CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-140

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

20 FEB 2008

NDA: 20-140/N-000 (AZ)(BC)(AC)(BI)(BZ)

Drug Product Name
Proprietary: ISO-Vorin™ for Injection
Non-proprietary: Levoleucovorin Calcium for Injection
Drug Product Priority Classification: S

Review Number: 4

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
(AZ)10 JULY 2007	11 JULY 2007	19 SEP 2007	28 SEP 2007
(BC)27 SEPT 2007	27 SEPT 2007	n/a	n/a
(AC)05 NOV 2007	06 NOV 2007	n/a	n/a
(BI)14 JAN 2008	15 JAN 2008	n/a	n/a
(BZ)06 FEB 2008	07 FEB 2008	n/a	n/a

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
11 JUNE 1991	1	13 AUG 1991
21 NOV 1991	2	04 FEB 1992
08 APR 1993	3	10 SEP 1993

Applicant/Sponsor
Name: Spectrum Pharmaceuticals, Inc.
Address: 157 Technology Dr.
Irvine, CA 92618
Representative: Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs
Telephone: 949-788-7600 x 210 (phone)
949-788-7609 (fax)
cletizia@spectrumpharm.com (email)

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommend approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** New Drug Application (Amendment)

2. **SUBMISSION PROVIDES FOR:** Approval for Marketing in the U.S.

3. **MANUFACTURING SITE:**

- Drug Substance:

Merck Eprova AG
Im Latemenacker 5
CH-8200 Schaffhausen
Switzerland
Contact: Martin Ulmann:
011-41 052 630 72 72 (phone)
011 -41 052 630 72 55 (fax)

- Drug Product:

Chesapeake Biological Laboratories Inc. (CBL)
111 South Paca St. Baltimore, MD USA 21230-2591
(410) 843-5005 (phone)
(410) 843-4414 (fax)

- Microbiological testing:

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder for injection, Intravenous, 50 mg per vial in a 10 ml Type I glass vial (rubber stoppered)

b(4)

5. **METHOD(S) OF STERILIZATION:**

6. **PHARMACOLOGICAL CATEGORY:** Rescue after High-Dose Methotrexate Therapy in Osteosarcoma

B. SUPPORTING/RELATED DOCUMENTS:

- The Applicant authorizes reference to NDA 20-141 for ISO-Vorin™ (levoleucovorin calcium) tablets.
- DMF # 20327; Merck Eprova AG (LOA dated 02 APR 2007 for drug substance manufacture)
- DMF # 14368; Chesapeake Biological Laboratories, Inc. (LOA dated 03 APR 2007 for drug product manufacture)
- ———— b(4)
- ————
- Microbiology Reviews #1-#3 (D. Hussong, 13 AUG 1991, 04 FEB 1992, 10 SEP 1993).
- Memo, Internal Meeting, 18 DEC 1990
- T-CON record (D. Hussong to E. Melendez) 19 DEC 1991
- T-CON record (R. Rivera to D. Hussong) 23 July 1992

C. REMARKS:

- There is no ONDQA PAL Initial Quality Assessment on file in DFS for this submission.
- The submission was provided in electronic CTD format and was available via the Global Submit Review system.
- The original NDA sponsor, Lederle Laboratories, responded on January 22, 1993 to the first deficiency letter on January 29, 1993. Ownership of the NDA was transferred from Lederle Laboratories to Merck Eprova, then to Targent, Inc. and finally to Spectrum Pharmaceuticals, Inc. Notification of change of ownership was submitted to CDER/ODE III on April 19, 2006. The applicant further references the pre-NDA meeting held by teleconference with Targent, Inc. and the Agency on July 15, 2005. These communications, a response to pre-NDA minutes and all outstanding deficiencies were included in Module 1. This submission includes revised product labeling, manufacturing, chemistry and controls for drug product and drug substance.
- On 12 DEC 2007 a T-con was held with the sponsor to discuss requirements for the additional studies the applicant needed to perform to support the label claim for a ' —— hold period for the drug product following reconstitution. The data were received for review in the 06 FEB 2008 amendment (Sequence #0010). Review of this data is found in Section P.2.5, Pharmaceutical Development, below. b(4)
- An information request concerning ———— qualification was submitted on January 8, 2008. The applicant requested that its contract manufacturer respond. That response, received on January 15, 2008, was received for review in the 14 JAN 2008 amendment (Sequence #0008). It was reviewed and incorporated into the body of this report. b(4)

Filename: N020140N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

b(4)

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Robert J. Mello, Ph.D.

B. Endorsement Block_____
Bryan S. Riley, Ph.D.

C. CC Block
In DFS

22 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology- 1

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/s/

Robert Mello
2/20/2008 09:32:52 AM
MICROBIOLOGIST

Recommend Approval

Bryan Riley
2/20/2008 09:36:01 AM
MICROBIOLOGIST
I concur with the conclusions in this review.

CONSULTATIVE REVIEW TO HFD 150

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS

Microbiologist's Review #1
August 13, 1991

A. 1. NDA 20-140

APPLICANT: Lederle Laboratories, Division of American Cyanamid Company
N. Middletown Road
Pearl River, New York 10965

2. PRODUCT NAMES: Isovorin^{R} (*l*-leucovorin calcium for injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The drug is lyophilized at —— vial, 50 mg/vial and ——— presentations in — 10 and —— mL vials, respectively. The reconstituted solution may be injected intramuscularly or intravenously. b(4)

4. METHOD(S) OF STERILIZATION: ——— b(4)
——— at Lederle Parenterals, Carolina, Puerto Rico

5. PHARMACOLOGICAL CATEGORY: An antidote to overdosage with antagonists of dihydrofolate reductase, particularly for recovery from methotrexate therapy. The drug is also useful to enhance the efficiency of 5-fluorouracil.

6. DRUG PRIORITY CLASSIFICATION: 2C

B. 1. DATE OF INITIAL SUBMISSION: 18 December 1990

2. DATE OF AMENDMENT: 11 June 1991 (assigned for review 29 July 1991

3. RELATED DOCUMENTS: DMF 3124 for Lederle Parenterals, Carolina, Puerto Rico

4. ASSIGNED FOR REVIEW: 14 April 1991

C. REMARKS: The consult request is for comments concerning manufacturing and controls from the perspective of sterility assurance, particularly review of filling operations, closure integrity and final product release specifications.

AUG 22 1991

D. CONCLUSIONS: The submissions are not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to Applicant". An inspection of the facility is recommended to assess the appropriateness of transporting open vials from the fill rooms of both areas (Parenterals I and Parenterals II) to the lyophilizers in Parenterals I.

8-14-91

David Hussong, Ph.D.

cc:

Orig. NDA 20-140
HFD 160/Consult File
HFD 150/CSO/PZimmerman
HFD 150/Chemist/SLook
drafted by: DHussong, 8/13/91
R/D init. by: PCooney, 8/14/91

8/14/91

5/21/91

14 Page(s) Withheld

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology- 2