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TITLE: Robust Bayesian model for the determination of the confirmatory cut point during the immunogenicity assessment

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ABSTRACT: Immunogenicity assessment consists in measuring antibodies that the body can create against a 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 cut point definition and validation 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. Moreover, to reduce the effects of potential outliers, a multivariate student distribution with low degrees of freedom is used for the likelihood. This model offers two main advantages; 1) it is consistent with the data distribution; 2) by being robust to outliers, it can be used directly on the data to derive the cut point without any prior outlier removal steps.
This model has been fitted in brms R package. The output of the model has been used for cut point determination. This assessment may lead to a more robust determination of the confirmatory cut points, and a comparative exercise with other existing methodologies will be provided.

BRIEF SPEAKER BIO: Jean-Francois Michiels

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Jean-François Michiels has been working as a statistical consultant in Cencora Pharmalex since 2013 and he is mostly involved in CMC projects. He has a bioengineering degree from the Université Catholique de Louvain (Belgium-2003). He has a PhD degree in animal cell culture (2004- 2011-UCL-Belgium). He accumulates more than 10 years of experience in several areas of pharmaceutical research and industry including bioassay and process development/validation, drug and vaccine discovery and manufacturing, with the usage various statistical tools such as design of experiments and advanced statistical models (e.g. nonlinear and mixed models). Drawing upon his extensive background and experience, he adeptly communicates statistical concepts to individuals with limited statistical knowledge and skillfully establishes appropriate analytical frameworks.