

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205776Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205776	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Rasuvo™ Established/Proper Name: Methotrexate sodium pre-filled manually triggered pen injector for subcutaneous injection Dosage Form: Pre-filled pen to be administered subcutaneously Strengths: 7.5 mg to 30 mg (in 2.5 mg increase increments)		
Applicant: Medac Pharma Inc.		
Date of Receipt: September 10, 2013		
PDUFA Goal Date: July 10, 2014		Action Goal Date (if different):
RPM: Sadaf Nabavian: 301-796-2777		
Proposed Indication(s): Rheumatoid Arthritis (RA), Polyarticular Juvenile Idiopathic Arthritis (pJIA), and Psoriasis.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	The sponsor relied on literature to support the safety and efficacy of the new route of administration (subcutaneous) for the Rheumatoid Arthritis (RA) and Psoriasis indications, as reflected in the Dosage and Administration section of the label (the subcutaneous route of administration is already an approved route for pJIA).
Dava, NDA 008085 (MTX Oral) Hospira, NDA 11719 (MTX IM)	The listed products were referenced for the entire label except the Dosage Forms and Strengths and Description sections. The listed products were referenced for Efficacy and Dosage information from the Indications, Dosage and Administration, Clinical Pharmacology, and Clinical sections of the label; and Safety information included in the Box Warning, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Population, Nonclinical Toxicology, and Over-dosage Sections of the label.

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
- 1 BA study (primary study) was conducted to bridge the proposed product to approved Oral MTX Product. The study evaluated the relative BA of the SC administration as compared to oral reference. The results of this study support the efficacy of SC dosing in RA and Psoriasis patients because, when compared to oral exposure, SC dosing yields higher systemic exposures, particularly after GI absorption is saturated at and above oral doses of 15 mg. The higher systemic exposure with SC administration encompasses the known efficacy with oral administration and is supported by substantial safety data with similar or higher systemic exposures when

MTX is administered by approved routes and at higher doses, all of which are represented in the labeling of the listed products referenced in the application.

- 1 BA study was conducted to bridge the proposed product to approval IM Product.
- 1 Human Factor Study-included administration of 2 doses of the proposed product in RA patients and review of body weight effect and injection site assessments included in the study.
- The sponsor also relied on the literature for the efficacy and safety of the SC administration for the RA and Psoriasis indications.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Methotrexate Oral Tabs	NDA 008085	Yes

Methotrexate Injection	NDA 11719	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: NDA 11719, NDA 8085

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: DESI 008085 (tablet and parenteral formulations) for the methotrexate oncology indications, which the sponsor is not seeking for in this NDA.

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a dosing regimen of subcutaneous administration for the indications of Rheumatoid Arthritis and Psoriasis.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “NO” **or** if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do **not** have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are*

listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDAs: 11719 (MTX Injection); 8085 (MTX Oral); NDA 204824 (Otrexup). ANDAs: 040632, 089341, 040632, 089342, 089343, 089340, A040263, 040716, 040768, 040767, 040385.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): None

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: NDA 205776

Name of Drug: Rasuvo™ (methotrexate) SC Injection in doses of 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, and 30 mg.

Applicant: Medac Pharma Inc

Submission Date: September 10, 2013, January 16, 2014, May 28, 2014, and June 12, 17, and July 3, 2014.

Receipt Date(s): September 10, 2013, January 16, 2014, May 28, 2014, and June 12, 17, and July 3, 2014.

Type of Labeling Reviewed: WORD/SPL

Background and Summary

The Sponsor submitted a new drug application dated September 10, 2013, for a drug/device combination of methotrexate injection as a 505(b)(2) application. This new drug application provides for methotrexate as a subcutaneous route of administration for the indications of Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (pJIA), and psoriasis.

Review

The following issues/deficiencies have been identified in the proposed labeling:

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.

Recommendations

The recommendations noted above from my review were conveyed to the sponsor in the Filing Communication Letter dated November 22, 2013, Medac then submitted the revised labeling incorporating our recommendations and submitted the revised labeling as amendments to the NDA dated January 16, May 28, June 12, 17, and July 3, 2014.

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

Supervisory Comment/Concurrence:

Ladan Jafari
Chief, Project Management Staff

Drafted: SNabavian/7.1.2014

Cleared: LJafari/7.1.2014

Finalized: SNabavian/7.3.2014

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW

Selected Requirements of Prescribing Information (SRPI)

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: Due to the Box Warning the HL Section is more than half a page, however if take out the BW the HL Section limit is met. A paragraph in the action letter will be provided in granting the HL Section limit.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information (SRPI)

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information (SRPI)

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment: *"Warnings" needs to be changed to "Warning"*

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *The revision date will be updated prior to approving the product.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

Selected Requirements of Prescribing Information (SRPI)

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references 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)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *No postmarketing adverse reaction listed*

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)*

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
07/09/2014

LADAN JAFARI
07/09/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

DATE: June 10, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Sadaf Nabavian, Regulatory Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: **NDA 205776**
Applicant: Medac Pharma, Inc
Device Constituent: prefilled peninjector
Drug Constituent: Methotrexate SQ
Intended Treatment: Rheumatoid Arthritis (RA), Juvenile RA, and Psoriasis
CDRH CTS Tracking No.: ICC 1400179

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

NDA 205776

Applicant: Medac Pharma

Device Constituent: peninjector

Drug Constituent: Methotrexate

Intended Treatment: Rheumatoid Arthritis (RA), Juvenile RA, and Psoriasis

CDRH Human Factors Involvement History

- 10/21/2013 – CDRH HFPMET was requested to review the human factors validation study report included in the IND.
- 3/25/2014 – CDRH HFPMET provided review recommendation. Three deficiencies were identified and sent to CDER project manager.
- 5/8/2014 – CDRH HFPMET was requested to review the Sponsor’s response to deficiencies.
- 6/10/2014 – CDRH HFPMET provided final review recommendation. There are no outstanding review issues.

Overview and Recommendation

The Division of Pulmonary, Allergy, and Rheumatology Products requested a consultative review from CDRH Human Factors Pre-Market Evaluation team to review a report titled “Evaluation of Rheumatoid Arthritis Patient Performance Using the Metoject® Prefilled Pen (Methotrexate 50 mg/mL, prefilled pen) for Subcutaneous Injection and Subsequent Pharmacokinetic Assessment of Drug Delivery.”

This report included an actual use component that was designed to evaluate use performance with representative users and to assess the pharmacokinetics of MTX across a range of body weights. This review focused on the evaluation of use performance. 104 patients were enrolled and completed the study at 5 sites. The actual use testing focused on the steps involved to perform self-injection, and four scenarios were identified to evaluate the potential risks associated with product use. The study results showed several failures associated with holding the needle in place for 5 seconds after activation, and two failures associated with the pinching technique for subcutaneous injection. This review identified three deficiencies requesting for additional clarifications regarding reported failures and use difficulties resulting in users not receiving a full dose, pinching techniques, and how the written exam was administered. The Sponsor provided a response to these deficiencies on 4/4/2014 (sequence # 10). [This consultant found the Sponsor’s response to be acceptable and did not have any further questions.](#)

Appendix 1: Human Factors Review of Sponsors' Response to IRs

Upon review of the human factors study report, CDRH HFPMET identified three deficiencies. The Sponsor provided a response to these deficiencies on 4/4/2014 (sequence # 10). The following section provides the deficiencies (in blue text) and evaluation of the Sponsor's response.

1. Your study results showed 4 failures and 4 reported difficulties where 8 study patients did not receive a full dose. Please note 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.

Please address the following:

- a. Please 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. Please clarify the source of the confusion of the click of the needle projector
- c. Please quantify the amount of dose that would be underdosed, 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.

Evaluation of Sponsor's Response:

- 1a. Medac reported that they chose BD's Physioject for its development of the drug/device combination product because it was specifically developed for patients with the most critical hand-disabilities. In addition, Medac also ensure that the Methotrexate 50 mg/ml prefilled pen is supplied with a patient leaflet including a patient instruction for use demonstrating graphically and in a detailed and comprehensive manner the correct administration of the drug product using the pre-filled pen including pinching tAnd the instruction for use was tested within the scope of the label comprehension test which was part of the actual use study (MC-MTX-15/HF). **This response was found acceptable.**
- 1b. Medac clarified that when the pre-filled pen is depressed against the thigh or abdomen, the needle protector shield retracts and upon contacting a stop point within the device, a very soft "click" sound is emitted. This sound is not as noticeable as the click sound that occurs when the button is pushed, but it is slightly detectable and was

interpreted as a “click” by one participant. Medac reported that this was a single occurrence. **This response was found acceptable.**

1c. Medac stated that while the instruction for use and subject training recommended that the pre-filled pen is to be held in place for at least 5 seconds, the delivery of the 0.3 mL study dose actually occurred in a shorter period of time (2-3 seconds). The study results showed that 3 patients did not receive any study medication, 3 patients received a partial amount of the study medication, which was not further specified and 1 subject received an estimated amount of 50 % of the study medication. Medac reported that the clinical impact of non-medication would be an absence of symptom relief or potential disease flare; however, given the long biological effect of methotrexate, this would be unlikely after a single missed dose. **This response was found acceptable.**

2. Regarding the issues associated with pinch, you did not discuss whether any of the techniques applied by test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences.

Evaluation of Sponsor’s Response:

The techniques applied by study participants did not have any adverse consequences to the participants. Therefore, no modification of the IFU is deemed necessary. **This response was found acceptable.**

3. In addition, please discuss how the studies design with respect to the duration between the two visits, and the written exam, and how they are representative of actual use.

Evaluation of Sponsor’s Response: Medac indicated that the written exam was performed before the next methotrexate injection during the second visit (8 ± 1 day after the first visit) to allow an interval of potential “training decay” and to reflect actual use. The written exam was conducted as part of the label comprehension portion. Medac suspected that due to this written exam at visit 2, participant’s awareness of correct self-administration might have been increased; however, the success rates of self-administration at visit 2 did not differ from those detected at visit 1, which did not indicate any issue associated with administering the written exam. **This response was found acceptable.**

Appendix 2: Human Factors Review of Study Report (previous review)

One hundred and four (104) patients were enrolled and completed the study at five sites. The actual use testing focused on the steps involved to perform self-injection, and four scenarios were identified to evaluate the potential risks associated with product use, which include premature needle withdrawal, incomplete ejection of all infusate in the syringe, premature release of skin pinch while injecting and management of known cytotoxic agent.

	Test Case	Objective	Scenario
1	Patient is required to hold the prefilled pen needle in place until all the medication is injected (about 5 seconds). This is necessary to be sure all the medication is delivered into subcutaneous tissue without excessive flow back or leakage.	Evaluate if the patient understands and is able and willing to hold the prefilled pen needle in place until all the medication is injected (about 5 seconds).	Patient will be observed performing the injection and a stopwatch will be used to determine the length of time the needle was held in place.
2	Patient will perform the required injection following all steps of the Patient Instructions for Use provided within the Medication Guide. Patient needs to check the optical window of the syringe to confirm that all medication was delivered.	Evaluate if the patient properly understands the need to check the optical window to verify the syringe is empty.	Patient will be observed performing an injection and after completion, will be monitored to be sure the optical window was checked and verified to be empty of any remaining medication.
3	Patient will perform all the required steps defined in the Patient Instructions for Use provided within the Medication Guide for performing injection. One step defines the requirement to pinch the skin at the site of injection. Pinching the skin helps to assure the patient performs a proper subcutaneous injection rather than an unwanted intramuscular injection. The skin must be pinched for the entire time of the injection.	Evaluate if the patient can properly perform the injection and continuously pinch the skin over the complete duration of the injection.	Patient will be observed performing an injection and performing a proper skin pinch procedure as defined in the Patient Instructions for Use provided within the Medication Guide. The skin pinch must remain in place during the overall injection period.
4	After completion of the injection procedure, the prefilled pen will be empty but will still contain cytotoxic drug residue. The patient will receive instructions for proper disposal of the spent syringe. It will be verified that disposal instructions are followed.	Evaluate if the patient is aware of the safe disposal requirements of the used prefilled pen device.	Patient will be observed performing the injection as defined in the Patient Instructions for Use provided within the Medication Guide. At the completion of injection, the used syringe must be disposed in accordance with instructions.

Medac Pharma indicated that based on their risk assessment, premature needle withdrawal was determined to be the greatest risk to patients because the patient may not receive a full dose of medication. The other risks included incomplete ejection of all infusate in the syringe, premature release of skin pinch while injecting and drug exposure (known cytotoxic) to individuals other than patients whom the product is prescribed. Therefore, the above four scenarios have been designed to evaluate these risks.

The actual use study included two sessions/visits. Visit 1 (Day 1) consisted of training on the use of the device, including the performance of a self-injection in the presence of a qualified healthcare professional. Visit 2 (Day 8 to 10) consisted of a written examination and a complete

panel of scenario test case observations, including a single observed self-injection. A written examination was given at the beginning of Visit 2 (Day 8 to 10) and evaluated the patients' retention of information given at the training visit (Visit 1, Day 1).

The study results are summarized as follows:

- Scenario 1:
 - 4 patients did not hold the needle in place for 5 seconds. Of the 4 patients who were marked “No”, 1 patient lifted the pen off the injection site at the same time he or she pushed the button on the pen, 1 patient was not properly seated, experienced difficulty in performing the skin pinch and lifted the pen slightly after pushing the button, 1 patient did not keep the pen in place (small drop of MTX on the skin) and was nervous about being observed, and 1 patient was confused by the first click.
 - 6 patients required assistance for this task, and 3 patients had no data for this category (CRF was blank). One patient requested assistance (“asked coordinator to confirm technique”), 8 patients received a prompt, 5 patients made an incorrect step, and 2 patients self-corrected a step.
 - Sponsor provided clarification on these failures (sequence 007, dated 2/28/2014). The four failures were reported at Visit 1. Two additional failures were seen at Visit 2. The possible causes of the failures were that the patients were inexperienced with using the new pen, and they were being nervous and confused about the click of the needle projector. However, the subjects that failed at Visit 1 were able to complete injections at Visit 2. In addition, the Sponsor clarified that the nature of the assistance provided:
 - There were 4 instances where assistance was provided to patients during the general injection process: reminding patient to hold pen firmly over skin; holding subject's shirt up, holding patient's skin on thigh, helping with patient's stiff hands.
 - There were 5 instances where assistance was provided to the task of holding the needle at the injection site for 5 seconds: guiding the step for pushing pen down before injection for two patients, reminding patient to take the cap off, and two unspecified assistance, where one patient failed the first injection completely but succeeded during second injection.
- Scenario 2, no failures were reported.
- Scenario 3:
 - One patient did not pinch the skin, and commented that he or she did not have good use of his or her hands to pinch the skin; however he or she was able to perform the injection in the upper thigh. One patient did not pinch the skin tight enough to allow visualization of the injection and was also confused by the click of the shield retracting.
- Scenario 4, no failures were reported.

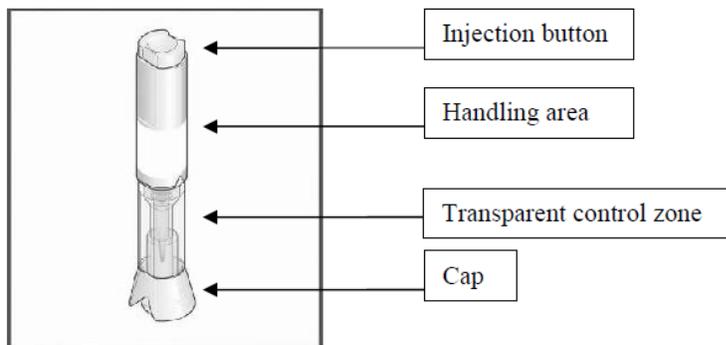
During participant debriefing, 5 patients indicated that they had difficulty using the prefilled pen. And of these instances, 4 patients did not receive a full dose.

This review identified three deficiencies that were communicated to the Sponsor.

Appendix 2: Device Description

Metoject® is a prefilled pen. The prefilled pen is designed to enable self-injection of an entire single dose. The dose is given once a week only. Each Metoject® prefilled pen is ready to use. No assembly is required. Metoject® is available in 10 dose strengths; they are 7.5 mg/0.15 mL, 10 mg/0.2 mL, 12.5 mg/0.25 mL, 15 mg/0.3 mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL, 25 mg/0.5 mL, 27.5 mg/0.55 mL and 30 mg/0.6 mL.

Metoject® prefilled pen components:



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



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
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Date: June 2, 2014
From: Keith Marin, Combination Products Team Leader, WO66, RM 2567
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Sadaf Nabavian, Sr. Program Management Specialist,
OMPT/CDER/OND/ODEII/DPARP
Subject: CDRH Consult, ICC 1300536/S003, NDA 205776, MAF (b) (4) PFS and
Autoinjector to deliver Methotrexate Final Review

1. **Issue**

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 205776. The device constituent of this combination product consists of a PFS and autoinjector to deliver Methotrexate.

2. **Device Description**

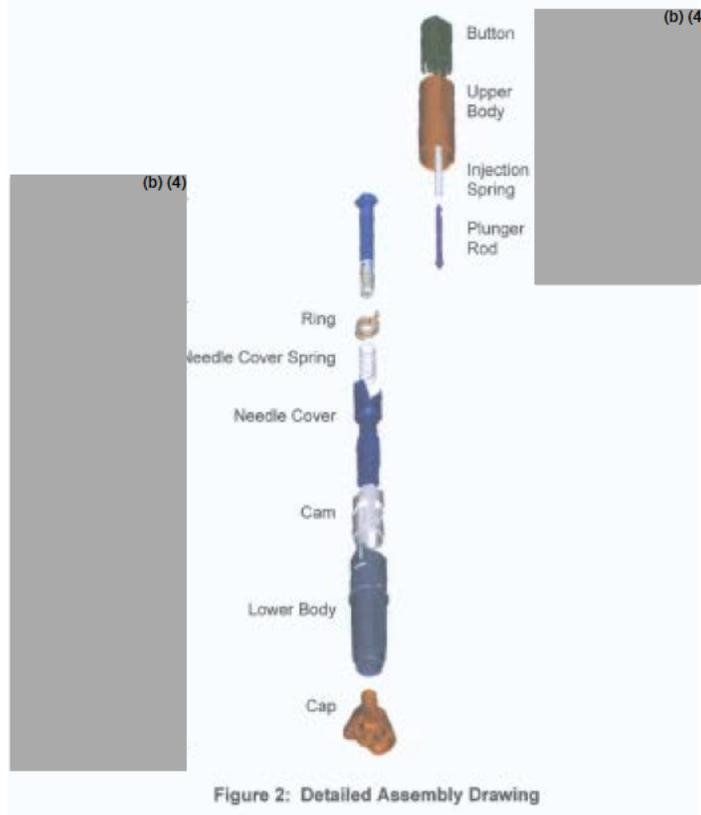
The primary container closure for drug product is the (b) (4) 1mL long syringe made of Type I (b) (4) glass barrel, embedded with 27 gauge, ½ inch stainless steel needle, needle shield and (b) (4) rubber plunger stopper.

The (b) (4) syringe is a disposable system for packaging and administering of parenteral medicinal product. The (b) (4) syringe system is comprised of:
Empty glass syringe barrel assembled with:

(b) (4)



The BD Physioject™ is a disposable, spring powered, single use autoinjector designed to subcutaneously inject drug product from a 1mL syringe



The user removes the BD Physioject™ Cap by pulling it straight off. Due to physical interference in the design, this action also removes the syringe's needle shield.

The autoinjector is then placed to the skin at a ninety degree angle and pressed downwards, which pushes the Needle Cover up and enables the Button. The Button is pressed, activating needle penetration and dose delivery. Internally to the BD Physioject™, depressing the Button releases the Injection Spring and causes the Plunger Rod to hit the syringe's plunger stopper. This causes the syringe to move forward, the needle to penetrate the skin, and the drug product to be delivered. Depressing the Button also causes the Needle Cover to be released.

The injection process can be viewed through (b) (4). The injection process is complete when the syringe's plunger stopper has reached the end of the syringe barrel (a permanent visual indication) or alternatively, when a specific time frame has passed. Once the injection is completed, BD Physioject™ is pulled straight out of the skin and the Needle Cover moves down over the needle, locking into place, and preventing reuse.

3. Documents Reviewed

NDA 205775 3.2.P.7
MAF (b) (4)
DMF (b) (4)

4. CDRH Review and Comments

(b) (4)

Cannula

The 27 gauge ½ inch staked cannula is made up of (b) (4) stainless steel. Acceptance specifications: Cannula is accepted by means of a supplier-issued certificate of conformance. (b) (4) also performs visual and dimensional inspections according to Standard Operating Procedures.



(b) (4)

Glass Barrel

- The glass material used (clear glass or Amber glass) meets the last edition of:
- USP <660> “Containers: glass”.
- Ph. Eur. 3.2.1. “Glass containers for pharmaceutical use” Type I.

All results were reported as “satisfactory.”

Reviewer’s Comments: Biocompatibility of the syringe and conformance with USP standards will be reviewed by the lead center as the syringe is also the primary drug container closure. The testing and documentation for the (b) (4) 1ml long syringe with staked needle is adequate for CDRH ODE – Device Evaluation review.

BD PHYSIOJECT AUTOINJECTOR

CDRH reviewed MAF (b) (4) and the performance data that (b) (4) provided within this document. We noted that none of the components of the Autoinjector come into physical contact with the drug product. The autoinjector encases the prefilled syringe that contains the drug product. Upon activation of the device, the autoinjector drives the prefilled syringe piston to deliver the drug product directly to the subcutaneous site of administration.

Device Performance

MAF (b) (4) demonstrates that the autoinjector conforms to ISO 11608-1, 2000, *Pen Injectors for Medical Use*.

	Free fall 1meter vertical direction onto the button Free fall 1meter vertical direction onto the cap Free fall 1meter horizontal direction	(b) (4)	1) Visual inspection 2) Container closure inspection 3) Dose accuracy	(b) (4)	Pass
BD Physioject + syringe 1.0 ml filling volume (ERD-20121235)	Cool atmosphere 5 ± 3°C (at least 4 hours)		Dose accuracy		Pass
	Standard atmosphere 23 ± 5°C RH 50%±25% (at least 4 hours)				Pass
	Warm atmosphere 40 ± 2°C RH 50%±10% (at least 4 hours)				Pass
	Free fall 1meter vertical direction onto the button Free fall 1meter vertical direction onto the cap Free fall 1meter horizontal direction		1) Visual inspection 2) Container closure inspection 3) Dose accuracy		Pass

Table 2: ISO 11608-1:2012 Test Results for BD Physioject (0.15ml Fill Volume)

Device Configuration (Test Report #)	Step 1 – Pre Conditionings		Step 2 – Test		Step 3 - Results						
	Preconditioning	Number of samples to prepare	Test	Number of samples to test	Number of surviving samples after preconditioning	Number of samples tested for dose accuracy	Test Results Mean X	Standard Deviation	Actual k	Target k	Conclusion (Pass if Actual k ≥ Target k)
BD Physioject + syringe 0.18 ml* filling volume (ERD-20121237)	Cool atmosphere 5 ± 3°C (at least 4 hours)	(b) (4)	Dose accuracy							(b) (4)	Pass
	Standard atmosphere 23 ± 5°C RH 50%±25% (at least 4 hours)										Pass
	Warm atmosphere 40 ± 2°C RH 50%±10% (at least 4 hours)										Pass
	Free fall 1meter vertical direction onto the button										Pass
	Free fall 1meter vertical direction onto the cap		Pass								
Free fall 1meter horizontal direction		1) Visual inspection 2) Container closure inspection 3) Dose accuracy									

*: A overfill of 30 µl is required due to dead volume in the syringe.

Table 1: MTX Pre-filled Pen, 50 mg/ml, Dose Accuracy of Different Dosage Volumes

Dosage [mg]	V _{set} [ml]	X [ml]	SD [ml]	X-(k*SD) [ml]	LLS [ml]	Result
7.5	0.150	0.1726	0.0051	0.1604	0.150	passed
10	0.200	0.2246	0.0048	0.2132	0.200	passed
12.5	0.250	0.2742	0.0032	0.2666	0.250	passed
15	0.300	0.3264	0.0029	0.3195	0.300	passed
17.5	0.350	0.3752	0.0037	0.3664	0.350	passed
20	0.400	0.4219	0.0066	0.4062	0.400	passed
22.5	0.450	0.4759	0.0040	0.4664	0.450	passed
25	0.500	0.5234	0.0040	0.5139	0.500	passed
27.5	0.550	0.5721	0.0052	0.5597	0.550	passed
30	0.600	0.6224	0.0037	0.6136	0.600	passed

Reviewer's Comment: A summary test matrix has been provided, but test reports were not included. CDRH requests complete test reports with notation and deviation from any ISO specified testing methods. Exposed needle length acceptance criterion 8mm± 2mm appears to be consistent with subcutaneous injection .

The MAF holder has not conducted studies of the needle shield according the CDRH Guidance for Sharps Injury Protection features, noting that this is not the intent of the needle shield. 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.

Packaging and Shipping

The shipping unit had to be tested according to the test program of Table 3 of client's plan 'Performance testing of shipping containers for MTX pen' document no.

05/03/05/QP 16072013 and in accordance to ASTM 04169- DC 2 (test program specified by the client).

Additional test conditions as per the client:

- Conditioning at "laboratory ambient" of 23°C / 50% r.h.
- "Schedule J - Concentrated Impact": Only two cardboard boxes were tested. The top face, one long and one short side face of the shipper were tested.
- "Schedule 1 - Low Pressure": Only ^{(b) (4)} test samples of the pallet will be tested due to the limited dimensions of the test chamber. Two cardboard boxes were identified by the client for the test, see section 7 of clients' plan. Furthermore this test schedule will be postponed at the end of the test program to avoid manipulation of the load securing by cutting of the stretch film as well as of the cardboard boxes by picking and dropping packages..

Table 2: Test sequence according to ASTM 04169-09 / Distribution Cycle 2, Ass- Level II (specified by the client)

Schedule	Test	Test Parameter	Test Load	Reference
-	Conditioning	Controlled room temperature: +2 c s T s +25 c	72 h	ASTD D4332
Schedule A Handling Mechanical Handling, Unitized Loads	10.3.2.1 Pick up, transport around test course, Method A fork lift	Test course	5 cycles (round trips)	ASTMD6055
	10.3.2.2 Impact Test	Impact velocity = 1.22 m/s	1 impact on all four sides	ASTMD880
	10.3.2.3 Rotational flat drop test	Drop ht. = 229 mm (S 226.8 kg)	1 drop over each bottom edge	ASTMD6179
Schedule E Vehicle Vibration	12.3 Vehicle vibration	Random Vibration Truck Spectrum frequency range 4...200 Hz (QRMS = 0.52)	3 h in shipping orientation	ASTMD4728
Schedule J Concentrated Impact	17 Free Fall Drop Test with impacting mass	Impacting mass Ace. To D6344 Impact faces: any endangered Top, 1 shorter side, 1 longer side	32 in. (0.8 m)	ASTMD6344

Table 2, continued: Test sequence according to ASTM 04169-09/ Distribution Cycle 2, Ass. Level II (specified by the client)

Schedule	Test	Test Parameter	Test load	Reference
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Schedule A Handling Mechanical Handling, Utilized Loads	10.3.2.1 Pick up, transport around test course, Method A fork lift	Test course	5 cycles (round trips)	ASTM D6055
	10.3.2.2 Impact Test	Impact velocity = 1.22 m/s		1 impact on all four sides
	10.3.2.3 Rotational flat drop test	Drop ht. = 229 mm (S 226.8 kg)	1 impact from each opposite edge	ASTM D6179

Results: On delivery no external damages on the shipping unit could be noticed. The compression test was passed by the shipping unit without a permanent deformation. Except for compressed cardboard box edges caused by stretch wrapping, no other observations could be noticed. During visual check on the folding boxes as well as the pens of cardboard box, no damaged test samples were detected.

Conclusion: All testing passed.

Reviewer notes: The sponsor indicated that there was no damage on the outer packaging after the transport. Based on the results of the testing and lack of failures, I would agree with the assessment. I have no further questions.

Sterility

The syringe component will be provided pre-filled and sterile. As a result, sterility will be addressed by CDER.

Shelf life

The Based on the available primary stability data and supportive data, an expiration date of (b) (4) is proposed when the product is stored below 25°C and protected from light. Support for the shelf life can be found in the stability testing section of 3.2.P.8.1.

Biocompatibility

MAF (b) (4) states that the skin contacting materials that the device is composed of conform to ISO 10993-1:1997, *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing*. The device is classified as intact dermal contact, limited contact duration.

LIST OF MATERIALS

Component	Material
Button	(b) (4)
Upper Body	
Injection Spring	
Plunger Rod	
Ring	
Needle Cover Spring	
Needle Cover	
Cam	
(b) (4)	
Lower Body	
Cap	

IN VITRO STUDIES, Test Article 13-0502-001

Protocol	Test	Result
42CC01.13	Cell Cytotoxicity/Elution 48-Hour Titration	Pass 1:1 USP Score = 0

IN VIVO STUDIES, Test Article 13-0502-001

Protocol	Test	Result
32PD04.09	Primary Dermal Irritation (SAL, PEG)	Negligible Irritant: SAL/PEG SAL: PII = 0; PEG: PII = 0 (PII = Primary Irritation Index)
32LL02.05	Murine Local Lymph Node Assay (SAL, PG)	Nonsensitizer: SAL/PG SAL: SI = 0.73; PG: SI = 0.86 (SI = Stimulation Index)

Reviewer's Comment: Test reports for biocompatibility are not provided. CDRH requires complete test reports to be submitted to the MAF for the device including for the dyes and colorants used in the proprietary injector.

In their March 6, 2014 IR response, the MAF holder provided a summary table of the biocompatibility testing. However, full test reports were not provided. This information is needed for full review of the material.

In their April 7, 2014 IR response, the MAF Holder provided the requested complete biocompatibility testing reports. Review of these materials demonstrates the device meets biocompatibility requirements.

5. CDRH Recommendation

Based on our review the following deficiencies should be conveyed to the MAF holder below: (b) (4)

CONTACT FOR FDA CORRESPONDENCE

(b) (4)

(b) (4)

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

Sponsor's Response: *The test report ERD20121237 Rev.02 Physioject™ Test Report: Dose Accuracy Tests with Low Filling Volume (0.15ml) (Attachment 1) is attached for your review. Please note that a newer version of ISO 11608-1 was released in 2012, and we evaluated the BD Physioject Autoinjector following the ISO 11608-1:2012 in place of ISO 11608-1:2000. The applicability and/or deviation from testing according to the Standard is discussed in Section 6.3 on page 12 of this report.*

CDRH Response: *The sponsor provided additional information related to dose accuracy. Based on the complete test reports, there were the following deviations to the protocol that did not have adequate explanation:*

- 5.5q: deviation states it is the user's responsibility
- 10.2: Accuracy testing was done only at ambient laboratory temperatures
- 10.6: Dry heat and cold storage testing was not done
- 10.9: Vibration testing was not completed

Discussion with CDER indicated that the device is labeled to be kept from small children so that should address the concern in 5.5q. However the deviations in the accuracy testing, dry heat and cold storage testing, and vibration testing is not acceptable. Looking over the testing, the MAF Holder really should be doing the accuracy testing according to the ISO standard. Just testing to ambient temperature will not cut it. The lack of vibration testing is more than simply a missing test. Vibration testing is also useful to determine how well a product wrapped/packed as well. We have had cases of syringes plungers falling out and auto injectors assembly becoming loose during shipping because the blister packs were not tight enough. The sponsor should provide dose accuracy testing at cool, standard and warm temperatures, not just ambient temperatures. We need to think about when the product is shipped via truck (hot as hell in the back) or in the plane's cargo area (freezing) that the product is cycled in extreme temperatures. Often drugs are shipped to a different continent for use, so most shipping containers are not temperature controlled on these long journeys at sea. When mobile hospitals are set up in the military, it was often on a hot tarmac in a tent, so the drugs are not temperature protected. This is also true when they use these drugs in Africa or PHS

deploys for the hurricanes/earthquakes. An IR was sent to the MAF holder on April 11, 2014 and communicated the following:

1. *In your March 6, 2014 response, you provided the dose accuracy testing that was requested. However, you have deviated from ISO 11608-1: 2012 and you have not provided all of the testing necessary to evaluate your device. Provide the following information:*
 - *Conduct an accuracy measurement of three different sets of systems at each of the conditions specified in Table 4 of ISO 11608-1:2012*
 - *Provide dry heat and cold storage testing according to 10.6 of ISO 11608-1:2012*
 - *Provide vibration testing according to section 10.9 of ISO 11608-1:2012*
 - *For all other deviations of ISO 11608, provide detailed justification for the deviation.*

CDRH Response: *After discussion with (b) (4) we became aware that they were confused related to what we were asking. Upon doing some investigating to figure out whether the NDA or MAF holder performed dose accuracy testing, it was discovered that the testing that (b) (4) provided was not connected to the summary matrix that was in the NDA. After some discussion, I believe the summary matrix table that was in the NDA may have been performed by the NDA holder, rather than (b) (4) which may explain some of (b) (4) confusion. Based on the summary report in the NDA, the testing was done based on ISO 11608-1:2000, a 12 year old standard that is no longer recognized by the Agency. I think in addition to providing the complete test reports we asked for in the IR, we may be able to save time by the sponsor providing a side by side comparison of the standard that they did testing based on (prEN ISO 11608-2010) with what we currently recognize (ISO 11608-1 Second edition 2012-04-01, needle-based injection systems for medical use -requirements and test methods - part 1: needle-based injection systems) and show us if they are identical. If they can do that and provide us the complete testing reports, this could save significant time by not having to do these tests again. But they would have to provide detailed comparison showing us how they did this testing and how it is no different from the other standard. On May 14, 2014, we communicated the following deficiency to the NDA holder:*

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.

Sponsor Response:

Comparison of the ISO 11608-1: 2000 version to that of the current ISO 11608-1:2012 version

In general, the **DIN EN ISO 11608-1:2012** (Needle-based injection systems for medical use - Requirements and test methods – Part 1: Needle-based injection systems) differs from the previous edition **DIN EN ISO 11608-1:2000** (Pen-injectors for medicinal use – Part 1: Pen injectors – Requirements and test methods) as follows:

- a) Clause 1 “Scope” has been revised to apply to needle-based injection systems (NISs), previously pen-injectors;
- b) Clause 3 “Terms and definitions” has been revised;
- c) Clause 5 “Requirements” has been completely revised and rearranged taking into account the enlarged scope. DIN EN ISO 11608-1:2000 referred to pen-injectors, only, which were defined as pen-injectors containing a multi-dose container. No further designations were provided. In contrast, current edition DIN EN ISO 11608-1:2012 provides the system designations listed below. In addition, the appropriate test and dose accuracy method are clearly associated with each injection system.

Multi-dose container:

- A: Needle-based injection device with replaceable container. Each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).
- C: Needle-based injection device with integrated non-replaceable container. Each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).

Single-dose container

- B1: Needle-based injection device with replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled.
 - B2: Needle-based injection device with replaceable container. Each container holds a single dose, whereby a portion of the deliverable volume is expelled.
 - D1: Needle-based injection device with integrated non-replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled.
 - D2: Needle-based injection device with integrated non-replaceable container. Each container holds a single dose, whereby a portion of the deliverable volume is expelled.
- d) Clause 7: The “Determination of dose accuracy” has been revised so that the determination of dose accuracy limits is clearly associated with the different system designations. In addition, DIN EN ISO 11608-1:2012 introduces the one-sided tolerance interval for dose accuracy limits, whereas version 2000 only describes the two-sided tolerance interval;
- e) Clause 9 “Test matrix” has been added showing the test requirements for each system designation;
- f) The standard has been editorially revised.

In summary, with regard to the Rasuvo™ (methotrexate) injection pre-filled pen, an adequate system designation has been implemented (“D1”) and lower requirements for this system with regard to the dose accuracy (e.g., the one-sided tolerance interval for dose accuracy limits) have been introduced as compared to 11608-1:2000.

Comparison of the DIN prEN ISO 11608-1:2010 (D) version to that of the current ISO 11608-1:2012 version

DIN prEN ISO 11608-1:2010 (D) was a draft version of the current standard (ISO 11608-1:2012). This draft version was available at medac in German (D) language. ISO 11608-1:2010 was issued as final DIN EN ISO 11608-1:2012 with only minor editorial changes. No content changes were incorporated; therefore, it is in full compliance with the current version (DIN EN ISO 11608-1:2012).

Testing of Rasuvo (Methotrexate) injection in accordance with EN ISO 11608-1:2012

The Rasuvo™ (methotrexate) injection pre-filled pen is a ready-to-use, filled syringe assembled into a disposable auto-injector for subcutaneous (s.c.) use. The pre-filled pen is not re-usable and discarded in its entirety after single use; therefore, the “D1” designation applies in accordance with the current standard, ISO 11608-1:2012.

EN ISO 11608-1:2012, Section 9, specifies requirements and test methods for needle-based injection systems (NISs) intended to be used with needles and non-replaceable, single-dose syringe-based containers filled by the manufacturer (“D1”) as listed in the [Table 1](#).

For each test described in Table 1, the following evaluations after each pre-conditioning and testing requirement should be performed:

- a) Visual inspection/Container inspection
- b) Dose accuracy testing and evaluation of dose accuracy acceptance criteria
- c) Full functional testing

For system designations “D1”, V_{set} is defined to be equal to the manufacturer-filled volumes. In the instance of manufacturer-filled single-dose NISs designed to fully empty the container, accuracy can be evaluated as the minimum deliverable dose (i.e. the labelled volume). To pass the minimum deliverable dose requirement for system designations “D1” with manufacturer-filled containers, there shall be a 95 % confidence level that at least the probability content (p) of all doses delivered are above the lower specification limit. This is defined by the minimum deliverable dose specified by the drug labelling. The following lower specification limits apply to the Rasuvo™ pen:

7.5 mg:	0.15 ml
10 mg:	0.20 ml
12.5 mg:	0.25 ml
15 mg:	0.30 ml
17.5 mg:	0.35 ml
20 mg:	0.44 ml
22.5 mg:	0.45 ml
25 mg:	0.50 ml
27.5 mg:	0.55 ml
30 mg:	0.60 ml

In accordance with the current standard, the one-sided lower specification limit for the minimum deliverable dose is applicable for manufacturer-filled containers and determined from the drug labelling.

- Determination of the Dose Accuracy of MTX pre-filled pens (50 mg/ml) from the 10 produced dosage volumes in the range between 7.5 and 30 mg ([Study Report 2011/042/QEN-R](#)).

Tests were performed as listed in [Table 2](#).

- Physioject™ Test report: Dose accuracy tests with low filing volume (0.15 ml) according ISO 11608-1: 2012 ([Study Report ERD_683](#))

Tests were performed as listed in [Table 3](#).

- Physioject™ Dose accuracy test and results ([Study Report ERD_575](#))

Tests were performed as listed in [Table 4](#).

Table 2: Study Reports 2011/042/QEN-R: Overview of performed tests

Tests were performed in accordance with prEn ISO 11608-1:2010 (D), which is in compliance with the final issued DIN ISO 11608-1:2012.					
System designation "D1"	Brief description	Probab. content	Replicates per injector	Total measurements per V_{set}	One-sided target
		p	R	n	k
Standard atmosphere	Dose accuracy (DA) testing at <ul style="list-style-type: none"> ▪ Room temperature (for at least 4 hours) This atmosphere was chosen because this storage condition complies with the storage condition stated in the PI.	(b) (4)			
Test material: Methotrexate 50 mg/ml pre-filled pen (Rasuvo™ (methotrexate) injection) 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml, 0.60 ml					
Visual Inspection and functional testing are normally observed during dose accuracy testing. No observations were determined.					

Table 3: Study Report ERD_683: Overview of performed tests

Tests were performed in accordance with DIN EN ISO 11608-1:2012.					
System designation "D1"	Brief description	Probab. content	Replicates per injector	Total measurements per V_{set}	One-sided target
		p	R	n	k
Cool, standard, warm atmosphere	Dose accuracy (DA) testing at <ul style="list-style-type: none"> ▪ $5 \pm 3^{\circ}\text{C}$ – no humidity requirement ▪ $23 \pm 5^{\circ}\text{C} / 50 \pm 25\%$ RH ▪ $40 \pm 2^{\circ}\text{C} / 50 \pm 10\%$ RH (each for at least 4 hours)	(b) (4)			
Free-fall	1 m drop \times 3 orientations				
Test material: NaCl 0.9 % solution, pre-filled pen of the lowest filling volume (0.15 ml)					
Visual Inspection, container inspection and functional testing were checked.					

Table 4: Study Report ERD_575: Overview of performed tests

Tests were performed in accordance with DIN EN ISO 11608-1:2000.	
System designation "D1"	Brief description
Cool, standard, warm atmosphere	Dose accuracy (DA) testing at <ul style="list-style-type: none"> ▪ 5 ±3°C – no humidity requirement ▪ 23 ± 5 °C / 50 ±25% RH ▪ 40 ±2°C / 50 ±10% RH (each for at least 4 hours)
Free-fall	1 m drop × 3 orientations
Test material 1: NaCl 0.9 %, pre-filled pen solution of 0.2 ml, 0.5 ml and 1 ml filling volume	
Visual Inspection, container inspection and functional testing were checked.	
<u>Acceptance criteria (two-sided dose accuracy limits):</u> As described by the ISO standard in table 4 chapter 9.2.1, for the current filling volume (Vset) we have the following specifications. A pen-injector's population accuracy satisfies the requirements when, for a given Vset, the following are fulfilled: $LLS \leq X - (k \cdot S)$ and $X + (k \cdot S) \leq USL$ with X the average delivered volume, k the tolerance limit factor, S the standard deviation, LLS and USL as below:	

In summary, the test requirements were fulfilled in accordance with the current standard (ISO 11608-1:2012). The free fall, cool and warm atmosphere test requirements were previously performed by (b)(4) and were deemed sufficient; therefore, medac did not perform these tests (please refer to Study Reports ERD_575 and ERD_683 and Table 3: Study Report ERD_683: Overview of performed tests).

In addition, the "vibration" test is a new requirement in accordance with ISO 11608-1:2012. This test was only previously required for devices with electronics in accordance with ISO 11608-1:2000.

Though dose accuracy testing was not performed after "vibration" it should be noted that a simulated shipping study for the Rasuvo pen was performed. Please refer to Module 3.2.P.3.5 and the following reports:

- [Test Report No. 238/13](#) - Transport simulation test according to ASTM 04169-09, DC 2 on one shipping unit containing (b)(4) filled auto injectors, type MTX
- [Report No. 2013/028/AC-R](#) - Methotrexate 50 mg/ml Pre-filled Pen: Additional analytical evaluation in the context of the transport validation test plan - Performance Testing of Shipping Units for MTX Pen: Pallet of (b)(4) containing sales units of one MTX Pen
- [Test Report No. 319/13](#) – Transport simulation test according to ASTM D4169-09 DC 2 on one shipping unit containing (b)(4) filled auto injectors, type MTX

CDRH Response: *The sponsor has provided a side by side comparison of the testing they have completed compared with the currently recognized ISO 11608-1:2012. Based on my evaluation, they have made several deviations to the standard. They have not conducted vibration testing, however they have done simulated shipping studies based on ASTM 04169-09, which has vibration as part of the testing schedule. Otherwise, I find the comparison of the testing they have done to ISO 11608-1:2012 to be sufficient. Additionally, after discussion with CDER and Dr. Lana Shiu, we came to the determination that since the auto*

*injector does not have a dial for dosing and the difference in dosing is a result of fill volume, a bracketed approach would be acceptable for dose accuracy where they had tested the highest and lowest doses. Additionally, the pen delivers the same force regardless of the fill volume. The sponsor did accuracy testing on all fill volumes to show that the entire dose could be delivered. As a result, I do not have any additional concerns related to the performance testing. **The response is acceptable.***

2. You have submitted a summary of biocompatibility testing. Test reports for biocompatibility according to ISO 10993-1:1997, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing, for a device in limited contact with intact skin were not provided. Submit complete test reports to the MAF for skin contacting materials in the device including all the dyes and colorants used in the proprietary injector.

Sponsor's Response:

(b) (4) Response:
The Biocompatibility/Testing Report can be found in (b) (4)
(b) (4) The following table lists the base material and colorant used for the skin contacting components of the BD Physioject configuration selected by Medac.

Skin Contacting Components	Base Material	Colorant
Button	(b) (4)	(b) (4)
Upper Body	(b) (4)	(b) (4)
Lower Body	(b) (4)	(b) (4)
Needle Cover	(b) (4)	(b) (4)
Cap	(b) (4)	(b) (4)

As requested, the Device Master File MAF (b) (4) will be updated to include this testing report during the upcoming annual update in July 2014.

CDRH Response: *The sponsor has not provided complete test reports for the biocompatibility testing. This will need to be provided. On April 1, 2014, the following IR was sent to the MAF Holder:*

*In your February 19, 2014 communication we requested the following:
You have submitted a summary of biocompatibility testing. Test reports for biocompatibility according to ISO 10993-1:1997, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing, for a device in limited contact with intact skin were not provided. Submit complete test reports to the MAF for skin contacting materials in the device including all the dyes and colorants used in the proprietary injector.*

In your March 6, 2014 response you provide summary biocompatibility information but not complete test reports. Please provide complete test reports for the biocompatibility testing including protocol, acceptance criteria, complete results, and conclusion.

On April 7, 2014, the sponsor provided the following response:

The requested information is enclosed as indicated in the table below. The acceptance criteria, complete results and conclusion can be found in the detailed documents accordingly.

Study Type	Report Type	Report # & Name	Attachment #
Cell Cytotoxicity	Protocol	42CC01.13	Attachment 1
	Test Report	Cell Cytotoxicity/Elution Test Test Article 13-0502-001	Attachment 2
Primary Dermal Irritation	Protocol	32PD04.09	Attachment 3
	Test Report	Primary Dermal Irritation Test Article 13-0502-001	Attachment 4
Sensitization	Protocol	32LL02.05	Attachment 5
	Test Report	Local Lymph Node Assay Test Article # 13-0502-001	Attachment 6

CDRH Response: *The sponsor's has provided the requested information. The response is acceptable.*

3. Simulated shipping studies to confirm functionality of the autoinjector after shipping were not provided. Provide testing to demonstrate the that autoinjector is functional after simulated shipping according to ASTM-D 4169, Standard Practice for Performance Testing of Shipping Containers and Systems.

Sponsor's Response: *The sponsor did not address this question.*

CDRH Response: *The response is unacceptable. On April 11, 2014, the following deficiency was sent to the NDA holder:*

1. *Simulated shipping studies on the final finished device to confirm functionality of the autoinjector after shipping were not provided. Provide testing to demonstrate the that autoinjector is functional after simulated shipping according to ASTM-D 4169, Standard Practice for Performance Testing of Shipping Containers and Systems.*

Sponsor's Response: *Simulated shipping studies on the final finished drug/device combination product Methotrexate 50 mg/ml solution for injection, pre-filled pen were performed in accordance with ASTM 04169-09, DC2. Transportation validation results, including the results of the functionality of the pens after simulated transportation in two layers were provided in Module 3.2.P.3.5, Section G of the original NDA (SN0000). In addition, Module 3.2.P.3.5, Section G is now updated to include the results of the functionality of the pens after simulated transportation in three layers.*

CDRH Response: *The MTX pens examined for functionality and container content fulfilled the acceptance criteria. The mean container content was 0.43ml. The response and supportive information provided by the sponsor is acceptable.*

4. You have not conducted studies of the needle shield according the CDRH Guidance for Sharps Injury Protection features, noting that this is not the intent of the needle shield. 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. Explain why this testing is not necessary or provide testing according to the Guidance.

Sponsor's Response: *The BD Physioject Autoinjector is the subject of Device Master File for components and not a finished medical device. The CDRH Guidance for Sharps therefore does not apply to BD Physioject, and we do not claim the needle shield as a Sharps Injury Prevention Device.*

CDRH Response: *The response is unacceptable. If (b) (4) states that they do not provide a finished device, then the NDA holder will need to provide the testing (or pay (b) (4) to complete it). On April 4, 2014, the following deficiency was sent to the NDA holder:*

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. As the finished device manufacturer you should conduct studies of the needle shield according the CDRH Guidance for Sharps Injury Protection features.*

Sponsor's Response:

The drug product Methotrexate 50 mg/ml solution for injection is a ready-to-use, pre-filled syringe assembled into a disposable pen (auto-injector) for subcutaneous use (Methotrexate 50 mg/ml Pre-filled Pen). The drug/device combination product is intended for single use. The pre-filled pen is supplied to the patient completely assembled with the pre-filled syringe as a single integral product; i.e. BD's Physioject is not a finished medical device but BD's Physioject is supplied to the manufacturer (b) (4)

The guidance, referenced by the FDA (Medical Devices with Sharps Injury Prevention Features, August 9, 2005.), has been developed to assist in preparing premarket notification submissions for medical devices that incorporate a sharps injury prevention feature. It focuses mainly on the specific content requirements of a premarket notification submission of medical devices that contain a sharps injury prevention feature (510(k) submission). The scope of the guidance is therefore, limited to medical devices that contain a sharps injury prevention feature.

Of note, medac's drug/device combination product was developed in accordance with the Guidance "Technical Considerations for Pen, Jet and Related Injectors Intended for use with Drug and Biological Products".

The following protective features as discussed in the 2005 guidance were addressed for medac's drug /device combination product:

- The user is able to easily tell whether the the syringe's needle cover of the BD Physioject is locked into place after the injection to avoid any injury.
- Once locked, the the syringe's needle cover of the BD Physioject cannot be deactivated and remains protective through disposal.
- The shield completely encloses the needle and prevents accidental finger access when activated.
- The housing extends beyond, i.e., fully covers the needle and prevents unintended finger access.

The Actual Use/Human Factor study (MC-MTX.15/HF) included a pen robustness evaluation and the data support that the protective needle shield is appropriate for its intended use. In addition, the test parameter of functionality of the protective shield is included in the proposed product specifications. Batches tested to date support the functionality of the protective needle shield. A summary of the studies and data to support the prevention of sharps injuries are summarized below.

Robustness Study

Of note, within the Actual Use Study (MC-MTX.15/HF "Evaluation of Rheumatoid Arthritis Patient Performance Using the Metoject[®]1 Prefilled Pen (Methotrexate 50 mg/mL, prefilled pen) for Subcutaneous Injection and Subsequent Pharmacokinetic Assessment of Drug Delivery") a pen robustness evaluation was included. Pen robustness was evaluated using i. a. criterion 4 "Did the protective needle shield move back into place to cover the needle?"

A total of 104 patients were enrolled in the study and completed the study at five sites. After the patients completed the self-injection, the pen used by each patient for self-injection at Visit 1 (Day 1) and Visit 2 (Days 8 to 10) was collected and checked for evidence of failure (robustness).

All prefilled pens used in the study were examined and all were found to be intact with all pieces remaining as one unit. The protective needle shield of all pre-filled pens moved into the correct position immediately after the pre-filled pen was lifted from the injection site. The pre-filled pen functioned without any device robustness failure during or as a result of the actual use self-injection procedure.

Visit 1, n = 106

Did the protective needle shield move back into place to cover the needle?

Yes: n = 106 (100.0%)

No: n = 0

Visit 2, n = 106

Did the protective needle shield move back into place to cover the needle?

Yes: n = 104 (98.1%)

No: n = 0

Missing: n = 2 (1.9%)

The number and percentage of patients who evaluated pen robustness were provided in a summary table and listed based on the safety population in the study report MC-MTX.15/HF. Refer to Section 9.5.2.3 for a detailed description of determining pen robustness. Post-text Table 14.2.1.8 provides a summary of pen robustness. A by-patient presentation of the data is provided in Listing 16.2.6.7.

No accidental needle-stick injuries by using the pre-filled pen, malfunctions (problem with the syringe's needle cover that may lead to an injury) or any other observation from the RA patients/health care professionals concerning the protective shield were determined within the actual use study.

As there are no standardized, validated methods to simulate clinical use of sharps injury prevention features it is considered justified that the results of the above Actual Use Study (instead of a simulated use testing) provide appropriate evidence that the protective needle shield is appropriate for its intended use.

In addition, medac GmbH (the parent company of Medac Pharma Inc, the applicant of the NDA 205776) has been granted marketing authorisations for the identical pre-filled pen (methotrexate 50 mg/ml solution for injection in a pre-filled syringe assembled in BD's Physioject) in various Member States of the European Union. Since grant of marketing authorisation a number of (b) (4) methotrexate pre-filled pens were supplied to the market. Medac is not aware of any complaints regarding accidental needle-stick injuries or any malfunction of the protective needle shield of the pre-filled pen.

Functionality of the protective needle shield

In addition, it should be noted that at release of the drug/device combination product each batch is tested according to the proposed specification as listed in Module 3.2.P.5.1. The test parameter "Functional Test, Auto-injector" is part of the drug/device combination product specification. The limit is set "The pre-filled pen expels the solution without interruption and the needle cover pushes forward afterwards". For the performance of the test, the pre-filled pen is injected into a dedicated vial with septum.

In addition, stability studies according to the stability protocol as described in Module 3.2.P.8.1 have been initiated considering long term ($25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$), intermediate ($30^{\circ} \pm 2^{\circ}\text{C}/65\% \pm 5\% \text{RH}$) and accelerated storage conditions ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$). All release/stability batches tested so far met the specified limit. Therefore, the functionality of the protective needle shield is assured.

Though medac's methotrexate 50 mg/ml pre-filled pen is not a medical device but a drug/device combination product we would additionally like to note that that sterility testing of the drug/device combination product (as requested in the above-FDA guidance for medical device) is part of the specification of the drug/device combination product. In addition, the biocompatibility was tested for BD's Physioject. A biocompatibility statement is included in the NDA (Please refer to Module 3.2.P.7).

CDRH Response: There are several issues with the needlestick prevention feature testing that the sponsor provided. There are two devices missing for the question "did the

protective needle shield move back into place to cover the needle?” It is not clear what “missing” indicates. Additionally, they have not provided any details of the protocol, testing population, acceptance/failure criteria, and results to test this needle stick feature. These details are needed in order to support that the testing demonstrates that the needle stick feature adequately protects the user from inadvertent needle stick injury. Finally, the clinical testing the sponsor has 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. As a result, on April 11, 2014, we sent the following IR:

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. 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.*

Sponsor’s Response: *The MC-MTX.15/HF Clinical Study Report (CSR) Table 14.2.1.8 gives the frequency distribution of the pen robustness evaluation for the n=106 patients included in the Safety Population. However, two patients (refer to CSR Table 10-1) discontinued the study prematurely prior to visit 2 (i.e., without conducting the second injection at visit 2). These patients were labeled as “missing” in the respective table.*

CDRH Response: *The sponsor’s explanation seems reasonable as the data for these two patients was incomplete due to the patients discontinuing the study prematurely prior to visit 2. **The response is acceptable.***

- 2. 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>.*

Sponsor's Response:

As compared to CDRH Guidelines for Sharps Injury Protection features, study MC-MTX.15/HF was designed as an actual use study to demonstrate that patients with RA can use the prefilled-pen to self-administer Methotrexate (MTX); the study also included a device robustness evaluation. For evaluation of the pen robustness, 6 questions were specified. The respective results are shown in the CSR MC-MTX.15/HF, Table 14.2.1.8. One of these questions specifically evaluated the proper function of the needle shield during the injection process (“Did the protective needle shield move back into place to cover the needle?”). A by-patient presentation of the data are provided in Listing 16.2.6.7 of the CSR.

At visit 1 and at visit 2, the patients completed a self-injection. After each injection the pens were collected and checked for evidence of failure (pen robustness).

A total of 210 injections were documented for visit 1 and visit 2. All pens were found to be intact after usage with all pieces remaining as one unit. After all injections the protective needle shield completely moved back into place and completely covered the needle. No accidental needle-stick injuries by using the prefilled-pen were determined within this study (refer to Section 12.2.1 Brief Summary of Adverse Events and Adverse Device Effects and Listing 16.2.7.1 Adverse Events of the CSR).

CDRH Response: *The sponsor has provided additional information on the use of the needlestick prevention feature. **The response is acceptable.***

- 3. 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.*

Sponsor's Response:

Medac conducted the MC-MTX.15/HF study, where the pen robustness was evaluated, in 210 performed injections. In these performed injections, no defects or damages of the protective needle shield were observed when inspected by the Sponsor's designee.

Within the development program of the BD Physioject™, Becton Dickinson (BD) conducted a study entitled “Evaluation of the convenience of use and functionality of BD Physioject™ via simulated injections performed by patients with destructive inflammatory rheumatism”. This study is part of (b) (4) Device Master File filed with the Center for Devices and Radiologic Health (MAF- (b) (4)). A letter of authorization to cross-reference MAF- (b) (4) is provided in Module 1.4.2 of the original NDA (SN0000). Among other objectives, this study evaluated the deployment and locking of the needle shield. In total, 390 injections were performed by 65 subjects. All of the auto-injectors [100% (390/390)] had their needle cover automatically activated.

Considering the injections performed in both trials, a total of 600 devices were tested. In all these injections, the protective needle shield worked properly.

CDRH Response: *When comparing both studies the Medac study with 210 injections and the 390 devices in the (b) (4) functionality study that is present in MAF (b) (4) the number of devices and the fact that no devices experienced failure of the needlestick prevention*

*feature, I believe the testing is sufficient to show that the feature works as intended. **The response is acceptable.***

The sponsor has addressed the performance and biocompatibility concerns. CDRH/ODE does not have any additional questions.

If you have any further questions, please contact LCDR Keith Marin at 301-796-2462.

Digital Signature Concurrence Table	
Reviewer Sign-Off Keith Marin	
Branch Chief Sign-Off Richard Chapman	

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/s/

SADAF NABAVIAN
06/05/2014

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 30, 2014

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP) Office of Drug Evaluation II
Office of New Drugs

FROM: Michael F. Skelly, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 205-776, Methotrexate
injection, sponsored by Medac Pharma, Inc.

At the request of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: MC-MTX.14/PK (sponsor); 070/11-032.ME
Study Title: "Relative bioavailability of four different doses of methotrexate 50 mg/mL administered subcutaneously by a disposable autoinjector compared to oral administration of methotrexate tablets, USP (Dava) in healthy male and female subjects, single center, open label, randomized, two-period, two-sequence, single dose crossover study in four dose groups"

The inspection of the clinical portion was conducted by
Alexandra B. Pitkin (ORA Investigator, LOS-DO) at CRS Clinical
Research Services Mannheim GmbH, in Mannheim, Germany, from May
12 to May 23, 2014. There were no objectionable findings during
the inspection and Form FDA-483 was not iss n

by (b) (4)

(b) (4)

(b) (4)

(b) (4) There were no

objectionable findings during the inspection and Form FDA-483
was not issued.

We are aware of the 12/27/2011 Meeting Request-Preliminary
Responses provided to the sponsor under PIND 109,543, and the
response to Question 2: "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."

The substance of this advice was communicated by Medac to CRS,
and consequently CRS did not retain reserve samples for either
test or reference formulations. In the opinion of this
reviewer, the study was not a bioavailability study described in
21 CFR 320.38(b)(1), for which reserve samples of a reference
oral solution, suspension, or injection would not be required.
Instead, it appeared to be a relative bioavailability study
described in 21 CFR 320.38(b)(2), for which reserve samples of
both reference and test products should have been retained. The
tablet reference product appeared to be an "appropriate
reference material" described in 21 CFR 320.25(c) and (e), as
amended and discussed at 67 FR 77674, December 19, 2002, and
with established stability during storage. However, for this
specific study, the four purposes of bioequivalence reserve
samples expressed in the Final Rule at 58 FR 25918, April 28,
1993, are not compromised by lack of their retention:

- Identity of the products would not likely be confused, for
oral tablets in their original containers, and the
prefilled autoinjector syringes.
- Repeating tests of strength, content uniformity, and
dissolution of the reference tablets would be a challenge
to the reference listed drug product, and not useful to
evaluating the test product. The strength of a test
solution would not normally be confirmed with a reserve
sample.

- Repeating the entire in vivo bioequivalence study with reserve samples has not been performed in the 23-year history of the regulation.
- Post-approval questions on product safety or failure would be investigated with currently manufactured product instead of reserve samples.

Conclusion:

Following review of the inspectional findings, I recommend that:

- The results from the clinical and bioanalytical portions of study MC-MTX.14/PK are acceptable for Agency review.

Michael F. Skelly, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

**Clinical Research Services, Mannheim, Germany - NAI
(FEI# 3006660278)**

(b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernett/CF

OSI/DBGLPC/BeB/Haidar/Choi/Skelly

OSI/DBGLPC/GLPB/Bonapace/Dasgupta

CDER/OND/ODEII/DPARP/Nabavian

CDER/OND/OCP/Agarwal/Tran

ORA/LOS-DO/Pitkin

Draft: MFS 5/29/2014

Edits: YMC 5/29/2014; SHH 5/30/2014

OSI: File BE6593; O:\BE\EIRCOVER\205776.med.Met.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 8732598

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/s/

MICHAEL F SKELLY
05/30/2014

SAM H HAIDAR
05/30/2014

WILLIAM H TAYLOR
06/03/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 8, 2014

To: Sadaf Nabavian, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer (Rheumatology)
Puja Shah, Regulatory Review Officer (Dermatology)
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP
Adora Ndu, Acting Group Leader, OPDP

Subject: NDA 205776
OPDP labeling comments for RASUVO (methotrexate) injection, for
subcutaneous use

In response to DPARP's consult request dated October 21, 2013, OPDP has reviewed the draft labeling (Package Insert [PI] and Carton/Container labeling) for RASUVO (methotrexate) injection, for subcutaneous use (Rasuvo) and offers the following comments. OPDP's comments regarding the proposed patient labeling (Patient Package Insert [PPI] and Instructions for Use [IFU]) were incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP, and were provided under separate cover on May 2, 2014.

OPDP's comments on the PI are provided directly below and are based on the proposed draft marked-up labeling titled "NDA 205776 Rasuvo SCPI 2016-1-16n_DPARP 2014-4-3.doc" that was provided via email from DPARP on April 28, 2014. We note that according to the Medical Officer Memo to File dated September 26, 2013, for the competitor, Otrexup (NDA 204824), CDER is requesting that the labeling for originator methotrexate products be updated to bring them up to current labeling standards, after which time newer methotrexate formulations, such as Rasuvo and Otrexup, will need to revise their labeling for consistency.

OPDP has reviewed the proposed carton and container labeling submitted by the applicant on September 10, 2013, and located in the EDR (eCTD Sequence Number 0000). We offer the following comments:

- We note that the proprietary name and established name are presented in several locations on the proposed carton label (representative example attached below). We recommend that the established name be presented in a manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.
- We recommend that the proposed carton and container labeling be revised to replace [REDACTED] ^{(b) (4)} with the approved proprietary name, "Rasuvo."

OPDP appreciates the opportunity to provide comments on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
05/08/2014

PUJA J SHAH
05/08/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: October 30, 2013

TO: Arthur Shaw, CDER/OPS/QNDQA, HF800, WO21-RM2506
arthur.shaw@fda.hhs.gov

Prasad Peri, CDER/OPS/ONDQA. HFD-820, WO21-RM2618
prasad.peri@fda.hhs.gov
Office of combination products at combination@fda.gov

Through: Carl Fischer, Ph.D., Chief, General Hospital Devices Branch,
Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3526

From: LT Neil A. Mafnas, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3500

Applicant: Medac Pharma, Incorporated
29 North Wacker Drive, Suite 704
Chicago, Illinois 60606
Phone: 312-854-0500
Fax: 312-750-1082
FEI# 123459

US Agent:
B&H Consulting Services, Incorporated
50 Division Street, Suite 206
Somerville, New Jersey 08876
Phone: 908-704-1691 ext. 288
Fax: 908-704-1693

Application # NDA #205776

Product Name: Methotrexate Pre-filled Pen Injector (methotrexate 50 mg/ml solution for injection)

Consult NDA 205776 is a new NDAS submitted by Medac Pharma Inc. It indicates that (b) (4) is a device kit assembly site. Please advise if this site needs an inspection.

Instructions:

The Office of Compliance at CDRH received a consult request from CDER on October 16, 2013, requesting that CDRH evaluate NDA 205776 and determine “whether an inspection is necessary for (b) (4)

Methotrexate is a folic acid antagonist indicated for the treatment of autoimmune diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and psoriasis. It primarily acts by competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has immunosuppressive and anti-inflammatory effects. Methotrexate belongs to the disease-modifying antirheumatic drugs and immunosuppressant drugs.

Methotrexate 50 mg/ml concentration in a pre-filled pen is indicated for use in the treatment of:

- Severe, active RA in adults
- Active polyarticular-course JIA following an insufficient therapeutic response to, or intolerance of, an adequate trial of first-line therapy, including full dose non-steroidal anti-inflammatory agents (NSAIDs)
- Severe, recalcitrant disabling psoriasis that is not adequately response to other forms of therapy but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.

The pre-filled pen injector consists of the following parts:

- 1 ml barrels of neutral, colorless glass (USP Type I) with embedded injection needle protected by a rigid needle shield (syringe barrel with or without graduation)
- Plunger stoppers of (b) (4) rubber (Type I rubber stoppers)
- (b) (4) button, upper body, injection spring and plunger rod
- (b) (4) lower body, ring, needle cover spring, needle cover, cam, cap

The primary packaging is the pre-fillable (b) (4) syringe of 1 ml capacity. The Physioject auto-injector pen is supplied to the manufacturer (b) (4). The manufactured pre-filled syringe is assembled into a device for a pre-filled pen, forming a complete system for self administration. The device is not reusable and should be discarded, in its entirety, after single subcutaneous use.

The pre-filled pen injector is activated by pressing a button which automatically pushes the needle forward and delivers the solution. Once the device is removed from the injection site, a needle cover automatically moves down over the needle for safe disposal.

Illustrations and a photograph of the device are included below:

Figure 2.3.P.1-1: Assembled pre-filled pen, exemplary version



Figure 3.2.P.7-1: Illustration of the Pre-Filled Pen (Exemplary Version)

(b) (4)



Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was no information available for review regarding compliance with 21 CFR 820.50, Purchasing Controls.
2. Regarding compliance with 21 CFR 820.30, there was no information pertaining the design of the combination product in the application.

3. There was no information available for review regarding the establishment of a Corrective and Preventive Action (CAPA) system compliant with 21 CFR 820.100.

This application was deficient overall. Additional information is required for an adequate desk review.

Regulatory History Evaluation

After reviewing the application, the (b) (4) site located at (b) (4) was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that a drug inspection conducted on (b) (4) revealed no deficiencies and was classified NAI. The inspection report did not include enough information about the facility and the manufacture of the finished combination product to evaluate the facility's compliance with applicable 21 CFR part 820 regulations.

Deficiencies to be Conveyed to the Applicant

Stephanie Pierson

Vice President

B&H Consulting Services, Incorporated
50 Division Street, Suite 206
Somerville, New Jersey 08876

The following information should be submitted for review to evaluate the extent of the firm's compliance with applicable 21 CFR 820 regulations under NDA # 205776:

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>

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA # 205776 and has the following recommendation:

CDRH Office of Compliance recommends a pre-approval inspection under the Medical Device Regulation be conducted for the following facility:

(b) (4)
[Redacted]

Additionally, CDRH Office of Compliance cannot issue a recommendation regarding the adequacy of Application NDA #205776 under the applicable Medical Device Regulations until a full desk review of the requested documentation can be completed.

LT Neil A. Mafnas, USPHS

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/s/

YOUBANG LIU
05/02/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 2, 2014

To: Badrul Chowdhury, M.D.
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Roberta Szydlo, RPh, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): Rasuvo (methotrexate)

Dosage Form and Route: Injection, for subcutaneous use
Application

Type/Number: NDA 205776

Applicant: Medac Pharma

1 INTRODUCTION

On September 10, 2013, Medac Pharma submitted for the Agency's review an original new drug application (NDA) for Rasuvo (methotrexate) injection for subcutaneous use. Rasuvo (methotrexate) injection is indicated for the treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) after treatment with other medicines including non-steroidal anti-inflammatory (NSAIDS) have been used and did not work well. In addition, Rasuvo (methotrexate) injection is indicated to control the symptoms of severe, resistant, disabling psoriasis when other types of treatment have been used and did not work well.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on October 21, 2013, and October 21, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed PPI and IFU for Rasuvo (methotrexate) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 23, 2014.

2 MATERIAL REVIEWED

- Draft Rasuvo (methotrexate) injection PPI and IFU received on September 10, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 28, 2014.
- Draft Rasuvo (methotrexate) injection PPI and IFU received on September 10, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on April, 28, 2014.
- Draft Rasuvo (methotrexate) injection Prescribing Information (PI) received on September 10, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 28, 2014.
- Draft Rasuvo (methotrexate) injection, Prescribing Information (PI) received on September 10, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on April 28, 2014.
- Approved Otrexup (methotrexate) injection comparator labeling dated October 11, 2013.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for*

People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
05/02/2014

ROBERTA T SZYDLO
05/02/2014

MELISSA I HULETT
05/02/2014

LASHAWN M GRIFFITHS
05/02/2014

LABEL AND LABELING AND HUMAN FACTORS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 23, 2014

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: NDA 205776

Product Name and Strength: Rasuvo (Methotrexate) Injection
7.5 mg/0.15 mL, 10 mg/ 0.20 mL, 12.5 mg/0.25 mL,
15 mg/0.30 mL, 17.5 mg/ 0.35 mL, 20 mg/0.40 mL,
22.5 mg/0.45 mL, 25 mg/0.50 mL, 27.5 mg/0.55 mL,
30 mg/0.60 mL

Product Type: Combination (drug + device)

Rx or OTC: Rx

Applicant/Sponsor Name: Medac Pharma

Submission Date: September 10, 2013

OSE RCM #: 2014-91, 2013-2505

DMEPA Primary Reviewer: Teresa McMillan, PharmD

DMEPA Associate Director: Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review responds to a request from DPARP to evaluate the applicant's Human Factor Validation Study Results as well as the container label, carton labeling, Prescribing Information, and Instructions for Use (IFU) associated with the proposed new product Rasuvo (Methotrexate), to ensure the intended population is able to use the product safely and effectively.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews {N/A}	C
Human Factors Study (single-use autoinjector)	D
ISMP Newsletters	E-(N/A)
Other	F-(N/A)
Container Label, Carton Labeling, and Instructions for Use (IFU) or Medication Guide	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Overall, the human factors study results demonstrated that participants were able to use the methotrexate single-use autoinjector safely and effectively. However, some trained (with and without an 8-10 day decay time) participants encountered difficulties (i.e. removing the autoinjector prior to the 5 second hold time and not pinching the skin) and required assistance (i.e., assistance with holding the pen, skin, or shirt) to complete the injection. It was also noted that users who encountered difficulties at Visit 1 did not report issues at Visit 2 and vice versa. Thus, a systematic problem could not be determined. We also note that the difficulties the trained users encountered have also been reported with the use of other autoinjector devices and therefore we do not believe that the risks are unique to the proposed autoinjector. Failure to hold for the allotted 5 second hold time may result in an under-dose in most instances. However, we note that all participants held for a minimum of three seconds and the injection is complete in one second although the IFU requires users to hold for five seconds. We defer to DPARP to determine the appropriateness of holding the skin while administering this product. The Applicant recommends training for all first time users. However, we also recommend the applicant provide instructions in the IFU for users to contact a healthcare provider regarding re-dosing if the autoinjector is removed from the site of the injection prematurely.

We note that the labels and labeling can be improved to promote the safe use of this product and to clarify important information. Since the frequency of administration of methotrexate may vary, it is important that the “once weekly “statement is presented on the labels and labeling if space permits. (b) (4)

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Study demonstrated that trained users are able to use the autoinjector safely and effectively. However, some users may encounter difficulties while administering this product. We also note that the difficulties the trained users encountered have also been reported with the use of other autoinjector devices and therefore the risks are not unique to the proposed autoinjector. In addition to training all first time users as the applicant proposes, DMEPA also recommends instructing users to contact a healthcare provider regarding re-dosing if an incomplete injection occurs.

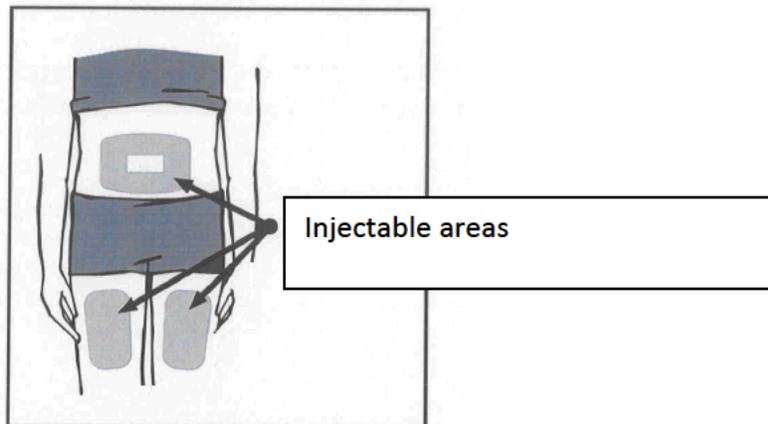
The proposed IFU, container label, carton and insert labeling can be improved to increase readability and prominence of important information to promote the safe use of the product to mitigate any confusion and to clarify information.

4.1 RECOMMENDATIONS FOR THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Instructions For Use

1. In Figure 4, add arrows that point to and identify the abdomen and thigh areas to be injected. See example below:



2. Add the following statement after the [REDACTED] (b) (4)

Contact a healthcare provider if the pen is removed from the skin before the end of the injection before using another pen.

B. All Labels and Labeling

1. Remove all instances of the name [REDACTED] (b) (4) and replace with "Rasuvo".

C. Single-Use Pen Container Label [Trade and Professional Sample]

1. To make space for more important information delete the (b) (4) statement and move the strength statement in its place.
2. Add the following statement under the “FOR SUBCUTANEOUS USE ONLY”
Single Use Pre-filled Pen

D. Single-Use Pen Container Labels [Professional Sample]

1. (b) (4)
Each product sample unit must bear a label that clearly denotes its status as a drug sample (e.g., “sample,” “not for sale,” “professional courtesy package” (21 CFR 203.38(c)). Add the following statement:
PROFESSIONAL SAMPLE. NOT FOR SALE.

E. Carton Labeling [Trade and Professional Sample]

1. Add a “Once weekly” statement after the strength statement on the principal display panel to denote the frequency of administration for this subcutaneous formulation of methotrexate.
2. Ensure that the image of the prefilled pen accurately represents the, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.³
3. Reduce the prominence of the manufacturer’s logo on the principal display and side panels.

F. Carton Labeling [Trade]

1. Revise the statement (b) (4) to the following:

This carton contains 4 single-use pre-filled pens .

³<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

G. Carton Labeling [Professional Sample]

1. Revise the statement  (b) (4)
to the following:

This carton contains 1 single-use pre-filled pen.

2. Relocate the “Not for individual sale. Sample only” statement to appear above the “For single use only” statement and revise the to the following:

PROFESSIONAL SAMPLE. NOT FOR SALE.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rasuvo (Methotrexate) that Medac Pharma submitted on September 10, 2013.

Table 2. Relevant Product Information for Rasuvo (Methotrexate)	
Active Ingredient	Methotrexate
Indication	Treatment of severe, active rheumatoid arthritis including polyarticular juvenile idiopathic arthritis and psoriasis
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	7.5 mg/0.15 mL, 10 mg/ 0.20 mL, 12.5 mg/0.25 mL, 15 mg/0.30 mL, 17.5 mg/ 0.35 mL, 20 mg/0.40 mL, 22.5 mg/0.45 mL, 25 mg/0.50 mL, 27.5 mg/0.55 mL, 30 mg/0.60 mL
Dose and Frequency	7.5 mg to 30 mg once weekly. Max dose-30 mg
How Supplied	Single-dose pre-filled autoinjectors pack size of 1 or 4 pens
Storage	Excursions permitted to 15°C to 30°C (59°F to 86°F); protect from light and do not freeze

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 16, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date Range	January 16, 2013-January 16, 2014 Date of last search from OSE review #2013-120, 2013-997
Drug Names	*METHOTREXATE SODIUM* [active ingredient]
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 113 cases, of which 6 cases described errors possibly associated with the current labels and labeling for Methotrexate. We excluded 107 cases because they described medication errors involving the tablet formulation (n=54), cases that listed methotrexate as a concomitant medication (n=37), duplicate cases (n=9), adverse events unrelated to a medication error (n=6), and accidental exposure unable to determine medication error (n=1).

Following exclusions 6 methotrexate medication error cases remained. Three involved the wrong dose of the injectable formulation of methotrexate. All three cases were overdoses and one case attributed the wrong dose to the pharmacy technician selecting the incorrect vial and not being accustomed to methotrexate. The other two wrong dose cases did not report a cause

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

or outcome. The remaining three cases described wrong routes of administration (e.g. subcutaneous) and no cause or outcome was reported. We reviewed the current methotrexate prescribing information and labels and labeling and found it adequate to mitigate these errors.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	Manufacture control number
9145543	US-PFIZER INC-2013076820
9369351	US-MYLANLABS-2013S1013434
9464963	FR-MYLANLABS-2013S1017440
9467834	
9560057	US-PFIZER INC-201327416

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

This was an actual use study with 106 Rheumatoid Arthritis (RA) patients ranging from 16 years and over. It assessed whether RA patients can use the device by evaluating four critical tasks (Figure 1), device robustness (each device was evaluated after use) and it also evaluated the pharmacokinetics of the proposed product. The study consisted of two visits. During visit 1, one hundred six patients were evaluated. However, in visit 2, only 104 patients were evaluated because one patient dropped out due to physician advice (unable to make it to visit 2) and the other patient dropped out voluntarily.

Visit 1, Day 1 (training visit)- All patients were trained by a qualified healthcare professional on the proper use of the pen. After training, patients performed a self-injection with the health care professional. Participants were able to ask questions and assistance was provided if needed. Healthcare professionals also completed a questionnaire on day 1.

Visit 2, Day 8-10 –Written exam was given to test the retention of the patients knowledge from Visit 1. Patients then self-injected without any assistance or training.

Also, open ended questions were asked regarding the device and the four critical tasks assessed.

Figure 1

Four Critical Tasks

- Held the device in place for 5 seconds
- Checked the window of device to confirm delivery
- Pinched the skin for subcutaneous administration
- Proper disposal

D.2 Results

VISIT 1 {DAY1}

Number of participants N=106		Reasons for Unsuccessful Injections, Assistance, and Difficulties
Number of Successful Injections	105	
Number of Unsuccessful injections	1	No reason given by the Applicant but I assumed that the start of injection startled 1 patient causing her to pull the pen out before the injection was completed. This was stated as a reason for difficulty below.
Number of participants requiring assistance	4	<ul style="list-style-type: none"> • Reminder to hold the pen firmly over skin • Holding up a patient's shirt • Assistance to hold the skin pinched on the thigh • Assistance with stiff hands
Number of participants experiencing difficulties using the device	7	<ul style="list-style-type: none"> • Patient somewhat hesitant to initiate injection due to anticipation of pain • Start of injection startled 1 patient causing her to pull the pen out before the injection was completed; some patients just pulled the pen out too soon • Holding pinched skin and trying to press the injection button • Due to patient's arthritic hands it was difficult to: hold pinched skin, and press the injection button

VISIT 2 DAY 8-10

***Note that the applicant also evaluated the mean time participants held the device at the site of injection. Per the applicant 23 held for exactly 5 seconds, 22 less than 5 seconds, and 59 for more than 5 seconds. The applicant also states that in one case, lifting the prefilled pen away from the injection site in less than 5 seconds resulted in a small drop of drug on the skin, but the patient commented that he or she was nervous about being observed. The minimal amount of time any one participant held was 3 seconds. The injection is delivered within 1 second.

Critical Tasks Number of participants=104	Number of Successful Number of Unsuccessful	Reasons for Unsuccessful Completion of Critical Tasks
<ul style="list-style-type: none"> Held the device in place for 5 seconds 	Successful=100 Unsuccessful=4	<ul style="list-style-type: none"> patient lifted the pen off the injection site at the same time he or she pushed the button on the pen patient was not properly seated experienced difficulty in performing the skin pinch and lifted the pen slightly after pushing the button patient did not keep the pen in place (small drop of MTX on the skin) and was nervous about being observed patient was confused by the first click
<ul style="list-style-type: none"> Checked the window of device to confirm delivery 	Successful=104 Unsuccessful=0	
<ul style="list-style-type: none"> Pinched the skin for subcutaneous administration 	Successful=102 Unsuccessful=2	<ul style="list-style-type: none"> patient commented that he or she did not have good use of his or her hands to pinch the skin; however he or she was able to perform the injection in the upper thigh due to the fact that the thigh area was sufficiently firm to allow successful depression of the protective shield at the beginning of the injection patient did not

		pinch the skin tight enough to allow visualization of the injection and was also confused by the click of the shield retracting.
<ul style="list-style-type: none"> • Proper disposal 	Successful=104 Unsuccessful=0	

Per the applicant, a systematic problem could not be deduced from the incomplete injections, participants requiring assistance and experiencing difficulties since all subjects with issues at visit 1 or visit 2 had at least one successful injection. Therefore, the IFU was not modified. It was also taken into consideration that the physician has to determine if it is appropriate for a subject to self-inject. The Applicant also stated that section 4 “How to prepare the injection” advises the user to ask a caregiver for assistance, if they are unable to push the pen to the stop point. Based on these assessments, the applicant determined that additional risk mitigations are not required.

DEVICE ROBUSTNESS

All pens were found to be intact but there was one pen with evidence of fluid within the transparent control zone (noted this was a failed injection and the MTX deposited on the wall of the shield) and one pen had a bent needle (degree of bending not noted).

The following comments regarding the device were given:

- 3 patients indicated they had difficulty holding the prefilled pen down after pushing the button or were confused with the sound of the “shield being pushed in”
- 1 patient expected to hear a click at the end of injection as occurs with another pen
- 1 patient forgot to remove the yellow cap

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following methotrexate labels and labeling submitted by Medac Pharma on September 10, 2013.

- Container label
- Carton labeling
- Professional Sample Carton Labeling
- Instructions for Use

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

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

TERESA S MCMILLAN
04/23/2014

LUBNA A MERCHANT
04/23/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

DATE: March 20, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Sadaf Nabavian, Regulatory Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: **NDA 205776**
Applicant: Medac Pharma, Inc
Device Constituent: prefilled peninjector
Drug Constituent: Methotrexate SQ
Intended Treatment: Rheumatoid Arthritis (RA), Juvenile RA, and Psoriasis
CDRH CTS Tracking No.: ICC 1400179

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

NDA 205776

Applicant: Medac Pharma

Device Constituent: peninjector

Drug Constituent: Methotrexate

Intended Treatment: Rheumatoid Arthritis (RA), Juvenile RA, and Psoriasis

CDRH Human Factors Involvement History

- 10/21/2013 – CDRH HF was requested to review the human factors validation study report included in the IND.
- 3/25/2014 – CDRH HF provided review recommendation. Three deficiencies were identified and sent to CDER project manager.

Overview and Recommendation

The Division of Pulmonary, Allergy, and Rheumatology Products requested a consultative review from CDRH Human Factors team to review a report titled “Evaluation of Rheumatoid Arthritis Patient Performance Using the Metoject® Prefilled Pen (Methotrexate 50 mg/mL, prefilled pen) for Subcutaneous Injection and Subsequent Pharmacokinetic Assessment of Drug Delivery.” This report included an actual use component that was designed to evaluate use performance with representative users and to assess the pharmacokinetics of MTX across a range of body weights. This review focused on the evaluation of use performance.

104 patients were enrolled and completed the study at 5 sites. The actual use testing focused on the steps involved to perform self-injection, and four scenarios were identified to evaluate the potential risks associated with product use. The study results showed several failures associated with holding the needle in place for 5 seconds after activation, and two failures associated with the pinching technique for subcutaneous injection.

This review identified one deficiency that should be communicated to the Sponsor:

1. Your study results showed 4 failures and 4 reported difficulties where 8 study patients did not receive a full dose. Please note 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), section (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.

Please address the following:

- a. Please 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. Please clarify the source of the confusion of the click of the needle projector
 - c. Please quantify the amount of dose that would be underdosed, 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. Regarding the issues associated with pinch, you did not discuss whether any of the techniques applied by test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences.
 3. In addition, please discuss how the studies design with respect to the duration between the two visits, and the written exam, and how they are representative of actual use.

CDRH Human Factors Review

One hundred and four (104) patients were enrolled and completed the study at five sites. The actual use testing focused on the steps involved to perform self-injection, and four scenarios were identified to evaluate the potential risks associated with product use, which include premature needle withdrawal, incomplete ejection of all infusate in the syringe, premature release of skin pinch while injecting and management of known cytotoxic agent.

	Test Case	Objective	Scenario
1	Patient is required to hold the prefilled pen needle in place until all the medication is injected (about 5 seconds). This is necessary to be sure all the medication is delivered into subcutaneous tissue without excessive flow back or leakage.	Evaluate if the patient understands and is able and willing to hold the prefilled pen needle in place until all the medication is injected (about 5 seconds).	Patient will be observed performing the injection and a stopwatch will be used to determine the length of time the needle was held in place.
2	Patient will perform the required injection following all steps of the Patient Instructions for Use provided within the Medication Guide. Patient needs to check the optical window of the syringe to confirm that all medication was delivered.	Evaluate if the patient properly understands the need to check the optical window to verify the syringe is empty.	Patient will be observed performing an injection and after completion, will be monitored to be sure the optical window was checked and verified to be empty of any remaining medication.
3	Patient will perform all the required steps defined in the Patient Instructions for Use provided within the Medication Guide for performing injection. One step defines the requirement to pinch the skin at the site of injection. Pinching the skin helps to assure the patient performs a proper subcutaneous injection rather than an unwanted intramuscular injection. The skin must be pinched for the entire time of the injection.	Evaluate if the patient can properly perform the injection and continuously pinch the skin over the complete duration of the injection.	Patient will be observed performing an injection and performing a proper skin pinch procedure as defined in the Patient Instructions for Use provided within the Medication Guide. The skin pinch must remain in place during the overall injection period.
4	After completion of the injection procedure, the prefilled pen will be empty but will still contain cytotoxic drug residue. The patient will receive instructions for proper disposal of the spent syringe. It will be verified that disposal instructions are followed.	Evaluate if the patient is aware of the safe disposal requirements of the used prefilled pen device.	Patient will be observed performing the injection as defined in the Patient Instructions for Use provided within the Medication Guide. At the completion of injection, the used syringe must be disposed in accordance with instructions.

Medac Pharma indicated that based on their risk assessment, premature needle withdrawal was determined to be the greatest risk to patients because the patient may not receive a full dose of medication. The other risks included incomplete ejection of all infusate in the syringe, premature release of skin pinch while injecting and drug exposure (known cytotoxic) to individuals other than patients whom the product is prescribed. Therefore, the above four scenarios have been designed to evaluate these risks.

The actual use study included two sessions/visits. Visit 1 (Day 1) consisted of training on the use of the device, including the performance of a self-injection in the presence of a qualified healthcare professional. Visit 2 (Day 8 to 10) consisted of a written examination and a complete panel of scenario test case observations, including a single observed self-injection. A written

examination was given at the beginning of Visit 2 (Day 8 to 10) and evaluated the patients' retention of information given at the training visit (Visit 1, Day 1).

The study results are summarized as follows:

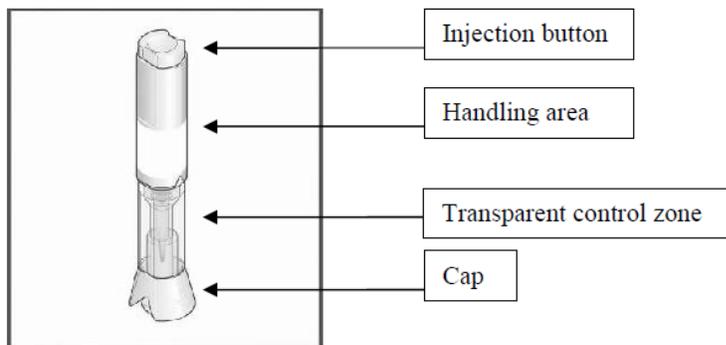
- Scenario 1:
 - 4 patients did not hold the needle in place for 5 seconds. Of the 4 patients who were marked “No”, 1 patient lifted the pen off the injection site at the same time he or she pushed the button on the pen, 1 patient was not properly seated, experienced difficulty in performing the skin pinch and lifted the pen slightly after pushing the button, 1 patient did not keep the pen in place (small drop of MTX on the skin) and was nervous about being observed, and 1 patient was confused by the first click.
 - 6 patients required assistance for this task, and 3 patients had no data for this category (CRF was blank). One patient requested assistance (“asked coordinator to confirm technique”), 8 patients received a prompt, 5 patients made an incorrect step, and 2 patients self-corrected a step.
 - Sponsor provided clarification on these failures (sequence 007, dated 2/28/2014). The four failures were reported at Visit 1. Two additional failures were seen at Visit 2. The possible causes of the failures were that the patients were inexperienced with using the new pen, and they were being nervous and confused about the click of the needle projector. However, the subjects that failed at Visit 1 were able to complete injections at Visit 2. In addition, the Sponsor clarified that the nature of the assistance provided:
 - There were 4 instances where assistance was provided to patients during the general injection process: reminding patient to hold pen firmly over skin; holding subject's shirt up, holding patient's skin on thigh, helping with patient's stiff hands.
 - There were 5 instances where assistance was provided to the task of holding the needle at the injection site for 5 seconds: guiding the step for pushing pen down before injection for two patients, reminding patient to take the cap off, and two unspecified assistance, where one patient failed the first injection completely but succeeded during second injection.
- Scenario 2, no failures were reported.
- Scenario 3:
 - One patient did not pinch the skin, and commented that he or she did not have good use of his or her hands to pinch the skin; however he or she was able to perform the injection in the upper thigh. One patient did not pinch the skin tight enough to allow visualization of the injection and was also confused by the click of the shield retracting.
- Scenario 4, no failures were reported.

During participant debriefing, 5 patients indicated that they had difficulty using the prefilled pen. And of these instances, 4 patients did not receive a full dose.

Appendix 1: Device Description

Metoject® is a prefilled pen. The prefilled pen is designed to enable self-injection of an entire single dose. The dose is given once a week only. Each Metoject® prefilled pen is ready to use. No assembly is required. Metoject® is available in 10 dose strengths; they are 7.5 mg/0.15 mL, 10 mg/0.2 mL, 12.5 mg/0.25 mL, 15 mg/0.3 mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL, 25 mg/0.5 mL, 27.5 mg/0.55 mL and 30 mg/0.6 mL.

Metoject® prefilled pen components:



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

Signed on behalf of CDRH

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 26, 2013

TO: Chief,
Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, High Priority User Fee NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 205-776
DRUG: Methotrexate injection
SPONSOR: Medac Pharma, Inc., Chicago, IL

This memo requests that you arrange for inspections of the clinical and analytical portions of the following relative bioavailability study. Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to June 14, 2014.**

Do not reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study: MC-MTX.14/PK
Study Title: "Relative bioavailability of four different doses of methotrexate 50 mg/mL administered subcutaneously by a disposable autoinjector compared to oral administration of methotrexate tablets, USP (Dava) in healthy male and female subjects, single center, open label, randomized, two-period, two-sequence, single dose crossover study in four dose groups"

Clinical Site: CRS Clinical Research Services Mannheim GmbH
Grenadierstrasse 1
68167 Mannheim, German
TEL: +49 (0) 621-15045-0
FAX: +49 (0) 621-15045-150

Investigator: Dr. Wolfgang Timmer
TEL: +49 (0) 621-15045-110
FAX: +49 (0) 621-15045-151
Email: wolfgang.timmer@crs-group.de

SECTION A - RESERVE SAMPLES

Because this relative bioavailability study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies
(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples
(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or

the samples are not adequate in quantity, notify the DBGLPC POC immediately.

- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.

- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

SECTION C - AUDIT OF ANALYTICAL DATA

Analytical Site:

(b) (4)

Contact person:

Methodology:

LC-MS/MS

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical method used for the measurement of analyte concentrations in human plasma.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method to analyze the subject samples.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the Applicant for their content.

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Page 6 - BIMO Assignment, NDA 205-776, Methotrexate injection, sponsored by Medac Pharma, Inc.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC (Foreign sites only):

Arindam Dasgupta, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

DARRTS cc:

CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Choi/Dasgupta/Chen/Dejernett
OSI/DBGLPC/Bonapace/Mada
CDER/OND/DPARP/Nabavian

Email cc:

ORAHQ/OMPTO/DMPTI/BIMO/Turner/Arline/Montemurro/Colon

Draft: XC 11/26/2013

Edit: MFS 11/26/2013

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/

(b) (4)

OSI file #: BE 6593

FACTS: 8732598

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/s/

XIKUI CHEN
11/26/2013

SAM H HAIDAR
11/26/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205776 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD (Proposed Proprietary name, (b) (4) denied by OSE on October 16, 2013) Established/Proper Name: Methotrexate as pre-filled pen injection Dosage Form: Injection, SC Strengths: 50mg/ml solution		
Applicant: Medac Pharma Agent for Applicant (if applicable):		
Date of Application: September 10, 2013 Date of Receipt: September 10, 2013 Date clock started after UN:		
PDUFA Goal Date: July 10, 2014		Action Goal Date (if different):
Filing Date: November 9, 2013		Date of Filing Meeting: November 5, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Rheumatoid Arthritis, JRA, and Psoriasis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 109543 and IND 113735				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Only established name is listed as the proposed proprietary name, (b) (4) was denied by OSE on 10/16/13.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: 3 Years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non-US sites
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it 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 in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC scheduled for April 4, 2014.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE denied sponsor's proposed proprietary name, (b) (4) dated October 16, 2013. Sponsor plans to submit a new proposed proprietary name request.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	October 21, 2013
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	October 21, 2013
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	October 21, 2013
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH consult requests for the device and Human Factor study was placed on October 21, 2013
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 17, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 5, 2013

BLA/NDA/Supp #: NDA 205776

PROPRIETARY NAME: New proposed name will be submitted by the sponsor

ESTABLISHED/PROPER NAME: Methotrexate Injection

DOSAGE FORM/STRENGTH: 50mg/ml pre-filled pen injection

APPLICANT: Medac Pharma, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): RA, JIA, Psoriasis

BACKGROUND: This is a new drug application in which the sponsor is proposing a SC route of administration of methotrexate injection in a pre-filled syringe indicated for RA, JRA, Ps.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sadaf Nabavian	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Janet Maynard		Y
Clinical	Reviewer:	Peter Starke	Y
	TL:	Janet Maynard	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Yongman Kim	Y
	TL:	Joan Buenconsejo	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jane Sohn	Y
	TL:	Timothy Robison	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Arthur Shaw	Y
	TL:	Craig Bertha	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	TBD	
	TL:	TBD	
OSE/DMEPA (proprietary name)	Reviewer:	Teresa McMillan	Y
	TL:	Lubna McMillan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	CDRH (Jackie Ryan and Quying Nguyen)		N
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO The sponsor provided relative BA study of the pen vs. oral and provided a PK bridge of the SC to the PO route.
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: No comments.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If no, explain: this is a 505(2) application</p>	
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: comments to be conveyed to the sponsor in the 74 Day Letter from the DDDP perspective.</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<p><input checked="" type="checkbox"/> YES (OSI consult request placed in DARRTS 11/14/2013) <input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p>

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Comments to be conveyed in the 74 Day letter.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments: comments to be conveyed in the 74 Day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: None at this time.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: SarahYim, M.D., Supervisory Assistant Director, DPARP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
11/21/2013

LADAN JAFARI
11/21/2013



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: November 7, 2013
From: Jacqueline Ryan, GHDB Combination Products TL, WO66, RM 2556
General Hospital Devices Branch, DAGID, ODE, CDRH
To: Sadaf Nabavian, Senior Program Manager,
OMPT/CDER/OND/ODEII/DPARP
Subject: CDRH Consult, ICC 1300548, NDA 205776
PFS and Auto injector to deliver Methotrexate, Filing Review Memo

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 205776. The device constituent of this combination product consists of a PFS and Auto injector to deliver Methotrexate. This memo is a filing review.

2. Device Description

The pre-filled pen consists of the following parts:

- 1 ml barrels of neutral, colorless glass (USP Type I) with embedded injection needle protected by a rigid needle shield (syringe barrel with or without graduation)
- plunger stoppers of (b) (4) rubber (Type I rubber stoppers)
- (b) (4) button, upper body, injection spring and plunger rod
- (b) (4) lower body, ring, needle cover spring, needle cover, cam, cap

The primary packaging of the auto-injector pen (Physioject™) is supplied to the manufacturer (b) (4) is the pre-fillable (b) (4) syringe of 1 ml capacity made of a Type I, colorless (b) (4) glass barrel, embedded with a stainless steel injection needle, protected by a rigid needle shield, and (b) (4) rubber plunger stopper (Type I).

The manufactured pre-filled syringe is assembled into a device for a pre-filled pen forming a complete system for self-administration.

The pre-filled pen is supplied to the patient completely assembled with the pre-filled syringe which forms a single integral product that is not reusable; it is discarded in its entirety after a single subcutaneous use. The pre-filled pen does not have any fluid path components and does not have any contact with the drug product solution contained in the pre-filled syringe.

The pre-filled pen is activated by pressing the button which automatically pushes the needle forward and delivers the solution. Once the device is removed from the injection site, the needle cover automatically moves down over the needle for safe disposal.

The proposed drug/device combination product includes a range of ten different filling volumes, each having an identical composition of 50 mg/ml. The following filling volumes are intended for registration:

- 0.15 ml pre-filled pen containing 7.5 mg methotrexate
- 0.20 ml pre-filled pen containing 10 mg methotrexate
- 0.25 ml pre-filled pen containing 12.5 mg methotrexate
- 0.30 ml pre-filled pen containing 15 mg methotrexate
- 0.35 ml pre-filled pen containing 17.5 mg methotrexate
- 0.40 ml pre-filled pen containing 20 mg methotrexate
- 0.45 ml pre-filled pen containing 22.5 mg methotrexate
- 0.50 ml pre-filled pen containing 25 mg methotrexate
- 0.55 ml pre-filled pen containing 27.5 mg methotrexate
- 0.60 ml pre-filled pen containing 30 mg methotrexate

(b) (4)



Figure 3.2.P.7-1: Illustration of the Pre-Filled Pen (Exemplary Version)



3. Documents Reviewed

NDA 205776, 3.2.P.3.5, 3.2.P.7

MAF (b) (4)

MAF (b) (4)

4. CDRH Review and Comments

A letter authorizing FDA to reference DMF No. (b) (4) is provided in Module 1.4.2. Additionally, a technical dossier from (b) (4) for the (b) (4) syringe is provided.

The (b) (4) syringe is composed of two main parts:

- (b) (4) 1 mL Long Syringe Barrel with 27 Gauge ½ IN (b) (4) Needle and Rigid Needle Shield (RNS), (b) (4) (Rubber Manufacturers DMF No. (b) (4)). A letter authorizing FDA to reference DMF No. (b) (4) is provided in Module 1.4.2.
- (b) (4) 1 mL Long Plunger Stopper, (b) (4) Black (Rubber Manufacturers DMF No. (b) (4)). A letter authorizing FDA to reference DMF No. (b) (4) is provided in Module 1.4.2.

(b) (4) holds a device master file (MAF No. (b) (4)) BD Physioject™ device. A letter authorizing FDA to reference MAF No. (b) (4) is provided in Module 1.4.2. Additionally, a technical dossier from (b) (4) for the Physioject™ device is provided.

Reviewer's Comment:

All relevant LOA for device components/ constituents have been provided.

Safety Features

The syringe's needle is covered with a shield until the patient removes the cap of the auto-injector by pulling it straight off. Once the injection is completed, the auto-injector is pulled straight out of the skin and the needle cover automatically moves down over the needle, locking into place and protecting the needle from body contact. Details regarding the safety features are provided in the technical dossier for the BD Physioject™ device.

Reviewer's Comment:

(b) (4)
We will review the MAF to see if this testing is provided.

Human Factor Design Considerations

Human factor design considerations and supporting studies for the auto-injector were conducted by (b) (4). Details regarding the studies are provided in the technical dossier from (b) (4) for the Physioject™ device.

Reviewer's Comment:

These studies will be reviewed by CDRH-ODE Human Factors Team.

Biocompatibility

BD Physioject™ is classified as a surface contacting device (contacting skin) with limited exposure (< 24 hours) per Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing. Testing has been conducted on the dermal contact components of the device for cytotoxicity, irritation and sensitization. The [Biocompatibility/Toxicology Summary](#) issued by (b) (4) is provided.

Reviewer's Comment:

The description of the test articles is adequate and the test reports are provided.

Dose Accuracy of the Pre-Filled Auto-Injector

BD Physioject™ is a single use, disposable auto-injector, designed to enable self-injection of an entire dose of drug product from a pre-filled glass syringe with attached needle in a single injection. It does not enable the adjustment of the dose. The auto-injector does not have any fluid path components and does not have any contact with the drug within the syringe.

For the drug/device combination product (methotrexate 50 mg/ml solution for injection, pre-filled pen), dose accuracy has been shown using the range of volumes intended for all of the proposed strengths (7.5 mg to 30 mg of methotrexate) from the final auto-injector pen. Partial use of the pre-filled pen is not intended since the entire contents of the pre-filled syringe are administered in one subcutaneous injection. There is no risk of overdosing or underdosing. The full study report is provided in

“Determination of the Dose Accuracy of MTX pre-filled pens (50 mg/mL) from the 10 produced dosage volumes in the range between 7.5 and 30 mg”
([Report No. 2011/042/QEN-R](#)).

Reviewer’s Comment:

The pens were tested for dose accuracy under standard conditions for the filling volumes intended for registration.

Additionally, dose accuracy according to ISO 11608-1 with preconditioning was performed by the MAF holder and test methods, summaries and reports and included in MAF (b) (4)

Depth and Route of Injection

A clinical trial was conducted by (b) (4) in accordance with Good Clinical Practices to evaluate the injected volume in the subcutaneous tissue with the Physioject™ handled by subjects (healthy volunteers) using an instruction for use, as compared to the conventional technique (healthcare practitioners with the pre-filled syringe not equipped with auto-injector). Injections were performed at the abdomen and the thigh, with the auto-injector equipped with the pre-filled syringe or with the pre-filled syringe as alone. The mean fluid depot depth was statistically not different between the auto-injector (8.2 mm; SD: 2.5) and the prefilled syringe as alone (8.3 mm; SD: 2.2). The details regarding the study are provided in the excerpt from the technical dossier for the BD Physioject™ device.

The results of the study are considered representative for Methotrexate 50 mg/ml Pre-filled Pen since the injection depth is controlled by functionality of the Physioject™

Reviewer’s Comment:

This study with additional documentation of exposed needle length may be adequate to assure appropriate depth of penetration.

Shelf-life and Expiration Dating

The stability data for Methotrexate 50 mg/ml Pre-filled Pen is provided in [Module 3.2.P.8](#).

Sterilization Methods

The primary packaging materials (syringe barrels and plunger stoppers) are delivered sterilized by the manufacturers. Information regarding sterilization is provided in the DMF No. (b) (4) for the (b) (4) syringe.

Reviewer’s Comment:

Sterilization of the device components is reviewed by CDRH. However, as the sterility of the final finished combination product is tested and reviewed by CDER, we will defer final sterility issues to CDER.

Simulated Shipping

The performance testing of shipping units for MTX Pen follows the ASTM standard "Standard Practice for Performance Testing of Shipping Containers and Systems (Designation 04169-09)".

Reviewer's Comment:

Shipping tests were conducted according to ASTM 4169 which is a CDRH recognized standard.

5. CDRH Recommendation

The CDRH ODE Engineering filing review has not indentified any issues that would preclude filing of the NDA.

Digital Signature Concurrence Table	
Reviewer Sign-Off Jacqueline Ryan	
Branch Chief Sign-Off Mary Brooks-Acting Branch Chief- GHDB	

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
11/08/2013