Potency Specifications for Serial Release and Throughout Dating

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Preface

Several points to consider throughout this presentation...

– Potency Specification for Release: the minimum potency result required in order to release the final product serial for sale, distribution, and use

– Potency Specification Throughout Dating: the minimum potency result that the final product serial is expected to maintain during the entirety of its shelf life or expiry period
  • For many regulatory authorities (human and veterinary) this specification is equal to the potency of the dose which is demonstrated to protect during the efficacy study and applies to both live and inactivated products
Preface

Several points to consider throughout this presentation...

– Specific definition of release and throughout dating specifications should be driven by the following:
  • Setting of appropriate regulatory policy. Policy should be defined prior to description of any statistical methods used to define potency specifications
  • Policy discussions should consider what risk(s) are to be controlled/minimized and what is the acceptable level of risk allowed.

– The AHI maintains that such policy should sufficiently minimize the risk that the mean of a final product serial will fall below the demonstrated protective dose throughout expiry and that the acceptable level of risk is based on 95% confidence
The Current State

-CVB Antigen Overage Concepts:
  Alignment Terminology and Graph
  -Most Recent CVB Guidance
  -Alternate Approach for Discussion
The Current State
CVB Antigen Overage Concepts for Live Vaccines

• Basic terminology:
  – Minimum Protective Dose (MPD)
    • This dose is termed “minimum protective dose”. However, unless
      specific study design is applied at the time of efficacy this is often a
      dose for which a protective response has been demonstrated and is
      perhaps better termed “demonstrated protective dose” (DPD).
  – Minimum Through Dating titer (MTD)
    • \[ MTD = MPD + 0.7 \log_{10}(\text{a standard overage}) \]
  – Minimum Release Titer (MRT)
    • \[ MRT = MTD + 0.5 \log_{10}(\text{a standard stability overage}) \]
    • \[ MRT = MPD + 1.2 \log_{10}(\text{a potency increase of 16x}) \]
  – Formulation Target: MRT + overage for loss during
    processing (lyophilization, etc.)

Could be adjusted by the CVB after analysis of product stability data
The Current State
CVB Antigen Overage Concepts for Live Vaccines

- Formulation target (tier loss due to processing, e.g. lyophilization, etc.)
- MRT (Minimum release titer)
- MTD (Minimum through dating)
- MPD (Demonstrated protective dose)
- Actual MPD (as confirmed through specific dose-titration studies)

Titer loss in average based on stability data

- Standard Stability Overage: $0.5 \log_{10}$
- Standard Overage: $0.7 \log_{10}$

Graph showing titer loss over time with time (months) on the x-axis and titer (log10) on the y-axis.
The Current State
Most Recent CVB Guidance

- Real-time product stability data are generated via confirmation of dating (COD) study, 3 serials tested for potency at regular time intervals
- Data are statistically modeled in order to calculate:
  - Overage 1 = 3\cdot s, where s = square root of residual variance
  - Overage 2 = mean titer loss through desired length of expiry

\[
\text{Assay/Vial Variance; lack-of-fit } \rightarrow 3\cdot s \rightarrow \text{Mean Titer Loss Through Dating}
\]

\[
\text{Risk Throughout Dating} \rightarrow \text{Responsibility of Firm to include additional overage that minimizes risk of falling below MTD throughout dating}
\]

\[
\text{Stability Overage} \rightarrow \text{Mean Titer Loss Through Dating}
\]
The Current State
Most Recent CVB Guidance

*Probability of an individual vial to fall below MTD

Distribution of the population of vials in a serial (includes assay & vial variance)

Titer loss in average based on stability data

*Note: probability to be below MPD is very, very small. Is this necessary?

*This probability assumes all vials are consumed at the given time point

\[ \text{Theoretical Risk of the Individual Vial in a Serial to Fall Below MTD when Serial is Released at MRT} \]

*Using BioMath analysis of real-time stability data: Overage 1 = 3s = 0.5, Overage 3 = 3s = 0.5, Overage 2 = Loss in Average = 0.3
The Current State
Most Recent CVB Guidance

- Current CVB guidance would require 20 times \((10^{1.3} = 19.95)\) more antigen than what was demonstrated to protect the animal in order to release the serial.

- This 1.3 \(\log_{10}\) increase in antigen comes from the following:
  - Overage 1 = 3\(\cdot\)s = 0.5 \(\log_{10}\), accounts for assay/vial variance; lack-of-fit
  - Overage 3 = 0.5 \(\log_{10}\), added by the firm to minimize risk of an individual test of the serial to fall below MTD during expiry
  - Overage 2 = 0.3 \(\log_{10}\), mean titer loss through desired length of expiry
Product Stability Determination for Human Biologics and Pharmaceutical Products

- Real-time data are generated via product stability study, multiple serials tested for potency at regular time intervals
- Data are statistically modeled in order to calculate:
  - Expected Loss = the expected potency loss during the dating period
  - Error Term = combined error from estimate of potency loss and potency measure at release

\[
\text{Expected Potency Loss During the Dating Period} = \text{MPD} \times \text{Statistical Constant} \times (\text{Assay Variability} + \text{Lack-of-Fit})
\]

*Statistical Constant that corresponds to the desired degree of confidence, usually 95%
Product Stability Determination for Human Biologics and Pharmaceutical Products

Theoretical Risk of an Individual Potency Measure to Fall Below MPD when Serial is Released at MRT

*Based on BioMath analysis of real-time stability data: MRT = MPD + Expected Loss + Error Term

- Distribution of the population of potency measures

- Titer loss in average based on stability data

- Probability of an individual potency measure to fall below MPD

- Probability of an individual potency measure to be below MPD at end of dating is acceptably low
Product Stability Determination for Human Biologics and Pharmaceutical Products

- Human Biologics/Pharmaceutical approach would require 4 times \((10^{0.6} = 3.98)\) more antigen than what was demonstrated to protect the animal in order to release the serial.

- This \(0.6 \log_{10}\) increase in antigen comes from the following:
  - \(\text{MPD} + \text{Expected Loss} + \text{Error Term} = \text{MRT}\)
  - \(6.4 \log_{10} + 0.3 \log_{10} + 0.3 \log_{10} = 7.0 \log_{10}\)

CVB approach yields a \(1.3 \log_{10}\) (20x) overage compared to \(0.6 \log_{10}\) (4x) overage using Human Bio/Pharma approach; CVB overage is 5 times greater than the Human Bio/Pharma overage.
The Future State

-Policy First → Math Second

-Points to Consider when Setting Policy
The Future State
Policy First → Math Second

• Most of the AHI-CVB exchange to date has been purely a mathematical exercise, not a discussion of policy

• In order to find the best path forward, AHI strongly believes a discussion of policy should take place (we are happy to realize that discussion this week)
The Future State
Points to Consider when Setting Policy

• AHI encourages CVB to consider the following when establishing future policy for release and throughout dating potency specifications:
  – Minimize/control risk at a 95% level of confidence
    • (fully consistent with other regulatory authorities; many, many doses released without need to adjust)
  – The throughout dating specification should be set equal to the Demonstrated Protective Dose
    • (fully consistent with other regulatory authorities; many, many doses released without need to adjust)
  – While termed “the MPD”, this dose is often the level for which efficacy was reported (unless confirmed via specific study design, the actual MPD is likely lower)
The Future State
Points to Consider when Setting Policy

– The practical risks/probabilities are often much lower than theoretical:
  
  • According to member company figures regarding sale, distribution, use, and buy-back/discard trends, very little (if any) of a typical live product serial is available for use at the last day of expiration (current risk mitigation assumes that all vials are used on the last day of expiry).
  
  • Products at or slightly below the demonstrated protective dose (“the MPD”) do not drop to zero protection (live and inactive antigen loads + relative immunity levels).
The Future State
Points to Consider when Setting Policy

– Identified risks associated with the current policy:
  • Safety (precautionary labels) / Veterinary client-patient concerns
  • Efficacy / Immuno-supression / Antigen interference
  • Product manufacturing / availability concerns

– Setting Policy that allows for data-driven overage reductions and potency specifications will encourage firms to tighten the performance of processes and analytical methods during product development
Thank You for Your Attention and Attendance