Abstract

Title: Anti-drug antibody immunogenicity studies in singlicate? Exploring some additional challenges faced and quantifying their impact

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Bio:

Joe Watson is a Principal Statistician at GSK, where he has primarily supported nonclinical research into biologics. In addition to his program support work, he also researches methodological improvements to ADA immunogenicity cut point analyses and explores novel methods for addressing the types of censored data commonplace in nonclinical research.

Joe attained his Doctoral degree from the University of British Columbia and his Master's degree from the University of Bath. After graduating, he completed two post-doctoral research fellowships at the University of British Columbia where he performed methodological research in the areas of spatio-temporal statistics, statistical ecology, and censored data.

Summary of presentation

During the development of therapeutic biologics, immunogenicity studies focusing on anti-drug antibodies (ADA) are routinely performed. A key aspect of these studies is immunogenicity cut point analysis. Cut points, determined from validation data, are used to categorize subjects into ADA-positive and ADA-negative status based on clinical screening and confirmatory assay data. The overarching goal of these cut points is to detect true ADA positive samples with high probability, whilst keeping the rate of false positives to a known (small) value. Extensive statistical literature exists on ADA assay validation and cut point estimation (e.g. Devanarayan et al 2017 and references within).

Traditionally, ADA immunogenicity assays have been conducted with samples appearing in duplicate on plates. Statistical analyses are then performed on the duplicate-averaged responses. However, scientific advancements have significantly enhanced ADA assay precision, sparking interest in the feasibility of conducting ADA validation, screening, and confirmation in singlicate. This topic is frequently discussed in bioanalysis conferences and scientific journals.

Theoretical results from Jiang et.al 2021 show that cut points estimated using singlicate and duplicate data are likely to be similar, provided the well-well variance doesn't exceed 50% of the total variability. The authors justify their theory with empirical evidence from a real-world case study in which they retrospectively analyse an ADA study in both singlicate and duplicate, with similar classification results achieved.

However, performing ADA studies in singlicate faces additional complications which have not been explored. These challenges include the detection of analytical and biological outliers, the QC-ing of plates, and the quantification of declines in classification accuracy (which are sensitive to the unknowable ADA-positive distribution). In this presentation, we will explore all these challenges and use simulated data examples to shed light on the current limitations of our understanding.

Note:

This abstract is subject to change, conditional upon approval, after which new details can be added.