CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205776Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205776/000	Sponsor:	MEDAC PHARMA INC
Org. Code:	570		50 DIVISION ST STE 206
	5		SOMERVILLE, NJ 08876
Date:	10-SEP-2013	Brand Name:	METHOTREXATE 50 MG/ML SOLUTION FOR INJEC
PDUFA Date:	10-JUL-2014	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	11-MAY-2014	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; METHOTREXATE; 50MG

FDA Contacts:	A. SHAW	Prod Qual Reviewer		3017961460
	Y. LIU	Product Quality PM		3017961926
	S. NABAVIAN	Regulatory Project Mgr	(HFD-570)	3017962777
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 08-JUL-2014	by T. SHARP	()	3017963208
	PENDING	on 21-NOV-2013	by EES_PROD		
	PENDING	on 30-SEP-2013	by EES_PROD		
	PENDING	on 30-SEP-2013	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
Dmf No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE PACKAGER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-SEP-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN:	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	DEVICE KIT ASSEMBLER	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** **FEI:** 3009238374		
	ONCOTEC PHARMA PRODUKTION GMBH AM PHARMAPARK		
	DESSAU ROSSLAU, SACHSEN-ANHALT, GERMANY		
DUNS No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

MARY GRACE LUBAO
07/21/2014

Chemistry Review Cover Sheet

NDA 205776
Rasuvo® (methotrexate) injection for subcutaneous use
Arthur B. Shaw, Ph.D.
ONDQA/DNDQIII/DPARP

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Chemistry Review Data Sheet

1. NDA 205776
2. REVIEW #1
3. REVIEW DATE: June 5, 2014
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) reviewed/Communications	Document Date	Comment
Original	9/10/2013	
CDRH Intercenter Combo Consult	10/16/2013	Request to determine if (b) (4) device assembly site, needs inspection
CMC Filing review	10/21/2013	Fileable
CDRH Intercenter Combo Consult	10/21/2013	Review Device
CDRH Consult Review	11/08/2013	Filing review
Filing Letter	11/22/3013	Request for placebo sample, stability data plots, notification about possible expiry date effect of unknown impurity at RRT (b) (4) sterility validation.
Response to IR	1/15/2014	Response to Filing letter
CMC IR	1/17/2014	Request SAS transport files for stability
Response to IR	1/23/2014	Response to 1/17 IR letter
Stat Consult request	1/30/2014	Request evaluation of stability data
Stat Consult review	3/19/2014	Recommend expiry of 17 months based on unknown Impurity at RRT (b) (4)
CMC/Device IR	04/04/2014	Request info about sharps protection of device
Response to IR	4/8/2014	Response to 4/04/2014 letter
CMC/Device IR	4/11/2014	Request more info about sharps protection of device
Response to IR	4/17/2014	Response to 4/11/2014 letter
Consult review CDRH	05/02/2014	Memo to file Original email (10/02/2014) Consult review regarding CDRH compliance for facility in Germany
CMC/Device IR	05/02/2014	See 05/02/2014 Consult review
CMC/Device IR	05/08/2014	Request info about dose accuracy testing
Response to IR	05/9/2014	Response to 5/08/2014
CMC/Device IR	05/12/2014	Request more info about dose accuracy testing
Response to IR	5/16/2014	Response to 05/02/2014 CDRH Compliance IR Letter
CMC IR Letter	05/22/2014	Request info on Container integrity testing.

Response to IR	5/23/2014	Response to 05/12/2014 Letter
Response to IR	5/29/2014	Response to 5/22/2014 IR Letter
Pharm/tox Consult request	05/30/2014	Request evaluation of leachables
Pharm/tox Consult review	05/30/2014	Leachables acceptable
CMC IR	05/30/2014	Request info on stability of test samples
Microbiology review	06/02/2014	Acceptable
CDRH review	06/05/2014	Acceptable
Response to IR	06/04/2014	Response to 5/30/2014 IR.

7. NAME & ADDRESS OF APPLICANT:

Applicant:	Medac Pharm Inc
Address	29 N. Wacker Drive Suite 704 Chicago, IL 60606
Contact Person	Terri Shoemaker
Telephone	312-854-0500
Email	tshoemaker@medacpharma.com
Agent	B&H Consulting Services, Inc.
Address	50 Division Street, Suite 206 Somerville, NJ 08876
Contact Person	Stephanie Pierson
Telephone:	908-704-1691 x288
Email	spierson@bhconsultingservices.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): methotrexate
c) Code Name/# N/A
d) Chem. Type/Submission Priority
   - Chem. Type: 5
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: folate analog metabolic inhibitor
11. DOSAGE FORM: Solution; injection

12. STRENGTH/POTENCY: 50 mg/mL

Volume (mL)	mg
0.15	7.5
0.20	10
0.25	12.5
0.30	15
0.35	17.5
0.40	20
0.45	22.5
0.50	25
0.55	27.5
0.60	30

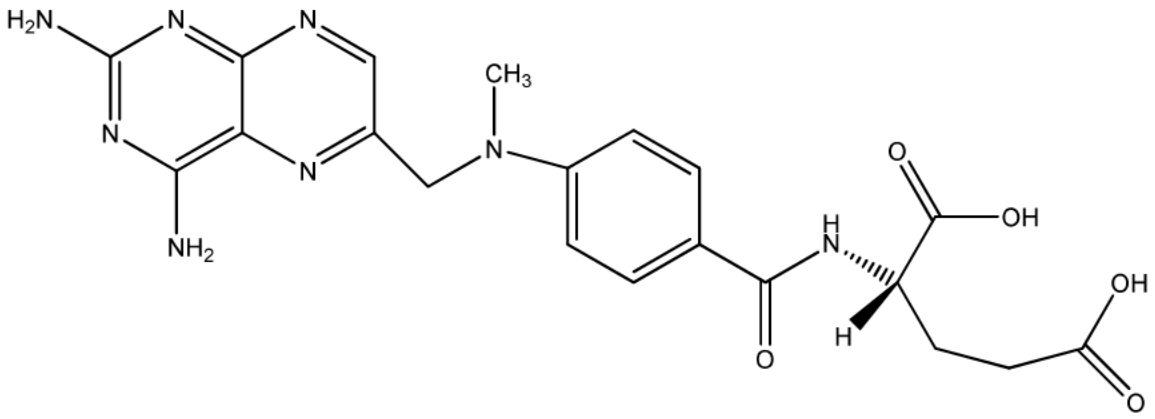
13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

l-Glutamic acid, N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-;



$C_{20}H_{22}N_8O_5$

MW= 454.44

CAS RN N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-(+)-glutamic acid (IUPAC, CAS)

N-[p-[(2,4-diamino-6-pteridinylmethyl)methylamino]benzoyl]-L-(+)-glutamic acid (WHO)

4-amino-10-methylpteroyl-glutamic acid

4-amino-10-methylfolic acid

CAS Registry Number:

59-05-2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Holder	DMF Subject	Item reviewed	LOA Date	Review Date	Reviewer
[redacted] (b) (4)				05/28/2013	5/16/2014	A.Shaw
				05/10/2012	07/22/2013	A.Shaw
				3/22/2013	2/13/2014	A.Shaw
				8/306/2013	2/03/2014	D.Miller

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109543	Development of drug/device combination for arthritis
IND	113755	Development of drug/device combination for psoriasis

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS:

	RECOMMENDATION	**DATE**	**REVIEWER**
EES	Pending		N/A
EA	Categorical Exclusion granted	No review needed	N/A
Microbiology	Acceptable	06/02/2014	Robert Mello
Statistics	Recommend 17 month expiry	03/19/2014	Xiaoyo Dong
Device	Acceptable	06/02/104	Keith Marin
Methods Validation	Not necessary		N/A
Pharm/tox Leachables	Acceptable	05/30/2014	Jane Sohn

.

The Chemistry Review for NDA NUMBER

- ## Recommendations

A. Recommendation and Conclusion on Approvability: Approvable pending completion of satisfactory inspections.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

- ## Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Methotrexate is a yellow to orange, crystalline powder, insoluble in water. It was first approved as a treatment for cancer in 1959 and is cytotoxic, which requires care in handling. There are a number of approved tablets and injections using methotrexate and the indication has been expanded to include treatment of forms of arthritis and psoriasis. The current application is a 505(b)(2). The CMC information for methotrexate is covered in DMF (b) (4) which has been reviewed many times and has been found acceptable. A recent amendment contains a number of changes in the manufacturing which have been reviewed and found acceptable. The specifications and testing for the drug substance are provided in the NDA, both in terms of COAs from the supplier and in terms of complete testing by the manufacturer of the drug product. The testing conforms to both the USP and the Ph.Eur. All process-related impurities are well-controlled and degradation is minimal. Note that the major degradant, (b) (4) and has no additional toxicity. The applicant has proposed a reduced testing program for release of the drug substance by the drug product manufacturer after the first commercial batches. This is acceptable.

2. Drug Product

The drug product is formulated by (b) (4) No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is (b) (4) into glass syringes and closed with a plunger with a rubber stopper. The safety of leachables that have been observed from the packaging components in direct contact with the drug product was evaluated by the Pharm/Tox staff and found to be acceptable. The preparation, including sterilization, of the syringes and the plunger are covered in DMFs which have been reviewed by the Microbiology Staff and found acceptable. The sterility aspects of the drug product manufacturing have been reviewed by the Microbiology Staff and found acceptable. The drug is formulated at one strength (50 mg/mL) to be delivered at a 10 different fixed volumes to achieve different strengths to be delivered to the patients.

Volume (mL)	Mg
0.15	7.5
0.20	10
0.25	12.5
0.30	15
0.35	17.5
0.40	20
0.45	22.5
0.50	25
0.55	27.5
0.60	30

The drug product specifications are adequate to support release of the drug. However an unidentified impurity at RRT = (b) (4) min increases steadily on storage at (b) (4) eported in the application. The Agency's statistical analysis shows that the upper 95% Confidence Limit for this impurity exceeds the acceptance criterion of (b) (4) at 17 months. This will be the recommended expiration date.

The pre-filled syringes (PFS) are loaded manually into a custom device, covered by a device master file. The syringe inside the device is the to-be-marketed product, a drug-device combination. The device incorporates a number of features. It is designed to deliver a fixed volume with no measuring by the patient. The needle is completely covered when not in use both before and after activation of the device so that the chances of accidental injection or exposure to the needle are minimized. When the device is activated the force of delivery is controlled by a spring in the device, not the patient. The needle is the correct length to ensure that the drug is administered subcutaneously. After the device is actuated there is no drug remaining in the syringe so that safe disposal is not an issue. The device performance was found acceptable the CDRH reviewer.

B. Description of How the Drug Product is Intended to be Used

The drug is intended to be used by patients with rheumatoid arthritis including polyarticular-course, juvenile rheumatoid arthritis, and moderate to severe psoriasis on a weekly basis after instruction by a doctor or other health care professional. The drug is injected subcutaneously in a fixed dose. Different strengths (same concentration, different fills) are available to permit a range of doses.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance and drug product are manufactured and controlled adequately to deliver the labeled dose of the drug.

- **Administrative**

See DARRTS signatures and cc's

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/s/

ARTHUR B SHAW
06/05/2014

CRAIG M BERTHA
06/09/2014
signing for E. Duffy, PhD

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 205776

2. Drug Name: methotrexate injection (single-use prefilled autoinjector); Strengths: 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, and 30 mg doses from appropriate corresponding prefilled solution (0.15-0.60 mL) with concentration of 50 mg methotrexate per mL

Route of administration: subcutaneous (or intramuscular as well for polyarticular-course juvenille idiopathic arthritis)

Indications: Adult rheumatoid arthritis (RA), polyarticular-course juvenile arthritis, and psoriasis

Pharmacological Class: Methotrexate is a folic acid antagonist that is said to act by competitive inhibition of the enzyme dihydrofolate reductase, inhibiting DNA synthesis and leading to immunosuppressive and anti-inflammatory effects

Applicant: Medac Pharma Inc. (Chicago, IL 60606)

3. RECEIVED DATE: 9/10/2013

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

	TYPE	HOLDER	ITEM	LOA DATE	COMMENTS
(b) (4)			(b) (4)	5/24/2013	this is a Device Master File (not a DMF)
	II			6/04/2013	This DMF was reviewed on 7/22/2013 and

					found to be adequate for an injection drug product.
(b) (4)	III		(b) (4)	5/30/2013	
	III			5/28/2013	
	III			5/22/2013	

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	X	There is no statistical analysis of the stability data provided in support of the shelf life even though impurities are observed to increase with time and assay decreases with time. See below for more detailed discussion of stability data and expiry.
Clin Pharm	☐	X	
EES	X	☐	EES entered on 30-SEP-2013
Pharm/Tox	X	☐	There is no apparent reason to consult the pharm/tox team regarding the drug substance, which complies with the USP monograph acceptance criteria for impurities. However, the USP monograph for methotrexate injection does not include tests or acceptance criteria for impurities. Thus, it is appropriate to ask the pharm/tox team to evaluate the acceptance criteria for the (b) (4) impurity (a degradant) that exceeds the ICH Q3B qualification threshold of 0.5%. The pharm/tox team should be consulted regarding the toxicological assessment of leachables that has been provided in P.7.
Methods Validation	☐	☐	This will be a review decision, if there is a special reason to have the FDA St. Louis laboratory perform validation or verification on one or more methods. Methotrexate is not an NME.
EA	☐	X	The categorical exclusion claim is to be evaluated by the reviewer (contact Dr. Ranaan Bloom, OPS). The applicant claims in 1.12.14 that action on this NDA

			would not increase the use of the active moiety. No extraordinary circumstances are known to the applicant.
New Drug Micro	X	☐	
CDRH	X	☐	The appropriate CDRH group should be asked to review the device master file (in addition to any consult from the clinical team regarding human factors studies) that supports this application. The reviewer should contact the DPARP PM as the consults may be routed through the Office of Combination Products.
Other	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		109543	methotrexate pre-filled syringe
IND		113735	methotrexate solution, injection

d. Previous Communications with the Applicant to note (if any)*:

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
meeting minutes	07/17/2013	IND 109543	includes CMC related issues
meeting responses	12/27/2011	IND 109543	includes additional CMC related comments
pre-NDA meeting minutes	11/8/10	IND 109543	includes CMC comments

*See also Module 1.6 for other correspondence, including pre-IDE meeting minutes.

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes (minor):		
• Provide placebo samples of the drug product. • Provide plots of drug product stability data on a parameter basis for each strength and storage condition.		

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	1. Biopharmaceutics is not included in this review.

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☐	☐	Biopharmaceutics is not included in this review.

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	X	
Combination Products	X	☐	
Nanotechnology	☐	X	
PAT	☐	X	
QbD Elements	☐	X	
SPOTS	☐	X	

Is a team review recommended?

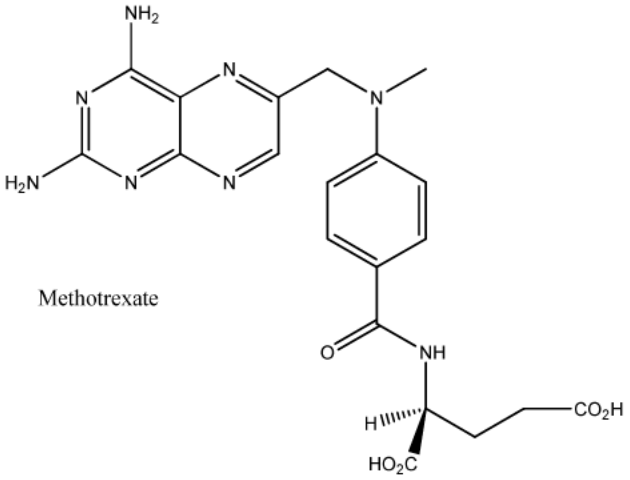
Yes	No	Suggested expertise for team
☐	X	

CMC Summary:
Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Drug substance:

- The referenced DMF [redacted] (b) (4) was previously reviewed and found adequate on 7/22/2013 for methotrexate drug substance for use in an injection drug product.
- The drug substance solid state form is said to "resemble" the crystal hydrate form [redacted] (b) (4)
- Methotrexate is:



Methotrexate

(*S*)-2-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzamido)pentanedioic acid

Molecular formula: $C_{20}H_{22}N_8O_5$
Molecular mass: 454.45 g/mole

Drug product:

- The drug formulation is a sterile solution that does not include a preservative. The sterilization is done by [(b) (4)]
- The drug product is for a single use and delivers varying amounts of a single formulation to provide the proposed multiple strengths (0.15 – 0.60 mL): 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, and 30 mg (as methotrexate [(b) (4)]) per injection.
- The single formulation is [(b) (4)] with sodium chloride and the pH is adjusted to a target of [(b) (4)] methotrexate, which is practically insoluble in water)
- Proposed dose is once weekly by subcutaneous [(b) (4)] injection.

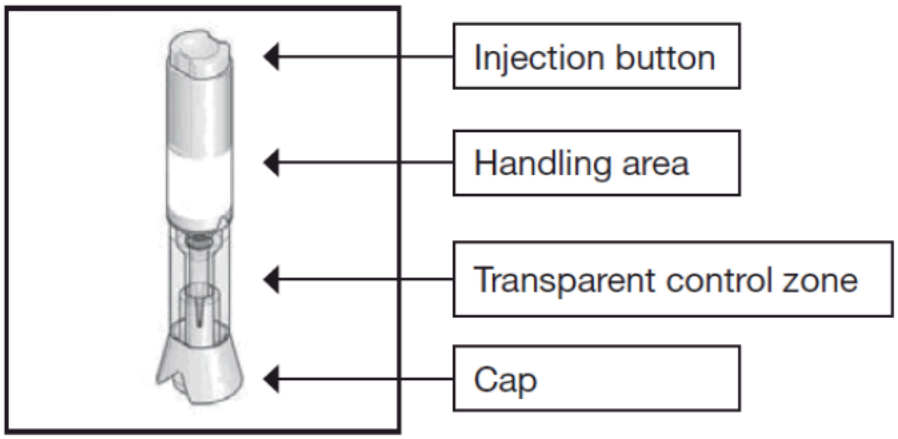
Drug product container closure system (pre-filled injector device):

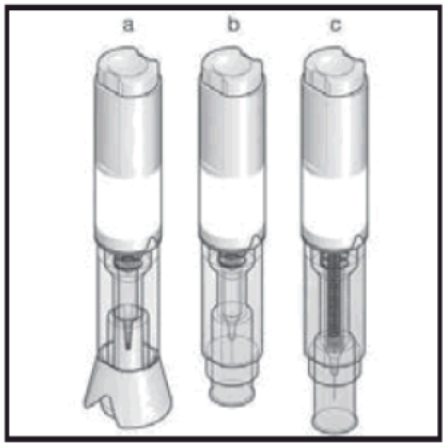
- The device consists of:
  - 1 mL USP Type I glass syringe barrel with embedded needle with a shield
  - [(b) (4)] rubber plunger
  - [(b) (4)] button, upper body, injection spring, plunger rod
  - [(b) (4)] lower body, ring, needle cover spring, needle cover, cam, cap

Drawing of device:

Start of Applicant Material

[(b) (4)] **Pre-filled Pen components:**





a) Pre-filled pen **with cap before injection**

b) Pre-filled pen **after cap removal before injection**

c) Pre-filled pen **after injection**

End of Applicant Material

The application reports on the following drug product leachables from the syringe components after 6 months of storage at 40°C/75%RH: (b) (4) Although, with the exception of the (b) (4) the levels of these leachables reported are low, it is recommended that the reviewer consult with the pharmacology/toxicology team to determine whether an official consult is necessary for evaluation of the toxicological report in P.7.

The to-be-marketed drug product was used in a relative bioavailability/pharmacokinetic (PK) study in healthy subjects (MC-MTX.14/PK) and in a handling/usability/PK/safety study in RA patients (MC-MTX.15/HF), as well as in other trials the applicant considers to be supportive. The drug product is said to be currently marketed in Germany and other European countries.

The specification for the drug indicates for the description parameter that the solution is clear to yellow-brown in color, but this is only confirmed visually. As such, it is appropriate that the applicant have a quantitative test to assess color with a limit that is based on product with an acceptable impurity profile. The specification does not currently include a parameter for leachables. Depending on the toxicological evaluation of the leachables report, there may be a need to request the applicant to monitor for various leachables and include acceptance criteria in the specification. Although there is a test for container content of formulation for each of the strengths, and a corresponding functional test for the auto-injector performed manually, there is no specific test for the dispensed volume. Based on development [e.g., "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," "Dye Tests on syringes filled with Methotrexate 50 mg/mL batch released and assembled in (b) (4)"] and other pertinent data (e.g., results of functional test

in stability studies), it is recommended that the reviewer consider the possibility that additional testing for dispensed volume (for each or bracketing strengths) is appropriate to include in the specification in addition to the proposed functionality test in conjunction with fill volume. Other test parameters included in the specification appear to be consistent with what the ICH Q6A guideline recommends for parenteral drug products.

Typically, the Office strongly recommends that all applications, not just those for new molecular entities and associated drug products, follow the ICH Q1A guideline and include 12 months of long term stability data. In this particular case, even though the applicant indicates that they have followed Q1A, there are only 9 months of long term stability data provided for three bulk batches of formulation (split amongst the highest and lowest strengths, i.e., auto-injectors delivering 7.5 and 30.0 mg of methotrexate) of drug product in the proposed auto-injector. These three bulk batches are also used to fill intermediate strength devices, but with only a single bulk batch used per strength (refer to table P.8.1-2) This would appear to be a reasonable bracketing scheme for stability testing. It is noted by the applicant that the primary stability batches were placed on stability in August 2012 whereas the bulk formulation was actually filled into prefilled syringes in May 2012. Thus, the initial time-point is really a 3 month post-manufacturing time-point. Considering this, and the supportive data (*vide infra*), the provision of only 9 months of long term stability data in the submission is not considered a filing issue. However, as a result of the limited nature of these primary stability data, the expiration dating period for the drug product may be limited, dependent on the stability data profile and evaluation, particularly with regard to the increase in the (b) (4) degradant levels.

In addition to the primary stability data, the application includes "supportive" stability data collected on pre-filled syringes (as opposed to the to-be-marketed pre-filled pens or auto-injectors). The applicant indicates in P.2.2 that medac GmbH has developed both pre-filled syringes and pre-filled pens (auto-injectors) of the 50 mg/mL methrotrexate solution. They further state that the container closure system (CCS) for the pre-filled syringes, for which supportive stability data are provided, are "comparable with the primary packaging material (pre-filled syringe) proposed for the US pre-filled pen." Thus, the CCS is comparable, not identical. The formulation is said to be identical in composition, however. In P.8.1 the applicant states that "the manufacturing process of the pre-filled pen for EU market is similar to that used for the US market." As the CCS and manufacturing is stated to be "comparable" and "similar," respectively, and not identical, it is recommended that the reviewer compare the accelerated stability for the primary versus the supportive drug product to gauge comparability and decide how pertinent the supportive data are to the assessment of the drug product stability and appropriate expiration dating period.

Refer also to the notes in the filing table later in this review.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.
The drug substance and product are manufactured by other companies and there are other firms involved in testing for both.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	X	☐	☐	The application is organized in the CTD format.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
3.	Are all the pages in the CMC section legible?	X	☐	☐	For those pages examined for this IQA/filing review.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☐	☐	☐	With regard to items/issues discussed at meetings, the adequacy of the proposed specification for the combination drug product is considered a review decision, as will be the importance of the supportive stability data.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	This readiness for inspection is indicated in check boxes on Form FDA 356h and its continuation sheets, for each facility.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	A categorical exclusion is claimed based on 21 CFR 25.31(a). They claim that there are no extraordinary circumstances.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	☐	*See table on cover page.* There are references to a MAF for the device, and DMFs for the drug substance, syringe and rubber components.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☐	X	☐	DMF (b) (4) is referenced.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☐	X	☐	See comment for 13. above.
15.	Does the section contain information on impurities?	X	☐	☐	Some information is provided as well as a reference to DMF (b) (4)
16.	Does the section contain information regarding the characterization of the DS?	X	☐	☐	By reference to comparison to a USP reference standard.
17.	Does the section contain controls for the DS?	X	☐	☐	DMF (b) (4) is referenced for current specifications of drug substance at (b) (4) (drug substance manufacturer). Information is provided for specifications and analytical methods used by Oncotec upon receipt of the drug substance.
18.	Has stability data and analysis been provided for the drug substance?	☐	X	☐	DMF (b) (4) is referenced for all drug substance stability data.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	X	☐	None mentioned in the NDA, however most information for the drug substance is provided by reference to DMF (b) (4)
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	See response for 19. above.
21.	Does the section contain container and closure information?	☐	X	☐	Only very briefly summarized, details are referenced to DMF (b) (4)

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	☐	All excipients are compendial and certificates of analyses are provided.
23.	Does the section contain information on composition?	X	☐	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	Note that the analysis performed for the pre-filled syringes is done as per the specification in P.3.3 and the methods in P.5.2 (validation data in P.5.3).
26.	Is there a batch production record and a proposed master batch record?	X	☐	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	Section P.2.2 provides information regarding the development of the formulation but no formulations other than that proposed for marketing are provided.
28.	Have any biowaivers been requested?	☐	X	☐	None could be found
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	Information is in P.7. Note that in addition, the autoinjector device is referenced to MAF (b) (4)
30.	Does the section contain controls of the final drug product?	X	☐	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	See the more detailed discussion above in section on critical issues and complexities.

32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	X	☐	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	X	☐	☐	The MV "package" is a page of references to information elsewhere in the NDA. It is missing a link to the drug product formulation section, but this is easily found in P.1.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	X	☐	☐	See P.2.5, P.3.3, and P.3.5

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	X	☐	☐	
37.	Have the immediate container and carton labels been provided?	X	☐	☐	
38.	Does section contain tradename and established name?	X	☐	☐	The trademark is (b) (4) and the established name proposed is methotrexate injection.

J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	

40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	☐	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X	☐	☐	Requesting placebo drug product and stability data plots (see comments on p. 4).

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, Ph.D., Acting CMC Lead (10/16/2013)
Prasad Peri, Ph.D., Branch Chief

{See appended electronic signature page}

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

/s/

CRAIG M BERTHA
10/16/2013

PRASAD PERI
10/21/2013
I concur