CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205776Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

NDA NO.	205776
CONSULT REQUESTED BY ONDQA	January 30, 2014
ESTABLISHED NAME	methotrexate
TRADE NAME	NA
DOSAGE FORM	solution for injection
STRENGTHS	50 mg/ml
ROUTE OF ADMINISTRATION	for subcutaneous use
INDICATION	Treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and psoriasis
APPLICANT	MEDAC PHARMA INC
REVIEW FINISHED	March 19, 2014
STATISTICAL REVIEWER	Xiaoyu Dong
PROJECT MANAGER	Youbang Liu
ONDQA REVIEWER	Arthur Shaw

_____

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Concur: _____

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I. EXECUTIVE SUMMARY

I.1. CONCLUSIONS AND RECOMMENDATIONS

As a result of the statistical evaluation of the 12-months primary long-term stability data of the drug product, it is concluded that the proposed shelf-life of (b) (4) is not supported mostly due to the failure of Unspecified Impurity at approx. RRT (b) (4) with an estimated shelf life of 17 months. In addition, Container Content data at intermediate strengths only support a much shorter shelf life. This may be caused by the limited data points available for analysis. Please note, the analysis of Container Content is based on the original data scale and specifications.

We recommend sponsor submit more stability data to have a more reliable estimated shelf life.

I.2. STATISTICAL ISSUES AND FINDINGS

We evaluated the sponsor's stability analysis and performed independent statistical analyses of 12-months long-term stability data of primary stability batches. Our statistical findings and analysis results are presented below.

- The sponsor's stability analysis method is inappropriate for the following reasons:
  - The sponsor did not perform data analysis for Container Content.
  - For other testing parameters, the sponsor performed the regression analysis on the average value of all 14 batches against time. Such an average method is incorrect because it ignores the inter-batch variability. Instead, stability analysis should be conducted using indiviudal batch values.
  - The sponsor used 99% confidence limit to estimate the shelf life. Based on ICH Q1A, 95% confidence limit should be used. In addition, the sponsor used two-sided 99% confidince limits for all stability testing parameters. This is incorrect because if the acceptance criterion is one-sided, then one-sided confidence limit should be applied.
  - For Unspecified Impurity at approx. RRT (b) (4) the sponsor compared the projected (model predicted) value, which is the estimate of the true mean stability value, with the acceptance criterion. This is incorrect because confidence limit of the true mean value, not the estimated mean value, should be used to evaluate the shelf life.
  - It is not clear on what basis the sponsor concluded that "*there is a greater than 99% probability that both* (b) (4) *and Total Related Compounds*

will not exceed their respective limits at [redacted] *under long-term storage conditions*".

- In addition, the sponsor did not include the interaction between Batch and Time in their two-way ANOVA analysis. As a result, the sponsor's pooling analysis is invalid.

- Our analyses of primary stability data summarized in Table 1 show the shelf life of [redacted] is not supported, especially for Unspecified Impurity at approx. RRT [redacted] and Container Content:
  - The estimated shelf life from Unspecified Impurity at approx. RRT [redacted] stability data is 17 months.
  - Applying by-strength analysis, 95% confidence limits of Container Content at 7.5 mg and 30 mg strengths are within the acceptance criteria during [redacted] At other intermediate strengths, except at 17.5 mg strength, the stability data do not support the shelf life of [redacted] This may be caused by the limited data points at intermediate strengths considering only up to 12-months data from one batch were available for the analysis. In addition, we may need to take the assay variability into account.
  - 95% Confidence limits of Assay, [redacted] and Total Related Compound are within their acceptance criteria during the proposed shelf life of [redacted]

Table 1: Estimated Shelf Life from Long-term Stability Data based on FDA Statistics Reviewer's Analysis

Testing Parameters	Acceptance Criteria		Estimated Shelf Life
Assay	[redacted] LC		[redacted]
[redacted]	NMT [redacted]		
Total Related Compounds	NMT [redacted]		
Unspecified Impurity at approx. RRT [redacted]	NMT [redacted]		
Container Content	Strength = 7.5 mg	0.15 to 0.19 ml	
	Strength = 10 mg	0.20 to 0.24 ml	
	Strength = 12.5 mg	0.25 to 0.29 ml	
	Strength = 15 mg	0.30 to 0.34 ml	
	Strength = 17.5 mg	0.35 to 0.39 ml	
	Strength = 20 mg	0.40 to 0.44 ml	
	Strength = 22.5 mg	0.45 to 0.49 ml	
	Strength = 25 mg	0.50 to 0.54 ml	
	Strength = 27.5 mg	0.55 to 0.59 ml	
	Strength = 30 mg	0.60 to 0.64 ml	
[redacted]			

II. INDRODUCTION

The sponsor proposed a shelf life of (b) (4) for Methotrexate 50 mg/mL Pre-filled Pen. To support this proposal, the sponsor analyzed the ongoing long-term stability data up to 12 months of primary batches for quantitative stability test in Table 2. The total batch number from all strengths is 14. Their analysis report can be found in 3.2.P.8.1 "Stability Summary and Conclusion".

Table 2 – List of Stability Tests Analyzed by the Sponsor

Strength	Batch No.	Tests
7.5 mg	1205017A 1205018C 1205019A	Assay; Container Content; (b) (4) Total Related Compound; Unspecified Impurity at approx. RRT (b) (4)
10 mg	1205017F	Assay; Container Content; (b) (4) Total Related Compound;
12.5 mg	1205017B	
15 mg	1205018D	
17.5 mg	1205019B	
20 mg	1205019D	
22.5 mg	1205018B	
25 mg	1205017C	
27.5 mg	1205017D	
30 mg	1205017E 1205018A 1205019C	Assay; Container Content; (b) (4) Total Related Compound; Unspecified Impurity at approx. RRT (b) (4)

To evaluate the validity of proposed shelf life of (b) (4) FDA Statistics Reviewer conducted an independent statistical analysis of 12 months primary long-term stability data at multiple strengths. The conclusions are summarized in Section I and detailed analyses are shown in Section VI in this review.

III. SPONSOR'S ANALYSIS

To support the proposed shelf life of (b) (4) for the drug product, the sponsor applied the linear regression model on the average value of all 14 batches for Assay, (b) (4) Unspecified Impurity at approx. RRT (b) (4) and Total Related Compounds. The sponsor's analysis each testing parameter is summarized below.

III.1 Container Content

MEDAC did not perform any statistical analysis for Container Content stability. MEDAC concluded that "*the data clearly show that all results are above the minimum content and that there is no loss or increase in the contents of any of the containers over time*".

III.2 Assay

The 12-month long-term stability data of Assay were analyzed by pooling the data of all 14 batches. In addition, MEDAC computed the average value of 14 batches at each time point and performed linear regression on those five average values in Table 3.Based on the results in Table 4, MEDAC concluded that "there is no significant loss of assay over time" based on the non-significance of the slope obtained from the linear regression.

Table 3 : Table 5 of MEDAC's Primary Stability Data – Statistical Analysis

Table 5: Average of Primary Stability Assay Results Over Time (25° ± 2°C/60% ± 5% RH)

Time Point (Months)	0	3	6	9	12
Average (n = 14)	101.9	99.9	100.6	100.8	101.8

Table 4 : Table 8 of MEDAC's Primary Stability Data – Statistical Analysis

Table 8: Regression Coefficients and Confidence Limits of Average Primary Assay Results (25° ± 2°C/60% ± 5% RH)

	Coefficients	Standard Error	t Stat	P-Value	Lower 95%	Upper 95%	Lower 99.0%	Upper 99.0%
Intercept	101.1988	0.80419	125.8385	6.31E-05	97.7386	104.6590	93.2173	109.1803
Slope	-0.09323	0.14328	-0.65071	0.58200	-0.70975	0.5232	-1.5153	1.3288

III.3 (b) (4)

MEDAC applied linear regression analysis similar to the method used for Assay. Their estimated shelf life is (b) (4) based on the upper limit of the two-sided 99% confidence interval of the mean stability as shown in Table 5. Their stability plot is shown in Figure 1.

Table 5 : Table 16 in MEDAC's Primary Stability Data – Statistical Analysis

Table 16: Estimated Expiration Period based on [redacted] Results (25° ± 2°C/60% ± 5% RH)

Parameter	Expiration Period (Months)
Upper 99% Confidence	[redacted]
Projected	
Lower 99% Confidence	

Figure 1 : Figure 1 in MEDAC's Primary Stability Data – Statistical Analysis

Figure 1: Projections for [redacted] Stability (25° ± 2°C/60% ± 5% RH)

[redacted]

III.4 Unspecified Impurity at approx. RRT [redacted]

MEDAC applied linear regression analysis similar to the method used for Assay. The obtained 99% confident limit is out of the acceptance criterion of NMT [redacted]% prior to [redacted] The sponsor used the projected value, which is the mean stability value, not the confidence limit to support the proposed shelf life of [redacted] Their project value is the red line in Figure 2.

Figure 2 : Figure 2 in MEDAC's Primary Stability Data – Statistical Analysis

Figure 2: Projections for Unspecified Impurity at approx. RRT (b) (4) Stability (25° ± 2°C/60% ± 5% RH)

III.5 Total Related Compounds

Again, MEDAC applied linear regression analysis similar to the method used for Assay. Their estimated shelf life is (b) (4) based on the upper limit of the two-sided 99% confidence interval of the mean stability as shown in **Table 6**. Their stability plot is shown in Figure 3.

Table 6 : Table 31 in MEDAC's Primary Stability Data – Statistical Analysis

Table 31: Estimated Expiration Period based on Total Related Compounds Results (25° ± 2°C/60% ± 5% RH)

Parameter	Expiration Period (Months)
Upper 99% Confidence	(b) (4)
Projected	
Lower 99% Confidence	

Figure 3 : Figure 3 in MEDAC's Primary Stability Data – Statistical Analysis

Figure 3: Projections for Total Related Compounds Stability (25° ± 2°C/60% ± 5% RH)

IV. FDA STATISTICS REVIEWER'S ANALYSIS

We performed independent statistical analyses of 12-months long-term stability data of primary batches. The summarized results are provided in Table 1 in Section I. The detailed analysis for each testing parameter is presented below.

IV.1 Container Content

Due to different acceptance criterion among the strengths, we performed by-strength analysis for Container Content long-term stability data. Our results are summarized as:

- At 7.5 mg and 30 mg strengths, 95% confidence limits of Container Content are within the acceptance criteria during (b) (4)
- At other strengths, except at 17.5 mg, the stability data do not support the proposed shelf life of (b) (4) This may be caused by the limited data points at intermediate strengths considering only up to 12 months data from

one batch were available for the analysis. In addition, we may need to take the assay variability into account. The stability plots are provided in Figure 4 below.

Table 7: Estimated Shelf Life from Long-term Container Content Stability Data based on FDA Statistics Reviewer's Analysis

Testing Parameters	Acceptance Criteria		Estimated Shelf Life
Container Content	Strength = 7.5 mg	0.15 to 0.19 ml	(b) (4)
	Strength = 10 mg	0.20 to 0.24 ml	
	Strength = 12.5 mg	0.25 to 0.29 ml	
	Strength = 15 mg	0.30 to 0.34 ml	
	Strength = 17.5 mg	0.35 to 0.39 ml	
	Strength = 20 mg	0.40 to 0.44 ml	
	Strength = 22.5 mg	0.45 to 0.49 ml	
	Strength = 25 mg	0.50 to 0.54 ml	
	Strength = 27.5 mg	0.55 to 0.59 ml	
	Strength = 30 mg	0.60 to 0.64 ml	

(b) (4)

Figure 4 : Stability Plots of Container Content at Intermediate Strengths from FDA Statistics Reviewer's Analysis

Primary Stability Analysis of Content (ml) at 25C and 60 RH at Strength = 10 mg

Batch=1205017F

(b) (4)

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(b) (4)

IV.2 Assay

Long-term stability data of Assay support the proposed shelf life of (b) (4)

The pooling analysis in Table 8 shows that the interaction between batch and time is non-significant with a p-value of 0.9752, and the batch effect is significant with a p-value of 0.0780. Thus the slope of various batches can be pooled. The stability analysis results are summarized in Table 9. As it shows, the change of Assay over time is 0.0243%LC per month with a non-significant p-value of 0.5172. All lower and upper 95% confidence limits are within the acceptance criterion of (b) (4) %LC.

Table 8: Pooling Analysis of Assay Stability Data based on FDA Statistics Reviewer's Analysis

Source	DF	Type I SS	Mean Square	F Value	Pr > F
month	1	(b) (4)			
BATCH	13				
month*BATCH	13				

Table 9: Primary Stability Results of Assay Data based on FDA Statistics Reviewer's Analysis (AC = (b) (4) %LC)

Batch	Strength (mg)	Bulk Batch Volume [L]	Est. Mean at t = 0 (%)	Slope (% per Mon)		95% Confidence Limit at (b) (4)		Est. Shelf Life (Month)
				Estimate	P-value	Lower	Upper	
1205017A	7.5	57	101.4	0.0243	0.5172			(b) (4)
1205017B	12.5		101.3					
1205017C	25		100.8					
1205017D	27.5		100.7					
1205017E	30		100.4					
1205017F	10		101.8					
1205018A	30	65	101.9					
1205018B	22.5		99.01					
1205018C	7.5		99.77					
1205018D	15		99.77					
1205019A	7.5	64	101.7					
1205019B	17.5		101.4					
1205019C	30		100.9					
1205019D	20		101.1					

IV.3 (b) (4)

Long-term stability data of (b) (4) support the proposed shelf life of (b) (4)

The pooling analysis in Table 10 shows that the interaction between batch and time and batch effect are all significant with a p-value of 0.0031 and <0.0001, respectively. Thus by-batch analysis was performed. The stability analysis results are summarized in Table 11. As it shows, the change over time is significant for all batches. All the upper 95% confidence limits at (b) (4) are less than the acceptance criterion of NMT (b) (4)%. Thus, the proposed shelf life of (b) (4) is supported by (b) (4) data.

Table 10: Pooling Analysis of (b) (4) based on FDA Statistics Reviewer's Analysis

Source	DF	Type I SS	Mean Square	F Value	Pr > F
month	1				(b) (4)
BATCH	13				
month*BATCH	13				

Table 11: Primary Stability Results of [redacted] based on FDA Statistics Reviewer's Analysis (AC = NMT [redacted] %)

Batch	Strength (mg)	Bulk Batch Volume [L]	Est. Mean at t = 0 (%)	Slope (% per Mon)		Upper 95% Confidence Limit at [redacted]	Est. Shelf Life (Month)
				Estimate	P-value		
1205017A	7.5	57	0.1960	0.0723	0.0001	[redacted]	[redacted]
1205017B	12.5		0.1594	0.0812	<.0001		
1205017C	25		0.1714	0.0825	<0.0001		
1205017D	27.5		0.1592	0.0836	<0.0001		
1205017E	30		0.1814	0.0809	<0.0001		
1205017F	10		0.1720	0.0796	<.0001		
1205018A	30	65	0.2080	0.0827	<0.0001		
1205018B	22.5		0.1714	0.0832	<0.0001		
1205018C	7.5		0.1954	0.0785	<0.0001		
1205018D	15		0.1744	0.0815	<0.0001		
1205019A	7.5	64	0.2134	0.0775	<0.0001		
1205019B	17.5		0.1862	0.0826	<0.0001		
1205019C	30		0.1940	0.0829	<0.0001		
1205019D	20		0.1918	0.0817	<0.0001		

IV.4 Unspecified Impurity at approx. RRT [redacted]

Long-term stability data of Unspecified Impurity at approx. RRT [redacted] do not support the proposed shelf life of [redacted] The estimated shelf life is 17 months based on the 12-months data.

Analysis was performed at Strength = 7.5 mg and 30mg separately. The stability analysis results are summarized in Table 12. As it shows, the change over time is significant for all batches. All the upper 95% confidence limits at [redacted] except Batch 1205017E, are out of the acceptance criterion of NMT [redacted] %. The estimated shelf life is 17 months. The stability plots are provided in Figure 5 below.

Table 12: Primary Stability Results of Unspecified Impurities at approx. RRT (b) (4) based on FDA Statistics Reviewer's Analysis (AC = NMT (b) (4) %)

Batch	Strength (mg)	Est. Mean at t = 0 (%)	Slope (% per Mon)		Upper 95% Confidence Limit at (b) (4)	Est. Shelf Life (Month)
			Estimate	P-value		
1205017A	7.5	0.0516	0.0058	0.0004	(b) (4)	
1205018C	7.5	0.0502	0.0076	0.0002		
1205019A	7.5	0.0588	0.0074	0.0003		
1205017E	30	0.0376	0.0054	<0.0001		
1205018A	30	0.0668				
1205019C	30	0.0540				

Figure 5 : Stability Plots of Unspecified Impurities at approx. RRT (b) (4) from FDA Statistics Reviewer's Analysis

Primary Stability Analysis of Unspecified Impurity at RRT (b) (4) (%) at 25C and 60 RH
Prefilled Pen=7.5 Batch=1205017A

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IV.5 Total Related Compounds

Long-term stability data of Total Related Compounds support the proposed shelf life of (b) (4)

The pooling analysis in Table 13 shows that the interaction between batch and time and batch effect are all significant with a p-value of 0.0006 and <0.0001 respectively. Thus by-batch analysis was performed.

The stability analysis results are summarized in Table 14. As it shows, the change of Total Related Compounds over time is significant for all batches. All the upper 95% confidence limits at (b) (4) are less than the acceptance criterion of NMT (b) (4)%. Thus, the proposed shelf life of (b) (4) is supported by this parameter.

Table 13: Pooling Analysis of Total Related Compounds based on FDA Statistics Reviewer's Analysis

Source	DF	Type I SS	Mean Square	F Value	Pr > F
month	1	(b) (4)			
BATCH	13				
month*BATCH	13				

Table 14: Primary Stability Results of Total Related Compounds based on FDA Statistics Reviewer's Analysis (AC = NMT (b) (4) %)

Batch	Strength (mg)	Bulk Batch Volume [L]	Est. Mean at t = 0 (%)	Slope (% per Mon)		Upper 95% Confidence Limit at (b) (4)	Est. Shelf Life (Month)
				Estimate	P-value		
1205017A	7.5	57	0.3972	0.0829	0.0006	(b) (4)	
1205017B	12.5		0.2610	0.1023	<.0001		
1205017C	25		0.2616	0.1045	<0.0001		
1205017D	27.5		0.2556	0.1048	<0.0001		
1205017E	30		0.3724	0.0922	0.0004		
1205017F	10		0.2736	0.1011	<.0001		
1205018A	30	65	0.4242	0.1013	0.0001		
1205018B	22.5		0.2596	0.1088	<0.0001		
1205018C	7.5		0.3892	0.0956	0.0002		
1205018D	15		0.2668	0.1054	<0.0001		
1205019A	7.5	64	0.4424	0.0939	0.0002		
1205019B	17.5		0.3016	0.1078	0.0001		
1205019C	30		0.4256	0.0991	0.0002		
1205019D	20		0.2944	0.1079	0.0001		

IV.6 Conclusions

As a result of the statistical evaluation of the 12-months primary long-term stability data of the drug product, it is concluded that the proposed shelf-life of (b) (4) is not supported mostly due to the failure of Unspecified Impurity at approx. RRT (b) (4) with estimated shelf life of 17 months. In addition, Container Content data at intermediate strengths only support a much shorter shelf life. This may be caused by the limited data points available at those strengths. Please note, the analysis of Container Content is based on the original data scale and specifications

We recommend sponsor submit more stability data to have a more reliable estimated shelf life.

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/s/

XIAOYU DONG

03/19/2014

This is a replacement of previous review. A few typos are fixed and more stability plots are added. Please use this review as the final version.

MEIYU SHEN

03/19/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: NDA 205776 **Applicant: Medac Pharma, Inc.** **Stamp Date: 9/10/2013**

Drug Name: Methotrexate **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			x	No clinical efficacy data for review
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			x	No clinical efficacy data for review
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			x	No clinical efficacy data for review
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			x	No clinical efficacy data for review
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	No clinical efficacy data for review
Appropriate references for novel statistical methodology (if present) are included.			x	No clinical efficacy data for review
Safety data organized to permit analyses across clinical trials	x			Assessed by

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

in the NDA/BLA.				clinical team
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			x	No clinical efficacy data for review

Yongman Kim	11/19/2013
Reviewing Statistician	Date
Joan Buenconsejo	11/19/2013
Supervisor/Team Leader	Date

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/s/

YONGMAN KIM
11/19/2013

JOAN K BUENCONSEJO
11/20/2013
I concur