Animal and Plant Health Inspection Service

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Technical Notes Regarding Establishing Control Chart Parameters

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1 Introduction

Veterinary Services Memorandum 800.XX (Draft 440) provides guidance for setting potency specifications for serial release of biological products that are administered to animals. Different options are presented that allow for different methods of establishing potency specifications based on the amount of testing conducted for serial release. Option 3 allows for the possibility of an increment of zero for the potency specification for the mean of 6 vials, but requires monitoring of the potency testing results in time for each serial released to the market. This document describes a monitoring procedure when the degradation is either linear or not able to be distinguished from the expected variance. For nonlinear degradation, please work with CVB on developing a monitoring method. This monitoring method has been designed to detect only the most egregious changes in the potency degradation profile. It has been designed with a goal of not falsely indicating a change when a change has not occurred.

This document describes monitoring the difference in means between time 0 and time 1 month and the difference in means between time 0 and end

of dating using control charts. This will require the use of 2 control charts and this document describes setting the control chart limits. The limits will be set using information obtained from the models fit to the confirmation of dating data.

2 Notation

This section provides notation that will be used throughout.

Let

- $\mathbf{Y}= (y_{1,1}, y_{1,2}, \ldots, y_{1,6}, y_{2,1}, \ldots, y_{2,6}, y_{3,1}, \ldots, y_{3,6})^{\mathbf{T}}$ be the observed potency from every vial tested for a serial released to the market under Option 3 that has reached its expiration dating. The first subscript indicates the time point where $i = 1$ denotes the initial testing, $i = 2$ denotes testing after 1 month and $i = 3$ denotes the testing at the end of the dating period. The second subscript indicates the vial tested at the respective time point.
- $y_{i,j} = \beta_0 + b_0 + (\beta_1 + b_1)x_{i,j} + \epsilon_{i,j}$ where b_0, b_1 and $\epsilon_{i,j}$ are random and b_0 and b_1 will vary by serial.
- $\mathbf{X} = \mathbf{Z} = \begin{pmatrix} 1 & 0 \\ \vdots & \\ 1 & 0 \\ 1 & 1 \\ \vdots & \\ 1 & 1 \\ 1 & x \\ \vdots & \\ 1 & x \end{pmatrix}$ where x is the dating period in months of the product.
- $\boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}$ represents the fixed intercept and fixed slope.
- $\bar{y}_{1,\bullet} = (\frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)\ \mathbf{Y}$, the mean potency at the initial testing.

- $\bar{y}_{2,\bullet} = (0, 0, 0, 0, 0, 0, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, 0, 0, 0, 0, 0, 0)$ $\mathbf{Y}$, the mean potency at one month.
- $\bar{y}_{3,\bullet} = (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6})$ $\mathbf{Y}$, the mean potency at the end of dating.
- $C_1 = (\frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, 0, 0, 0, 0, 0, 0)$
- $C_2 = (\frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, \frac{1}{6}, 0, 0, 0, 0, 0, 0, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6}, -\frac{1}{6})$
- $t_1^* = \bar{y}_{1,\bullet} - \bar{y}_{2,\bullet} = C_1\mathbf{Y}$ be the difference in mean potency of the 6 vials tested intially and the mean potency of the vials tested after 1 month.
- $t_2^* = \bar{y}_{1,\bullet} - \bar{y}_{3,\bullet} = C_2\mathbf{Y}$ be the difference in mean potency of the 6 vials tested intially and the mean potency of the vials tested at the end of dating.
- $\mathbf{G} = \begin{pmatrix} \sigma^2_{b_0} & \sigma_{b_0 b_1} \\ \sigma_{b_0 b_1} & \sigma^2_{b_1} \end{pmatrix}$, the variance/covariance matrix of the random effects.
- $\mathbf{R} = \sigma^2\ \mathbf{I}$, where σ^2 is the squared practical standard deviation and $\mathbf{I}$ is the 18×18 identity matrix.
- $\mathbf{\Sigma} = \mathbf{ZGZ^T} + \mathbf{R}$
- $\mathrm{E}(C_1\mathbf{Y}) = C_1\mathbf{X}\boldsymbol{\beta}$
- $\mathrm{E}(C_2\mathbf{Y}) = C_2\mathbf{X}\boldsymbol{\beta}$
- $\mathrm{Var}(C_1\mathbf{Y}) = C_1\mathbf{\Sigma}C_1^\mathbf{T}$
- $\mathrm{Var}(C_2\mathbf{Y}) = C_2\mathbf{\Sigma}C_2^\mathbf{T}$

3 Confirmation of Dating Study

A confirmation of dating study (COD) is necessary to estimate the parameters of $\mathbf{\Sigma}$. It is not uncommon for one or more parameters of $\mathbf{G}$ to be estimated as zero, specifically $\sigma_{b_0 b_1}$ and $\sigma_{b_1^2}$

4 Monitoring

Two metrics will be used to monitor all serials released to the market under Option 3, namely t_1^* and t_2^*. These parameters (t_1^* and t_2^*) will be control charted separately. A threshold is set at $\mathrm{E}(C_1\mathbf{Y}) + 4.5\sqrt{\mathrm{Var}(C_1\mathbf{Y})} = C_1\mathbf{X}\boldsymbol{\beta} + 4.5\sqrt{C_1\boldsymbol{\Sigma}C_1^{\mathbf{T}}}$ for the control chart of t_1^*. Likewise, a threshold is set at $\mathrm{E}(C_2\mathbf{Y}) + 4.5\sqrt{\mathrm{Var}(C_2\mathbf{Y})} = C_2\mathbf{X}\boldsymbol{\beta} + 4.5\sqrt{C_2\boldsymbol{\Sigma}C_2^{\mathbf{T}}}$ for the control chart of t_2^*. If three consecutive serials produce values above the threshold for either t_1^* or t_2^*, the reviewer should be notified and a new stability study should be conducted.

Because the COD study is necessary to establish the threshold, the comparison of t_1^* and t_2^* to their respective thresholds cannot begin until after the COD study is completed. However, these values should be charted for all serials released to the market, including those released prior to completion of the COD.