Current industry practices for in-study cut point setting for clinical immunogenicity assays

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Introduction

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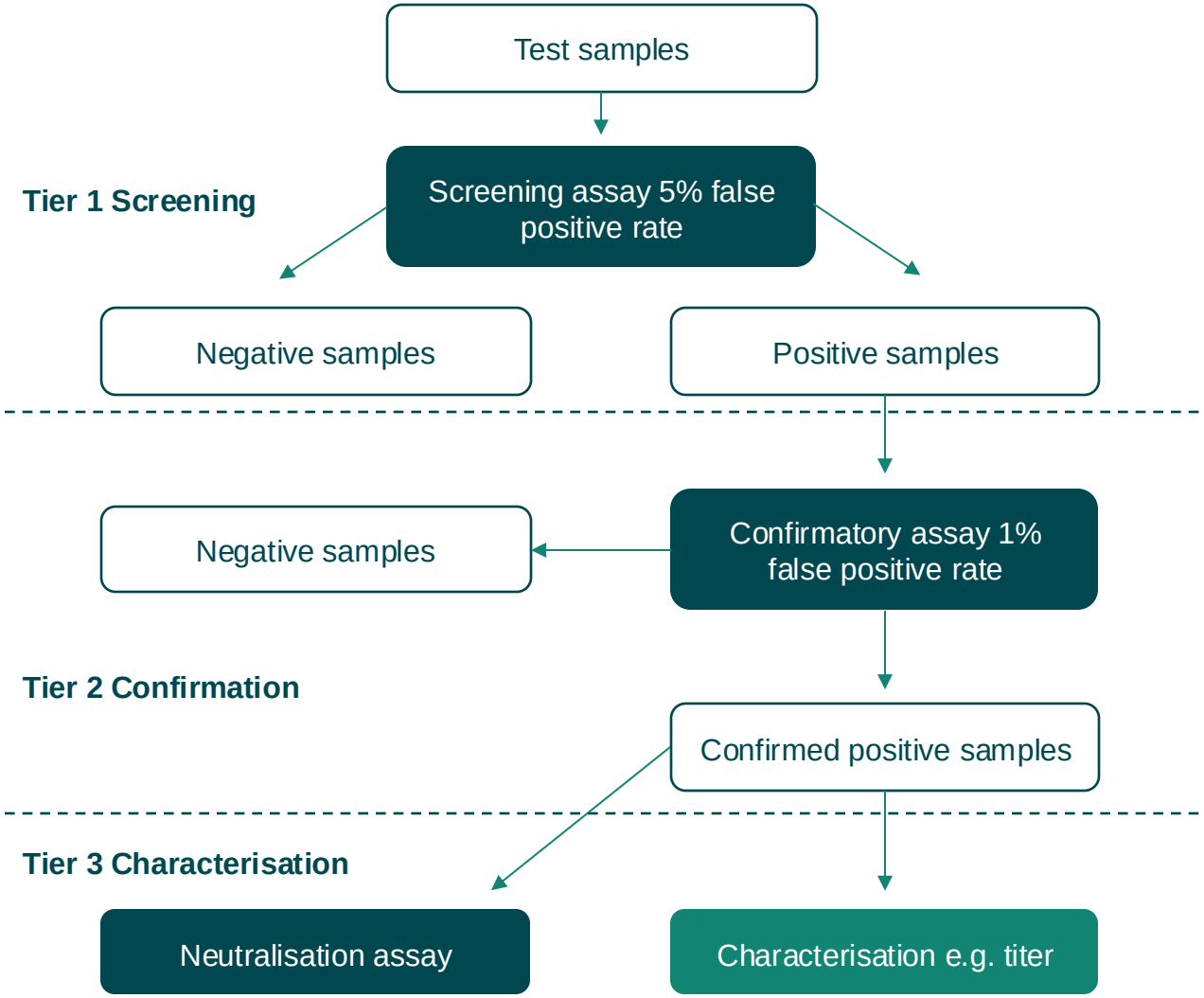
- Anti-drug antibodies (ADA) assays monitor unwanted immunogenicity
- Tiered approach
- Response thresholds (cut points, CP) set during method validation

Assay responses to set CPs can vary between subject populations

False positive or false negative samples

Need for verification of validation CP in each clinical study

Adjustment of CP's (in-study CP) if needed



Introduction

White papers:

Best practices for in-study CP verification and calculation

Different approaches applied based on differences in:

- Interpretation
- Sponsor specific practices
- Context of use

Presented here:

ICON's observations of current practices for in-study CP verification and calculation

When to use an in-study cut point

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CP should be calculated from treatment naïve subjects

Challenging because:

- Availability of pre-dose samples
- Often many different disease states

As a result, common practice is:

- CP determined on samples from healthy subjects
- In-study cut point determined later

When to use an in-study cut point

Evaluate pre-dose samples with the validation CP:

- False positive range (FPR) in screening within 2-11%, validation CP can be used
- If not, a study specific cut point can be calculated / applied
  - Depending on the context; early stage, low number of pre-dose samples
  - >11%: little impact, no need for in-study CP
  - <2%: risk for false-negativity, need for in-study CP

Additional statistical evaluations can be applied:

- Compare study pre-dose and validation CP samples
  - Means (Levene's test), variances (ANOVA) and visualized (boxplots)
- Pre-emptive calculation of in-study CP for each disease states
  - In case of clear differences, prevents complex statistical evaluation
  - Risk of unnecessary changes in CP

How to set an in-study cut point

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Validation CP: Extensively documented

6 * 50 drug-naïve samples, 3 days, 2 technicians, balanced design

In-study CP: Various approaches

During sample analysis, as soon as sufficient pre-dose samples have been analysed

- Samples analysed only once
- Distributed over multiple runs to capture biological and analytical variability

Pre-dose samples analysed separately in similar fashion for setting a validation CP

- Samples analysed multiple times

Hybrid options

- Initial analysis data from pre-dose samples plus dedicated runs to increase statistic power of the assessment
- Volume, number of F/T and informed consent to be considered

Consequences of using an in-study cut point

Consequences of using an in-study cut point

Potential impact on assay reproducibility and data interpretation when a CP shifts:

Altered assay characteristics, such as sensitivity and drug tolerance

– Re-evaluate and consider repeating sensitivity and drug tolerance assessments

In case in-study CP > validation CP: Risk of failure of the low positive control (LPC)

– Re-evaluate and consider to re-establish the LPC

In case of significant shift in CP: Different scoring results

– Establish an in-study CP as soon as possible to prevent re-evaluation of study sample results

Conclusion

Conclusion

- Monitoring CPs is a critical process
  - Ensures reliable immunogenicity assessments in different trial phases and study populations
- CPs may need adjustment to avoid false positives or negatives
  - Based on statistically evaluation of clinical study populations
- Setting in-study CP challenging compared to validation CP
  - Less straightforward
  - More context dependent
- Therefore, on a case-by-case basis
  - Essential to thoroughly evaluate the experimental and statistic methodology

Acknowledgements

Hendrik Folkerts and Peter van Bommel

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