiencies.

A. Deficiencies:

1. Your response to the fill volume issue is not adequate.
 - (a) An overage for permeability is not justified by your weight loss data.
 - (b) We are concerned that the entire contents of a vial may be emptied thinking the vial contains the labeled amount of the drug when the vial actually contains more than the labeled amount.
 - (c) The USP recommends 0.5 mL and not mL overage for a 10 mL container. See USP <1151>.
 - (d) As requested in Deficiency #3 per our March 5, 1999 Facsimile, the fill volume (Target and Range) should be adjusted per USP 23 or the current overfill justified (e.g. overfill data of the Referenced Listed Drug).
2. The definition for finished product specification (defines the level of quality that must be met from the time of manufacture through the shelf life of the product) and stability specification (assures the product meets a quality standard over the shelf life) appears to be the same. Please clarify.

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

1. Your response must also address the labeling deficiencies.

2. Please provide any additional stability data that may be available.
3. Your sterility assurance information is pending review.

Sincerely yours,

/S/

RS

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 10 1999

Chemistry Comments to be Provided to the Applicant

ANDA: 40-333 APPLICANT: Gensia Sicor
Pharmaceuticals, Inc.

DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL

The deficiency presented below represents a MINOR deficiency:

A. Deficiency:

The 18-month stability data cause concern: At the 18-month test station, the assay has declined significantly with the lack of detection of a corresponding level of impurities. Please provide additional information as described below:

- (1) Assay data for the Referenced Listed Drug obtained from the market place showing similar low assay prior to the expiration date, or
- (2) Reduce your proposed expiration dating period to 12-months, or
- (3) Elucidate the degradation pathway and demonstrate that the Referenced Listed Drug has similar levels of degradants.
- (4) In any case, please commit to extend the expiration dating period only by prior approval supplement unless the degradation pathway has been elucidated and appropriate limits have been approved.

In addition to responding to this deficiency, please note and acknowledge the following:

Your sterility information is pending review.

Sincerely yours,

JSI

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs

38. Chemistry Comments to be Provided to the ApplicantANDA: 40-333 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. The grade, acceptance tests/specifications and representative Certificate of Analysis for _____ of the batch record for the manufacturing process are not provided.
2. Has the container resin, medical grade _____, been approved for use in an aqueous injectable product? If so, the specific reference to the approval (NDA or ANDA #, Date of Approval) should be provided. If the resin has not been previously approved, Pharmacological/Toxicity information for a safety consult should be provided.
3. The vial overfill of approximately % exceeds the USP 23 <1151> recommendation of 5% (Supplement 8, page 4437). The fill volume (Target and Range) should be adjusted per USP 23 or the current overfill justified (e.g. overfill data of the Referenced Listed Drug.).
4. The finished product specifications for assay and impurities also include release specifications. Please describe the difference between Finished Product and Release specification.
5. Individual impurities (release and stability) allowed above % should be justified with data from analysis of the Referenced Listed Drug. Additionally, the release and stability specifications should have a limit for individual unidentified impurities.
6. _____ test specification is based on an evaluation of an expired lot of the Reference Listed Drug. It should be based on testing of the Reference Listed Drug prior to expiry.
7. Please provide a copy of the _____ finished product test,

8. For stability studies, Bacterial Endotoxin and Sterility testing should be performed annually.
 9. Your proposal to possibly extend the expiration dating period beyond 24 months in the future conflicts with the current USP monograph.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Since the subject product is an official article in the United States Pharmacopeia (USP), the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.
2. The microbiologist's review of the submission for sterility assurance is pending.
3. Your response must also address the labeling deficiencies.
4. Please provide any additional stability data that may be available.

Sincerely yours,

RS

cc Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research