CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205776Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

28 May 2014

NDA: **205-776/N000**

Drug Product Name
Proprietary: Rasuvo™
Non-proprietary: methotrexate injection

Review Number: **1**

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10 September 2013	10 September 2013	13 September 2013	17 September 2013
15 January 2014	15 January 2014	n/a	n/a

Submission History (for 2nd Reviews or higher): N/A

Applicant/Sponsor
Name: Medac Pharma Inc.
Address: 29 N Wacker Drive Suite 704
Chicago, IL 60606
Representative: Stephanie Pierson, Vice President
B&H Consulting Services, Inc. (US Agent)
50 Division Street, Suite 206
Somerville, NJ 08876
Telephone: 908-704-1693

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

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing Authorization

3. MANUFACTURING SITE: Oncotec Pharma Produktion GmbH
Am Pharmapark
06861 Dessau-Roßlau
Germany
FEI: 3009238374

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile solution, subcutaneous injection, 50mg/mL (bulk concentration) packaged as pre-filled syringes (1mL barrels) assembled in disposable, manually activated pen-injectors. Dosing is controlled by the individual syringe fill volume. The following presentations will be manufactured:

- 7.5 mg/0.15 mL methotrexate
- 10 mg/0.20 mL methotrexate
- 12.5 mg/0.25 mL methotrexate
- 15 mg/0.30 mL methotrexate
- 17.5 mg/0.35 mL methotrexate
- 20 mg/0.40 mL methotrexate
- 22.5 mg/0.45 mL methotrexate
- 25 mg/0.50 mL methotrexate
- 27.5 mg/0.55 mL methotrexate
- 30 mg/0.60 mL methotrexate

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Folic acid antagonist: Treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and psoriasis

B. SUPPORTING/RELATED DOCUMENTS:

- BD DMF # (b) (4) Syringe System Drug Master File (DMF-(b) (4)) dated February 15, 2013.
- Microbiology Review of DMF #(b) (4) (D. Miller, DARRTS dated 2/31/2014).

C. REMARKS: The submission is in eCTD format located in the electronic document room (EDR).

filename: N205776N000R1.docx

Executive Summary

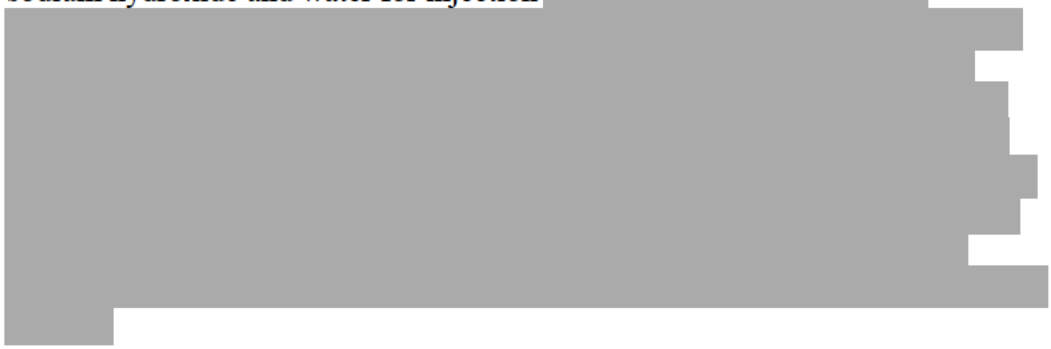
I. Recommendations

A. Recommendation on Approvability - Recommended for 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 – The drug substance is formulated with sodium chloride, sodium hydroxide and water for injection (b) (4)



B. Brief Description of Microbiology Deficiencies - None

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

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

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

B. Endorsement Block _____
Neal J. Sweeney, Ph.D.
Senior Microbiology Reviewer

C. CC Block: NDA 205776

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/s/

ROBERT J MELLO
06/02/2014

NEAL J SWEENEY
06/02/2014

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 205-776 **Applicant: Medac Pharma, Inc.** **Submit Date: 10 September 2013**

Drug Name: Methotrexate 50mg/ml solution for injection (pre-filled pen) **NDA Type: 505(b)(2)** **Received Date: 10 September 2013**

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		Submission is in eCTD format located in 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		Section 3.2.P.3.3. Environmental monitoring, bioburden, filter integrity test.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	Syringe/stoppers sterilization referenced to DMFs (b) (4) Media fill data were in Section 3.2.P.3.5. No equipment sterilization information was provided. See 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?	N/A	N/A	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity (CCI) studies?	X		Product is not preserved. Microbial immersion and dye ingress methods were used. (see below)
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Table 3.2.P.5.1-1. Sterility USP<71> membrane filtration; endotoxins USP<85>
7	Has the applicant submitted the results of analytical method verification studies?	X		Sterility, endotoxin, and CCI in Section 3.2.P.5.3
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	N/A	N/A	Product is a single use sterile solution that is ready for injection.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: See comments below.

Robert J. Mello, Ph.D. Senior Review Microbiologist Date

John W. Metcalfe, Ph.D. Senior Review Microbiologist Date

Product Quality Microbiology Assessment

Component/Equipment Sterilization Processes:
The Applicant referenced relevant Drug Master Files for the [redacted] syringe and stopper sterilization process validations. However, the submission contained no description of, or sterilization validation for, the critical product contact equipment such as [redacted] Such information was alluded to in the process development report as being available for review on site of the contract manufacturer Oncotec.

[redacted]

The applicant will be requested to provide this information for review in the submission or else obtain a Letter of Authorization from the contract manufacturer to review a relevant Drug Master File which contains this information.

Container Closure Integrity Testing:
CCI dye immersion testing procedures were summarized in 3.2.P.5.2 and microbial immersion studies were used during process validation. It appears that the dye immersion procedures are used at release as well as within the stability program. However, there remains some ambiguity on this issue. The Applicant stated the following footnote to the specifications for sterility, bacterial endotoxins and container closure integrity test in Table 3.2.P.5.1-1:

[redacted]

It is unclear what this means. It is assumed, here, to mean that these tests will be performed on the filled syringes prior to their assembly into the final drug product/pen-injector (the drug - device combination). Also it is assumed to mean that the finished drug - device combination underwent each of these tests during the initial validation of the [redacted] manufacturing process. The applicant will be asked to clarify this statement.

The following Microbiology Information Request will be forwarded to the Applicant:

Microbiology Information Request:

1. Your submission contained no description of, or sterilization validation for, the critical product contact equipment such as [redacted] Provide this information within the submission or else obtain a Letter of Authorization from the contract manufacturer to review a relevant Drug Master File which contains this information.
2. The following footnote to the specifications for sterility, bacterial endotoxins and container closure integrity test is listed in Table 3.2.P.5.1-1:

(b) (4)

It is unclear what this means. Clarify if the intent is that these tests will be performed on the filled syringes prior to their assembly into the final drug product/pen-injector (the drug - device combination). Also, clarify how the finished drug - device combination underwent each of these tests during the initial validation of the (b) (4) manufacturing process.

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/s/

ROBERT J MELLO
09/19/2013

JOHN W METCALFE
09/19/2013
I concur.