

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201517Orig1s000

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

NDA Number: 201-517
Drug Name: morphine sulfate oral solution 20mg/mL
Indication(s): Chronic Pain, Opioid
Applicant: Lannett Holdings, Inc.
Date(s): Received on May 5, 2011
Review Priority: Standard
Biometrics Division: VI
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1. EXECUTIVE SUMMARY

This review describes statistical findings on the impurity stability data so that FDA office of New Drug Quality Assessment can make informed decisions on the sponsor's proposal of 18-month shelf life.

The FDA statistician conducted a stability analysis to estimate the shelf life of the impurity of the drug product based on 18-month stability data. The data did not satisfy the batch selection requirement stated in the 2003 FDA Guidance. Only two batches are provided for 30 and 120 mL packages whereas the guidance requires at least three batches for each package configuration.

For a shelf life estimation, two acceptance criteria - (b) (4) - are used. Two different criteria resulted in two different shelf lives. With (b) (4) acceptance criterion, 18-month shelf life is granted. However, only (b) (4) shelf life is granted when (b) (4) acceptance criterion is used. In this case, the sponsor's proposal of 18-month shelf life is not acceptable.

2. INTRODUCTION

This review describes statistical findings on the impurity stability data so that FDA office of New Drug Quality Assessment can make informed decisions on the sponsor's proposal of 18-month shelf life.

The stability parameter of being reviewed is impurity whose acceptance criterion is not more than (NMT) (b) (4). However, the statistical software calculates confidence limits up to 9 decimal places. A shelf life is determined as the time at which the 95 percent one-sided confidence limit for the mean curve intersects the acceptance criterion. In other words, a shelf life is estimated by comparing the confidence limit with the acceptance criterion. Therefore, the values of both confidence limit and the acceptance criterion are to have the same unit for comparability.

The statistical reviewer addressed the issue of difference in unit between the acceptance criterion and the confidence limit in Section 3. The data will be discussed in Section 3.1 and the reviewer's statistical analysis in Section 3.2.

3. REVIEWER'S ASSESSMENT

3.1 Data

The FDA statistical reviewer received the data in MS Excel format (NDA 201517 Stbaility RRT (b) (4)) from FDA project manager. Table 1 displays the summary of the impurity stability data.

Table 1 Impurity Stability Data

| Package | Batch | Available Data |
|---------|---------|----------------|
| 30 mL | 7801003 | 18 months |
| | 8801017 | 18 months |
| 120 mL | 7801005 | 18 months |
| | 8801017 | 18 months |
| 240 mL | 7801005 | 18 months |
| | 8801001 | 18 months |
| | 8801017 | 18 months |

It can be noted that there are only two batches available for 30 and 120 mL packages. FDA Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products (2003)¹ requires providing at least three batches to establish a shelf life applicable to all future batches of the drug product. The data did not satisfy this requirement so that the batch-to-batch variation for 30 and 120 mL packages cannot be assessed properly.

3.2 Statistical Evaluation

¹ This will be referred as 2003 FDA Guidance.

The FDA statistician evaluated the sponsor's 18-month stability data in accordance with the 2003 FDA Guidance. The reviewer conducted ANCOVA analyses to estimate the shelf life of the drug for each package separately using Statistical Analysis Software, SAS.

First, the reviewer performed batch poolability tests. For 30 mL packaging configuration, only slopes are pooled. The fitted regression lines have common slope but different intercepts. For 120 mL, both intercepts and slopes are pooled. The fitted regression lines for two batches are the same. For 240 mL, the batches are not poolable resulting three different fitted regression lines for three batches. The Figure 1 displays the stability data with both the fitted regression lines (solid lines) and one-sided 95% confidence limits of the regression means (dashed lines).

Figure 1 Fitted Regression Lines with 95% One-Sided Confidence Limit

(b) (4)



Second, the reviewer estimated the shelf life by comparing the 95% confidence limits shown above with the acceptance criterion, NMT (b) (4). SAS estimates the confidence limits up to 9 decimal points for precision. Therefore, the reviewer needs to round the confidence limits in order to compare them with the one decimal place long acceptance criterion. The reviewer also rounded the results to two decimal places since the original data are 2 decimal places long, i.e. using (b) (4) as an acceptance criterion. These different criteria lead to different shelf life estimates from the same data. For example, if a batch's the confidence limit at 18 month is (b) (4) 18-month shelf

life is granted when (b) (4) criterion is used. It is because (b) (4) becomes (b) (4) after being rounded to one decimal place. However, 18-month shelf life cannot be granted when (b) (4) criterion is used (see APPENDIX). Table 2 shows three sets of shelf life estimates for three scenarios without rounding; with being rounded to one decimal place, Rounded (b) (4) with being rounded to two decimal places, Rounded (b) (4)

Table 2 Shelf Life Estimation for Impurity

| Package | Batch (Batch Name in Figure 1) | Estimated Regression | | Estimated Shelf Life (Month) | | |
|---------|-----------------------------------|----------------------|------------------|------------------------------|--------------------|--------------------|
| | | Intercept | Slope (b) (4) | Without Rounding | Rounded (b) (4) | Rounded (b) (4) |
| 30 ml | 7801003 (BATCH1) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | 8801017 (BATCH2) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| 120 ml | 7801005 (BATCH1) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | 8801017 (BATCH2) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| 240 ml | 7801005 (BATCH1) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | 8801001 (BATCH2) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | 8801017 (BATCH3) | (b) (4) | (b) (4) | (b) (4) | (b) (4) | (b) (4) |

When (b) (4) acceptance criterion is used, the shortest shelf life among all package configurations is (b) (4) for 30 mL, (b) (4) for 120 mL, and (b) (4) for 240 mL. However, when (b) (4) acceptance criterion is used, all the estimated shelf lives across the package configurations are shorter than (b) (4): (b) (4) for both 30 and 120 mL, and (b) (4) for 240 mL. In latter case, the shelf life is (b) (4), which are shorter than (b) (4) the shelf life proposed by the sponsor. Therefore, which acceptance criterion is used is critical for the shelf life determination.

4. CONCLUSIONS AND RECOMMENDATIONS

The FDA statistician conducted a stability analysis to estimate the shelf life of the impurity of the drug product based on 18-month stability data. Two acceptance criteria - NMT (b) (4) and NMT (b) (4) - are used. Two different criteria led to two different shelf lives. With (b) (4) acceptance criterion, 18-month shelf life is granted. However, only (b) (4) shelf life is granted when (b) (4) acceptance criterion is used. In this case, the sponsor's proposal of 18-month shelf life is not acceptable.

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/s/

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05/13/2011

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