

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-023**

**MICROBIOLOGY REVIEW**

# Product Quality Microbiology Review

13 DEC 2007

**NDA:** 22-023 BC and BI

**Drug Product Name**

**Proprietary:** EMEND® for Injection  
**Non-proprietary:** Fosaprepitant dimeglumine  
**Drug Product Priority Classification:** 2

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Consult Sent	Assigned to Reviewer
31-OCT-2007	31-OCT-2007	N/A	N/A
04-DEC-2007	04-DEC-2007	N/A	N/A

**Submission History (for amendments only)**

Submission Date(s)	Microbiology Review #	Review Date(s)
31-MAR-2006	1	26-MAR-2007

**Applicant/Sponsor**

**Name:** Merck & Co., Inc.  
**Address:** 770 Sumneytown Pike  
P.O. Box 4, BLA-20  
West Point, PA 19486-0004

**Representative:** Nicholas Andrew  
Associate Director, Worldwide Regulatory Affairs  
**Telephone:** 732-594-5585

**Name of Reviewer:** Anastasia G. Lolas

**Conclusion:** Recommended for approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Amendments to New Drug Application
  2. **SUBMISSION PROVIDES FOR:** Microbial growth studies in support of the 24-hour storage period following reconstitution of the product
  3. **MANUFACTURING SITE:** DSM Pharmaceuticals, Inc.  
5900 NW Greenville Blvd.  
Greenville, NC 27834  
  
Release and stability testing: Merck & Co., Inc.  
770 Sumneytown Pike  
West Point, PA 19486-0004
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Lyophilized powder (single-dose, 10 mL glass vial with 115 mg fill) for reconstitution and further dilution
    - Intravenous infusion
    - 115 mg reconstituted with 5 mL sterile saline and further diluted with 110 mL sterile saline
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** Anti-emetics/seratonergics and others
- B. **SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review #1 (dated 26-MAR-2007) of NDA 22-023; product quality microbiology was reviewed and recommended for approval. However, the 24-hour storage period after reconstitution was not covered and data were not requested at the time.
- C. **REMARKS:** This is an electronic submission in the CTD format. The application was recommended for approval from the product quality microbiology perspective. However, there were other discipline deficiencies and an approvable letter was sent to the applicant on 03-MAY-2007. The application was resubmitted on 27-JUL-2007. In preparation for the labeling meetings, it was discovered that the applicant proposed a 24-hour holding time at room temperature for the reconstituted and diluted product solution prior to administration. There was concern that due to the high amount of lactose in the product that microbial growth could be supported during that time compromising the sterility of the drug. The original submission did not contain any data or any information regarding the microbial growth potential of the drug.

b(4)

A letter was sent to the applicant on 18-OCT-2007 stating that without any data, no more than a 4-hour holding time at room temperature would be allowed for the product following reconstitution. The applicant submitted an amendment on 31-OCT-2007 using USP <797> as a reference and stating that microbial studies were not necessary. A teleconference took place on 09-NOV-2007 when the concern was again expressed to the applicant and a description was given regarding the studies that would need to be completed to determine the most acceptable post-reconstitution holding time (see also minutes in DFS). The applicant performed the microbial growth studies and submitted an amendment on 04-DEC-2007.

APPEARS THIS WAY  
ON ORIGINAL

**file name:** N022023R2.doc

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**Executive Summary****I. Recommendations**

- A. Recommendation on Approvability – Recommended for approval based on product quality microbiology**
- 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 – The product consists of a lyophilized powder supplied in a single-dose 10 mL glass vial (115 mg). The microbial growth studies submitted on 04-DEC-2007 in support of the 24-hour storage time of the product following reconstitution and dilution are assessed on the next page.**
- B. Brief Description of Microbiology Deficiencies – None**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

**III. Administrative**

- A. Reviewer's Signature \_\_\_\_\_  
Anastasia G. Lolas**
- B. Endorsement Block  
Bryan S. Riley, Ph.D.**
- C. CC Block  
N/A**

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/s/

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Anastasia Lolas  
12/17/2007 09:08:56 AM  
MICROBIOLOGIST

Bryan Riley  
12/17/2007 09:13:29 AM  
MICROBIOLOGIST

# Product Quality Microbiology Review

26 MAR 2007

**NDA:** 22-023  
22-023 BC (2) & BI

**Drug Product Name**

**Proprietary:** EMEND® for Injection  
**Non-proprietary:** Fosaprepitant dimeglumine  
**Drug Product Priority Classification:** 2

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Consult Sent	Assigned to Reviewer
31-MAR-2006	03-APR-2006	17-MAY-2006	31-MAY-2006
08-DEC-2006	11-DEC-2006	N/A	N/A
21-FEB-2007	22-FEB-2007	N/A	N/A
16-MAR-2007	19-MAR-2007	N/A	N/A

**Submission History (for amendments only) – N/A**

**Applicant/Sponsor**

**Name:** Merck & Co., Inc.  
**Address:** 770 Sumneytown Pike  
P.O. Box 4, BLA-20  
West Point, PA 19486-0004

**Representative:** Vijay K. Tammara, Ph.D.  
Director, Regulatory Affairs

**Telephone:** 267-305-6713

**Name of Reviewer:** Anastasia G. Lolas

**Conclusion:** Recommended for approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** New Drug Application
  2. **SUBMISSION PROVIDES FOR:** New drug product
  3. **MANUFACTURING SITE:** DSM Pharmaceuticals, Inc.  
5900 NW Greenville Blvd.  
Greenville, NC 27834  
  
Release and stability testing: Merck & Co., Inc.  
770 Sumneytown Pike  
West Point, PA 19486-0004
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Lyophilized powder (single-dose, 10 mL glass vial with 115 mg fill) for reconstitution and further dilution
    - Intravenous infusion
    - 115 mg reconstituted with 5 mL sterile saline and further diluted with 110 mL sterile saline
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** Anti-emetics/seratonergics and others
- B. **SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review #1 (dated 20-OCT-2006) of DMF 14141; the sterile operations on Line 3 were reviewed and the DMF was found inadequate to support the manufacture of Emend® for Injection
  - Microbiology Review #2 (dated 17-JAN-2007) of DMF 14141; the responses to the microbiology deficiencies identified in the first review were found adequate to support the manufacture of Emend® for Injection
- C. **REMARKS:** EMEND® is also available in 80 and 125 mg capsules (NDA 21-549).

b(4)

**The PAL's Initial Quality Assessment (dated 11-MAY-2006) identified the most critical issues to be related to the "low solubility of aprepitant and the procedures and controls that are used to limit this impurity in the drug product".**

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This is an electronic submission in the CTD format. The validation studies for all \_\_\_\_\_ and sterilization processes are located in DMF 14141 (DSM Pharmaceuticals, Inc., contract manufacturer for the product).

b(4)

The applicant was contacted on September 22, 2006 to provide the filling line number where the product will be manufactured. The reviewer was referred to the DMF holder who stated that Line 3 in the \_\_\_\_\_ facility will be used for the product and provided the relevant sections of the DMF (telephone communication, September 22, 2006).

b(4)

An information request was sent to the NDA applicant on November 7, 2006 to provide the following:

- Studies that demonstrate the integrity of the container-closure system
- Identify the sterilizing filters and provide a product-specific bacterial retention study

The applicant included the response to the microbiology questions in the BC amendment submitted on December 8, 2006. This additional information is reviewed under the relevant sections of the review.

A second information request was sent to the applicant on January 24, 2007 regarding the bacterial filter retention study because the response in the 08-DEC-2006 BC amendment was incomplete. Another BC amendment was submitted on February 21, 2007 responding to this request as well as to Chemistry requests. See Section P.3.5 of the review for an **assessment of the applicant's response**.

An electronic communication was sent to the applicant by the OND PM requesting additional information including if a \_\_\_\_\_ ze control filter was used in the filter retention studies. An amendment was submitted on March 16, 2007 and the response has been incorporated into the relevant section of this review.

b(4)

**file name:** N022023R1.doc

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**Executive Summary****I. Recommendations**

- A. Recommendation on Approvability – Recommended for approval based on product quality microbiology**
- 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 – The product consists of a lyophilized powder supplied in a single-dose 10 mL glass vial (115 mg). The sterilization validation of operations and product quality microbiology are reviewed here.**
- B. Brief Description of Microbiology Deficiencies – None**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

b(4)

**III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Anastasia G. Lolas
- B. Endorsement Block**  
James L. McVey
- C. CC Block**  
N/A

7 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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Anastasia Lolas  
3/26/2007 08:39:27 AM  
MICROBIOLOGIST

James McVey  
3/27/2007 07:53:02 AM  
MICROBIOLOGIST