Case Study

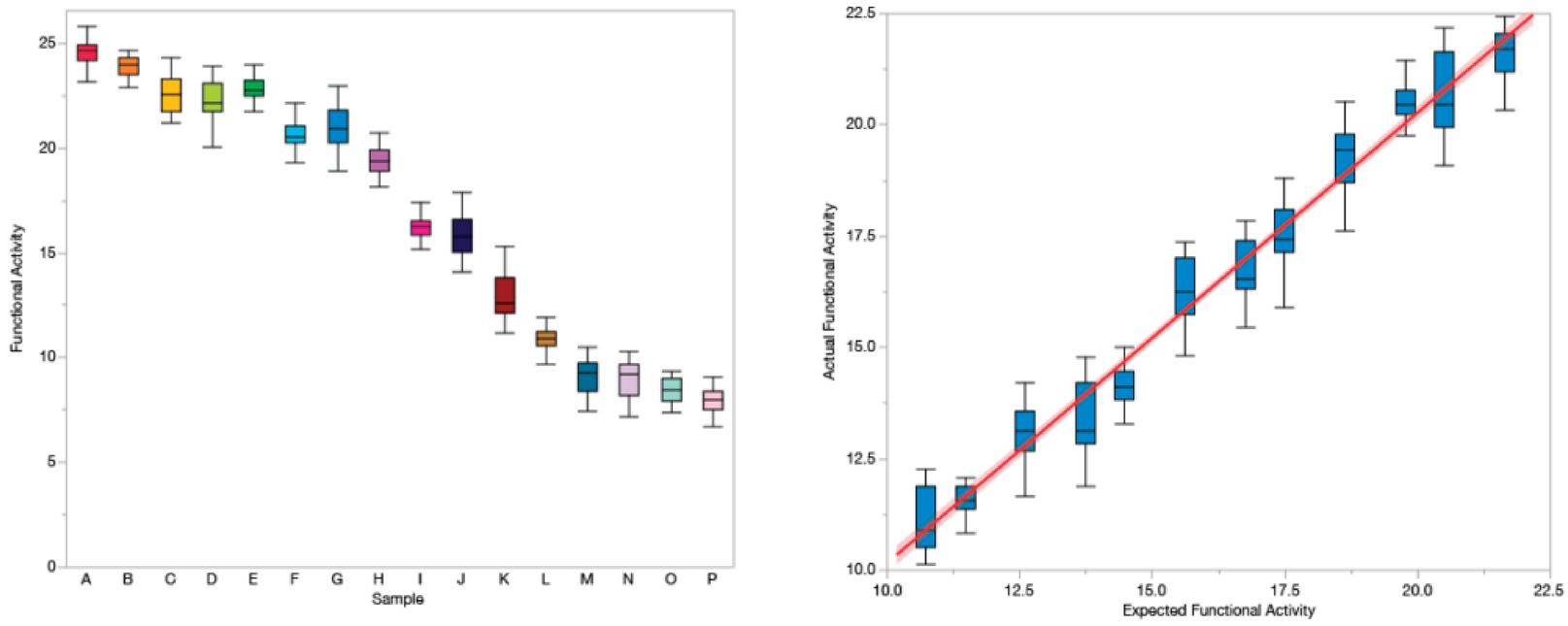
Characterization & Assay Development/ Qualification

Context

Historically, vaccine design efforts have focused on eliciting high titers of neutralizing antibodies, resulting in the development of highly reproducible assays to measure these functions. While our understanding of the importance of extra-neutralizing antibody functions in protection from infection has increased, the routine measurement of these functions as clinical endpoints in clinical trials has been hampered by the lack of qualified or validated assays to measure them. However, beyond being used to identify potential correlates of protection in pre-clinical trials or exploratory analyses, the Systems Serology assays can be rapidly qualified and validated to GCLP standards, allowing for the robust and reproducible measurement of extra-neutralizing antibody functions in late-stage clinical trials.

Problem

To date, neutralizing antibody titers have been the predominant focus of vaccine efforts against SARS CoV2. However, evidence from pre-clinical studies has suggested that extra-neutralizing antibody functions may be critical to vaccine-mediated protection from infection and development of severe COVID. However, as the assays used to generate the pre-clinical data may not be robust or reproducible enough to support regulatory filings, additional assay development and qualification is frequently required. During assay development the conditions that potentially affect the assay's reliability are evaluated with the goal of making the assay as reliable and reproducible as possible.



The precision (left) and linearity (right) of the GCLP-qualified functional assay used for the analysis of clinical trial specimens from SARS CoV2 vaccine clinical trials.

Assay qualification serves to provide documented evidence that the assay is operating accurately and reproducibly and is suitable for its intended purpose. Typically, qualifying an assay consists of evaluating the parameters outlined in the Harmonized Tripartite Guideline to Validation of Analytical Procedures: Text and Methodology and defining acceptable ranges for parameters such as accuracy, precision, limit of detection, limit of quantitation, specificity, linearity and range, and robustness. Here, one of the Systems Serology assays was formally developed and qualified to GCLP standards, allowing for its use to support an ongoing phase 1/2a SARS CoV2 vaccine clinical trials as well as a secondary endpoint for the regulatory filings following phase 3 clinical trials.

Systems Serology Application

During development of the SARS CoV2-specific antibody-dependent functional assay, the specific assay parameters that could potentially impact the ability to accurately and reliably measure SARS CoV2-specific activity were identified and systematically evaluated. Each of these components were rigorously evaluated across multiple experiments to ensure that the optimal parameters that allowed for a robust and precise assay were selected. After the completion of assay development, formal qualification of the SARS CoV2-specific assay was conducted using the WHO guidelines for analytical method qualification under GCLP standards with predetermined acceptance criteria. This qualification approach involved evaluating the assay for (1) repeatability and intermediate precision, (2) specificity and sensitivity, (3) linearity, and (4) the limits of detection and quantitation. The assay resulting from this development and qualification process was highly reproducible and is currently being used to support Phase 3 SARS CoV2 vaccine clinical trials.

Conclusion

The development and qualification process conducted here ultimately resulted in the development of a highly reproducible assay that measures a specific antibody dependent functional activity of SARS CoV2-specific antibodies. Critically, as this assay meets the standards outlined in the GCLP requirements, it can be used to evaluate samples from clinical trials and support regulatory filings. As additional extra-neutralizing antibody functions that are linked to efficacy or protection are identified, the development and qualification process can be applied to any of the Systems Serology suite of assays offered by SeromYx to ultimately support evaluation of these potential correlates of protection in late-stage clinical trials and any necessary regulatory filings.