

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203568Orig1s000**

**MICROBIOLOGY REVIEW(S)**

## MEMORANDUM

**Date:** 04-Jan-2013

**From:** Joseph Leginus, Review Chemist, Branch VII/DPA III/ONDQA

**To:** NDA 203568, Kynamro™ (mipomersen sodium) Injection

**Subject:** Acceptable Microbiology Recommendation

### Background:

- In Chemistry Review #2 (4-Dec-2012), a recommendation for Approval for NDA 203568 from the standpoint of chemistry, manufacturing and controls was provided. As part of the Executive Summary in the review, it was noted that the microbiology review consult had not yet been finalized.
- On 04-Jan-2013, a recommendation for approval from a microbiology product quality standpoint was provided by the Microbiology Reviewer, R. Mello.

### Conclusion:

- NDA 203568 is recommended for Approval from the standpoint of chemistry, manufacturing and controls and a recommendation for approval from a microbiology product quality standpoint has been provided.

Joseph Leginus, PhD  
Review Chemist

Ali Al-Hakim, PhD  
Branch VII, Chief, ONDQA

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/s/  
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JOSEPH LEGINUS  
01/04/2013

ALI H AL HAKIM  
01/04/2013

# Product Quality Microbiology Review

02 January 2013

**NDA:** 203-568/N-000

**Drug Product Name**

**Proprietary:** Kynamro™  
**Non-proprietary:** mipomersen sodium

**Review Number:** 1

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

Submit	Received	Review Request	Assigned to Reviewer
29 March 2012	29 March 2012	03 April 2012	04 April 2012
20 June 2012	20 June 2012	-	-
30 November 2012	30 November 2012	-	-

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

**Applicant/Sponsor**

**Name:** Genzyme Corporation  
**Address:** 500 Kendall Street  
Cambridge, MA 02142  
**Representative:** Jill P. Hillier Ph.D.  
Senior Director, Regulatory Affairs  
**Telephone:** 781-434-3443

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

**Conclusion:** The application is recommended for approval from microbiology product quality standpoint.

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** 505(b)(1)
  2. **SUBMISSION PROVIDES FOR:** Marketing Authorization
  3. **MANUFACTURING SITE:**
    - 200mg/ml vial: Hospira Inc., 1776 North Centennial Drive McPherson, KS 67460
    - 200 mg/mL pre-filled syringe (PFS): Genzyme Ridgefield, 1125 Pleasant View Terrace, Ridgefield, NJ 07657
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution, subcutaneous injection, 200mg/ml packaged in two forms:
    - Vial: Single-use (b) (4) 2 mL (1 ml fill), clear glass vial, (b) (4) with flip-off cap
    - Pre-filled Syringe: (b) (4), 1 mL, (b) (4) clear glass syringe with (b) (4) needle and a needle shield, (b) (4) rubber plunger stopper
  5. **METHOD(S) OF STERILIZATION:** Sterile filtration (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Adjunct treatment for patients with homozygous familial hypercholesterolemia.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- (b) (4)
- C. **REMARKS:**
- An ONDQA Initial Quality Assessment was filed in DARRTS on 14 May 2012.
  - The submission was available in eCTD format within the Electronic Document Room. No specific microbiology comments were noted. A microbiology consult was requested.
  - During the initial microbiology filing review, some information deficiencies were noted. The following microbiology information request was transmitted to the applicant in the NDA Filing Letter dated 25 May 2012:

Microbiology

6. Provide protocols and final reports supporting (b) (4) processing operations for both the vial presentation and the prefilled syringe presentation. Include information on the sterilization (b) (4) (b) (4) of the primary containers/closures and filling equipment. Also, include information on the environmental monitoring program.
7. Provide protocols and final reports supporting container closure integrity testing for both the vial presentation and the prefilled syringe presentation.

The Applicant responded to this information request in their 20 June 2012 amendment submission. Their responses are incorporated into the body of this review. In addition, the following information request was transmitted to the Applicant on 15 November 2012:

*We note that your drug product manufacturing process for both the vial and pre-filled syringe presentations includes (b) (4). Please note that determination of the bioburden (b) (4) does not provide you with an accurate understanding of the microbiological quality of your manufacturing process prior to sterilization. Provide a commitment to perform bioburden sampling (b) (4). You may, in addition, continue to perform the bioburden sampling (b) (4), if you so desire.*

The Applicant responded to this information request in their 30 November 2012 amendment submission. Their responses are incorporated into the body of this review.

**Filename:** N203568N000R1.doc

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**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 - Formulation processes are the same at the two manufacturing sites.** (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.  
Senior Microbiology Reviewer
- B. Endorsement Block:** \_\_\_\_\_  
Stephen Langille, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**  
N/A

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ROBERT J MELLO  
01/04/2013

STEPHEN E LANGILLE  
01/04/2013

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 203-568**

**Applicant: Genzyme Corp**

**Submit Date: 29 March 2012**

**Drug Name: KYNAMRO  
(mipomersen sodium) Injection,  
200mg/ml**

**NDA Type: 505(b)(1)**

**Received Date: 29 March 2012**

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Information is in eCTD format accessible via the Electronic Document Room (EDR)
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Separate sections labeled 3.2.P.3.3 were provided for both the pre-filled syringe and the vial presentations.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Only narrative summaries of results were provided in the vial and syringe sections (Section 3.2.P.2 and Section 3.2.P.3.5) See Comment #1 below
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Summary narratives of container closure testing for both presentations were submitted in separate Sections 3.2.P.2.5.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Provided in the vial and syringe Sections 3.2.P.5.1.
7	Has the applicant submitted the results of analytical method verification studies?	X		Provided in the vial and syringe Sections 3.2.P.5.3.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	Not Applicable
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	-	-	Not Applicable
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: See Attached page. Two (2) comments will be sent to the Sponsor.

Robert J. Mello, Ph.D.  
Senior Microbiology Reviewer

\_\_\_\_\_  
Date

John W. Metcalfe, Ph.D.  
Senior Microbiology Reviewer

\_\_\_\_\_  
Date

## **Product Quality Microbiology Assessment**

The drug product is a 1 ml solution containing 200mg of mipomersen sodium contained in either a 1ml prefilled syringe or in a 2ml (1ml fill) rubber stoppered glass vial. The dosage and administration information in the package insert indicates that 1 ml of the drug product is to be administered subcutaneously. The syringe and vial are both labeled as “single-use”. The drug product is sterile and preservative free.

### **Preliminary Microbiology Review Comments:**

**Comment #1:** Protocols and final reports supporting (b) (4) processing operations for both the vial presentation and the prefilled syringe presentation were not provided. The applicant provided only brief narratives and summary tables. No information was provided on the sterilization (b) (4) of the primary containers/closures and filling equipment. No information was provided on the environmental monitoring program.

**Comment #2:** Protocols and final reports supporting container closure integrity testing for both the vial presentation and the prefilled syringe presentation were not provided. The applicant provided only brief narratives.

The following information requests should be submitted to the applicant:

1. Please provide protocols and final reports supporting (b) (4) processing operations for both the vial presentation and the prefilled syringe presentation. Include information on the sterilization (b) (4) of the primary containers/closures and filling equipment. Also, include information on the environmental monitoring program.
2. Please provide protocols and final reports supporting container closure integrity testing for both the vial presentation and the prefilled syringe presentation.

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ROBERT J MELLO  
05/03/2012

JOHN W METCALFE  
05/03/2012  
I concur.