Assessing IVD quality where regulations are not as prescriptive as needed

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Outline

- Definitions
- The evaluation process
  - Review of manufacturer's data
  - Performance evaluation testing
- Resources

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Definition: Verification

- Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (ISO 9000:2005)

- Process of demonstrating the performance criteria included in the method can be met by the facility prior to introducing them for routine use. (NATA Technical Note 17)

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Definition: Validation

The process of proving that a procedure, process, system, equipment, or method works as expected and achieves the intended result. (CLSI)

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Definition: Evaluation

- An investigation that measures the performance capabilities of an assay (CLSI).

- at a point in time.

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The purpose of test kit evaluations

- Confirm that the test kit will perform satisfactorily according to its intended use.
- Minimise the risk of harm:
  - *Safety of blood products*
  - *Accurate clinical diagnoses and effective disease management*
- Provide comparative data for future evaluations

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The purpose of test kit evaluations

- Estimate test kit performance under local conditions, using specimens representative of the local population.
- Evaluations focus on test kit performance.
  - Not on quality of manufacture.
- Provides independent evidence of test kit performance.

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The evaluation process

- Two parts:
  - Review of manufacturer's evidence
    - Dossier or "desktop" review
  - Laboratory performance evaluation
- Either one or both

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Review manufacturer's evidence

- Manufacturers apply to a country's NRA for test kit registration
- A dossier of evidence is submitted, this will include:
  - Test kit Instructions for Use (IFU)
  - Performance data
    - Analytical (pre-clinical)
    - Clinical
    - Stability
- Review by NRA / evaluating laboratory

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The Instructions for Use

- Examine the intended use statement within the test kit IFU
  - What is the level of risk?
  - e.g. “Screening test” vs. “Genotyping test”
- Level of Risk informs how the evaluation is performed
- Examine the summary of performance characteristics

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Example: Intended use of a NAT screening test kit

The XXXXXXXXX Assay is a qualitative *in vitro* nucleic acid amplification test for the detection of human immunodeficiency virus type 1 and human immunodeficiency virus type 2 (HIV) RNA, hepatitis C virus (HCV) RNA, and/or hepatitis B virus (HBV) DNA in plasma and serum specimens from human donors, tested individually or in pools. It is also intended for use in testing plasma and serum to screen organ and tissue donors, including cadaveric (non-heart-beating) donors.

It is not intended for use on samples of cord blood.

This assay is not intended for use as an aid in diagnosis.

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Manufacturer's performance data

- Does the data presented support the test kit's intended use?
- Have sufficient tests been performed?
  - European Union "Common Technical Specifications (CTS) for In Vitro Diagnostic Medical Devices" are a useful guide
- Do the samples tested represent the local population?
- Are the data scientifically sound?
- Is more evidence required – does the evidence presented require clarification?

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Performance evaluation process

- Develop Performance Evaluations Process SOP

Consistent approach

Performance evaluation process

Protocol

- Develop a testing protocol that defines:
  - Aim
  - Parameters for investigation
  - Resources required / available
    - *Human, equipment, reagents, specimen panels*
  - Statistical analyses & acceptance criteria
  - Timeframe
  - Safety requirements
- Make use of testing regulations & guidelines e.g.
  - **NPAAC**; **NATA**: Technical note 17; **CLSI**

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Performance evaluation process

Specimens

- Performance characteristics
  - Sensitivity → positive panels
    → seroconversion panels?
  - Specificity → blood donor samples
    → hospitalised patients?
  - Pools?
  - Ability to detect different subtypes
  - Precision
  - Lot-to-lot variation
- How many samples is enough?
  - Statistical confidence

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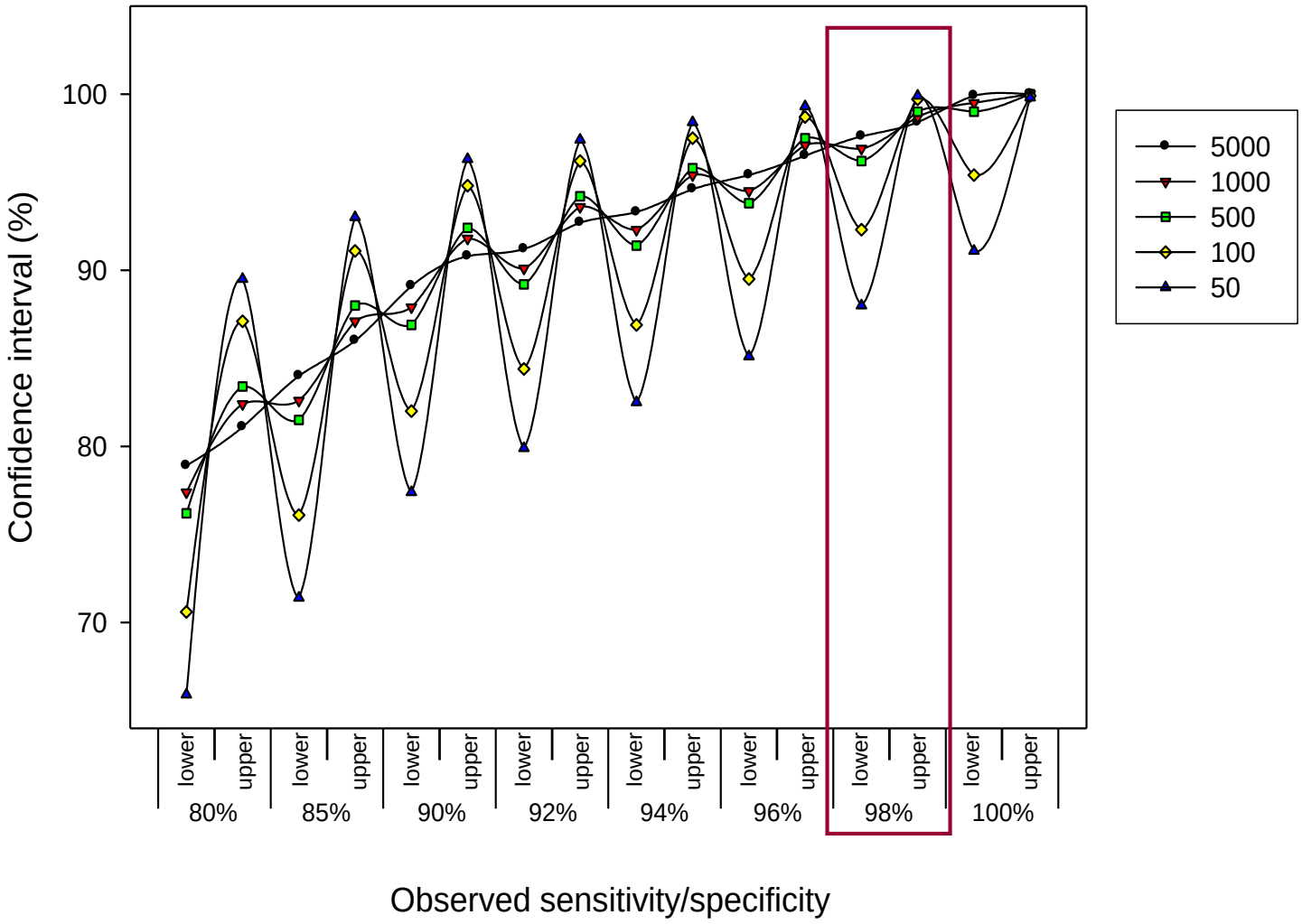
95% Confidence Interval



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Performance evaluation process

- Follow the protocol
  - Data for the validation should be generated from the final protocol
- Keep accurate and complete records
  - A third party needs to be able to analyse and interpret the data

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Performance evaluation process

Report

- Scientific format
- Communicate data effectively
- Include all relevant findings
  - Report confidence intervals
  - Summary tables
  - Appendix for complete data tables
- Correct labelling → tables and graphs
- Consistency of specimen numbers
- Peer review before submission

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Some resources

- **Clinical Laboratory Standards Institute (CLSI)** (clsi.org)
- **NATA**: Technical note 17 (www.nata.com.au)
- **NPAAC:** Requirements for the development and use of in-house and in vitro diagnostic devices
- (www.health.gov.au/npaac)

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Summary

- A test kit evaluation programme seeks to ensure that:
  - only *high quality* test kits are supplied
  - risks understood and minimised
- This ensures:
  - the safety of blood transfusions,
  - the accuracy of clinical diagnoses, and
  - effective donor / disease management
- Use available resources

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