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Practical Considerations in Using an Equivalence Approach to Establish Lot Release Limits for Vector Dose

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Abstract

The approval of several gene therapy products and gene-modified cell therapies over the last five years has led to increasing numbers of investigational new drug applications (INDs) using adeno-associated and lentiviral vectors. However, these successes have been tempered by the risks of dose-related toxicities. The therapeutic window for a product is derived from pre-clinical and clinical dose response models, which assume statistically that measurements of dose are exact. Whether vector is administered directly or used as a critical reagent to prepare a gene-modified cellular product, the assignment of a label concentration to a vector batch is critical for establishing consistency of product used in preclinical and clinical development.

Introduction

Measurement uncertainty and volume delivered contribute to potential dose errors. To avoid confounding dose with volume, dose escalation is often done by preparation of vector at target dose levels corresponding to the escalation increments (*e.g.*, half log) and administering the same volume of product. We have previously published a paper advocating for an equivalence approach to lot release for viral vector dose in that context. Implementation of this statistical technique has raised awareness of the importance of minimizing dose error and has been a welcome tool to address the practical challenges of dealing with measurement uncertainty. However, it has also highlighted several important issues where further clarification is needed.

Some of the questions we have received reflect a lack of understanding of basic statistical concepts while others reflect pragmatic problems that were not directly addressed in the original article. In service to remedying both issues, we have used select questions to organize this article. They include the following:

1. Doesn't a high coefficient of determination (R^2 value) for a dose response model curve fit mean that there is little error in dose?
2. If the confidence intervals of the dose measurements for any two batches don't overlap, doesn't adjusting for dose volume make sense?
3. What is the "order of operations" when it comes to establishing targets, equivalence bounds, offsets, type I and type II risk tolerance, and assay precision qualification?
4. How is the propagation of error caused by testing bulk drug substance and final container accounted for in setting the offset for final container?
5. Does this lot release strategy meet the emerging expectation for a total error approach to assay validation?
6. When using a forecasted confidence interval to establish lot release acceptance, how should the sample standard deviation be evaluated in each assay run?

Answers to these questions illustrate that to achieve a high lot acceptance rate and make minimal dose volume adjustments while maintaining a low tolerance for dose error, both low process variability and low measurement uncertainty are required. By adopting an equivalence lot release model, which includes a total error approach to assay qualification, specific testing strategies can be evaluated quantitatively for dose error and lot release decision risks.

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