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

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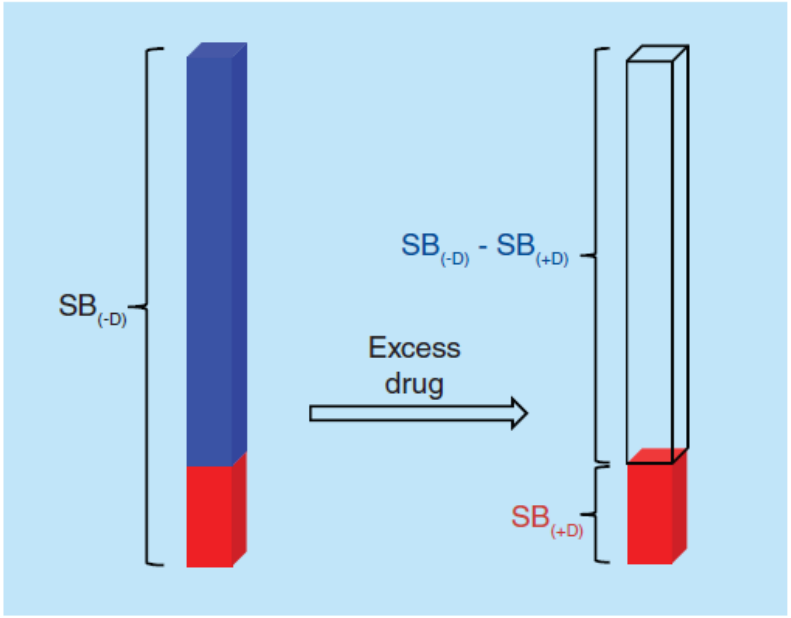
Some reminder

- Anti-drug-antibodies (ADAs): Immune response that can adversely affect the pharmacokinetics, bioavailability, and efficacy of biopharmaceuticals and in some cases may neutralize the activity of the drug (Tovey & al, 2011)
- Approach for testing presence of ADA in human body:
  - Tiered testing method: to be identified as positive and demonstrate that ADAs are specific for the therapeutic protein product, sample must be positive to the screening assay (tier I) and to the confirmatory assay (tier II) (Myler & al, 2021)
  - The cut-point should be determined statistically with an appropriate number of treatment-naïve samples (assumed negative) (FDA, 2019)
  - The cut-point should be determined during pre-study method validation (Myler & al, 2021)

Confirmatory cut point (Kubiak & al, 2020)

- $SB_{(+D)}$ is the signal generated in the presence of drug (inhibited)
  - Due to factor non-related to ADA as inhibition saturate specific interactions (background noise of the instrument, nonspecific binding…)
- $SB_{(-D)}$ is the total signal generated in the absence of drug (uninhibited)
  - Include non-related ADA factors and specific binding to the drug (including but not limited to ADA)
- In a hypothetical situation, ADA negative would mean these two signals are equivalent



Confirmatory cut point evaluation: Devanarayan & al, 2017

- Compute %inhibition data and analyze them (end point of interest)

$$\text{Signal Inhibition (\%)} = \left[1 - \left[\frac{\text{Mean signal of Drug Inhibited Sample}}{\text{Mean signal of Uninhibited Sample}}\right]\right] \times 100$$

- Remove potential outliers
- Investigate data distribution
- Compute cut point to yield an approximate 1% FPR (or a at least 1% false positive rate with 80% confidence level may also be used)

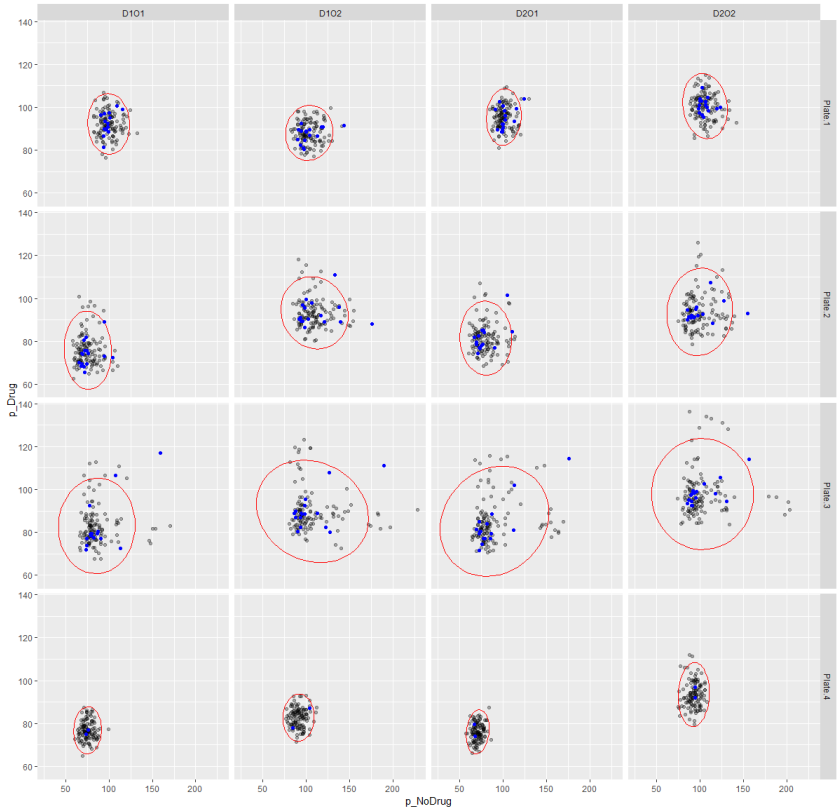
Confirmatory cut point evaluation: Bayesian framework

- Modeling of %inhibition
  - Easy to implement
  - Strong assumption: ratio of 2 normal distributions is normally distributed

- Alternative: model jointly (i.e., bi-response model) the inhibited and uninhibited signals
  - Easily coded with the R package **brms** (Bürkner P, 2017)
  - Assume correlations between the two responses at the minimal design levels (plates and subjects)
  - Outlier evaluation is done in 2 dimensions on the predictive distributions of inhibited and uninhibited signals

Confirmatory cut point evaluation: Bayesian outlier evaluation

- Grey = predictive distribution
- Red = Ellipse calculated from the predictive distribution
- Blue = data (modified after Kubiak & al [2018])



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  - Assume correlation between the two responses at the minimal design levels (plates and subjects)
  - Outlier evaluation is done in 2 dimensions on the predictive distributions of inhibited and uninhibited signals
  - The cut-point is calculated as a one-sided β, γ tolerance interval on predicted %inhibition (ratio of predicted inhibited / predicted uninhibited signals)

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Thank you

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