Development of an **adaptable** yet fully **automated end-user tool** that allows a harmonized and regulatory compliant calculation and evaluation of **immunogenicity cut-points**

Els Pattyn
Non-Clinical Efficacy and Safety Biostatistician

sanofi

NCS Non Clinical Statistics Conference

Louvain-la-Neuve, Belgium / October 19-21, 2022

Immunogenicity

Immunogenicity → ability of a substance to provoke an immune response

- **Wanted** – an appropriate immune response to a pathogen or vaccine
- **Unwanted** – immune response against a therapeutic antigen
  → production of **anti-drug-antibodies (ADAs)**

Immunogenicity

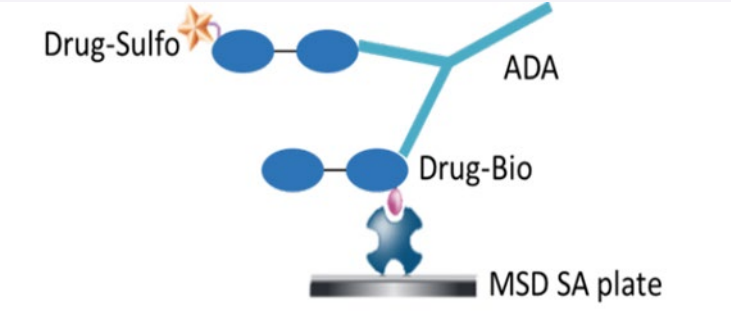
Risk of Potential Safety Concerns = **Probability of eliciting an Immune Response** x **Severity of consequences of an Immune Response**

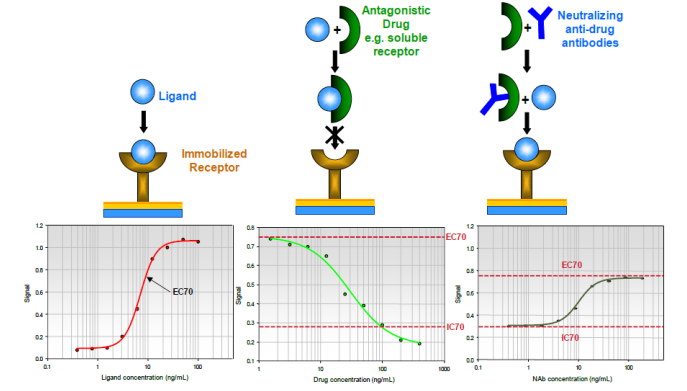
- **Safety Concerns**
  - Induction of inflammation or autoimmune disease
  - Hypersensitivity reactions:
    - Immediate (anaphylaxis, complement activation)
    - Delayed
  - Deficiency syndrome
  - Immune complex disease
- **Loss of Efficacy**
  - Decreased exposure or bioavailability
  - Neutralization (neutralizing Ab (NAb)) : lack or loss of efficacy
- **Changes in pharmacokinetics**
  - Accelerated elimination / loss of efficacy
  - Delayed elimination / unexpected toxicities

Immunogenicity

Multi-tiered approach

- Screening assay - bridging, direct or competitive ELISA, cytokine profile
- Confirmation assay - determination of specificity
- Characterization assay – titer, class/isotypes of antibodies, domain specificity, neutralizing capacity





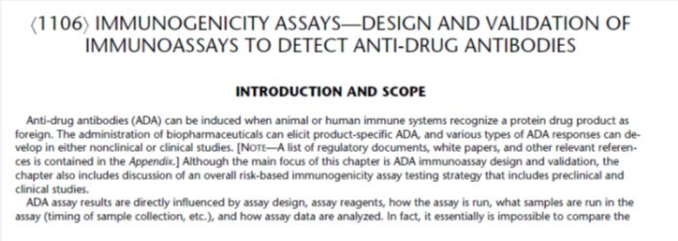
Immunogenicity

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP)

- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (2017). EMEA/CHMP/BMWP/14327/2006 Rev.1

US Department of Health and Human Services, US FDA, Center for Drug Evaluation and Research, Biologics Evaluation and Research.

- Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products (2014).
- *Guidance* for Industry, Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016)

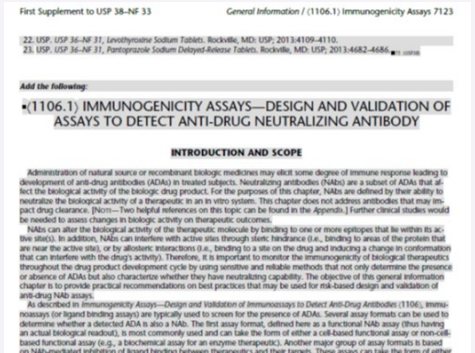


⟨1106⟩ IMMUNOGENICITY ASSAYS—DESIGN AND VALIDATION OF IMMUNOASSAYS TO DETECT ANTI-DRUG ANTIBODIES

INTRODUCTION AND SCOPE

Anti-drug antibodies (ADA) can be induced when animal or human immune systems recognize a protein drug product as foreign. The administration of biopharmaceuticals can elicit product-specific ADA, and various types of ADA responses can develop in either nonclinical or clinical studies. [NOTE—A list of regulatory documents, white papers, and other relevant references is contained in the *Appendix*.] Although the main focus of this chapter is ADA immunoassay design and validation, the chapter also includes discussion of an overall risk-based immunogenicity assay testing strategy that includes preclinical and clinical studies.

ADA assay results are directly influenced by assay design, assay reagents, how the assay is run, what samples are run in the assay (timing of sample collection, etc.), and how assay data are analyzed. In fact, it essentially is impossible to compare the



First Supplement to USP 38–NF 33 — *General Information* / ⟨1106.1⟩ Immunogenicity Assays 7123

22. USP, *USP 36–NF 31, Levothyroxine Sodium Tablets*. Rockville, MD: USP; 2013:4109–4110.
23. USP, *USP 36–NF 31, Pantoprazole Sodium Delayed-Release Tablets*. Rockville, MD: USP; 2013:4682–4686.

Add the following:

•⟨1106.1⟩ IMMUNOGENICITY ASSAYS—DESIGN AND VALIDATION OF ASSAYS TO DETECT ANTI-DRUG NEUTRALIZING ANTIBODY

INTRODUCTION AND SCOPE

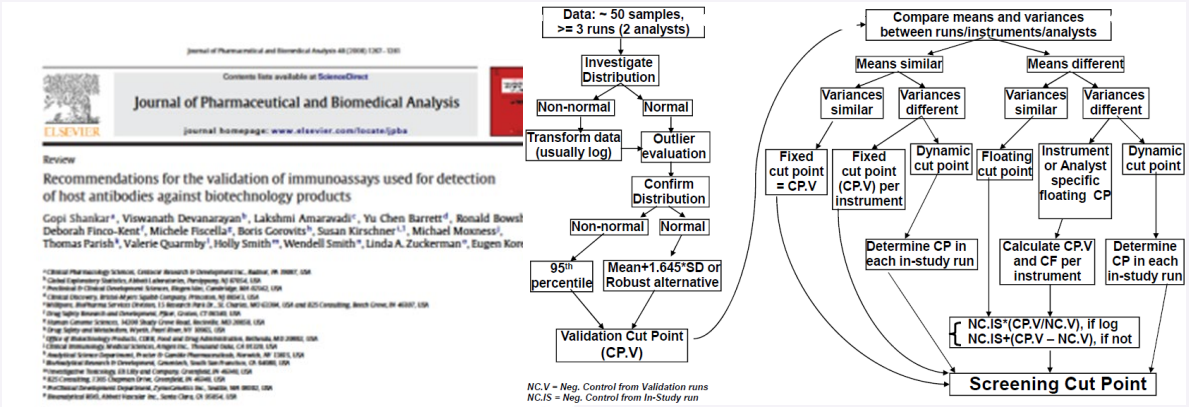
Administration of natural source or recombinant biologic medicines may elicit some degree of immune response leading to development of anti-drug antibodies (ADAs) in treated subjects. Neutralizing antibodies (NAbs) are a subset of ADAs that affect the biological activity of the biologic drug product. For the purposes of this chapter, NAbs are defined by their ability to neutralize the biological activity of a therapeutic in an in vitro system. This chapter does not address antibodies that may impact drug clearance. [NOTE—Two helpful references on this topic can be found in the *Appendix*.] Further clinical studies would be needed to assess changes in biologic activity on therapeutic outcomes.

NAbs can alter the biological activity of the therapeutic molecule by binding to one or more epitopes that lie within its active site(s). In addition, NAbs can interfere with active sites through steric hindrance (i.e., binding to areas of the protein that are near the active site), or by allosteric interactions (i.e., binding to a site on the drug and inducing a change in conformation that can interfere with the drug's activity). Therefore, it is important to monitor the immunogenicity of biological therapeutics throughout the drug product development cycle by using sensitive and reliable methods that not only determine the presence or absence of ADAs but also characterize whether they have neutralizing capability. The objective of this general information chapter is to provide practical recommendations on best practices that may be used for risk-based design and validation of anti-drug NAb assays.

As described in *Immunogenicity Assays—Design and Validation of Immunoassays to Detect Anti-Drug Antibodies* ⟨1106⟩, immunoassays (or ligand binding assays) are typically used to screen for the presence of ADAs. Several assay formats can be used to determine whether a detected ADA is also a NAb. The first assay format, defined here as a functional NAb assay (thus having an actual biological readout), is most commonly used and can take the form of either a cell-based functional assay or non-cell-based functional assay (e.g., a biochemical assay for an enzyme therapeutic). Another major group of assay formats is based

White Papers

Immunogenicity Cut-Point Setting



Journal of Pharmaceutical and Biomedical Analysis

Review

Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products

Gopi Shankar, Viswanath Devanarayan, Lakshmi Amaravadi, Yu Chen Barrett, Ronald Bowsher, Deborah Finco-Kent, Michele Fiscella, Boris Gorovits, Susan Kirschner, Michael Moxness, Thomas Parish, Valerie Quarmby, Holly Smith, Wendell Smith, Linda A. Zuckerman, Eugen Kor


ARTICLE INFO

ABSTRACT

Most biological drug products elicit some level of anti-drug antibody (ADA) response. This antibody response can, in some cases, lead to potentially serious side effects and/or loss of efficacy. In humans, ADA often causes no detectable clinical effects, but in the instances of some therapeutic proteins these antibodies have been shown to cause a variety of clinical consequences ranging from relatively mild to serious adverse events. In nonclinical (preclinical) studies, ADA can affect drug exposure, complicating the interpretation of the toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) data. Therefore, the immunogenicity of therapeutic proteins is a concern for clinicians, manufacturers and regulatory agencies.

In order to assess the immunogenic potential of biological drug molecules, and be able to correlate laboratory results with clinical events, it is important to develop reliable laboratory test methods that provide valid assessments of antibody responses in both nonclinical and clinical studies. For this, method validation is considered important, and is a necessary bioanalytical component of drug marketing authorization applications. Existing regulatory guidance documents dealing with the validation of methods address immunoassays in a limited manner, and in particular lack information on the validation of immunogenicity methods. Hence this article provides scientific recommendations for the validation of ADA immunoassays. Unique validation performance characteristics are addressed in addition to those provided in existing regulatory documents pertaining to bioanalyses. The authors recommend experimental and statistical approaches for the validation of immunoassay performance characteristics; these recommendations should be considered as examples of best practice and are intended to foster a more unified approach to antibody testing across the biopharmaceutical industry.

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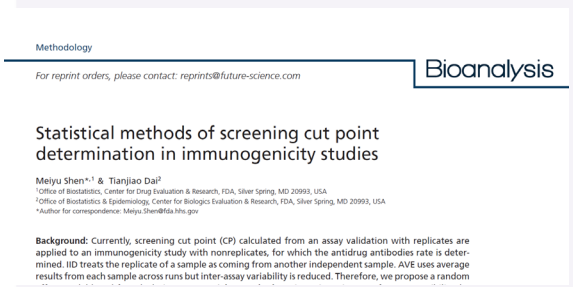

Methodology

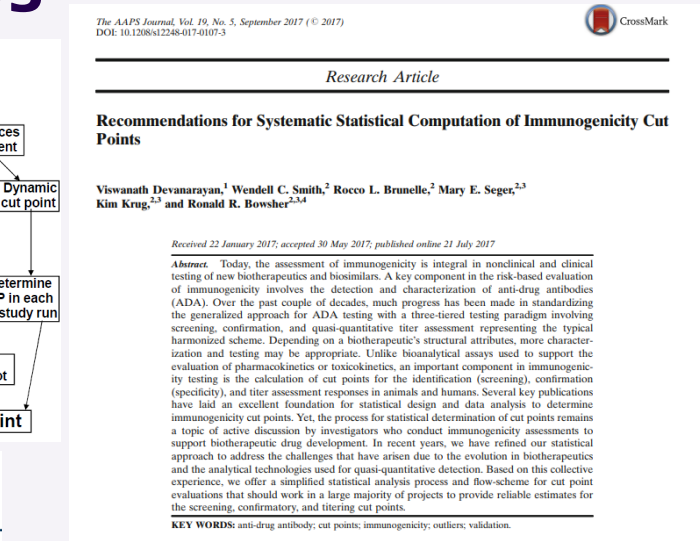
For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Statistical methods of screening cut point determination in immunogenicity studies

Meiyu Shen & Tianjiao Dai

Background: Currently, screening cut point (CP) calculated from an assay validation with replicates are applied to an immunogenicity study with nonreplicates, for which the antidrug antibodies rate is determined. IID treats the replicate of a sample as coming from another independent sample. AVE uses average results from each sample across runs but inter-assay variability is reduced. Therefore, we propose a random


The AAPS Journal, Vol. 19, No. 5, September 2017 (© 2017)
DOI: 10.1208/s12248-017-0107-3

CrossMark

Research Article

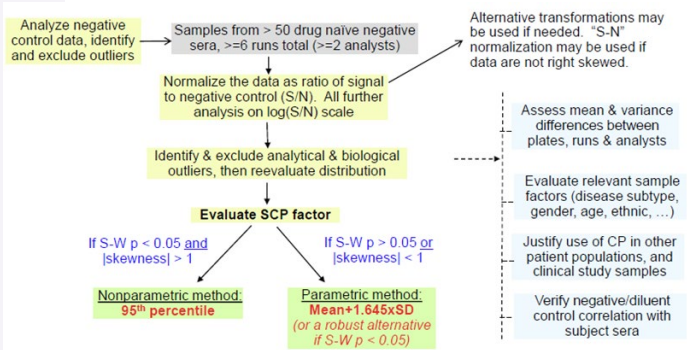
Recommendations for Systematic Statistical Computation of Immunogenicity Cut Points

Viswanath Devanarayan, Wendell C. Smith, Rocco L. Brunelle, Mary E. Seger, Kim Krug and Ronald R. Bowsher

Received 22 January 2017; accepted 30 May 2017; published online 21 July 2017

Abstract. Today, the assessment of immunogenicity is integral in nonclinical and clinical testing of new biotherapeutics and biosimilars. A key component in the risk-based evaluation of immunogenicity involves the detection and characterization of anti-drug antibodies (ADA). Over the past couple of decades, much progress has been made in standardizing the generalized approach for ADA testing with a three-tiered testing paradigm involving screening, confirmation, and quasi-quantitative titer assessment representing the typical harmonized scheme. Depending on a biotherapeutic's structural attributes, more characterization and testing may be appropriate. Unlike bioanalytical assays used to support the evaluation of pharmacokinetics or toxicokinetics, an important component in immunogenicity testing is the calculation of cut points for the identification (screening), confirmation (specificity), and titer assessment responses in animals and humans. Several key publications have laid an excellent foundation for statistical design and data analysis to determine immunogenicity cut points. Yet, the process for statistical determination of cut points remains a topic of active discussion by investigators who conduct immunogenicity assessments to support biotherapeutic drug development. In recent years, we have refined our statistical approach to address the challenges that have arisen due to the evolution in biotherapeutics and the analytical technologies used for quasi-quantitative detection. Based on this collective experience, we offer a simplified statistical analysis process and flow-scheme for cut point evaluations that should work in a large majority of projects to provide reliable estimates for the screening, confirmatory, and titering cut points.

KEY WORDS: anti-drug antibody; cut points; immunogenicity; outliers; validation.

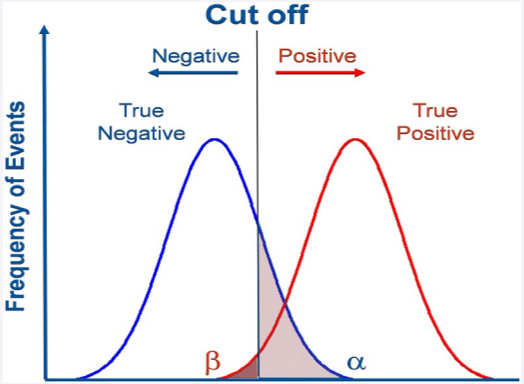


Devanarayan (AAPS-2013/WRIB-2015/EBF2016 presentations)

sanofi

Immunogenicity CP Setting

- **Cut-point (CP) (factors)** are determined
  to **discriminate** positive vs negative samples
  on **blank (naive) population**



Zhang et al 2020, *J Immunol Methods*

- **Blank population** should be
  - **Representative** - demographics & target disease
  - Incorporate all relevant **sources of variability**
    - **Biological** : Subject
    - **Analytical** : Analyst - Run - Plate
  - **Naive (pre-dose)** - free of outliers & pre-existing Abs

Immunogenicity CP Setting

To accommodate to plate effects, '**floating**' cut-point factors (**CPF**) are established by **subtraction** or **division** by sample's plate-specific negative control (NC).

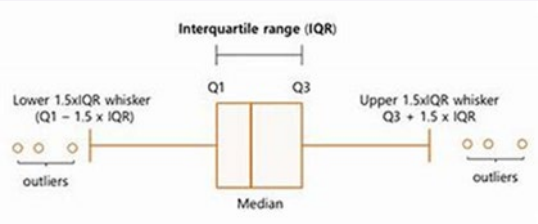
Two **distributions** of the blank population are considered:

- **Normal** distribution upon subtraction of NC → Additive CP
- **Lognorma**l distribution upon division of NC → Multiplicative CPF

Immunogenicity CP Setting

- Not-model based – 'BoxPlot' method

  Tukeys' criteria



- Based on mixed-effects model
  - Fixed effect : Analyst
  - Random effects : Plate ID[Run, Analyst], Run[Analyst], Subject ID

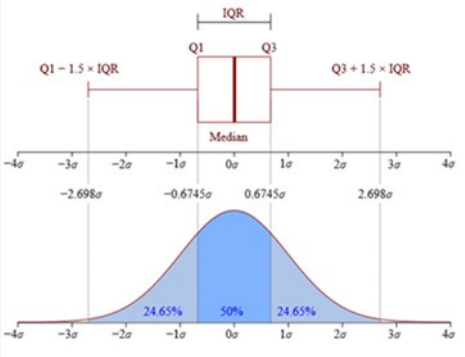
  → adequate handling sources of variability

  → REML-based: cope with imbalance and missingness

Immunogenicity CP Setting

- **Analytical outliers** - sample level
  - BoxPlot: outlying differences subject's response value from its median
  - Mixed Effect Model: outlying conditional residuals

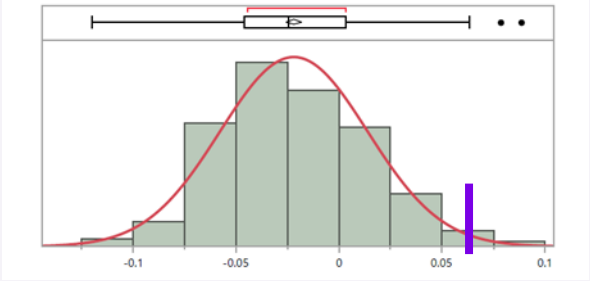
- **Biological outliers** - subject level
  - BoxPlot: outlying subject's median value
  - Mixed Effect Model: outlying subject's BLUPs

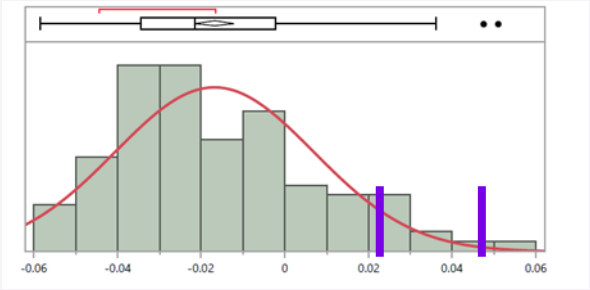


Immunogenicity CP Setting

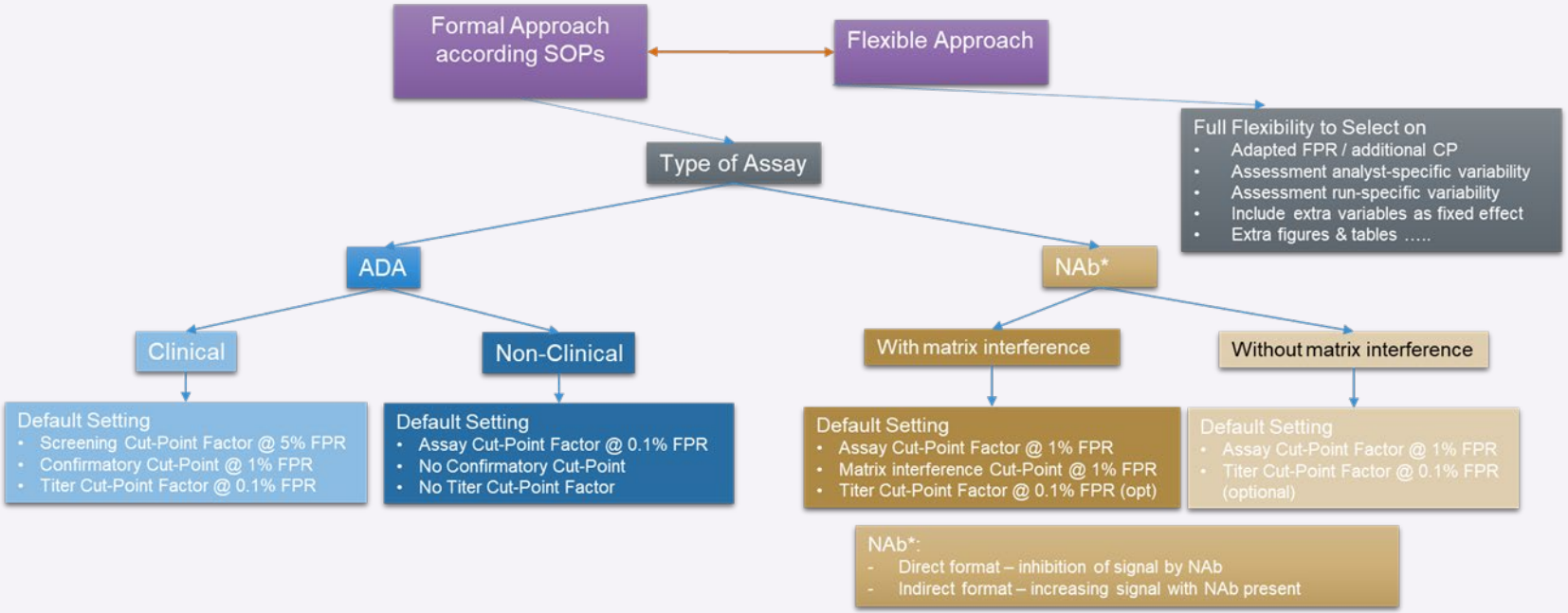
Method of CP Determination on Blank Population

- **Parametric** → mean & standard deviation
- **Parametric robust alternative** → median & MAD
- **Non-parametric** – 1-sided confidence limit on observed percentiles





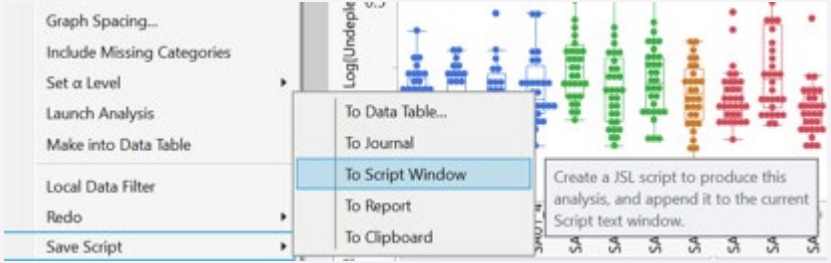
Immunogenicity CP Setting

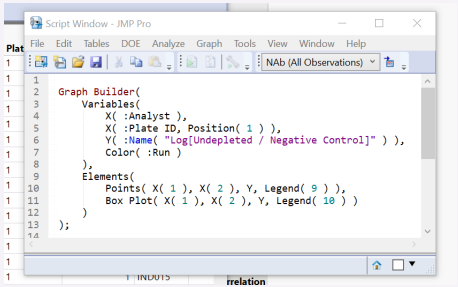


End-User Tool for Immunogenicity CP

Statistical Discovery.™ From SAS.

JSL – JMP Scripting Language





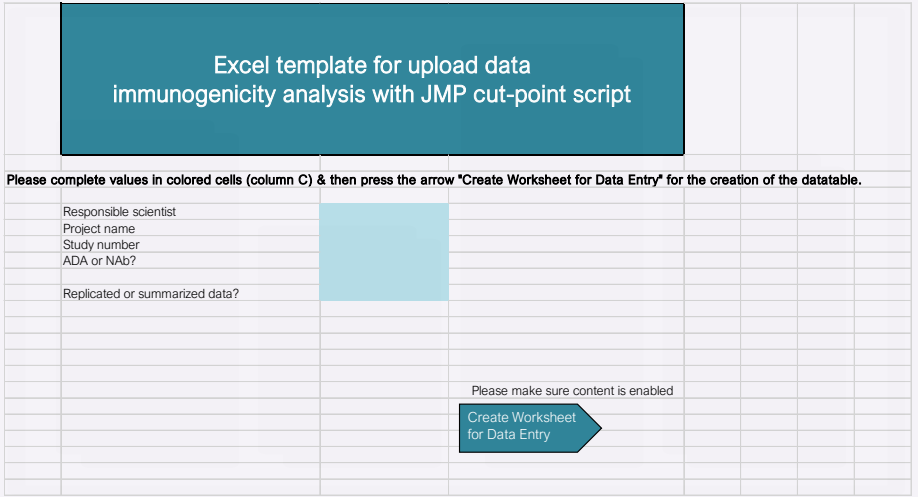
End-User Tool for Immunogenicity CP

- JSL enables automation of analysis / processes
- Also programmable towards outcome-dependent decisions

End-User Tool for Immunogenicity CP

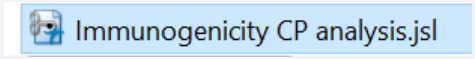
1. Populate Excel template with raw data

Immunogenicity Cut Point Calculation.xlsm

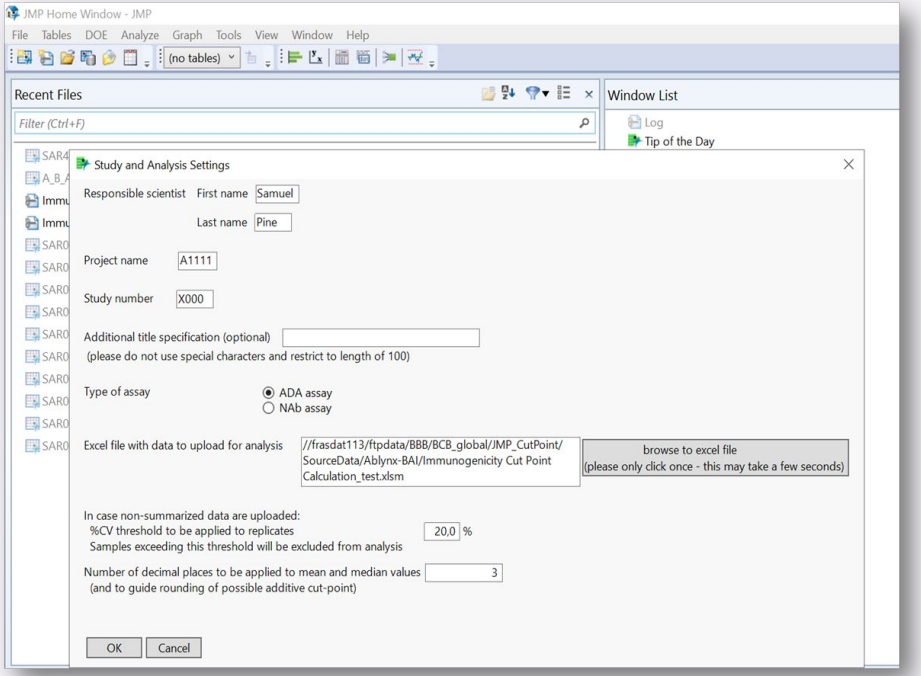


End-User Tool for Immunogenicity CP

2. Launch JSL Script



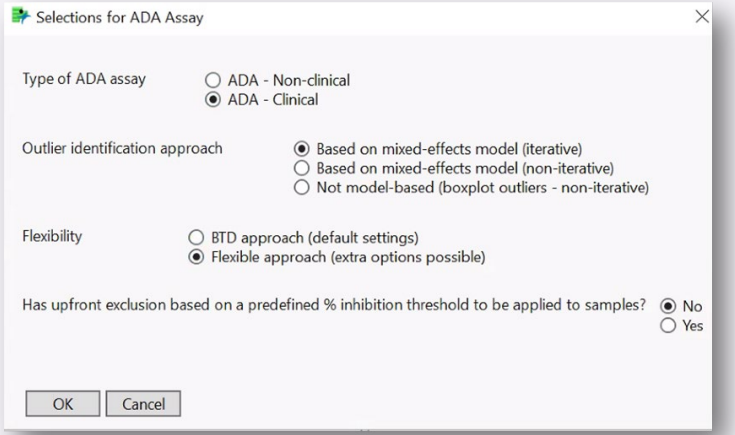
Interactive model window for upload of dataset and selection of analysis options

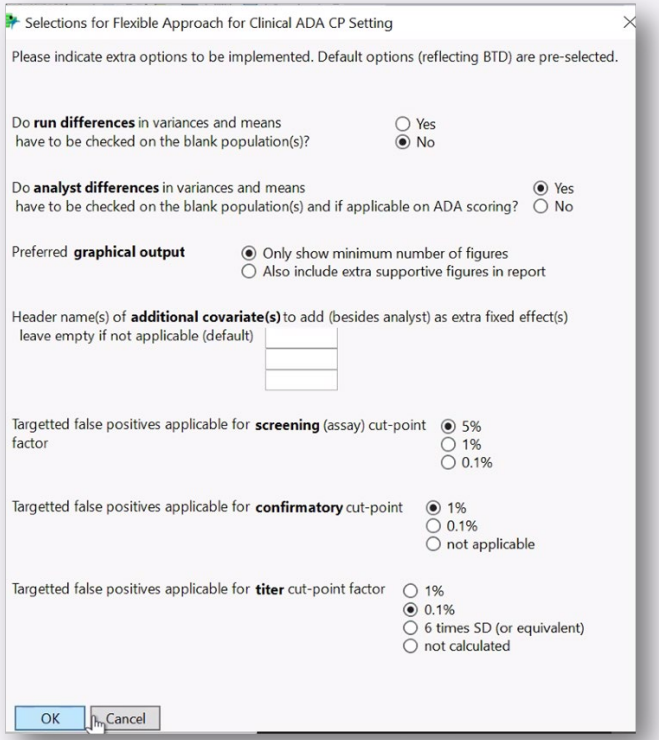


End-User Tool for Immunogenicity CP

2. Launch JSL Script

Dynamic menus
and options rely on previous selection

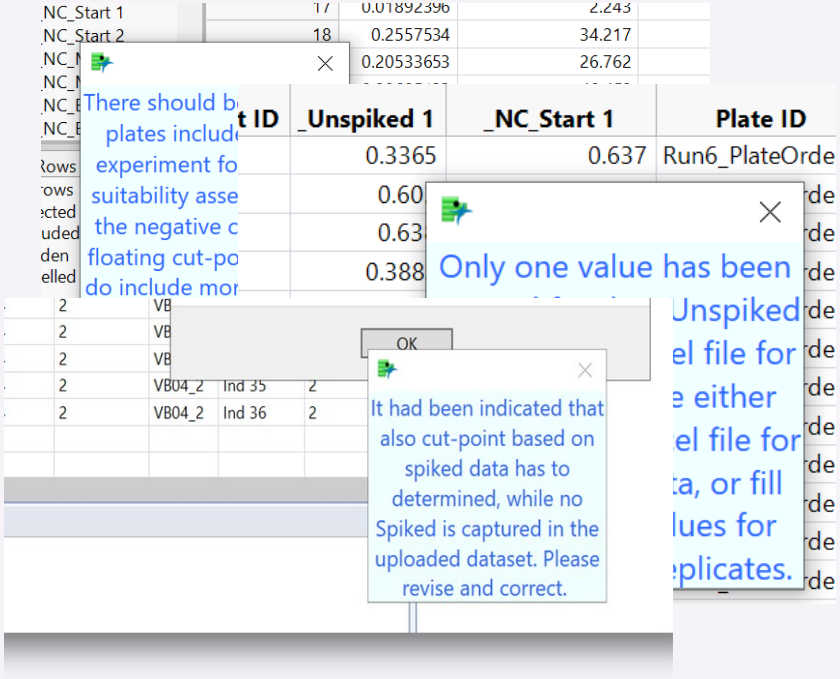




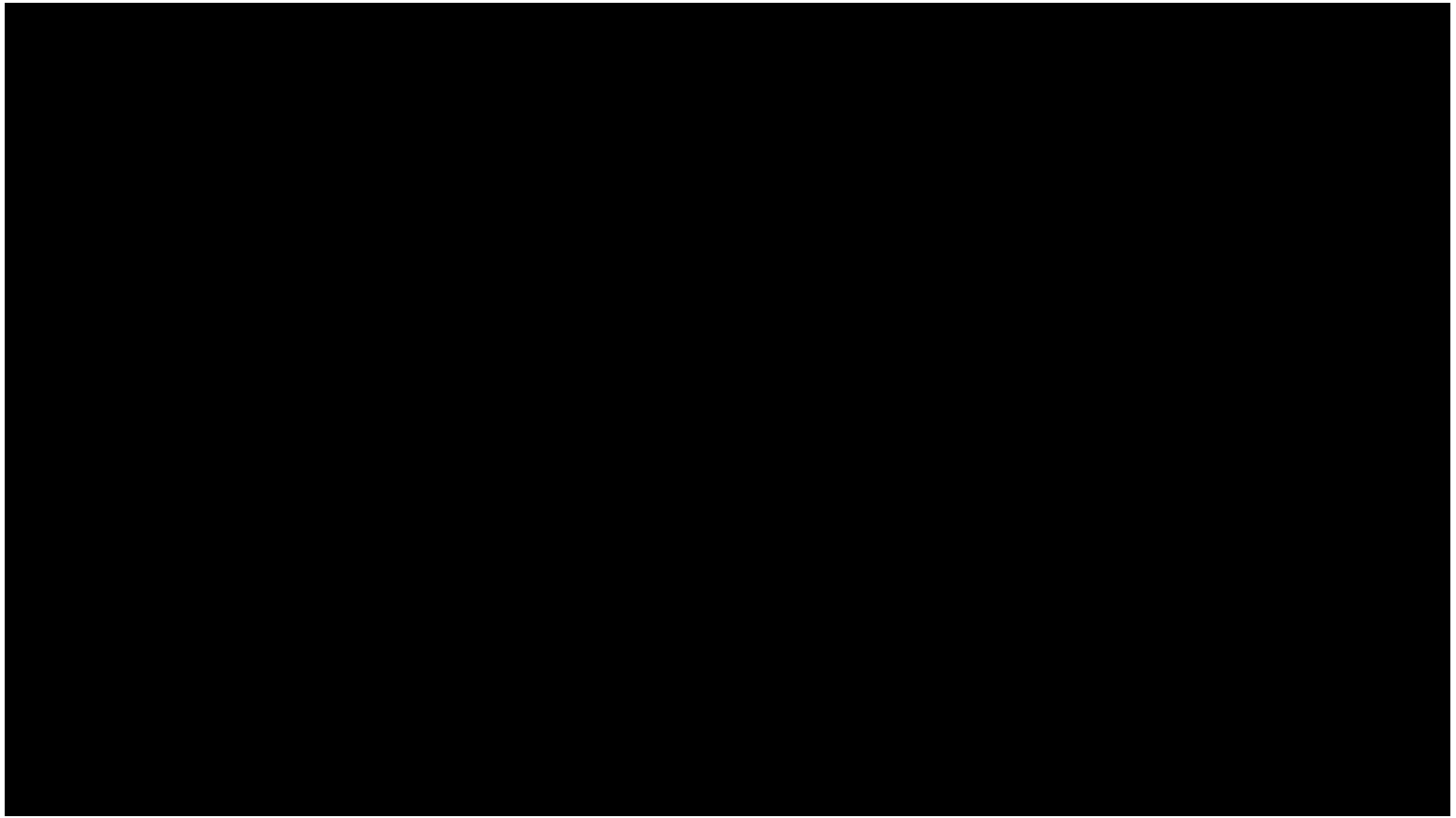
End-User Tool for Immunogenicity CP

2. Launch JSL Script

Includes data checks and acceptance testing



Video Demo



End-User Tool for Immunogenicity CP

1. Analysis Settings

1.1. System Settings

	System Values
Script version	Immunogenicity CP analysis_v01
Invoked from	//frasdat113/ftpdata/BBB/BCB_global/JMP_CutPoint/Script/Prod/
By (username)	I0407086
From (computername)	DESKTOP-PIQ1C87
On (date and time)	26Oct2021:10:38:27
Uploaded Excel file	//frasdat113/ftpdata/BBB/BCB_global/JMP_CutPoint/SourceData/Ablynx-BAI/Immunogenicity Cut Point Calculation_test2.xlsm

1.2. Selected Options

ADA Cut-Point Analysis	Selected Options for Study
Optional title specification	
Responsible scientist	Pine SAmuel
Assay type	Clinical ADA assay
Confirmatory data	Spiked data included in uploaded dataset
Upfront exclusion	No upfront exclusion of samples performed
Outlier removal approach	Based on mixed-effects model (iterative approach) including {:Analyst} as fixed effect and {:Plate ID[:Analyst,:Run], :Run[:An
Flexibility	Flexible approach
Data upload	Uploaded data already summarized over replicates
%CV threshold	No %CV check performed (no replicates in uploaded dataset)
Number of decimal places	Entered number of decimal places to guide precision for possible additive cut-point factor : 3

Description	Selected Option for Flexible Approach
Analysis for run-specific differences in variances and means on the analysis population(s)	Run differences assessed
Analysis for analyst-specific differences in variances and means on the blank population(s)	Operator differences assessed
Preferred graphical output	Extra supportive figures and tables included in report
Header name(s) of additional covariate(s) to add (besides analyst) as extra fixed effect's	{}

Cut-Point (Factor)	Targetted FPR
Screening cut-point factor	5% FPR
Confirmatory cut-point	1% FPR
Titer cut-point factor	0.1% FPR

2. Methodology

The cut-point (CP) analysis is based on guidelines described in BTD-010945, RDBTD-002228, RDBTD-002001, RDBTD-002002 and RDBTD-002217.

In order to accommodate to putative plate/run drifts, a floating screening cut-point factor (SCPF) is settled. Therefore, log-transformed ratios of unspiked values divided by their respective negative control (NC) values and unspiked values subtracted by their NC are both assessed as screening responses.

The transformation appropriateness is evaluated by distribution of the responses on the dataset after exclusion of the outliers (so called blank population dataset). The blank population delineation is based on a mixed-effects model applying Tukey's outlier criterion on the conditional residuals and subject's Best Linear Unbiased Predictors (BLUP) for analytical and biological outlier identification, respectively. According to Tukey's outlier criterion, observations that fall below Q1 – 1.5*(Q3-Q1) or above Q3 + 1.5*(Q3-Q1) are considered as outliers, with Q1 and Q3 representing the 25th and 75th percentiles, respectively. Analytical outliers are removed before biological outliers, both in an iterative way.

The choice for the most appropriate blank population dataset (derived from either the difference of unspiked values and their NC or log-transformed ratios) is based on the normality assessment of the blank populations. If the blank screening population derived from the log-transformed ratios does not show significant evidence against normality by the Shapiro-Wilk test (p-value ≥ 0.05), SCPF setting is performed on this blank population. In case signifiant deviations from normality are seen on the log-transformed unspiked over NC ratios, the blank population delineated from unspiked values subtracted by their respective NC is evaluated. If no significant deviations from normality are seen here, this blank population is used for subsequent analysis. In case both blank populations return a p-value < 0.05 by the Shapiro-Wilk test, the blank population providing the smallest absolute value for the skewness coefficient is taken forward for SCPF setting.

Also the method of SCPF calculation is based on the normality properties of the obtained blank population. In case no evidence against normality is seen by the Shapiro-Wilk test (p-value ≥ 0.05), SCPF is determined by the parametric approach (mean + k (one-sided standard normal quantile) x SD (standard deviation)). This k value is based on the targetted false positive rate (FPR). If, however, evidence is provided for deviations from normality on the blank population dataset, but the absolute value of the skewness coefficient does not exceed 1, SCPF is obtained by the robust alternative method. Here, median is used instead of mean, and the SD is estimated by 1.4826 * median absolute deviation (MAD) to ensure robustness. In case the Shapiro-Wilk test shows significant deviations from normality (p-value < 0.05) and the absolute value of the skewness coefficient exceeds 1, both the robust alternative and the observed percentiles of the blank population (non-parametric method) are outputted for the determination of SCPF. In order to assure the selected FPR with a specified confidence level, the non-parametric SCPF are determined by their one-sided lower confidence limit as established by the smoothed empirical likelihood quantiles. For the 95th percentile a 90% one-sided confidence level, while for the 99th and 99.9th percentiles, the 80% one-sided confidence level is incorporated for the SCPF determination. In case log-transformed dataset is used, back-transformation is applied to obtain the SCPF.

In order to establish suitability of the SCPF, the NC results should represent the drug-naive matrix sample results of the target population. Therefore, the NC values should drift in the same direction as the individual subject samples. This is assessed by the correlation of the plate's median (- if applicable – log-transformed) screening values versus plate's median (log-transformed) NC on the blank screening dataset. Also the correlation of the run's median on the whole dataset. Both Pearson's and Spearman's correlation coefficients should be positive in order to confirm suitability.

Although formal assessment of the analyst-specific differences is performed on sample's final ADA scoring, differences in means and variances are also assessed on the blank population as supportive information. Differences in means are assessed by the mixed effects model including {:Analyst} as fixed effect and {:Plate ID[:Analyst,:Run], :Run[:Analyst], :Subject ID} as random effects. Analyst-specific differences in variances on the blank population are assessed by a Levene's test. If analyst-specific differences in either means or

All relevant data paths & analysis info captured

Dynamic text changes dependent on selected settings

End-User Tool for Immunogenicity CP

4. Screening Cut-Point Factor

4.1. Assay Response (Log[Unspiked / Negative Control])

4.1.1. Distribution of Screening Response before Outlier Exclusion

Figure 5: Boxplots of log-transformed screening response values before outlier exclusion by analyst and run colored by plate

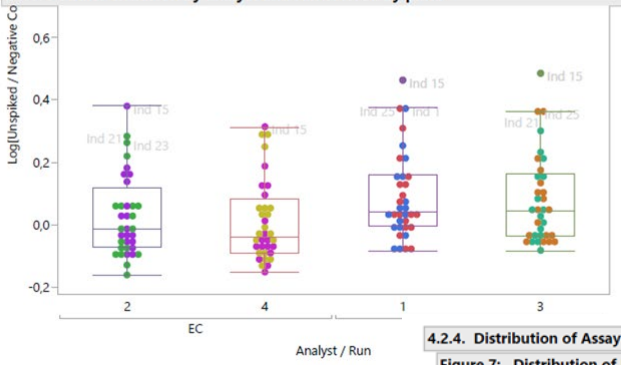
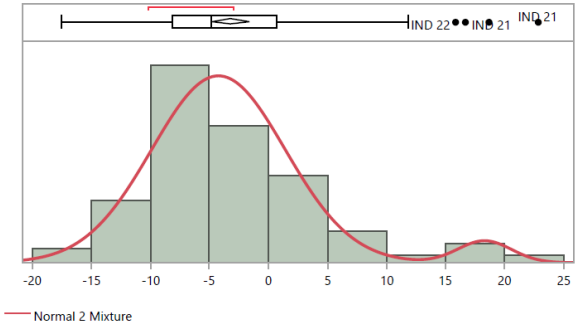


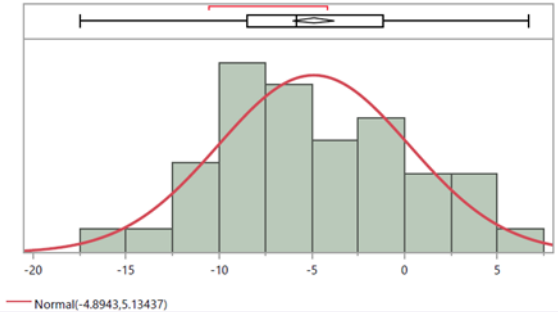
Figure 6: Distribution of the difference of unspiked values over their respective negative control values before outlier exclusion with parameter estimates for fitted mixture of 2 normal distributions and summary statistics

Unspiked - Negative Control



4.2.4. Distribution of Assay Response a...

Figure 7: Distribution of Unspiked - Negative Control assay response on dataset with analytical and biological outliers excluded



Descriptive Statistics

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4. Normalization Factor Determination for Screening and Titration Purposes

4.3. Evaluation of Most Appropriate Blank Population Dataset

Table 10: Assessment of distributional properties of blank populations delineated from untransformed and log-transformed ratios of unspiked values over their respective negative control

Assay Response	Log [Unspiked / Negative Control]	Unspiked - Negative Control
p-value Shapiro-Wilk test	0.14475	0.00972
Skewness Coefficient	0.24613	0.32241

As the Shapiro-Wilk test on the blank population derived on the log-transformed ratios did no over their respective NC values were taken forward as blank population for screening NF deter

4.5. Screening Factor Determination

Table 11: Obtained screening and titer cut-point factors derived from the blank population derived from the log-transformed response data

	Multiplicative Cut-Point Factor
Multiplicative screening cut-point factor targeted at a 5% FPR as determined by parametric approach	1.171 (1.17)
Multiplicative titer cut-point factor determined by parametric approach calculated by Mean + 6*SD	1.856 (1.86)

For the determination of the screening cut-point factor, a 5% FPR was targeted. In this blank screening population, 7.3% of the samples are ADA reactive based on the obtained

5.3. Evaluation of Most Appropriate Blank Population Dataset

Table 22: Assessment of distributional properties of blank populations delineated from untransformed and log-transformed ratios of Spiked values over their respective Unspiked values

-	Spiked/Unspiked (equivalent to % inhibition)	Log-transformed Spiked/Unspiked
p-value Shapiro-Wilk test	0.39437	0.3556
Skewness Coefficient	-0.2619	-0.281

The confirmatory cut-point has been determined on blank dataset derived on the Spiked over Unspiked response values (without log-transformation) (% inhibition scale), as this blank population did not provide evidence for deviations against normality as assessed by the Shapiro-Wilk test.

Analysis

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4.6. Suitability of Negative Control for Cut-Point Factor

Figure 8: Suitability testing of negative control on plate's median values on blank dataset

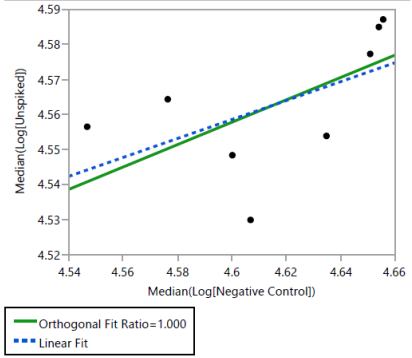

Table 10: Suitability testing of negative control on median values over plates on blank population dataset

-	Slope Deming regression	Slope simple linear regression	Pearson's correlation coefficient	Spearman's correlation coefficient
Estimate	0.31984	0.27062	0.55191	0.61905
p-value	.	0.1561	0.1561	0.10173

R^2 0.305

5.5. Identities of the Biological Outliers Identified and Excluded from the Spiked / Unspiked Blank Population Dataset

Table 23: Identities of subjects identified as biological outliers and excluded per iteration

Round 1	Round 2
2010373	2020053
2010411	
2010461	
2010687	
2020008	
2020171	
2020206	
2020499	

The blank confirmatory population contains 294 observations with data from 152 subjects. 4 observations were identified as analytical outliers, and 9 subjects (accounting for 18 observations) as biological outliers by the mixed-effects model.
As such, 6.96% of the samples of the original confirmatory analysis dataset have been identified as outliers and removed to constitute the blank confirmatory population for CCP determination.

View on outliers and description blank population
Suitability testing

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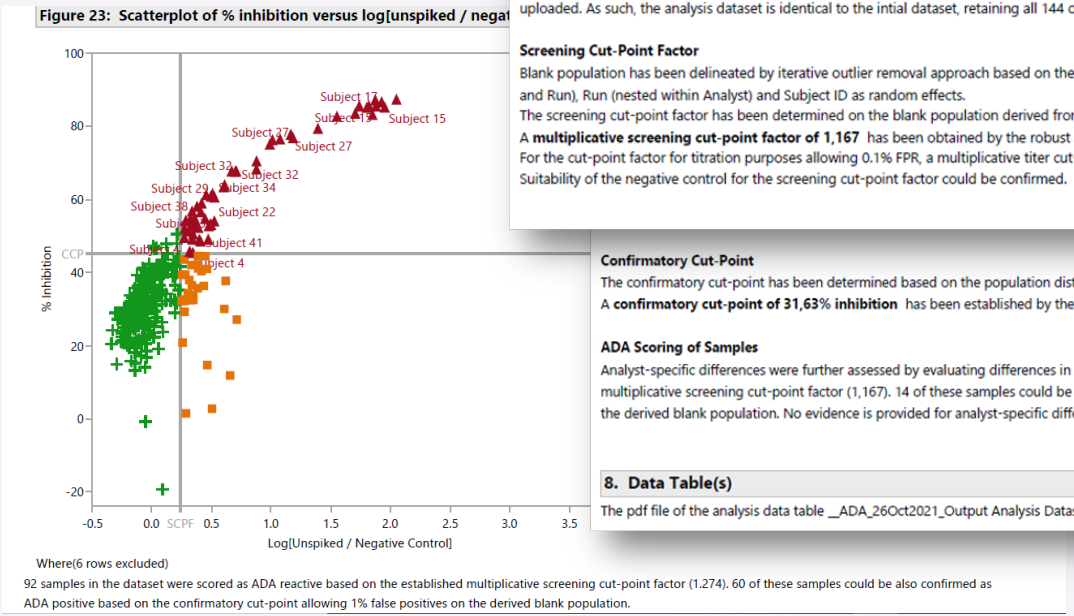

7. Final Conclusions

Dataset Descriptives

A total of 144 observations were included in the initial dataset with data of 36 distinct subjects. No %CV check has been performed in this analysis, as no replicate data has been uploaded. As such, the analysis dataset is identical to the intial dataset, retaining all 144 observations tested by 2 analysts in 4 runs.

Screening Cut-Point Factor

Blank population has been delineated by iterative outlier removal approach based on the mixed effects model including Analyst as fixed effect and Plate ID (nested within Analyst and Run), Run (nested within Analyst) and Subject ID as random effects.
The screening cut-point factor has been determined on the blank population derived from the Log[Unspiked / Negative Control] response values.
A **multiplicative screening cut-point factor of 1,167** has been obtained by the robust alternative approach allowing 5% FPR on the blank population.
For the cut-point factor for titration purposes allowing 0.1% FPR, a multiplicative titer cut-point factor of 1,337 has been established.
Suitability of the negative control for the screening cut-point factor could be confirmed.

Confirmatory Cut-Point

The confirmatory cut-point has been determined based on the population distribution of the untransformed ratios of Spiked over Unspiked values.
A **confirmatory cut-point of 31,63% inhibition** has been established by the robust alternative approach allowing 1% false positives on the untransformed blank population.

ADA Scoring of Samples

Analyst-specific differences were further assessed by evaluating differences in ADA scoring. 33 samples in the dataset were scored as ADA reactive based on the established multiplicative screening cut-point factor (1,167). 14 of these samples could be also confirmed as ADA positive based on the confirmatory cut-point allowing 1% false positives on the derived blank population. No evidence is provided for analyst-specific differences in sample's ADA scoring.

8. Data Table(s)

The pdf file of the analysis data table _ADA_26Oct2021_Output Analysis Dataset.pdf has been outputted to folder \\frasdat113\ftpdata\BBB\BCB_global\JMP_CutPoint\Report\.

Overview scatterplots
Final conclusions

Note : all presented data are fictive for illustration purposes only

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- √ Value comes in **automation**, **harmonization** & reduced operational complexity
- √ Allows state-of-the-art immunogenicity cut-point analysis, updates can be pushed to all teams simultaneously
- √ Standard preferred approach as default with flexible settings for many modalities & situations
- √ Uniform and automatic reporting
- √ Quick and efficient – **reduced effort** of human task for analysis & reporting
- √ Includes acceptance criteria checks and diagnostic analysis evaluations
- √ Run in a **validated** environment and suitable for regulatory submissions

Team credits

BAI – Ablynx, a Sanofi company
BCB & TMED - Sanofi
NCES – Sanofi

sanofi

Thank you

sanofi