CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

sNDA Number	205637
Drug Name	Bunavail (buprenorphine and naloxone) buccal film
Indication(s)	Maintenance Treatment of Opioid Dependence
Applicant	BioDelivery Sciences International
Date(s)	Date Received: March 14, 2014 Completion Date: April 10, 2014
Biometrics Division	VI
Statistical Reviewers	Sutan Wu, Ph.D.
Concurring Reviewer	Yi Tsong, Ph.D.
Chemistry Reviewer	Arthur B Shaw, Ph.D. (OPS/ONDQA)
Project Manager	Luz E Rivera (OPS/ONDQA)
Distribution: OTS/OB Y. Tsong, L. Patrician, OPS/ONDQA A. Shaw, L. Rivera	

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1. EXECUTIVE SUMMARY

The purpose of this review is to provide statistical assessments on sponsor's 12-month stability analysis for long-term storage condition, so that the FDA chemistry reviewer can have a formal decision on the proposed shelf life for this Bunavail (bi-layer) product.

There are 4 different strengths in provided data: [redacted] 2.1/0.35, 4.2/0.70, and 6.3/1.04 mg Buprenorphine/Naloxone (Bup/Nal). Each strength has 3 nested batches. For each batch, the available stability data are: 1) 6 month 40°C/75%RH (accelerated condition); 2) 6 month 30°C/65%RH (intermediate condition); and 3) 12 month 25°C/60%RH (long-term condition). The stability parameters to be analyzed are: Bupernorphine (BUP) assay, Naloxone (NX) assay and [redacted] (unidentified impurity).

Per the discussion with FDA chemistry reviewer, the stability analysis should be done by each strength based on the nature of this product. The sponsor followed ICH Q1E stability analysis guidance to analyze the data, but did not follow the shelf life Decision Tree in ICH Q1E (see Appendix A) to propose the corresponding shelf life.

The reviewers verified the sponsor's analyses and re-proposed the shelf life according to ICH Q1E (see Appendix A). The conclusions are listed below:

- [redacted] (impurity)

  No extrapolation time is allowed beyond the last observation time (12 month), because the observed changes were deemed as significant change by FDA chemistry reviewer at both the accelerated condition and the intermediate condition.

  The proposed shelf life is 12 month, for all four strengths.

- Bupernorphine (BUP) assay and Naloxone (NX) assay (potency assays)

  From the available data, the significant scientific changes were observed at both the accelerated condition and the intermediate condition. However, the significant changes for the two assays at the accelerated condition were decrease, while the significant changes at the intermediate condition were increase except for one instance. Per the discussion with FDA scientist, it is reasonable to conclude that extrapolation is permitted up to 1.5 times the length of real time data but limited to 6 months.

  The proposed shelf life for NX assay is [redacted] month, for all four strengths.

  The proposed shelf life for BUP assay is [redacted] month, for strengths [redacted], 4.2/0.70, and 6.3/1.04 mg. The proposed shelf life is [redacted] month, for strength, 2.1/0.35 mg.

Combining all the results, the shelf life permitted for this Bunavail (bi-layer) product is 12 month by ICH Q1E.

2. INTRODUCTION

The purpose of this review is to provide statistical assessments on sponsor's 12-month stability analysis for long-term storage condition, so that the FDA chemistry reviewer can have a formal decision on the proposed shelf life for this Bunavail (bi-layer) product.

There are 4 different strengths in provided data: (b) (4) 2.1/0.35, 4.2/0.70, and 6.3/1.04 mg Buprenorphine/Naloxone (Bup/Nal). Each strength has 3 nested batches. For each batch, the available stability data are: 1) 6 month 40°C/75%RH (accelerated condition); 2) 6 month 30°C/65%RH (intermediate condition); and 3) 12 month 25°C/60%RH (long-term condition). The stability parameters to be analyzed are: Bupernorphine (BUP) assay, Naloxone (NX) assay and (b) (4) (impurity).

The statistical reviewer received the consulting request on March 14, 2014. Per the discussion with FDA chemistry reviewer on April 3, this stability analysis will be evaluated by each strength because of the nature of the product.

3. Sponsor'e Submissions

For each stability parameters, the regression analysis was performed and the model building strategy from the sponsor was presented in Table 1. The one-sided 95% lower confidence bound was applied to two potency assays: BUP assay and NX assay. The corresponding spec limits for BUP assay and NX assay from sponsor are (b) (4) % (label claim). The one-sided 95% upper confidence bound was applied (b) (4), the unidentified impurity.

Based on the regression analysis, the sponsor proposed (b) (4) month shelf life for (b) (4), and (b) (4) month for BUP assay and NX assay.

Table 1: Sponsor's Model Building Strategy

Model Name	Terms in Model	p-value for Bt term. Are Batch Slopes Poolable?	p-value for B term. Are Batch Intercepts Poolable?	Next Step or Final Model
1	B t Bt	>0.25**	NA	Go to Model 2
		≤ 0.25*	NA	Model 1 is Final Model
2	B t	NA	> 0.25**	Model 3 is Final Model
		NA	≤ 0.25*	Model 2 is Final Model
3	t	NA	NA	

NA = not applicable.
* Answer to question is no, so poolability is not allowed and this term is included in final reduced model.
** Answer to question is yes, so poolability is allowed and this term is not included in final reduced model.

**Source: Table 5 in sponsor's 12 month stability analysis report*

The reviewer has following comments regards to the sponsor's approach:

- *The provided model building strategy follows the ICH Q1E guidance, but the proposed shelf life didn't.*

  For [redacted], *no extrapolation time is allowed beyond the last observation time (12 month), because the observed changes were deemed as significant change by FDA chemistry reviewer at both the accelerated condition and the intermediate condition.*

  For BUP assay and NX assay, the significant scientific changes were observed at the accelerated condition. Therefore, only 1.5 times the length of real time data extrapolation is allowed but limited to 6 months.

- *Because increase changes were observed for two potency assays, BUP assay and NX assay, the FDA chemistry reviewer concluded to use 2-sided 95% confidence bounds to evaluate the data. This decision is also supported by the nature of the product that the potency has a chance to be increased* [redacted] *in products.*

- *The spec limits for BUP assay and NX assay are 90% to 110% according to FDA chemistry reviewer and FDA general potency guidance.*

The reviewer's independent analyses, conclusions and recommendations are presented in next section.

4. REVIEWER'S ASSESSMENT

All the analyses are according to ICH Q1E guidance. Per the discussion with FDA chemistry reviewer, the analysis was done by each strength.

4.1 Statistical Evaluation

a) [redacted] **(% w/w, impurity):**

No extrapolation time is allowed beyond the last observation time (12 month), because the observed changes were deemed as significant change by FDA chemistry reviewer at both the accelerated condition and the intermediate condition.

The proposed shelf life is 12 month, for all 4 strengths.

b) BUP assay (sponsor specs: [redacted]**%, FDA specs: 90% -110% (from FDA chemistry reviewer)):**

The significant scientific changes were observed at both the accelerated and the intermediate conditions. However, the significant change at the accelerated condition was a decrease, while the significant change at the intermediate condition was an increase except for one instance.

Per the discussion with FDA scientist, it is reasonable to conclude that extrapolation is permitted up to 1.5 times the length of real time data but limited to 6 months. Table 2 and Table 3 presented the final reduced model and corresponding model estimates. These tables are provided by sponsor and are verified the statistical reviewer.

Table 2: Final Regression Model for BUP Assay

Strength Analyzed	p-value: Are Batch Slopes Poolable?	p-value: Are Batch Intercepts Poolable?	Final Model
(b) (4)			
2.1/0.35 mg Bup/Nal	0.5278**	<.0001*	Model 2:B t/Common Slope, Separate Intercepts
4.2/0.70 mg Bup/Nal	0.5284**	<.0001*	Model 2:B t/Common Slope, Separate Intercepts
6.3/1.04 mg Bup/Nal	0.8246**	0.0254*	Model 2:B t/Common Slope, Separate Intercepts

**Source: Table 9 in sponsor's 12 month stability analysis report, and verified by the stat reviewer*
**B: batch term; t: time term*

Table 3: Final Regression Model Estimates for BUP Assay

Strength Analyzed	Batch	Intercept	Slope (per year)
(b) (4)			
2.1/0.35 mg Bup/Nal	3684238	96.38	5.961
2.1/0.35 mg Bup/Nal	3684239	98.84	5.961
2.1/0.35 mg Bup/Nal	3684240	90.39	5.961
4.2/0.70 mg Bup/Nal	3684242	96.48	2.199
4.2/0.70 mg Bup/Nal	3684243	97.41	2.199
4.2/0.70 mg Bup/Nal	3684244	90.91	2.199
6.3/1.04 mg Bup/Nal	3684245	95.75	2.366
6.3/1.04 mg Bup/Nal	3684246	97.92	2.366
6.3/1.04 mg Bup/Nal	3684247	94.87	2.366

**Source: Table 10 in sponsor's 12 month stability analysis report, and verified by the stat reviewer*

Figure 1 to Figure 4 present the worst case (shelf life) for each strength, respectively. The teal line and the brown line are the two-sided 95% confidence bounds, respectively.

It is clear that the two-sided 95% confidence bounds are within the 90% -110%, FDA proposed specs, at both (b) (4) month and 24 month extrapolation time, for strengths, (b) (4) 4.2/0.70, and 6.3/1.04 mg Bup/Nal. For strength 2.1/0.35 mg Bup/Nal, the upper confidence bound from the worst case (Batch 3684239) exceeds the upper spec 110% at (b) (4) month (see Figure 2).

Therefore, per ICH Q1E, only (b) (4) month shelf life is permitted for strengths, (b) (4), 4.2/0.70, and 6.3/1.04 mg. And (b) (4) month shelf life is permitted for strength, 2.1/0.35 mg. Also note here, the value of BUP assay shows an increase trend for all 4 strengths. (Note: 24 month extrapolation is for the FDA chemistry reviewer's information.)

The worst case (batch 3684236) for stgthc= (b) (4) mg Bup/Nal

(b) (4)

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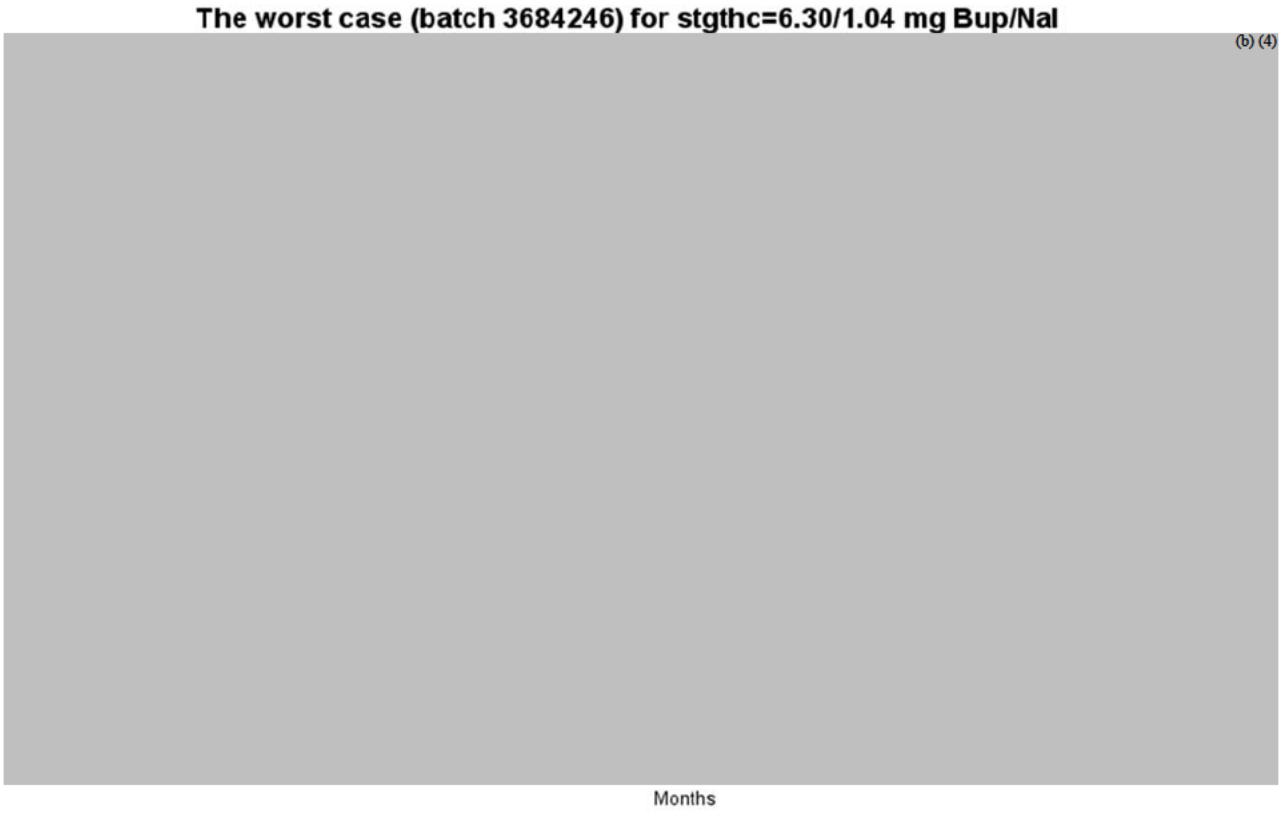

Figure 4: The Worst Case (Batch 3684246) for Strength 6.30/1.04 mg Bup/Nal: the teal line and the brown line are the 2-sided 95% confidence bounds; the red lines are spec limits; the black dots are observed data.

**Note: 24 month extrapolation is only for the FDA chemistry reviewer's information*

c) **NX Assay(sponsor specs: (b) (4) %, FDA specs: 90% -110% (from FDA chemistry reviewer)):**

The significant scientific changes were observed at both the accelerated and the intermediate conditions. However, the significant change at the accelerated condition was a decrease, while the significant change at the intermediate condition was an increase except for one instance.

Per the discussion with FDA scientist, it is reasonable to conclude that extrapolation is permitted up to 1.5 times the length of real time data but limited to 6 months. Table 4 and Table 5 presented the final reduced model and corresponding model estimates. These tables are provided by sponsor and are verified the statistical reviewer.

Table 3: Final Regression Model for NX Assay

Strength Analyzed	p-value: Are Batch Slopes Poolable?	p-value: Are Batch Intercepts Poolable?	Final Model
(b) (4)			
2.1/0.35 mg Bup/Nal	0.5815**	0.6886**	Model 3:t/Common Slope, Common Intercept
4.2/0.70 mg Bup/Nal	0.8928**	0.7988**	Model 3:t/Common Slope, Common Intercept
6.3/1.04 mg Bup/Nal	0.6170**	0.2910**	Model 3:t/Common Slope, Common Intercept

**Source: Table 11 in sponsor's 12 month stability analysis report, and verified by the stat reviewer*
**B: batch term; t: time term*

Table 4: Final Regression Model Estimates for NX Assay

Strength Analyzed	Batch	Intercept	Slope (per year)
(b) (4)			
2.1/0.35 mg Bup/Nal	all	96.20	3.740
4.2/0.70 mg Bup/Nal	all	95.04	0.997
6.3/1.04 mg Bup/Nal	all	95.71	0.427

**Source: Table 12 in sponsor's 12 month stability analysis report, and verified by the stat reviewer*

Figure 5 to Figure 8 present the worst case (shelf life) for each strength, respectively. The teal line and the brown line are the two-sided 95% confidence bounds, respectively. It is clear that the two-sided 95% confidence bounds are within the 90% -110%, FDA proposed specs, at both (b) (4) month and 24 month extrapolation time, for all 4 strengths.

Per ICH Q1E guidance, only (b) (4) month shelf life is permitted. Note that no strong increase or decrease trends were observed for all 4 strengths, except strength, 2.10/0.35 mg Bup/Nal. The data shows an increase trend for strength, 2.10/0.35 mg Bup/Nal. (Note: 24 month extrapolation is for the FDA chemistry reviewer's information.)

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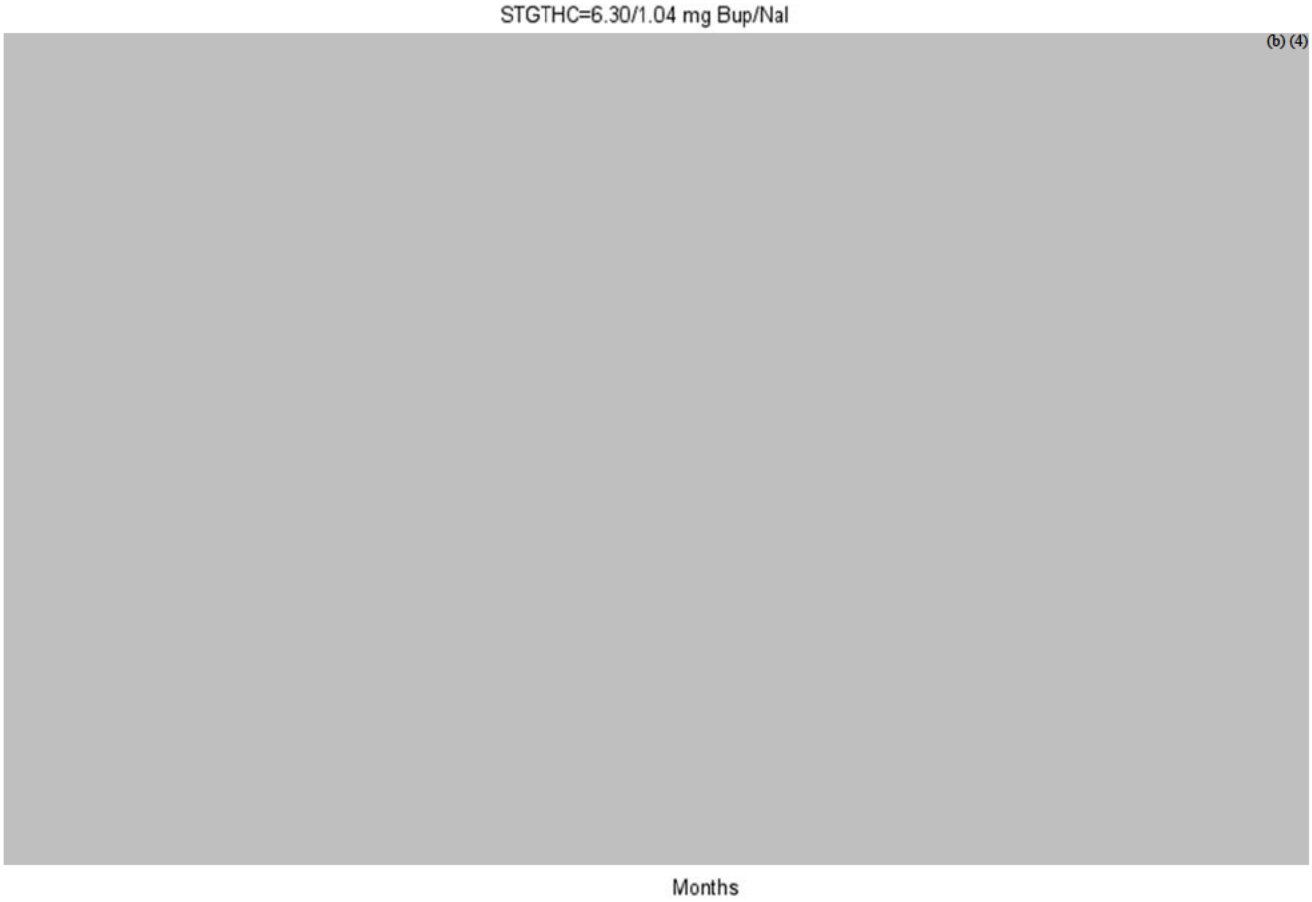


Figure 8: The stability profile (pooled analysis) for Strength 6.30/1.04 mg Bup/Nal: the teal line and the brown line are the 2-sided 95% confidence bounds; the red lines are spec limits; the black dots are observed data.

**Note: 24 month extrapolation is only for the FDA chemistry reviewer's information*

4.2 Conclusions and Recommendations

This 12-month stability analyses were done per ICH Q1E guidance. Please refer to the Statistical Evaluation Section for detailed statistics analyses and results, for each stability parameters.

Here the overall summaries are presented:

a) (b) (4) no extrapolation is allowed and the permitted shelf life is the last observation time, 12 month, for all 4 strengths.

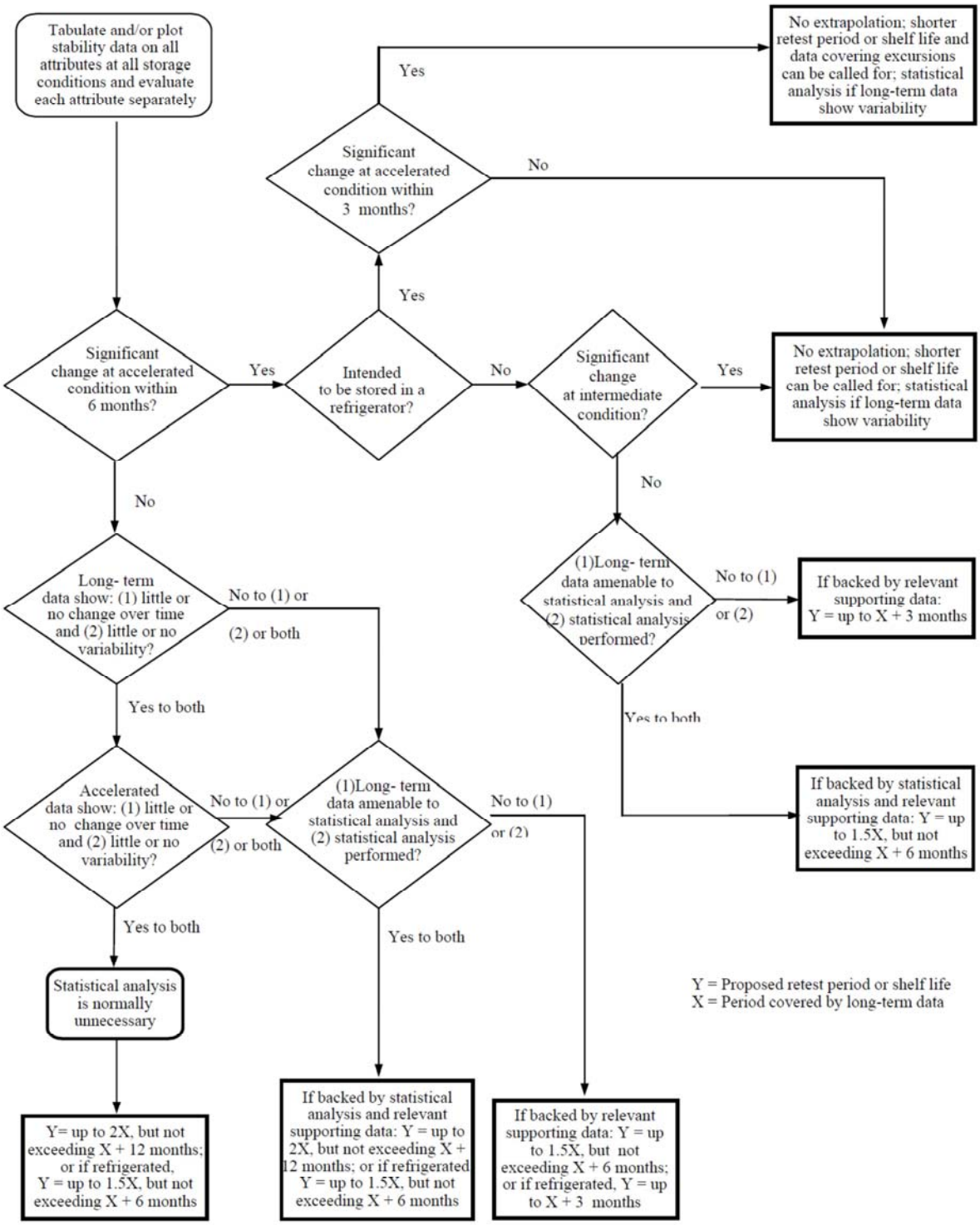
b) BUP assay, (b) (4) month shelf life is permitted for strengths (b) (4) 4.2/0.70, and 6.3/1.04 mg Bup/Nal. For strength 2.1/0.35 mg Bup/Nal, only (b) (4) month shelf life is permitted.

c) NX assay, (b) (4) month shelf life is permitted for all 4 strengths.

Also, the statistical reviewer noted that the change rate (slope estimate) for strength, 2.1/0.35 mg Bup/Nal is 5.961% for Bup assay, and it is 3.740% for NX assay. Both change rates (slope estimate) are much higher than the rates (slope estimate) for other strengths. The observed data also confirmed the same findings (See Figure 2 and Figure 6). All these findings in study suggest that the strength, 2.1/0.35 mg Bup/Nal may have different stability profiles compared to the other 3 strengths, regards to Bup assay and Nal assay, and may require more careful review considerations.

Appendix A: Shelf Life Decision Tree from ICH Q1E

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



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/s/

SUTAN WU
04/11/2014

YI TSONG
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