

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205776Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

June 27, 2013

**NO RELEVANT PATENTS CERTIFICATION**

**Reference: Methotrexate 50 mg/ml Pre-filled Pen  
(methotrexate 50 mg/ml solution for injection)**

In accordance with <21 CFR 314.50(i)(B)(ii), medac Pharma Inc. presents the following certification. In the opinion and to the best knowledge of medac Pharma Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

**EXCLUSIVITY STATEMENT**

According to the information in the Food and Drug Administration Orange Book Database (<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>), there is no unexpired exclusivity for the reference listed drugs.



Terri Shoemaker  
President & CEO  
Medac Pharma, Inc.

## EXCLUSIVITY SUMMARY

NDA # 205776

SUPPL #

HFD #

Trade Name Rasuvo

Generic Name Methotrexate Injection

Applicant Name Medac Pharma Inc.

Approval Date, If Known July 10, 2014

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant conducted a relative bioavailability (BA) study (MC-MTX.14/PK) in healthy adults that showed equal or greater bioavailability of methotrexate SC administered via the applicant's autoinjector compared to the exposure obtained with orally administered methotrexate tablets. The applicant also relied on published literature to support the safety and efficacy of the new route of administration for their proposed product, methotrexate (MTX) injection, to be administered subcutaneously (SC) (as a single-use prefilled autoinjector) for the indications of rheumatoid arthritis (RA) and psoriasis. The applicant also relied on FDA's previous finding of safety and efficacy of MTX for those indications as well as the indication of polyarticular juvenile idiopathic arthritis (pJIA), which is already approved for treatment via the subcutaneous

route of administration. Finally, the applicant conducted an actual use study (MC-MTX.15/HF) to demonstrate that patients and caregivers can be taught to successfully administer the product.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 08085 Dava

NDA# 11719 Hospira

NDA#

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
!  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
! YES   
! NO   
! Explain:

Investigation #2  
!  
! YES   
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Sadaf Nabavian  
Title: Senior Regulatory Project Manager  
Date: June 23, 2014

Name of Office/Division Director signing form: Sarah Yim  
Title: Associate Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
07/10/2014

SARAH K YIM  
07/10/2014



June 10, 2013

To Whom It May Concern,

**Debarment Certification**

**Methotrexate 50 mg/ml Pre-filled Pen  
(methotrexate 50 mg/ml solution for injection)-  
New Drug Application 505(b)(2)**

The undersigned hereby certifies that Medac Pharma Inc. did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in connection with this application.

A handwritten signature in cursive script, appearing to read "T. Shoemaker".

Terri Shoemaker  
President & CEO  
Medac Pharma, Inc.

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205776 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Rasuvo Established/Proper Name: Methotrexate injection Dosage Form: Subcutaneous (SC)		Applicant: Medac Pharma Inc. Agent for Applicant (if applicable):
RPM: Sadaf Nabavian		Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 10, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval on 7/10/2014
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> <li>Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input checked="" type="checkbox"/> Included 7/3/2014
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 9/10/2013
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input checked="" type="checkbox"/> Included 6/12/2014
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 9/10/2013
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	6/17/2014
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included 7/3/2014
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (indicate date(s))</li> <li>Review(s) (indicate date(s))</li> </ul>	Acceptable: 3/6/2014 Review: 2/28/2014 Not Acceptable: 10/13/2013
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> 7/9/2014 DMEPA: <input checked="" type="checkbox"/> 4/23/2014 DMPP/PLT <input checked="" type="checkbox"/> 5/2/2014 (DRISK): <input type="checkbox"/> OPDP: <input checked="" type="checkbox"/> 5/8/2014 SEALD: <input type="checkbox"/> CSS: <input type="checkbox"/> Other: <input type="checkbox"/>
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review: 11/21/2013  <input type="checkbox"/> Not a (b)(2) 6/19/2014 (action cleared via email received by Mary Ann Holovac)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included 7/10/2014
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>4/2/2014</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	6/10/2014;6/5/2014;5/30/2014;5/22/2014;5/14/2014;5/12/2014;5/8/2014;5/2/2014;4/11/2014;4/4/2014;3/27/2014;3/6/2014;2/19/2014;1/24/2014;1/17/2014;12/12/13; 11/22/2013; 9/23/2013
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Memo to file: 11/26/2014 PeRC Meeting Minutes: 4/21/2014
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	7/17/2013; 11/8/2010
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	Pre-IND MTG (Written Responses during PIND stage: 12/27/2011)
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    7/10/2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    6/19/2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	DPARP: 6/2/2014; 11/6/2013 DDDP: 6/4/2014; 11/15/2013
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review dated: 6/2/2014; Page 22

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	11/20/2013
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None DPARP: 6/2/2014; 11/7/2013 DDDP: 5/8/2014; 11/8/2013
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested 6/3/2014
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/28/2014; 10/22/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/30/2014
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/9/2014; 3/19/2014; 10/21/2013
<b>❖ Microbiology Reviews</b>	<input type="checkbox"/> Not needed 6/2/2014; 9/19/2013
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input type="checkbox"/> None CDRH/DAGID: 6/10/2014; 3/27/2014 CDRH/GHDB: 6/5/2014;11/8/2013
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Granted, CMC Review: Page 62, dated 6/9/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<b>❖ Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 7/8/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
07/14/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review and we have the following labeling comments noted below. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

#### Prescribing Information

1. Ensure that all of the to-be-marketed product presentations, including single and multiple packaging units, are represented and have NDCs listed in the "How Supplied" section.
2. Correct mismatched font sizes in the "How Supplied" section.

#### Carton Labels

3. Since it is not used in the Prescribing Information, remove all references to the term (b) (4) or (b) (4). Instead, use the term "auto-injector". If you wish to retain the term (b) (4) for use on the carton/container labels or in the Instructions for Use, propose new wording to match in the Prescribing Information.
4. Remove all references to (b) (4) on the carton labels. Methotrexate is (b) (4). The description should match that which is in the Prescribing Information. Therefore, it should read "Each 0.xx mL of Rasuvo contains xx mg methotrexate."
5. Increase the font size of presentation of strength "xx mg per 0.xx mL" on the 4-pack cartons.
6. Delete the yellow bars in the background behind the presentation of strength, as it detracts from the ability to read the strength of the product.
7. Revise (b) (4) to "Keep out of the reach of children".
8. Hyphenate the term "preservative-free".

#### Container/Device Labels

9. We agree with your approach to the presentation of dose and concentration for each dosage strength of Rasuvo on the Carton labels. However, you have not carried that approach to the Container/Device labels. Revise the Container/Device labels to add the total dose of methotrexate in each dosage strength, e.g., "10 mg" for the 10 mg per 0.20 mL dosage strength. This should be prominently displayed with a colored background, similar to the approach you took to label the cartons for each dosage strength. Likewise, the presentation of the concentration for each dosage strength can be less prominently displayed without a colored background.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB, Tuesday, June 17, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/6.10.2014

Cleared by: LJafari/6.10.2014  
PStarke/JMaynard/6.10.2014

Finalized by: SNabavian/6.10.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
06/10/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the requested information in the attached label via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB, Thursday, June 12, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/6.5.2014

Cleared by: LJafari/06.5.2014  
PStarke/JMaynard/6.5.2014

Finalized by: SNabavian/6.5.2014

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
06/05/2014

## Liu, Youbang

---

**From:** Stephanie Pierson <spierson@bhconsultingservices.com>  
**Sent:** Friday, May 30, 2014 9:18 AM  
**To:** Liu, Youbang  
**Cc:** Helen Ribbans; Patricia Nee  
**Subject:** RE: Information Request for NDA 205776, May 30 of 2014

Dear Youbang,

On behalf of Stephanie Pierson, who is out of the office, I acknowledge receipt of the information request provided below.

Best regards,

Patricia Nee

---

**From:** Liu, Youbang [<mailto:Youbang.Liu@fda.hhs.gov>]  
**Sent:** Friday, May 30, 2014 9:02 AM  
**To:** Stephanie Pierson  
**Subject:** Information Request for NDA 205776, May 30 of 2014

B&H Consulting Services, Inc.  
US Agent for Medac Pharma Inc.  
Attention: Stephanie Pierson  
Vice President  
50 Division Street, Suite 206  
Somerville, New Jersey 08876

Dear Ms. Pierson:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205776, Methotrexate 50 mg/ml solution for injection in pre-filled pen. We have the following comments and information requests:

1. Amend the analytical procedure (SOP-PM-294) for the assay of the purity of the drug product to include instructions to prepare the test solution for the drug product sample fresh, since an unknown impurity at RRT = (b) (4) is unstable in the test solution (See Methods Validation Report Q-MV-B-0 1094, Page 196)
2. Provide an evaluation of the sample stability for SOP-PM-292 in terms of the stability of (b) (4)
3. If the sample preparation used in SOP-PM-292 was shown to be unstable in terms of the stability of (b) (4) provide data to show that the samples were analyzed in a time frame that provides assurance that the measurement of (b) (4) was accurate when the samples were assayed as part of the long-term stability studies.

Please acknowledge the receipt of this email and provide the amendment submission by June 5, 2014.

Regards,

*Youbang Liu, Ph.D.*

Regulatory Project Manager

Division III, ONDQA/OPS/CDER/FDA

10903 New Hampshire Avenue

Building 21, Room 2525

Silver Spring, MD 20993

Phone: (301) 796-1926

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

YOUBANG LIU  
05/30/2014

## Liu, Youbang

---

**From:** Stephanie Pierson <spierson@bhconsultingservices.com>  
**Sent:** Thursday, May 22, 2014 3:00 PM  
**To:** Liu, Youbang  
**Cc:** Patricia Nee; Helen Ribbans  
**Subject:** RE: Information Request for NDA 205776

Dear Youbang,  
I confirm receipt of the requested information.  
Kind regards,  
Stephanie

---

**From:** Liu, Youbang [<mailto:Youbang.Liu@fda.hhs.gov>]  
**Sent:** Thursday, May 22, 2014 2:33 PM  
**To:** Stephanie Pierson  
**Subject:** Information Request for NDA 205776

B&H Consulting Services, Inc.  
US Agent for Medac Pharma Inc.  
Attention: Stephanie Pierson  
Vice President  
50 Division Street, Suite 206  
Somerville, New Jersey 08876

Dear Ms. Pierson:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205776, Methotrexate 50 mg/ml solution for injection in pre-filled pen. We have the following comments and information requests:

1. Specify which test will be used to assess container closure integrity, the dye ingress test described in P.5.2 or the bacterial ingress test described in the validation in P.5.3.
2. If the dye ingress test is used provide a validation report in Section P.5.3.
3. If the bacterial ingress test is used provide a complete description of the test in Section P.5.2.
4. Amend the specifications to include a test for actuation force. Alternatively refer to a specification for actuation force in the Device Master File.

Please acknowledge the receipt of this email and provide the amendment submission by May 29, 2013.

Regards,

*Youbang Liu, Ph.D.*  
Regulatory Project Manager  
Division III, ONDQA/OPS/CDER/FDA  
10903 New Hampshire Avenue  
Building 21, Room 2525  
Silver Spring, MD 20993  
Phone: (301) 796-1926

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

YOUBANG LIU  
05/22/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

We also have the following comments for the carton and container labels:

1. Replace (b) (4) with the approved proprietary name, "Rasuvo" and resubmit all carton and container labeling.
2. Consistent with 21 CFR 201.10(g)(2), ensure that the font size of the established name is at least half the size of the letters comprising the proprietary name and has a prominence consistent with the proprietary name in terms of type, size, color, and font.

Submit revised labeling incorporating the requested information in the attached label via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by the close of business on COB Wednesday, May 28, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/05.12.2014

Cleared by: LJafari/05.13.2014  
PStarke/JMaynard/05.14.2014

Finalized by: SNabavian/05.14.2014

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
05/14/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

We are reviewing your submission dated, May 9, 2014, which was in response to our information request dated May 8, 2014, for methotrexate injection, NDA 205776. We have the following additional comment and request for information.

- You have provided a summary test matrix to demonstrate ISO 11608-1:2000 conformance of the BD Physioject autoinjector. However, you have tested your device with a standard from 12 years ago that does not meet our current review standards. Compare the ISO 11608-1: 2000 version of the standard to that of the current ISO 11608-1:2012 version to perform tests that have different requirements or additional new testing for each dosage volume in the summary text matrix. If there are any deviations from the standard, provide clear justifications for the deviation.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB, Tuesday May 27, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/5.12.2014

Cleared by: LJafari/5.12.2014  
JMaynard/5.12.2014

Finalized by: SNabavian/5.12.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
05/12/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review and we have the following comment and request for information.

- A summary test matrix has been provided to demonstrate ISO 11608 conformance of the BD Physioject autoinjector, but test reports were not included.
  1. Provide complete test reports with notation and explanation of any deviation from testing specified in ISO 11608-1, 2000, Pen Injectors for Medical Use. If there are any deviations that were made to the ISO standard, provide detailed justification for this deviation.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB, Friday May 9, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/5.8.2014

Cleared by: LJafari/5.8.2014

Finalized by: SNabavian/5.8.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
05/08/2014

## Liu, Youbang

---

**From:** Liu, Youbang  
**Sent:** Friday, May 02, 2014 11:06 AM  
**To:** spierson@bhconsultingservices.com  
**Cc:** Nabavian, Sadaf  
**Subject:** Information Request for NDA 205776

B&H Consulting Services, Inc.  
US Agent for Medac Pharma Inc.  
Attention: Stephanie Pierson  
Vice President  
50 Division Street, Suite 206  
Somerville, New Jersey 08876

Dear Ms. Pierson:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 205776, Methotrexate 50 mg/ml solution for injection in pre-filled pen. We have the following comments and information requests:

1. Information regarding finished combination product design activities that cover all regulatory aspects of 21 CFR 820.30.
2. Information regarding purchasing control activities that cover all regulatory aspects of 21 CFR 820.50. Please also include the procedure that covers Purchasing Controls.
3. Information about the firm's CAPA system that cover all regulatory aspects of 21 CFR 820.100. Please also include the CAPA procedure.
4. Information regarding the final acceptance activities of the finished combination product.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Please acknowledge the receipt of this email and provide the amendment submission by May 16, 2014.

Sincerely,

*Youbang Liu, Ph.D.*  
Regulatory Project Manager  
Division III, ONDQA/OPS/CDER/FDA  
10903 New Hampshire Avenue  
Building 21, Room 2525  
Silver Spring, MD 20993  
Phone: (301) 796-1926

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

YOUBANG LIU  
05/02/2014

**PeRC PREA Subcommittee Meeting Minutes  
April 2, 2014**

**PeRC Members Attending:**

Lynne Yao  
Jane Inglese  
Wiley Chambers  
Tom Smith  
Peter Starke  
Gregory Reaman  
Daiva Shetty  
Julia Pinto  
Kevin Krudys  
Lily Mulugeta  
Barbara Buch

**Agenda**

NDA	205776	Rasuvo (methotrexate) RA/pJIA Partial Waiver_Assessment Psoriasis Full Waiver	RA including pJIA and severe, recalcitrant psoriasis
-----	--------	---	--

(b) (4)

**Rasuvo (methotrexate) RA/pJIA Partial Waiver Assessment; Psoriasis Full Waiver**

- NDA 205776 seeks marketing approval for Rasuvo (methotrexate) for the treatment of RA including pJIA, and severe, recalcitrant psoriasis.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA a goal date of July 10, 2014.
- *PeRC Recommendations:*
  - For RA/pJIA the PeRC agreed with a partial waiver in pediatric patients aged birth to less than 2 years because studies would be impossible or highly impracticable because the pJIA does not occur in pediatric patients of this age. The PeRC agreed that the product would be adequately labeled for pediatric patients aged 2 to less than 17 years.
  - For severe, recalcitrant psoriasis the PeRC agreed with a full waiver because the product would be unsafe for use by pediatric patients. The safety information and concern must be incorporated into section 8.4 of labeling.
  - The Division expressed concerns about inconsistent labeling of safety information in section 8.4 for this product as well as a recently-approved product, Otrexup, and a generic methotrexate labeling. The Division also noted that generic methotrexate labeling is being reviewed for PLR conversion by the generic labeling conversion contractor. The PeRC acknowledged that there may be some inconsistencies in section 8.4 of labeling until the PLR conversion for generic labeling is complete. However, the PeRC reminded the Division of the statutory requirement to include safety information in section 8.4 if a waiver for safety in any or all pediatric populations is granted. The PeRC also suggested that PMHS may be consulted for any pediatric labeling issues. In addition, any pediatric safety labeling changes included in 8.4 for this product should also be incorporated into the labeling for Otrexup.

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JANE E INGLESE  
04/21/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

We are reviewing your submission dated, April 8, 2014, which was in response to our information request dated April 4, 2014, for methotrexate injection, NDA 205776. We have the following additional comments and request for information.

1. Additional clarification is needed regarding the following points:
  - a. For our question, “did the protective needle shield move back into place to cover the needle?” you responded that two devices were “missing”. It is unclear on what “missing” indicates, please elaborate and state if the needle shield was missing from the device or were the results missing.
  - b. You have not provided any details of the protocol, testing population, acceptance/failure criteria, and results to test this needle stick feature. Provide these details in order to support that the testing demonstrates that the needle stick feature adequately protects the user from inadvertent needle stick injury. For additional information, see the CDRH Guidance for Sharps Injury Protection features at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>.
2. The clinical testing you have provided appears to only be with 212 devices. As noted in the CDRH Guidance for Sharps Injury Protection Features, Section 10 "Sample Size Determination", we recommend that the simulated use testing of your device include a sufficient number of devices to provide confidence in the performance of the device. We believe that for many devices with sharps safety features it is feasible to test 500 devices, which will enable detection of grossly defective devices at a 1% level. Thus, we request testing of a total of 500 devices. If you anticipate that the requested data regarding 500 devices cannot be obtained within the requested time period, we can have a teleconference to discuss the request.
3. Simulated shipping studies on the final finished device to confirm functionality of the autoinjector after shipping were not provided. Provide testing to demonstrate that the autoinjector is functional after simulated shipping according to ASTM-D 4169, Standard Practice for Performance Testing of Shipping Containers and Systems.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB Friday, April 18, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

*See appended signature*

---

Sadaf Nabavian, Pharm.D.  
Sr. Regulatory Project Manager  
Division of Pulmonary, Allergy, and  
Rheumatology Products

Drafted by: SNabavian/4.10.2014

Cleared by: LJafari/4.11.2014  
JMaynard/4.11.2014  
KMarin/4.11.2014

Finalized by: SNabavian/4.11.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN

04/11/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review and we have the following request for information.

1. It appears that your device has a sharps injury protection feature. The shield does cover the needle before, during, and after the injection and locks to prevent re-use. It may therefore be considered a sharps injury protection feature. Clarify whether you have conducted studies of the needle shield according per CDRH Guidance for Sharps Injury Protection features.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB Tuesday, April 8, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/4.4.14

Cleared by: LJafari/4.4.14

Finalized by: SNabavian/4.4.14

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
04/04/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We have the following comments and requests for information.

1. Your study results showed 4 failures and 4 reported difficulties where 8 study patients did not receive a full dose. For future reference, instances where study participants required assistance during task performance should be recorded as failures.

You reported that these failures can be attributed to premature lifting the pen prior to the drug delivery is complete. Some possible causes were identified which included patient's disease state which presents a challenge for them to hold the pen tight against the skin and push the start button at the same time, patient's experience, nervousness, and confusion about the click of the needle projector.

When asked about mitigating these risks, you stated that the Instruction For Use (IFU), (b) (4) already states explicitly in bold that subjects should count slowly to 5 seconds from the moment of pressing the button before lifting the pen. However, your study results showed that multiple users continue to experience failures and difficulties.

In response to our comments above, address the following:

- a. Discuss how you have designed the device taken into consideration pertinent characteristics of the intended users i.e. arthritic patients with varying level of manual dexterity.
  - b. Clarify the source of the confusion of the click of the needle projector.
  - c. Quantify the amount of dose that would be under-dosed, and describe the associated clinical impact and risk implications to actual users. If the clinical impact and risk implications indicate that additional action necessary to improve user performance, describe how you plan to demonstrate the effectiveness of those actions.
2. With regard to the issues associated with the pinch, information was not provided on whether any of the techniques applied by test participants had any potential negative consequences to the patient or the user. Therefore, if any of the techniques applied result in patient harm, the Instructions for Use and labeling should be modified to warn users of those potential consequences.
  3. Provide details on the study design with respect to the duration between the two visits, and the written exam, and how they are representative of actual use.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by COB Wednesday, April 2, 2014, followed by an official submission to the NDA.

If there are any questions, you may contact me at 301-796-2777.

*{See appended electronic signature page}*

---

Sadaf Nabavian, Pharm.D.  
Sr. Regulatory Project Manager  
Division of Pulmonary, Allergy and Rheumatology  
Products (DPARP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Drafted by: SNabavian/3.27.2014

Cleared by: LJafari/3.27.2014

Finalized by: SNabavian/3.27.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
03/27/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205776

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Medac Pharma, Inc.  
c/o B&H Consulting Services, Inc.  
50 Division Street  
Suite 206  
Somerville, NJ 08876

ATTENTION: Stephanie Pierson, RAC  
Vice President

Dear Ms. Pierson:

Please refer to your New Drug Application (NDA) dated September 10, 2013, received September 10, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Sodium Injection, 50 mg/mL.

We also refer to your December 20, 2013, correspondence, received December 20, 2013, requesting review of your proposed proprietary name, Rasuvo. We have completed our review of the proposed proprietary name, Rasuvo and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 20, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Sadaf Nabavian, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
03/06/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We have the following comments and requests for information.

1. Provide the following information for Study MC-MTX.15/HF:
  - a. The training script used by the instructors in Study Visit 1. If no training script was used, explain why a standardized instruction set was not tested in the study.
  - b. The study report uses the term Metroject® to denote the prefilled pen device used in the study. However, you have not used this term in the rest of the NDA submission. Explain any differences between the Metroject device and the to-be-marketed device.
  - c. Provide specific details of the results for each observation/performance measure taken during Study Visit 2, as outlined in Section 9.5.2.1.2 on pages 57-8 of the study report.
  - d. We note that you have identified failures (i.e., incomplete injections, participants needing assistance and experiencing difficulties using the device, unsuccessful completion of the following critical tasks: held device in place for 5 seconds and pinched the skin for subcutaneous administration) during Visit 1 and Visit 2 in the study. However, no risk mitigations for these failures have been provided. Provide risk mitigations for these failures or provide a rationale for why risk mitigations are not needed.
  - e. The point of requesting an evaluation of pen robustness during a study is to allow for a specific root-cause inspection / *in vitro* evaluation when there is evidence of device failure. However, the study report does not provide this information. Therefore, we request that you submit the following. If a detailed inspection and evaluation of device failures was not performed, explain why this was not carried out.
    - i. Provide specific details of a root-cause inspection / evaluation of the pen that showed evidence of having malfunctioned with evidence of fluid within the transparent control zone after the injection.
    - ii. Provide specific details of a root-cause inspection / evaluation of the pen that showed evidence of having a bent needle after the injection.
2. You state that the needle length for the proposed drug product is ½ inch, but do not state whether the needle guards/sheath prevent the needle from fully penetrating the skin to the hilt. Since the exposed needle length is a critical element of the device function, provide the following:
  - a. Data regarding the exposed needle length for the injection.
  - b. Specifications for the exposed needle length.

3. Provide details, including specifications, regarding the force to fire for an injection.
4. Most injection devices for subcutaneous injection do not require pinching of the skin as part of the injection routine. For rheumatoid arthritis patients, this step may increase the difficulty of using the product. Support your reasoning for why patients must be instructed to pinch the skin as part of the injection of the proposed drug product.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by Monday, February 24, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/2.19.2014

Cleared by: LJafari/2.19.2014

Finalized by: SNabavian/2.19.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
02/19/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We have the following comment and request for information.

1. Submit final study report, raw and calculated pharmacokinetic parameters in SAS Transport format (.xpt), bioanalytical report, and associated bioanalytical method validation report (including adequate long-term storage stability data) for your relative bioavailability trial, MC-MTX.12/PK, as soon as the results become available. Update the Division if you anticipate delays from your proposed timeline of end of April 2014.

Submit the requested information via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) as soon as the results are available and as stated above, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/1.24.2014

Cleared by: LJafari/1.24.2014

Finalized by: SNabavian/1.24.2014

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
01/24/2014

## Liu, Youbang

---

**From:** Liu, Youbang  
**Sent:** Friday, January 17, 2014 11:50 AM  
**To:** 'spierson@bhconsultingservices.com'  
**Cc:** Nabavian, Sadaf  
**Subject:** Information Request for NDA 205776

NDA 205776

Medac Pharma Inc.  
US Agent: B&H Consulting Services, Inc.  
Attention: Stephanie Pierson  
Vice President  
50 Division Street, Suite 206  
Somerville, NJ 08876

Dear Ms. Pierson:

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 205776 dated September 10, 2013. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

- Please submit the stability data in a SAS transport file that can be readily analyzed by our statistics reviewers

Please acknowledge the receipt of this email and the time line of the amendment submission.

Sincerely,

*Youbang Liu, Ph.D.*  
Regulatory Project Manager  
Division III, ONDQA/OPS/CDER/FDA  
10903 New Hampshire Avenue  
Building 21, Room 2525  
Silver Spring, MD 20993  
Phone: (301) 796-1926

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

YOUBANG LIU  
01/17/2014

NDA 205776  
Methotrexate injection  
Medac Pharma, Inc.

Dear Ms. Pierson:

Your NDA submission dated, September 10, 2013, for methotrexate injection is currently under review. We are providing you with our proposed labeling requesting that you fill-in the information requested and highlighted throughout the attached labeling. Please note that we may have additional labeling comments as we continue our review.

Submit revised labeling incorporating the requested information in the attached label via email to [Sadaf.Nabavian@fda.hhs.gov](mailto:Sadaf.Nabavian@fda.hhs.gov) by the close of business on Tuesday, January 14, 2014, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/12.12.2013

Cleared by: LJafari/12.12.2013

Finalized by: SNabavian/12.12.2013

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
12/12/2013



NDA 205776

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Medac Pharma, Inc.  
c/o B&H Consulting Services, Inc.  
50 Division Street, Suite 206  
Somerville, NJ 08876

Attention: Stephanie Pierson, RAC  
Vice President

Dear Ms. Pierson:

Please refer to your New Drug Application (NDA) dated September 10, 2013, received September 10, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Methotrexate 50 mg/ml Pre-filled Pen.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

Therefore, the user fee goal date is July 10, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 12, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. We note that you have submitted a protocol for a relative bioavailability study, MC-MTX-12/PK, to your NDA. However, a study report was not provided. Provide the status of this study.
2. Provide raw pharmacokinetic data for study MC-MTX.9/PH in SAS Transport (.xpt) format.
3. For study MC-MTX.9/PH: Provide analysis of relative bioavailability (C<sub>max</sub> and AUC) between the subcutaneous (SC) route and the intramuscular (IM) route. The analysis should be stratified by formulation strengths (i.e., 10 mg/mL and 50 mg/mL) as well as based on pooled data from both strengths. Also, provide detailed formulation composition information for the drug products used in this study.
4. Provide placebo samples of the drug product.
5. Provide plots of drug product stability data for the following parameters for each strength and storage condition, including a statistical analysis to evaluate the confidence bands:
  - a. Container content
  - b. Assay
  - c. Purity
6. We note that an unidentified impurity with RRT is increasing on storage at (b) (4). Include this impurity in the statistical evaluation. This impurity may affect the expiration date and may need to be identified and/or qualified.
7. Your submission contained no description of, or sterilization validation for, the critical product contact equipment such as (b) (4). 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.
8. 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)

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.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

#### Highlights (HL)

1. The Initial U.S. Approval must be in bold type and placed on the line immediately beneath the product title. Therefore, there must NOT be a space between the product title and Initial U.S. Approval lines.
2. For the Revision Date, the preferred format is “Revised: Month Year” or “Revised: M/YYYY”.

#### Full Prescribing Information (FPI)

3. If there is more than one contraindication, use a bullet for each contraindication instead of subsection headings.
4. In the Drug Interactions section, a table may be the most effective format to enhance communication of multiple drug interactions. The table can list, when applicable, the co-administered drugs, mechanism of action, and clinical comments (clinical concern and practical instructions for preventing or managing interactions, e.g., dose adjustments or advice regarding monitoring).
5. In the Pharmacokinetics section, include all PK information under subsection 12.3 Pharmacokinetics. Organize information under descriptive subheadings (e.g., Absorption, Distribution, Metabolism, Excretion, Specific Populations, and Drug Interaction Studies).

#### In Section 17, Patient Counseling Information

- Organize information by subsection headings or bulleted items. Numbered subsections (e.g., 17.1, 17.2) are not recommended because they may be redundant with subsection titles elsewhere in the labeling.
- The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use):
  - i. Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - ii. Information Following Section 17
    - The revision date at the end of highlights replaces the “revision” or “issued” date at the end of the FPI and should not appear in both places. However, a revision date may appear at the end of FDA-approved patient labeling.

We request that you resubmit labeling that addresses these issues by January 15, 2014, as we may have additional labeling comments that will be forthcoming. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for the indication of psoriasis for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We also acknowledge receipt of your request for a partial waiver of pediatric studies from birth to 2 years of age for the indication of Polyarticular Juvenile Idiopathic Arthritis for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Sadaf Nabavian, Sr. Regulatory Project Manager, at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SARAH K YIM  
11/22/2013  
Signing for Badrul Chowdhury, M.D., Ph.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

IND 109543

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

medac GmbH  
c/o B&H Consulting Services, Inc.  
50 Division Street  
Suite 206  
Somerville, NJ 08876

ATTENTION: Mohamed Abdelnasser  
Director CMC Regulatory Affairs

Dear Dr. Abdelnasser:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methotrexate Injection, 50 mg/mL.

We also refer to your May 8, 2013, correspondence, received May 8, 2013, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

We note that you have proposed an alternate proprietary name in your submission dated May 8, 2013. In order to initiate the review of the alternate proprietary name, <sup>(b) (4)</sup> submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

IND 109543

Page 4

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sadaf Nabavian, at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
CAROL A HOLQUIST  
10/16/2013



NDA 205776

**NDA ACKNOWLEDGMENT**

Medac Pharma, Inc.  
c/o B&H Consulting Services, Inc.  
50 Division Street, Suite 206  
Somerville, NJ 08876

Attention: Stephanie Pierson, RAC  
Vice President

Dear Ms. Pierson:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Methotrexate 50 mg/ml Pre-filled Pen

Date of Application: September 10, 2013

Date of Receipt: September 10, 2013

Our Reference Number: NDA 205776

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 9, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Sadaf Nabavian, Sr. Regulatory Project Manager, at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Sadaf Nabavian, Pharm.D.  
Sr. Regulatory Project Manager  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SADAF NABAVIAN  
09/23/2013



IND 109543

**MEETING MINUTES**

Medac GmbH  
c/o B&H Consulting Services, Inc.  
50 Division Street, Suite 206  
Somerville, NJ 08876

Attention: Helen M. Ribbans, RAC, FRAPS  
President, Regulatory Consultant

Dear Ms. Ribbans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methotrexate injection.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2013. The purpose of the meeting was to discuss your development program in support of a future registration for methotrexate injection as a 505(b)(2) application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Sadaf Nabavian, Pharm.D.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA meeting

**Meeting Date and Time:** June 17, 2013, from 8:30-10:00 A.M. EST  
**Meeting Location:** Conference Room 1419

**Application Number:** IND 109543  
**Product Name:** Methotrexate Injection

**Indication:** Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriasis  
**Sponsor Name:** Medac GmbH

**Meeting Chair:** Badrul A. Chowdhury, M.D, Ph.D.  
**Meeting Recorder:** Sadaf Nabavian, Pharm.D.

### FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sarah Yim, M.D., Supervisory Associate Director, DPARP

Janet Maynard, M.D., MHS, Acting Clinical Team Leader, DPARP

Peter Starke, M.D., Clinical Reviewer, DPARP

Theresa Michele, Clinical Team Leader, DPARP

Nikolay Nikolov, M.D., Clinical Reviewer, DPARP

Arthur Shaw, Ph.D., CMC Reviewer, ONDAQ (via telecon)

Craig Bertha, Ph.D., Acting CMC Lead, DNDQA III, ONDQA

Arun Agrawal, Ph.D., Clinical Pharmacology Reviewer

Timothy Robison, Ph.D., Pharmacology/Toxicology Supervisor (via telecon)

Quynh Nguyen, Biomedical Engineer/Injection Systems Human Factors Specialist  
Human Factors Pre-Market Evaluation Team

Lubna Merchant, Pharm.D., Safety Evaluator Team Leader, Office of Surveillance and Epidemiology (OSE)

Teresa Mcmillan, Pharm.D., Safety Evaluator, OSE

Snezzana Trajkovik, M.D., Clinical Reviewer, Division of Dermatology and Dental Products (DDDP)

Tatiana Oussova, M.D., Clinical Team Leader, DDDP

Sadaf Nabavian, Pharm.D., Regulatory Project Manager, DPARP

### SPONSOR ATTENDEES

*Medac GmbH*

Kirsten Brab, PhD, Head Drug Regulatory Affairs International

Hans-Jürgen Kuehnel, PhD, Medical Director

Uwe Pichlmeier, PhD, Head of Biometrics and Data Management (via telecon)

Michaela Rehberg, PhD, Director, Drug Regulatory Affairs/Pharmaceutical Development  
Gretel Sass, Director, Research and Development  
*B&H Consulting Services, Inc.*

Elizabeth Dupras, RAC, Associate Director, CM&C and Regulatory Affairs (telecon)  
Stephanie Pierson, RAC, US Agent for Medac Pharma  
Helen M. Ribbans, RAC, FRAPS, President, Regulatory Consultant

(b) (4)

## 1.0 BACKGROUND

The purpose of the meeting is to discuss Medac's drug development plan in support of a future registration for methotrexate injection as a 505(b)(2) application. Medac submitted a request for a meeting on March 26, 2013, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on April 16, 2013. The briefing package was submitted on May 3, 2013. The Division provided the preliminary responses to Medac on June 12, 2013, and in response Medac requested for further clarification and discussion under General Comments (2 bullet point in context of Question 15), Questions 4, 10, 11, 15, 16, and 25. For Questions 4, 10 and 11, Medac provided handouts prior to the meeting and the information has been captured under the discussion sections and as well included in Section 8, Handout and Attachment.

## 2. DISCUSSION

### *Questions and Responses*

#### General comments:

*In general, the summary of your development plan in support of a 505(b)(2) NDA submission for methotrexate (MTX) is consistent with the advice provided by the Division during our type B meeting on October 14, 2010, and our written responses communicated on December 27, 2011. Therefore, it appears that your program is generally acceptable to support submission of your application. In addition to the information provided, the following aspects should be addressed in your new drug application (NDA) submission:*

- *Pharmacokinetic (PK) differences due to different body weights and sites of administration in RA patients (see our response to your Question 15)*

- *Data pertaining to dosing in special populations such as renal and hepatic impairment, elderly patients etc. seem to be available in the public domain. We encourage you to undertake a literature search to check if some of the known information is of sufficient quality to be incorporated into the product label.*

*If a 505(b)(2) application seeks to rely on the Agency's previous findings of safety or efficacy for a product, then that product should be identified as a listed drug. In some cases, more than one listed drug may be applicable; for example, your application may list both Hospira's NDA 011719 (MTX injection) and Dava's NDA 008085 (Oral MTX) as reference products.*

Discussion:

Refer to the discussion section under Question 15

A. 2.1. CHEMISTRY, MANUFACTURING AND CONTROLS

**Question 1:**

***Does the Agency agree that the proposed drug substance specifications are adequate to control the quality of the drug substance?***

FDA Response:

*Yes, we agree.*

Discussion:

No discussion occurred.

**Question 2:**

***Does the Agency agree that the proposed specifications for the drug/device combination product are adequate to control the quality of the Methotrexate 50 mg/ml Pre-filled Pen?***

FDA Response:

*The adequacy of your proposed Specification will be a review issue. However we have the following comments:*

- 1. Specify the measurement units and target values used for the test "Uniformity of dosage units."*
- 2. The acceptance criteria for Extractable Volume should have an upper limit.*
- 3. We note that the acceptance criteria for Assay and Osmolality are broad, while the batch analysis shows a narrow range of values.*

Discussion:

No discussion occurred.

**Question 3:**

***Does the Agency agree that this validation concept is acceptable for manufacturing drug product batches in the range of*** (b) (4)

**FDA Response:**

*A response will be provided at the meeting.*

**Discussion:**

The following responses were provided to the sponsor via email correspondence dated June 14, 2013, and no further discussion was requested by the sponsor.

*“Agency neither approves process validation approaches or protocols (including the number of batches or a batch size to be used for a single or multiple product strengths in process validation studies) nor does it prescribe how to accomplish that goal. However, success of a process validation is predicated on (i) science and risk-based product and process design, (ii) development of scientifically justified product and process knowledge for a commercial process (iii) leveraging product and process development knowledge for a process validation protocol design, (iv) careful execution of a properly designed process validation protocol, and (v) verification of pre-established protocol outcome via scientifically and statistically justified accept/reject criteria for product quality and batch disposition.*

*Adequacy of an actual process validation protocol, its execution and study outcome is typically evaluated on an inspection and not through application review. Hence submission of any such information into an application is neither required, nor evaluated as a condition of application approval. Please note that the Process Validation guidance (see below for the reference) states, “The decision to begin commercial distribution should be supported by data from commercial-scale batches.”*

*In support of your proposal, it is expected that the process validation protocol among other deliverables will include certain objective measures (e.g., acceptance criteria [see 21 CFR 210.3(b)(20)], and appropriate process capability/performance metrics) to demonstrate and assure that the manufacturing process is robust and capable of reliably delivering a product of uniform character and quality across intended product strengths and production scales (i.e., variable batch size).*

*Establishing and maintaining a validated manufacturing process, capable of delivering a product of intended quality characteristics consistently and reliably throughout its lifecycle, remains the primary goal of process validation activities and a sole responsibility of a drug product manufacturer. For additional information, you are encouraged to refer to “Guidance for Industry, Process Validation: General Principles and Practices” posted at the following link. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.”*

**Question 4:**

***Does the Agency agree that the results from the primary and supportive stability studies can be used to establish the initial expiration date of [REDACTED] (b) (4) for commercial batches of Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)?***

**FDA Response:**

*In order to provide you with a response we will need to know the similarities and differences among the batches used for supportive stability, the batches used for the primary stability studies, and the batches for the to be marketed product.*

**Discussion:**

The Sponsor summarized the table pertaining to the batches which listed a comparison of primary stability, supportive stability and to-be-marketed drug product batches. The sponsor noted that all the batches were made with the same manufacturing process, batch formula, manufacturing equipment, manufacturing process, and same container closure system. The sponsor also stated that in terms of analytical testing, the primary stability batches and to-be-marketed batches the requirements were met and exceeded the USP requirement (see enclosure). The sponsor concluded that any differences found in the batches were not expected to impact any physical or chemical characteristics of the drug product and insured the Division that the stability studies were identical to the to-be-marketed product. The sponsor also informed the Division that they plan to submit the complete information in the future NDA package.

The Division replied that the information provided by the sponsor is acceptable, however the information in terms of the supportive stability batches will be a review issues and further comments will be provided as a post-meeting note in the final minutes.

**Question 5:**

***Does the Agency agree that a fully translated blank batch record and a single representative executed batch record in German with English annotations are acceptable?***

**FDA Response:**

*Yes, we agree.*

**Discussion:**

No discussion occurred.

**Question 6:**

***Does the Agency agree with medac's proposal to provide sterile process validation data for three bulk batches; three batches each at the lowest (0.15 ml) and the highest (0.60 ml) fill volumes, and one batch at each of the intermediate fill volumes (0.20 ml to 0.55 ml)?***

**FDA Response:**

*Yes, your proposal is acceptable.*

*We also refer you to the following Guidance and MaPP:*

- *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Nov 1994. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf>)*
- *MaPP 5040.1 Product Quality Microbiology Information in the Common Technical Document - Quality (CTD-Q) (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm079570.pdf>)*

Discussion:

No discussion occurred.

Question 7:

*Does the Agency agree that samples for methods validation testing can be limited to samples from two drug product batches, i.e., one batch filled at 0.15 ml (the lowest fill volume) and one batch filled at 0.60 ml (the highest fill volume) and that samples of each of the 10 fill volume presentations are not required?*

FDA Response:

*Yes, we agree, use of 2 batches of product for method validation is acceptable.*

Discussion:

No discussion occurred.

2.2. Nonclinical

Question 8:

*Does the Agency agree that the Dava Pharmaceuticals' approved labeling (NDA 008085), published nonclinical literature and the local tolerance study in rabbits (LPT Report 20070/06) conducted by medac demonstrate the nonclinical safety of methotrexate in support of a marketing approval for Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection) and that no additional nonclinical studies need be conducted?*

FDA Response:

*Yes we agree that no further non-clinical studies are needed for the submission of an NDA. We also have the following comments:*

- *Provide relevant, published scientific literature with your NDA submission to support the evaluation of safety and labeling of your product. The literature should cover relevant pharmacology, ADME, general toxicology, pregnancy, carcinogenicity, genotoxicity, and fertility. You are encouraged to provide updated literature as much of the literature on methotrexate is old. Reference to the label of an approved US product (NDA 08085) is acceptable.*

- *Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Draft Consensus Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 2 Version dated February 6, 2013).*
- *A safety assessment of extractables and leachables should be provided for all components of the container closure system and device that are in contact with the drug product during storage.*

Discussion:

No discussion occurred.

**Question 9:**

***Does FDA agree that the results are as expected and have no impact on the benefit/risk profile of Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection) for the treatment of RA, JIA and psoriasis?***

FDA Response:

*As noted in our written responses communicated on December 27, 2011, bioequivalence of oral and SC methotrexate is not expected to be demonstrated in light of the different routes of administration. An assessment of the benefit/risk profile of Methotrexate 50mg/ml Pre-filled Pen for the treatment of RA, JIA, and psoriasis will be determined during the review of your new drug application (NDA).*

Discussion:

No discussion occurred.

**Question 10:**

***Since no efficacy studies have been conducted with the Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection) in support of the NDA and the efficacy of the drug product will be based on reference to approved labeling and published clinical literature, does the Agency agree that no Integrated Summary of Efficacy (ISE) is needed in the 505(b)(2) NDA?***

FDA Response:

*No, we do not agree. The integrated summary of efficacy (ISE) and integrated summary of safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports, are required by the regulations, and would be located in Module 5. However, if you believe section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and Module 5.*

Discussion:

The sponsor provided an overview of the data that will be submitted in terms of the efficacy and safety data. The sponsor added that for efficacy data they will include individual data for studies MC-MTX.14/PK and MC-MTX.15/HF in Module 2.7.3. Further, the Sponsor added that they do not intend to provide a separate integrated summary of efficacy (ISE) document evaluating the efficacy for methotrexate. In terms of safety, the sponsor stated that they plan to include individual data for studies MC-MTX.14/PK and MC-MTX.15/HF and supportive study MC-MTX.10 in module 2.7.4. The sponsor added that they do not think that is feasible to pool data from these two studies due to the differences including the study population, study design, the heterogeneity of the adverse events incidences, the differences in the number of doses administered, and data collected in the studies. Also, the sponsor noted that Study MTX.10/RH is not suitable for pooling due to the non-randomized study design with 3 administrations of 10mg/ml methotrexate followed by 3 administrations of 50mg/ml methotrexate using the prefilled syringes (see enclosure).

The Division reiterated that the integrated summary of safety (ISS) and the ISE are required by regulation and should be detailed integrated analyses. If the Sponsor believes that section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed the sponsor's proposal would be reasonable to include those data in Module 2 vs. Module 5. However, the Division asked that the sponsor provides an explanation in both Module 2 and Module 5 and links to all the supportive information including literature references and datasets in Module 5. The Division explained that the ISE and ISS do not require pooling of the study data. Rather, the ISE and ISS require integrated analyses. The Sponsor's rationale for not pooling the data due to differences in study design and patient populations seem reasonable.

Question 11:

*Does the Agency agree that it is appropriate to integrate the safety data from studies MC-MTX.15/HF (actual use study) and MC-MTX.14/PK (comparative bioavailability study [oral vs. SC]) in the 505(b)(2) NDA?*

FDA Response:

*We have discussed our expectations regarding the integrated safety data in our response to your Question 10. However, we do not agree with your proposal if your underlying question pertains to whether only integrated safety data from studies MC-MTX.15/HF and MC-MTX.14/PK can be provided. While integrated safety data can be provided, safety data from each individual study should also be provided.*

Discussion:

No discussion occurred.

2.3. Risk Evaluation and Mitigation Strategy

Question 12:

*Does the Agency agree that a waiver from submitting a Risk Evaluation and Mitigation Strategy (REMS) is appropriate?*

FDA Response:

*At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology, the Division of Risk Management, have insufficient information to conclusively determine whether or not a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of methotrexate 50 mg/mL Pre-filled Pen (methotrexate 50 mg/mL solution for injection) outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. The FDA approved Methotrexate Injection products do not currently have a required REMS program or a Medication Guide in labeling. We will make a final determination of the need for a REMS during the review of your proposed application.*

Discussion:

No discussion occurred.

Question 13:

***Does the Agency agree that these studies together with the published nonclinical and clinical literature, and reference to approved methotrexate labeling (NDA 008085, Dava Pharmaceuticals, Inc.) are sufficient to support a marketing approval for Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)?***

FDA Response:

*The purpose of this meeting is to determine the adequacy of your dossier for the submission of an NDA. A determination of whether the data are sufficient to support marketing approval of Methotrexate 50mg/ml Pre-filled Pen will occur after submission of your NDA. Thus, it is premature to assess whether the data are sufficient to support a marketing approval for Methotrexate 50mg/ml Pre-filled Pen. See our response to your Question 16 regarding concerns with your Actual Use Study.*

Discussion:

No discussion occurred.

Question 14:

***Does the Agency agree that these results demonstrate acceptable local tolerability of the Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)?***

FDA Response:

*As noted in our response to your Question 13, the purpose of this meeting is to determine the adequacy of your dossier for the submission of an NDA. Your question is premature as a determination of whether the data demonstrate acceptable local tolerability of the Methotrexate 50mg/ml Pre-filled Pen will be a review issue.*

Discussion:

No discussion occurred.

Question 15:

***Does the Agency agree that the relative bioavailability data adequately cover the***

***expected body weight range and patient population to be treated with Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)?***

FDA Response:

*Enrollment of RA patients in the Human Factors study in the <60 kg, 60-100 kg and >100 kg body weight ranges for the determination of pharmacokinetics is in line with Agency's recommendations. In the meeting package, we did not see a thorough discussion of the quantitative differences in the PK (a) between different body weight groups and (b) between abdomen and thigh administration sites and any potential labeling implications with respect to Dosage and Administration. We suggest that you carefully assess these data and determine if the dosage administration should take into consideration body weight of the patient and if the site of administration should be restricted to one of the two studied sites of administration.*

Discussion:

The Division acknowledged and agreed the fact that the Sponsor has conducted methotrexate relative bioavailability determinations for the three body weight ranges (<60 kg, 60-100 kg, and >100 kg) and the two sites of injections (abdomen and thigh) in RA patients. The Division further added that the Sponsor has not provided information in the meeting briefing package about the quantitative differences in the PK (Cmax and AUC) among different body weight groups and between different sites of drug administration, and any potential labeling implications with respect to Dosage and Administration. The Sponsor stated to submit the complete data analysis and potential implications for review when NDA is submitted. The Division responded that the Sponsor's data analyses and potential labeling implications will be review issues when NDA is submitted.

## 2.4. Human Factor Study

### **Question 16:**

***Does the Agency agree that study MC-MTX.15/HF provides adequate information to support approval of the auto-injector itself as well as the drug/device combination product - Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)?***

### **FDA Response:**

*No, we do not agree. You have submitted a synopsis of the Human Factors study (HFS) and have not provided all raw data for our review.*

*We have identified the following potential deficiencies that may affect the utility of the results:*

*The study results indicated task failures across three of the four scenarios, however, there was no analysis directed toward the understanding of those task failures. In addition, without a complete test report, we were unable to review the adequacy of your method and data. Please submit a complete test report that includes the following items:*

- *A clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.*
  - *Provide use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority.*
  - *Describe all activities in which your test participants will engage during the test.*
- *A description of the study participants, and discuss how they were representative of actual intended uses*
- *A description of the testing environment and realism of the simulated use in sufficient detail. Justify how they were appropriate for validation testing.*
- *The content of the training and how it was reflective of actual use*
- *We note that a written examination was given at the beginning of Visit 2 (testing visit Day 8 to 10), which evaluated the participants' retention of information*

*given at Visit 1 (training visit on Day1). Discuss how a written exam represents realistic use*

- *A rationale for measuring task times and whether they are any clinical significance*
- *An analysis of your study results. Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm, under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.*

Discussion:

The sponsor at first informed the Division that they planned to submit an amendment to the IND with a final human factor clinical study report including the background strategy followed in developing the human factor protocol, they also stated that every single point on the proposed protocol pointed out by the Division has been addressed and asked if it would be acceptable from the Division standpoint to submit that data as an amendment for review and if the Division would consider would provide feedback in a timely manner prior to the NDA submission. The Division recommended that instead of submitting the data for review to the IND for the sponsor to submit the data to the NDA in order to expedite the process and so the data can be formally reviewed.

The sponsor went into depth and briefed the Division on the concerns raised by the Division regarding the human factor study. Some of that information included the risk analysis that was conducted to identify the task in the human factor study which included many factors including features, functions of the pen itself, including the IFU of the MG. The sponsor informed the Division that they also looked at additional information from published data on the actual pen, validation data, and FDA database, etc. The sponsor also provided information on the pen usage including the study subjects such as RA patients, the timing of the pen, the level of patient education, the differences and the detailed setting of each visits from visits 1 (trained by the HCP) Visit-2 (self injectors 8-10 days later and observed) and etc. The sponsor stated that the analysis of performance also included the task failures and the clinical impact and that none of the failures cause any harms to the subjects. The sponsor plans to address all Division's questions and provide the complete data in the NDA submission and to also submit the study report, the protocol and the data needed to support the questions raised.

The Division asked a clarifying question regarding the type of population that the sponsor plans to recruit for the human factor study and asked if pediatric patients will be included. The Division replied that pediatric subjects will not be included and that only adult rheumatoid arthritis patients beyond the age of 18 years will be recruited in the study. The Division stated that since one of the proposed indications of methotrexate includes the pediatric population that it will be required for the sponsor to include a human factor study in pediatric patients for validation which is expected in a human factor study with active product and active patients. The Division further added that published data can be submitted as only supportive data for the conclusion of the study for the pediatric population. The Division sought clarification regarding the written exam, the sponsor clarified that the intent of the written exam was to see what information was retained by the participants in addition to the Instructions for Use and the Medication Guide that was provided. The Division recommended for the sponsor to keep in mind that a written exam is not representative of an actual use scenario and this may affect the utility of the results. The sponsor replied that they will think about amending the protocol to include the pediatric population.

## 2.5. DATA MANAGEMENT AND BIOSTATISTICS

### **Question 17:**

***Does FDA agree with the proposed format for submission of data sets?***

#### **FDA Response:**

*Yes, we agree.*

#### **Discussion:**

No discussion occurred.

### **Question 18:**

***Does FDA agree that no further analyses of the data from these two studies need be prepared for the NDA?***

#### **FDA Response**

*Based on your summary information, your proposal appears to be sufficient to support submission of a 505(b)(2) NDA. Whether additional analyses of the data are required will be determined during review of your NDA.*

#### **Discussion:**

No discussion occurred.

## 2.6. DEVICE

### **Question 19:**

***Does FDA agree that a LOA to MAF (b) (4) and the additional information related to***

***the device (Module 3.2.P.7) are sufficient and that no further device specific data are needed in the NDA?***

*FDA Response:*

*No, we do not agree. You have not provided a letter of authorization to review the Drug Master File (DMF) for the (b) (4) syringe. The syringe primary container closure is also a device which must be evaluated by the Center for Devices and Radiological Health (CDRH) for safety and efficacy. Provide a letter of authorization so we can review the DMF/ MAF for the (b) (4) syringe container closure.*

*You have not provided shipping data to demonstrate that the final finished combination product is functional after exposure to conditions during shipping. Submit simulated shipping data according to ASTM D4169:1999, Standard Practice for Performance Testing of Shipping Containers and Systems and ASTM F647, Testing to Assess Durability of Devices Following Interaction with Drugs to demonstrate that the final finished combination product is functional after exposure to conditions during shipping.*

*Discussion:*

No discussion occurred.

2.7. REGULATORY

***Question 20:***

***Does the Agency agree with the organization of the eCTD?***

*FDA Response:*

*Yes, we agree with the organization of the eCTD.*

*Discussion:*

No discussion occurred.

***Question 21:***

***Does the Agency agree with the Sponsor's proposal to submit only literature references cited in the Module 2 Summaries?***

*FDA Response:*

*Yes, we agree with your proposal to submit only literature references cited in the Module 2 Summaries and to have the other references available upon request.*

*Discussion:*

No discussion occurred.

***Question 22:***

***Does the Agency concur with the Sponsor's proposal not to include any Case Report***

***Forms in the NDA?***

FDA Response:

*The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drug or placebo (21 CFR §314.50(f)(2)). If no case report forms are submitted because there were no deaths or discontinuations secondary to adverse events in your clinical studies, then this should be noted in your submission.*

Discussion:

No discussion occurred.

2.8. Pediatric Waiver Request

**Question 23:**

***Does the Agency agree with the Sponsor's proposal concerning the partial pediatric waiver?***

FDA Response:

*See Section 3, PREA REQUIREMENTS. As noted in our letter dated March 6, 2013, the Pediatric Study Plan you have proposed, including a partial pediatric waiver, appears reasonable. On preliminary review, it appears that the safety and efficacy of methotrexate in children with juvenile rheumatoid arthritis (JRA) has been established based on the proposed listed drug's label and the available scientific literature. In your pediatric study plan, this information may be used to support the safety and efficacy of methotrexate in children, rather than as the basis for extrapolation of safety and efficacy data from adults to children.*

*You should be aware that an application for a new route of administration for psoriasis may trigger a requirement for pediatric assessments under the Pediatric Research Equity Act (PREA). This decision will be made when the NDA is submitted. A plan for addressing PREA requirements would need to be submitted with the NDA. It may be reasonable to request a full waiver from pediatric studies in psoriasis due to safety reasons.*

Discussion:

No discussion occurred.

2.9. Exclusivity

**Question 24:**

***Does the Agency agree that the Sponsor's 505(b)(2) application will support a request for (b) (4) ?***

FDA Response:

*(b) (4) determinations are made at the time of approval of an application and your NDA submission may include a request for (b) (4)*

Discussion:

No discussion occurred.

## 2.10. PDUFA

### **Question 25:**

***Assuming that the medac application is accepted for review prior to the Agency's approval of the pharmaceutically equivalent product, we request confirmation that review of medac's application will proceed as a 505(b)(2) NDA.***

### **FDA Response:**

*A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).*

*If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.*

*If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).*

*If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.*

*If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.*

*We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.*

*Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.*

Discussion:

The sponsor noted that they were aware from publically available information that another subcutaneous methotrexate product was currently being reviewed by the division. The sponsor requested feedback on the timing and the fileability of their NDA submission in light of this information. In addition, the sponsor asked the Division to assure that the NDA will be accepted as a 505(b)(2) vs. 505(j) if the NDA is submitted prior to the action due date of the pending application. The Division could not provide any additional comments except to remind the Sponsor that circumstances could change that would render a 505(b)(2) application for the product no longer appropriate.

2.11. LABELING

Question 26:

*Does the Agency agree with the general concept that a summary from the literature could support the approval of the Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection) for SC administration for the RA, JIA and psoriasis indications?*

FDA Response:

*Your proposal to submit a summary from the literature of the safety and efficacy of methotrexate in RA, JIA, and psoriasis appears to be sufficient to support submission of your NDA. A determination of whether the data support approval of the auto-injector itself as well as the drug/device combination product will occur after submission of your NDA.*

Discussion:

The Division asked the sponsor which reference listed product they intend to rely on. The sponsor confirmed that the reference listed products will be the NDAs from the Hospira and Dava and further confirmed that the labeling will be submitted in PLR format. The Division advised that from the administrative standpoint the sponsor lists the complete reference listed products in the appropriated fields on Form 356.

Question 27:

***Does the Agency agree with the plan for developing the label, including the Instructions for Use for the Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection) for SC self administration by the patient and/or caregiver?***

FDA Response:

*The currently approved Hospira and Dava Package Inserts, along with your Instructions for Use, supportive data from the literature, and clinical and safety data may be used as a starting point for creating the Methotrexate 50mg/ml Pre-filled Pen package insert. However, we remind you that the package insert for your product will be expected to conform to the Physician's Labeling Rule (PLR) format.*

Discussion:

No discussion occurred.

### **3.0 PREA REQUIREMENTS**

*Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:*

- o if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).*
- o if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.*

*The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:*

*<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).*

Discussion:

No discussion occurred.

#### **4.0 PRESCRIBING INFORMATION**

*Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:*

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.*
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.*
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see Warnings and Precautions (5.2)]".*

*Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:*

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.*

Discussion:

No discussion occurred.

**5.0 MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

<i>Site Name</i>	<i>Site Address</i>	<i>Federal Establishment Indicator (FEI) or Registration Number (CFN)</i>	<i>Drug Master File Number (if applicable)</i>	<i>Manufacturing Step(s) or Type of Testing [Establishment function]</i>
1.				
2.				

Corresponding names and titles of onsite contact:

<i>Site Name</i>	<i>Site Address</i>	<i>Onsite Contact (Person, Title)</i>	<i>Phone and Fax number</i>	<i>Email address</i>
1.				
2.				

Discussion:

No discussion occurred.

**6.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

## **7.0 ACTION ITEMS**

None

## **8.0 ATTACHMENTS AND HANDOUTS**

Medac's Slides for Question 4 and Question 10/11 (as combined).

**Comparison of Primary Stability, Supportive Stability and To-Be-Marketed Drug Product Batches**

<b>Parameter</b>	<b>Primary Stability and To-Be-Marketed Batches</b>	<b>Supportive Stability Batches</b>
Batch Formula (Briefing Package Section 10.2.3.2)	Same	Same
Manufacturing Equipment	Same	Same
Manufacturing Process (Briefing Package Section 10.2.3.3)	Same	Same
Pen Assembly	Semi-automatic	Table-top
Analytical Testing (Briefing Package Section 10.2.5)	USP	Ph. Eur. <sup>a</sup>
Container Closure System (Briefing Package Section 10.2.7)	Same	Same

<sup>a</sup> Ph. Eur. requirements meet or exceed USP/proposed commercial requirements.

CONFIDENTIAL

**Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)****June 17, 2013 pre-NDA Meeting**

---

**Questions 10 and 11****EFFICACY**

- medac plans to include individual data/results for Studies MC-MTX.14/PK and MC-MTX.15/HF in Module 2.7.3 (Summary of Clinical Efficacy)
- Since medac has not preformed clinical efficacy studies, medac does not plan to provide a separate ISE document which evaluates the efficacy of MTX.

**SAFETY**

- medac plans to include individual data/results for Studies MC-MTX.14/PK and MC-MTX.15/HF and supportive study MC-MTX.10 in Module 2.7.4 (Summary of Clinical Safety)
- medac does not plan to pool data from the MC-MTX.14/PK and MC-MTX.15HF due to differences in
  - study populations (healthy volunteers vs. RA patients),
  - study designs (two-period, two sequence crossover design with oral MTX treatment as control vs. uncontrolled design),
  - heterogeneity of AE incidences (32% vs. 3%) due to the fact that MTX.14/PK was conducted in healthy volunteers (leading to large frequency of AEs belonging to SOC GI) whereas in MTX.15/HF 93% of RA patients were already on MTX),
  - number of doses and doses administered, and data collected in the studies.
- MTX.10/RH is not considered suitable for pooling due to the non-randomized study design with 3 administrations of 10 mg/ml MTX followed by 3 administrations of 50 mg/ml MTX using prefilled syringes (without autoinjector).

---

CONFIDENTIAL

**Methotrexate 50 mg/ml Pre-filled Pen (methotrexate 50 mg/ml solution for injection)**

**June 17, 2013 pre-NDA Meeting**

---

Note: The full study reports for MC-MTX.14/PK and MC-MTX.15/HF and supportive study MC-MTX.10 will be included in Module 5.

---

CONFIDENTIAL

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
SADAF NABAVIAN  
07/17/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

PIND 109543

**MEETING REQUEST -  
Written Responses**

(b) (4)  
c/o Medac GmbH  
7400 West 110<sup>th</sup> Street, Suite 300  
Overland Park, Kansas 66210

Attention: (b) (4)  
Senior Consultant, Scientific Consulting

Dear (b) (4)

Please refer to your Pre-Investigational New Drug Application (PIND) file for Methotrexate 50mg/ml autoinjector.

We also refer to our October 11, 2011, communication notifying you that we would provide a written response to the questions in your September 14, 2011, meeting request within 60 days after receiving your background materials. The background materials were received on October 31, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Sadaf Nabavian, Pharm.D.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

### General Comments

We have reviewed your Pre-IND meeting package dated October 31, 2011, and have the following general comments regarding your development program:

- Your development program for rheumatoid arthritis has three goals: 1) to achieve approval of the subcutaneous route of administration for MTX, 2) to achieve approval of a 50 mg/ml formulation, and 3) to achieve approval of the 50 mg/ml formulation in the autoinjector presentation.
  1. In order to support your application of your MTX product for the subcutaneous route of administration:
    - a) Your 505(b)(2) application should contain a study or studies to bridge to any data necessary to support your application which are derived from the reference listed drug(s); e.g., a relative bioavailability study of your proposed subcutaneous formulation to approved oral MTX (to reference the established efficacy and safety of oral MTX in RA).
    - b) You would also need evidence that this change in route of administration does not negatively impact the efficacy and safety of MTX in RA. This evidence may be available in published literature or in the public domain.
  2. In order to support approval of a 50 mg/ml formulation of MTX, you would need to provide data to support the conclusion that subcutaneous injection of the proposed 50 mg/ml formulation results in acceptable exposures. Specifically, the aforementioned subcutaneous vs. oral MTX relative bioavailability study could be done using the 50 mg/ml formulation.
  3. You would need information to support approval of the autoinjector itself, as well as the drug in the autoinjector (technically, a drug/device combination product).
    - a) Additional information is needed to determine what will be necessary to support approval of the autoinjector. Provide a letter of authorization (LOA) so that CDRH may review the master file for the Physioject autoinjector. Ensure that the supplier BD references any deviations from the master file or customizations that apply specifically to your product. See additional comments pertaining to the autoinjector below.
    - b) To support your drug/device combination product, you will need to provide information to support a conclusion that your drug/device combination product results in the desired delivery of drug to the intended biospace, in the intended population. This information should include an actual use study, a label comprehension study, and an evaluation of device robustness. An actual use study is intended to demonstrate that RA patients can use the drug/device to self-administer the product, and should include an assessment of the PK of

the drug in RA patients across a range of body weights. In a label comprehension assessment, patients would receive instructions for use as would be employed in practice, followed by patient use of the device and evaluation of patient-perceived clarity of instruction and correctness of usage. In an evaluation of device robustness, in addition to traditional mechanical tests, we recommend device collection after actual use in patients, with analysis of the devices to look for evidence of failure. The label comprehension assessment and device robustness evaluation could be done as part of the actual use study.

Based on the information described in your briefing document, you may have adequate information to submit an NDA for either a 10 mg/ml in PFS presentation or a 50 mg/ml in PFS presentation if you provide a relative bioavailability study of the chosen PFS formulation(s) compared to oral MTX. You could subsequently submit an application with additional data (described in item 3.a. and b. above) to support the 50 mg/ml formulation in autoinjector.

**Question 1:**

***Does the Agency concur with conducting the pharmacokinetic study in healthy volunteers?***

**FDA Response:**

Refer to our General Comments. In general, your approach to do PK studies in healthy volunteers appears reasonable. However, the data required for approval of your product will depend on whether you intend to seek approval of the PFS presentation alone and/or the formulation in autoinjector. For approval of the PFS, the relative bioavailability study of subcutaneous vs. oral routes of administration can be performed in healthy volunteers, and no additional PK data would be required. For approval of the autoinjector, in addition to data on SC/oral relative bioavailability, PK data will be required for the drug/device combination in RA patients across a spectrum of body weights. These data could be obtained during the actual use study of the autoinjector.

Although bioequivalence is not expected to be demonstrated in light of the different routes of administration, we suggest that you include bioequivalence parameters (90% CI, 80-125% goal posts) in the statistical criteria for assessment of the relative bioavailability.

Also, note that the bioavailability can vary based on the site(s) of injection. Use the same site(s) of injection that you would propose for your final product.

**Question 2:**

***Please confirm that only one reserve sample of our drug and the comparator drug (consisting in total of 5 times the amount required for release testing) is required for a multisite BA study.***

**FDA Response:**

You are required to retain reserve samples for only studies that meet the regulatory definition of a bioequivalence study. Note that the proposed study is a relative bioavailability study and not a bioequivalence study and demonstration of bioequivalence is not expected because of the different routes of administration.

**Question 3:**

***Does the Agency concur with applying the ACR20 response at 12 weeks at the primary study end point in the proposed pivotal Phase III trial?***

**FDA Response:**

Yes, we agree with the proposed endpoint for an efficacy trial. However, the evidence to support your 505(b)(2) application could be obtained from published literature. Thus, it appears that an additional efficacy study would not be necessary for your 505(b)(2) application. If your application seeks comparative or superiority claims, e.g., that SC MTX is superior to oral MTX, then at least 2 adequate and well-controlled trials would be needed.

**Question 4:**

***Does the Agency concur to limit the confirmatory part of the pivotal Phase III trial to the 12-week efficacy data and to consider the additional 12-week extension phase (with dose modification possibility) as descriptive only?***

**FDA Response:**

See our response to your Question 3. It does not appear that an efficacy study would be necessary. If an efficacy study was to be performed, we agree that the additional 12-week extension phase could be descriptive only.

**Question 5:**

***Does the Agency concur with the approach for blinding the treatment arms in the proposed pivotal Phase III trial?***

**FDA Response:**

See our response to your Question 3. An efficacy study may not be necessary. If you did pursue an efficacy study, the proposed blinding procedure appears appropriate.

**Question 6:**

***Does the Agency agree that inclusion in the NDA of the results of an exploratory pharmacokinetic study of subcutaneously administered MTX in children/adolescents with polyarthritic forms of severe, active JRA along with comparison of the pediatric PK results with respective data obtained in adults would represent a pediatric assessment and thus fulfill***

***PREA requirements, as comparable PK are considered to provide evidence that safety and efficacy of MTX in JRA patients are not substantially different from that in adults?***

**FDA Response:**

Conclusions regarding the PREA-required pediatric plans and assessments will not be made until the NDA submission and review of your 505(b)(2) application.

It is possible that a pediatric assessment for the efficacy of SC MTX in JIA could be largely derived from the literature. Additional clinical data may be necessary to address gaps in the literature or answer questions related to your formulation. For example, a 50 mg/ml formulation would require that extremely small volumes be delivered to the youngest/smallest children, and it may be necessary to perform a study in this subgroup to provide evidence that this formulation can be used to provide consistent doses. It is unlikely that the single dose PK study you propose would be considered adequate to fulfill the PREA requirements. Additional considerations include your rationale for the selection of doses for pediatric patients, description of whether doses will be based on body weight and/or age of the patient, criteria for PK comparability, and whether the same autoinjector will be used for adult and children or if a smaller autoinjector will be developed for children.

**Question 7:**

***medac will propose labeling for MTX 50mg/ml solution for injection pre-filled syringe sealed in a disposable auto-injector allowing SC self-administration by the patient or their guardians after appropriate instruction and training in addition to SC route administered by healthcare professionals. Will the FDA accept SC self-administration for the auto-injector?***

**FDA Response:**

Refer to our General Comments above. You will need to provide evidence to support the conclusion that patients or their guardians can self-administer MTX with the proposed autoinjector after the instruction and training you propose to use for marketing.

**Question 8:**

***Does FDA agree that a 505(b)(2) NDA (or a clinical efficacy supplement to an approved NDA for use of medac MTX 50mg/ml auto-injector in psoriasis by the SC route), referring to NDA 008085 (Rheumatrex, MTX tablets, USP, 2.5 mg base, Dava Pharmaceuticals, Inc.) as the Reference Drug is appropriate as the legal basis for marketing authorization indicating the use of 50mg/ml MTX solution in pre-filled syringes sealed in disposable auto-injectors for treatment of RA and JRA in the United States by SC administration?***

**FDA Response:**

Refer to our General Comments.

### ADDITIONAL COMMENTS

Additional general comments regarding 505(b)(2) applications:

- FDA recommends that sponsors considering submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and FDA's Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, the FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).
- If you intend to submit a 505(b)(2) application that relies on approval of FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a bridge (e.g., via a relative bioavailability study) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference, but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.
- If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. The use of labeling statements taken from the labeling of other drug products may cause those products to also be listed drugs. It is important to identify all listed drugs at the time of the initial 505(b)(2) NDA submission.
- Circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product was approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

### Additional Comments Related to the Autoinjector:

Your submission does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Provide a comprehensive use-related risks and a justification for why an HF/usability validation study is not necessary for the proposed product.

If you choose to submit an HF/usability validation protocol, note the following comments (a-g):

#### a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials. In addition, to establish the scope and facilitate understanding of the testing you perform, please provide a graphical depiction of the user interface for your device. Also explain the overall interaction between users and the UI and refer to it as necessary when discussing task priority, specific test results or residual risk.

A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing. Based on your analysis of your intended users and the use of your device, you should determine the extent and type of training needed and indicated for users prior to using your device. After the training need is established and the training materials prepared, you should train the user participants for your human factors/usability validation testing in the same manner that actual users will be trained. You should provide at least some lag time between training and the testing. When you design your human factors/usability validation protocol, please include this analysis and ensure that representative (i.e., realistic) training is given to all test participants. Describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, we expect that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

#### b. User Tasks and Use-Related Risks Analysis

Provide a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the

device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Also describe all activities in which your test participants will engage during the test.

In addition, for human factors/usability validation testing, provide information to support that the tasks you choose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.

c. Use Environment and Conditions

Conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

Include as many representative users in your human factors/usability validation as your analysis indicates are necessary to achieve a reasonable validation. Note that FDA's expectations for the number of study participants to be used in Human Factors/Usability Validation are a minimum 15 per user group. Submit results of a study that includes minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g. level of disabilities/impairments) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total could be no less than 25.

In addition, we note that this device is intended to treat Juvenile Arthritis. Refer to FDA's Guidance on Premarket Assessment of Pediatric Medical Devices (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm>) has different subgroups for pediatric patients as follows:

<b>Pediatric Subgroup</b>	<b>Approximate Age Range</b>
Newborn (neonate)	from birth to 1 month of age
Infant	greater than 1 month to 2 years of age

Child	greater than 2 to 12 years of age
Adolescent	greater than 12 to 21 years of age

And adults should be greater than 21 years of age. To ensure that an adequate representation of different major groups that will be included in the study, provide a break-down of the participants using the above guidance. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment. Provide a discussion of how you assessed the participants' level of impairment in this response.

Regardless of the number of groups you test, provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Realism of simulated use

The testing environment and realism of the simulated use was not described in sufficient detail to determine if it is reasonable for a validation study of device use, however a "focus group" approach is not likely to represent actual use conditions. Determine the conditions under which the testing will be undertaken and include realistic and challenging scenarios of use that, in aggregate, include all critical user tasks which you have identified.

f. Data Collection and Analysis

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. We expect you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – We expect you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

g. Report

We expect to review a report of the human factors/usability evaluation and validation testing. The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

We strongly recommend that you submit your draft protocol in advance for us to review in order to ensure that your methods and the resulting data will be acceptable. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Additional CMC Comments:

- Provide complete container closure section for your combination drug product in the forthcoming submission. You need to demonstrate adequate dose performance for all drug product presentations to be used under the proposed studies. We note that you refer to the delivery volume of (b) (4) in your submission dated Oct 31, 2011, whereas the 7.5 mg drug product is delivered in 150 µL volume. Please address this discrepancy.
- Also, we would like to remind you of our previous Chemistry, Manufacturing and Control (CMC) comments communicated to you in the meeting minutes dated November 8, 2010.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
SADAF NABAVIAN  
12/27/2011



IND 109543

**MEETING MINUTES**

medac Gesellschaft fur klinische Spezialpreparate mbH

(b) (4)  
7400 West 110<sup>th</sup> Street, Suite 300  
Overland Park, KS 66210

ATTENTION: (b) (4)  
Senior Consultant, Scientific Consulting

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for methotrexate pre-filled syringe.

We also refer to the meeting between representatives of your firm and the FDA on October 14, 2010. The purpose of the meeting was to discuss the development program for methotrexate pre-filled syringe.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Sincerely,

*{See appended electronic signature page}*

Jessica Benjamin  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** October 14, 2010

**TIME:** 1:30 PM – 2:30 PM (EST)

**LOCATION:** Food and Drug Administration, Bldg. 22, Room 1415

**APPLICATION:** IND 109543

**PRODUCT:** methotrexate pre-filled syringe

**INDICATION:** (b) (4)

**SPONSOR:** medac Gesellschaft fur klinische Spezialpreparate mbH  
(b) (4)

**TYPE OF MEETING:** Type B, Pre-NDA

**MEETING CHAIR:** Sarah Yim, MD, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

**MEETING RECORDER:** Jessica Benjamin, Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Badrul C. Chowdhury, MD, PhD	Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD	Clinical Team Leader
Kathleen Coyle, MD	Clinical Reviewer
Molly Topper, PhD	Pharmacology/Toxicology Supervisor
Asoke Mukherjee, PhD	Pharmacology/Toxicology Reviewer
Yun Xu, PhD	Acting Clinical Pharmacology Team Leader
Jean Nashed, PhD	Product Quality Reviewer
Jessica Benjamin	Regulatory Health Project Manager
<b>medac Gesellschaft fur klinische Spezialpreparate mbH</b>	<b>Title</b>
Kirsten Brass, PhD	Head, Drug Regulatory Affairs International
Michaela Rehberg, PhD	Director, Drug Regulatory Affairs/Pharmaceutical Development
Uwe Pichmeier, PhD	Head of Biometrics and Data Management
Hans-Jurgen Keuhnel, MD	Medical Director

(b) (4)

**BACKGROUND:** medac Gesellschaft für klinische Spezialpreparate mbH (medac) submitted a Pre-NDA meeting package to the Agency for methotrexate pre-filled syringe for the (b) (4). Each of medac's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the sponsor on October 12, 2010.

**Summary Comment:**

After review of your PIND submission, the Agency does not believe a bioequivalence approach using the Hospira NDA as RLD is appropriate because this RLD is not approved (b) (4) for the administration routes you are proposing. It may be more feasible for you to develop your product in indications for which MTX parenteral routes are already approved, such as psoriasis or oncology indications. Nonetheless the responses below are provided for your consideration.

*Question 1. Does the FDA concur that the nonclinical and clinical bridging studies performed by medac, Germany, supplemented by relevant published literature, and reference to the safety and efficacy findings in approved NDA 011719 will be sufficient to demonstrate the safety and effectiveness of methotrexate 50 mg/mL given subcutaneously to treat*

(b) (4)

**FDA Response:**

Although methotrexate is approved for rheumatoid arthritis (RA) via oral administration, and this information is in the approved injectable methotrexate labels, the label does not contain dosing information for parenteral routes of administration, nor does it contain route-specific efficacy and safety information. Therefore, you will need to take this into account in your clinical development program. In addition to referencing the approved oral methotrexate for RA, you will need to provide substantial evidence of efficacy for the parenteral routes for which you plan to seek approval. Because oral methotrexate is already approved for RA, the additional evidence that would be expected for the NDA would include data from at least one adequate and well-controlled trial for each route of methotrexate administration proposed for approval. You may be able to meet this evidentiary requirement utilizing published trials.

Also, we recommend submission of a full chemistry, manufacturing, and controls (CMC) section, consistent with the stage of development. Provide letters of authorization (LOA) to DMFs supporting your application and complete list of manufacturing and testing facilities, with corresponding cGMP status. Note, that release and stability data are needed for all planned presentations of the drug product (currently 10 listed in your package), including evaluation of extractables/leachables from the syringe.

In addition, we recommend that you monitor impurities and degradation products of all active and inactive ingredients. Impurities or degradants that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for

**Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008) for assessment of impurities to support clinical studies for an IND and NDA. In addition, refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants such as Ames Assay for each impurity that needs to be qualified or alternatively, reduce the levels of these impurities as outlined in above referenced guidance for industry (2008): Recommendations for further non-clinical studies may be made upon review of the data when you submit the IND application.**

**Safety data for the leachable and extractable impurities from (b) (4) rubber stoppers and (b) (4) rods will also be required.**

Discussion:

The Division stated that the current Hospira label reflects the labeling standards of its time. Much of the label would be changed if the label were being developed currently; for example indications for the oral formulation would not be included in the parenteral formulation label unless there was sufficient information to do so. However, a US-approved RLD must be used. For methotrexate, the currently listed RLDs are Hospira for parenteral administration (psoriasis, oncology indications) and Dava for tablets (RA and JRA, psoriasis). The Hospira product is an appropriate RLD for the Sponsor's MTX (50 mg/ml) pre-filled syringe; however additional information would be needed to support the dosing, safety and efficacy of the parenteral routes of administration for indications which medac plans to seek approval (i.e., RA and JRA). Evidence to support efficacy of parenteral MTX for RA and JRA may be available in the literature. Any clinical trial being used to support filing of an NDA should meet the standards described in the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998).

Regarding the use of literature, the Division was also concerned that much of the literature on methotrexate is old and would not be considered substantial evidence today. Medac intends to update the literature references for the FDA filing and will include all of the latest available information. The Division also stated that treatment guidelines cannot be used to support the efficacy and safety of methotrexate. Instead, relevant scientific literature data must be provided. The Division encouraged medac to examine options for a methotrexate development program considering use of literature and data medac may have on methotrexate that was not included in the briefing document.

Discussion then turned to possible designs of clinical trials. The Division explained that for any trial involving an active comparator, a US-approved drug, preferably an RLD, must be used. The study can be performed anywhere in the world, as long as standard of care is comparable to the US, and all study records and data will be readily available for FDA review. A study conducted in predominantly Caucasian subjects would not be a problem as long as the disease state under study is either known to be, or can be shown to be, similar regardless of race/ethnic origin. It is not necessary to include the intramuscular (IM) route of administration unless medac

wants to include IM dosing in the label. Study duration should be at least 12 weeks; the 24-week duration suggested in the ACR treatment guidelines would be acceptable.

The Division indicated they were open to another meeting to discuss trial design for the methotrexate development program. A formal meeting request and information package will be required.

*Question 2. If FDA will require additional study of Methotrexate 50 mg/mL does FDA then agree that the pharmacokinetic study provided in section 11 (Study on the relative bioavailability of MTX 50 mg/mL compared to the FDA reference listed drug (MTX 25 mg/mL) when administered as a single subcutaneous or intramuscular dose of 15 mg MTX in healthy subjects could possibly satisfy this requirement?*

**FDA Response:**

**You will need to provide a summary of non-clinical information for the referenced product in support of the 505 b(2) application. In addition, you will need to provide safety data for IV, IM and SC route following once a week injection for one month when the treatment is repeatedly given at the same site of injection. However, the need for non-clinical data may be waived if you provide sufficient clinical safety data when methotrexate is injected repeatedly at the same site in humans. If you do not intend for the drug to be administered at the same sites of injection, the package insert should clearly state that the safety of the product at the site of injections when given repeatedly was not determined. Additional non-clinical safety data for the 505 b(2) application would be recommended upon review of the data.**

**The Agency does not believe**

(b) (4)

**If you plan to target your product development to other indications, we suggest you seek guidance from the relevant division(s).**

**Discussion:**

Medac requested clarification regarding the definition of "same site." The Division explained that this was intended to describe the same general area within 2-3 inches. Detailed instructions regarding injection site use should be described in labeling and will be expected to have data to support the proposed recommendations.

*Question 3. Medac intends to submit proposed labeling for Methotrexate 50 mg/mL that excludes use in the neoplastic indications in the approved labeling for the reference listed drug product. Does FDA accept omission of the neoplastic indications for Methotrexate 50 mg/mL solution for injection, pre-filled syringe as compared to the reference listed drug as approved in NDA 011719?*

**FDA Response:**

**Refer to the Agency's Summary Comment above.**

Discussion:

The label for the Sponsor's MTX product submitted would not be expected to necessarily conform to the Hospira label. The Division explained that clinical safety and efficacy data in accordance with today's standards will be required to file an NDA for methotrexate 50 mg/ml pre-filled syringe for the RA, JRA and psoriasis indications utilizing SC and IM or SC only administration. The label for the Sponsor's product would reflect the data submitted.

*Question 4. Similarly, medac intends to submit proposed labeling for Methotrexate 50 mg/mL that excludes administration routes related to the neoplastic indications currently approved for the reference listed drug product. Do you agree with removal of the intrathecal and intra-arterial administration routes for Methotrexate 50 mg/mL?*

**FDA Response:**

**Refer to the Agency's Summary Comment above.**

Discussion:

See discussion from Question #3.

*Question 5. Medac will also submit proposed labeling for Methotrexate 50 mg/mL allowing for s.c. self administration by the patient after appropriate instruction and training in addition to the i.m., i.v. and s.c. route administered by healthcare professionals. Will the FDA accept s.c. self administration for this product?*

**FDA Response:**

**Refer to the Agency's Summary Comment above.**

Discussion:

See discussion from Question #3.

*Question 6. Does FDA agree that a 505(b)(2) NDA referring to NDA 011719 (Hospira, Methotrexate Sodium preservative free) as the Reference Listed Drug is appropriate as the legal basis for marketing authorization of Methotrexate 50 mg/mL solution for injection, pre-filled syringe in the United States?*

**FDA Response:**

**See FDA Summary Comment and response to Question 1. NDA 011719 does not appear to be adequate to serve as the legal basis for marketing authorization of your product in (b) (4)**

Discussion:

There was no further discussion of this point.

Question 7.

(b) (4)  
Does FDA agree that this course of action is appropriate for the proposed NDA and indications sought for Methotrexate 50 mg/mL?

**FDA Response:**

You should be aware that an application for a new route of administration would trigger a requirement for pediatric assessments under the Pediatric Research Equity Act (PREA). A plan for addressing PREA requirements would need to be submitted with the NDA. (b) (4)

Discussion:

The Division explained that a pediatric assessment will be required for the NDA. Within the pediatric assessment, the Sponsor should make the case for any waiver or deferral of studies in pediatric populations, ensuring that the entire age range is covered, from 0 to 16 years.

Question 8. Based on the clinical data submitted to support Methotrexate 50 mg/mL solution for injection, pre-filled syringe, (b) (4)

Does FDA agree that the NDA as proposed is likely to provide sufficient data to support this request? (b) (4)

**FDA Response:**

(b) (4)

In 21 CFR 314.108, a "clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." The regulations define "essential to approval" as meaning that "there are no other data available that could support approval of the application." If there are sufficient data available in the published literature to support approval of your proposed routes of methotrexate administration for RA, then it is unlikely that additional studies would be considered essential to approval. However, the Agency will not make a determination about whether a study is essential for approval until the time of approval, after the data have been fully evaluated.

Discussion:

There was no further discussion of this point.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

LYDIA I GILBERT MCCLAIN

11/08/2010

Acting Division Director

Reference ID: 2861286

Reference ID: 3596786