Bayesian framework for the determination of the confirmatory cut point during the immunogenicity assessment

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Immunogenicity assessment consists in measuring the antibodies against the drug. This evaluation is essential for therapeutic protein products, since the risk they induce an immune reaction is high. This is commonly carried out using a two-tiered approach, where samples are defined positive or negative based on two different cut points. The first cut point is based on a screening assay and the second one on a confirmatory assay. The two assays differ only by the presence of excess drug in the confirmatory assay. Therefore, they are usually performed in parallel in the same analytical run. In addition, outlier removal is considered important as it could biased the cut point. This analysis is very sensitive and should be controlled by the false positive rate.

Bayesian methods provides several advantages to the reliable outlier and cut point determinations. We focus here on the confirmatory assay. The percent inhibition between the inhibited and uninhibited signals are classically used to determine the confirmatory cut point. However, most methods assume that the percent inhibition is normally distributed, whereas, as a ratio of two normal variables, it is theoretically not the case (it follows a Cauchy distribution). As an alternative, we propose to model inhibited and uninhibited signals in a bi-variate way. Because the two signals are measured on the same plate, their within plate correlation is an important element and is included the model. This model has been fitted in brms R package. The output of the model has been used for outliers and cut point determinations. This assessment may lead to a more robust determination of the confirmatory cut points.

Clément Laloux short bio:
I'm a Manager Statistics & Data Sciences at Pharmalex Belgium. I have a background in business engineering (bachelor and master) where I specialized in supply chain management and statistics (master). As a Manager Statistics & Data Sciences, I'm providing statistical support on various fields of business, such as clinical, pharmaceutical, or cosmetical activities. The projects I worked on are notably related to method validation, study of treatment effects or reporting and exploratory studies in clinical trials and mostly involve the use of Bayesian statistics.