CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205931Orig1s000

STATISTICAL REVIEW(S)

NDA #: 205931/ 0000(505 (b) (2) submission)
Drug Name: Doxycycline Hyclate Tablets USP
Applicant: Aqua Pharmaceuticals
Indication: Treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
Submission Date: September 25, 2013
Filing Meeting Date: November 19, 2013

This 505(b) (2) NDA application for doxycycline hyclate 75 mg and dual scored 150 mg tablets relies on FDA's previous findings of safety and effectiveness for the reference drug, Vibra-Tabs (doxycycline hyclate tablets 100 mg).

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The applicant is relying on previous findings of the efficacy and safety for the listed drug. However, safety assessments of adverse events were made for three pharmacokinetic studies (see Table 1) conducted to demonstrate bioequivalence of the applicant's Doxycycline Hyclate to listed drugs.

Table 1: Summary of Clinical Bioequivalence Studies

Study No.	Study Objectives	Test Product(s) Dosing Regimen Route of Administration	Number of Subjects	Treatment Duration
11060203	Evaluate bioavailability of new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 300 mg Dose Oral	26 (24 included in statistical analysis)	Single Dose
11060204	Evaluate bioavailability of new dosage strength of drug product under fasted and non- fasted conditions.	Doxycycline Hyclate Tablets, 150 mg (unscored) 150 mg Dose Oral	26 (25 included in statistical analysis)	Single Dose
11060201	Evaluate bioavailability of a new dosage strength of drug product relative to an equivalent dose of the RLD under fasted conditions.[a]	Doxycycline Hyclate Capsules, 150 mg300 mg Dose Oral	26 (22 included in statistical analysis)	Single Dose

The applicant reported that there were no deaths or serious adverse events reported in these limited studies. See Clinical review for the safety assessments.

The applicant has concluded that that three bioequivalence studies described in Table 1 have demonstrated bioequivalence of 150 mg tablets to the RLD [West-ward (ANDA 065095), 100 mg tablets].

Statistical comments:

This submission did not require statistical review since there were no clinical studies provided in the submission.

Mushfiqur Rashid, Ph.D.
Statistical reviewer

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/s/

MUSHFIQUR M RASHID
06/24/2014

THAMBAN I VALAPPIL
06/24/2014

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	205931
DATE RECEIVED BY ONDQA:	April 29, 2014
DATE OF DATA RECEIVED:	May 15, 2014
DATE OF SPONSOR'S ADDITIONAL ANALYSIS REPORT RECEIVED:	June 12, 2014 June 17, 2014
T-CON WITH THE SPONSOR	June 18, 2014
DRUG NAME:	Doxycycline Hyclate Tablets
DOSAGE FORM:	Tablets
STRENGTH	75 mg, 150 mg
INDICATION:	A tetracycline-class antimicrobial indicated for various infections. For a more detailed indication, see the reference listed drug (RLD) labeling.
SPONSOR:	AQUA PHARMACEUTICALS LLC
REVIEW FINIHSED:	June 18, 2014
NAME OF STATISTICAL REVIEWER:	Xiaoyu (Cassie) Dong, Ph.D.
NAME OF PROJECT MANAGER:	Navi Bhandari
CMC REVIEWER	Shrikant Pagay

_____
Reviewer: Xiaoyu Dong, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____
Meiyu Shen, Acting TL, Mathematical Statistician, CDER/OTS/OB/DB VI
Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI

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TABLE OF CONTENTS

I. EXECUTIVE SUMMARY *5*

II. STATISTICAL ISSUES AND FINDINGS **5**

III. SPONOR'S ANALYSIS *12*

IV. ATTACHMENT (STABILITY PLOTS) *15*

IV.1 Long-term Stability Plots of Assay **15**

IV.2 Long-term Stability Plots of (b) (4) **20**

IV.3 Long-term Stability Plots of (b) (4) **24**

IV.4 Long-term Stability Plots of (b) (4) **29**

IV.5 Long-term Stability Plots of Total Related Substance **33**

IV.6 Long-term Stability Plots of (b) (4) **37**

Reference ID: 3527136

List of Tables

Table 1: Available Long-Term Stability Data 5
Table 2: Predicted Mean Value and 95% Confidence Limits at 24 Months at 75 mg under the Long-term Storage Condition (Spec. = Specification, LCL = Lower Confidence Limit, UCL = Upper Confidence Limit, Pred. = Predicted Mean Value, Est. = Estimated) 10
Table 3: Predicted Mean Value and 95% Confidence Limits at 24 Months at 150 mg under the Long-term Storage Condition (Spec. = Specification, LCL = Lower Confidence Limit, UCL = Upper Confidence Limit, Pred. = Predicted Mean Value, Est. = Estimated) 11
Table 4: Predicted Mean Value and 95% Confidence Limits at 24 Months at 150 mg Dual Scored under the Long-term Storage Condition (Spec. = Specification, LCL = Lower Confidence Limit, UCL = Upper Confidence Limit, Pred. = Predicted Mean Value, Est. = Estimated) ... 12
Table 5 – Sponsor's Stability Analysis Results based on 12 months long-term Stability Data..... 13
Table 6 – Sponsor's Stability Analysis Results based on 12 months long-term Stability Data 13

Reference ID: 3527136

List of Figures

Figure 1 : Stability Plots of Assay for Failed Lot at 150 mg Dual Scored from FDA Statistical Reviewer's Analysis (the shaded band is the 95% confidence interval of the mean response, the dashed and solid lines are the mean response from regression analysis; the circle and cross points are the observed stability data; Spec. = (b) (4) %LC) 7
Figure 2 : Stability Plots of (b) (4) for Failed Lots at 75 mg, 150 mg and 150 mg Dual Scored from FDA Statistical Reviewer's Analysis (the upper shaded band limit is the upper 95% confidence limit of the mean response, the dashed and solid lines are the mean response from regression analysis; the circle and cross points are the observed stability data; Spec = NMT (b) (4) %) 7
Figure 3 – Sponsor's Stability Plot for Assay at 150 mg Dual Scored using Pooling Analysis..... 13
Figure 4 – Sponsor's Stability Plot for (b) (4) at 150 mg Dual Scored using Pooling Analysis..... 14

Reference ID: 3527136

I. EXECUTIVE SUMMARY

We performed statistical analysis of 24 months and 12 months long-term stability data with multiple packaging types and multiple strengths. Our conclusions on the shelf life are summarized in Table A below. Please note, the shelf life estimation using 12 month stability data is performed under the assumption that the stability time trend beyond 12 months (last observed time) remains the same.

Table A – FDA Statistics Reviewer's Estimated Shelf Life for each Package and Strength using Long-term Stability Data

	75 mg Tablets	150 mg Tablets	150 mg Dual Scored Tablets
(b) (4)			
60cc Bottle			
(b) (4) **Blister**			
(b) (4)			

In summary, the proposed shelf life of (b) (4) months is not supported by the long-term stability data.

II. STATISTICAL ISSUES AND FINDINGS

Statistics reviewer received the following stability data as listed in Table 1 from the sponsor on May 15, 2014.

Table 1: Available Long-Term Stability Data

Package	75 mg	150 mg	150 mg Dual Scored
(b) (4)			
60cc Bottle	24 months	24 months	12 months
(b) (4) **Blister**	12 months		12 months
(b) (4)			

The sponsor pooled all batches from different packages together for each strength, and concluded that the proposed shelf life of (b) (4) months is supported. Such poolabilty analysis is inappropriate for their submitted data due to the following reasons.

- ICH guidance is applicable for at least three batches for each configuration. However, the sponsor only has two batches for each package; Thus, the pooling test (p-value based) is not directly applicable for the current data;

Reference ID: 3527136

- The p-value based pooling method itself has limitations. More variability of the data, more likely we would have a non-significant p-value to conclude pooling is OK. The "failed" test parameter (b) (4) consistently show large variability within 12 month for all the strengths, thus it is easier to have a large p-value and pool the data;
- Because (b) (4) content shows less stable over the 12 months in Blister package than that in Bottle package for all the strengths. Thus, stability data of (b) (4) should not be pooled across all packages. In addition, there is inconsistent data variability among different batches.

Considering the above data issues, we should apply by-batch analysis which is a more conservative method in order to assess the worst case scenario, especially when by-batch and pooling method get very different results.

Based on our independent data analyses, the lots with an estimated shelf life shorter than 24 months are plotted in **Figure 1** and **Figure 2**. The detailed results are summarized in Table 2, Table 3, and Table 4 at each combination of strength and package. In these tables, those lots with the estimated shelf life less than 24 months are marked in red. All stability plots are listed in the Attachment at the end. Please note, we conducted by-strength and by-package analysis. In this way, we would be able to assess the worst case scanario of shelf life estimation.

- As **Figure 1** shows, At 150 mg Dual Scored pacakged with Blisters (b) (4), the 12 months long-term stability data of Assay (Lot 1202624 C) do not support the proposed shelf life of (b) (4) months because the lower 95% confidence limits at (b) (4) months is (b) (4) %LC (see Table 4), which is lower than the lower specification limit of (b) (4)

- As **Figure 2** shows, the upper 95% confidence limit of (b) (4) are out of specification for all strengths at the end of (b) (4) months. Thus, the proposed shelf life of (b) (4) months is not supported. Please refer to Table 2, Table 3, and Table 4 for detailed values of the confidence limits at the end of (b) (4) months and the estimated shelf life for specific packaging type.

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/s/

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06/18/2014

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