Applying the NPAAC Standard to validate a Class 3 in-house IVD

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Outline

- TGA requirements
- NPAAC Standard
- Documentation preparation
  - Method establishment
  - Method validation
  - Scientific Validation

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TGA requirements

- For laboratories that manufacture class 3 in-house IVDs
  - Annual notification to TGA
  - NATA accreditation
  - Laboratories must meet:
    - AS ISO 15189
    - NPAAC: Requirements for the development and use of in-house IVDs
  - Maintain **suitable documentation** to demonstrate compliance with NPAAC standard

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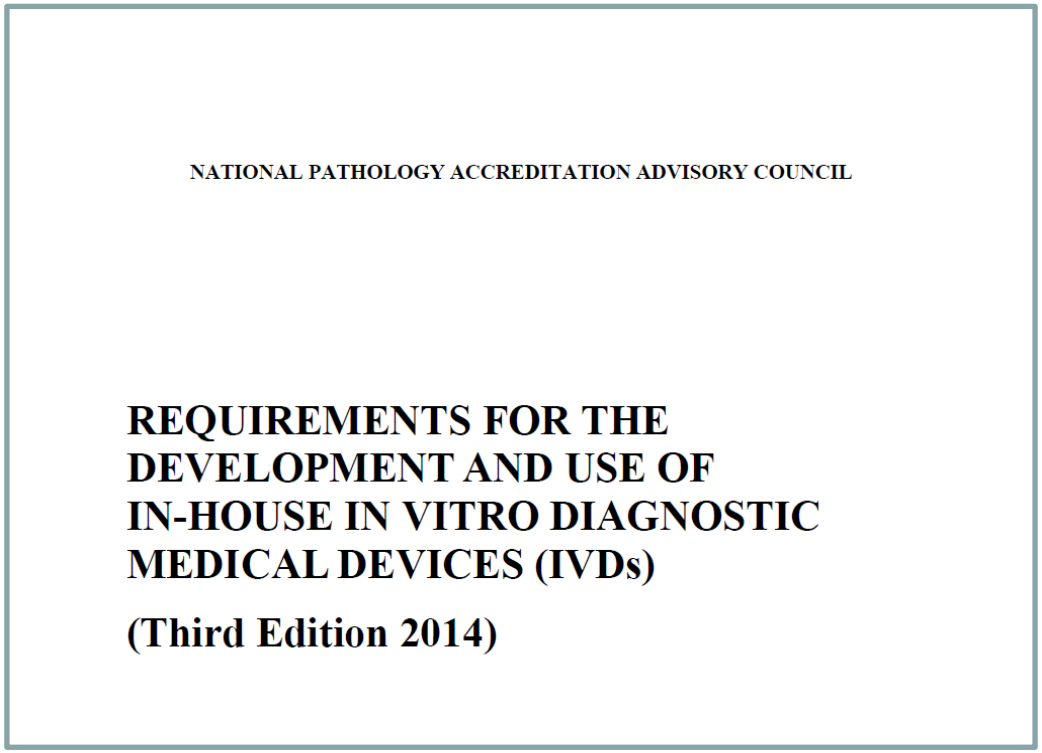
NPAAC Standard


NATIONAL PATHOLOGY ACCREDITATION ADVISORY COUNCIL

REQUIREMENTS FOR THE DEVELOPMENT AND USE OF IN-HOUSE IN VITRO DIAGNOSTIC MEDICAL DEVICES (IVDs)

(Third Edition 2014)

PDF Available to Download from:
http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd.htm

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Particular Requirements

- Design
- Production and Contracted Services
- Analytical Performance
- Scientific Validity
- Clinical Performance
- Clinical Utility
- Multivariate Index Analysis
- Monitoring, Analysis and Improvement
- Adverse Event reporting and recalls
- Documentation

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Documentation

- **Standard 11.1**

The laboratory must establish documented procedures for the design, development, production, validation and monitoring of an in-house IVD

- Documentation on method establishment
  - Reagents, standards, QC, stability, sample processing & storage, performance characteristics
- Method Validation Report
  - Summary information, method development, risk analysis, sample analysis, references

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Case Study

- HTLV-I proviral load PCR
  - To be used for monitoring and management of patients diagnosed with HTLV
  - Class 3 IVD
- Deadline for TGA notification of Class 1-3 in-house IVDs
  - **June 30th 2017**
  - Laboratory must hold information relating to QMS, IVD design & manufacture and performance monitoring

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In-house IVD review team

- Meets periodically to plan for notification process and review progress
- Staff involved:
  - Scientists
  - Director
  - Staff with relevant expertise as required
    - QC development, evaluations, quality manager

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Isolation of PBMC

DNA extraction

RT-PCR

Possible variations

Source material

- Whole blood
- DBS

Instrumentation

Controls and Standards

- non-amplification control
- HTLV –I positive control
- HTLV-II positive control
- HTLV standard

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Reviving Cells from Liquid Nitrogen

Remove cryovial of cells from liquid nitrogen and immediately thaw rapidly at 37ºC in a water bath, until ice just begins to melt.

Before the cells have completely thawed, transfer the contents of the cryovial to a 10 mL Falcon tube containing 10 mL of cold RPMI-1640. Mix gently.

Centrifuge the Falcon tube at 470 x g for 7 Minutes then pour off the supernatant.

Resuspend the cells in 10 mL of cold RPMI-1640 and incubate for 1 hour at 37ºC in 5% CO_2.

Centrifuge the Falcon tube at 470 x g for 5 Minutes then pour off the supernatant.

Resuspend the cells in 5 mL of warmed media (select media appropriate to the cell type) and transfer to a 25 cm^2 tissue culture flask.

Incubate the flask at 37ºC in 5% CO_2. Exchange the media when indicated.

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Documentation milestones

- 2 months
  - Description of analytical method
  - Procedure and work instructions
  - Specifications of reagents and their sources
  - Quality and identity of standards used
  - Outline of validation experiments
  - Description of stability studies

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Documentation milestones

- 6 months
  - Sample processing and storage information
  - Calculations applied to results
  - Preparation of standard curve and QC material, storage requirements and expiry dating
  - Methods of post-implementation monitoring
  - In-use criteria for acceptance / rejection of calibration curves and QC results
  - Definition of master mix batch, quarantine and lot release

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Documentation milestones

- 12 months
  - Measurement uncertainty estimate
  - Summary information on QC samples & method used to determine acceptance criteria
  - Validation report

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Scientific validation milestones

- 6 months
  - Establishment of standard curve and QC acceptance criteria
  - Stability of HTLV DNA in sample types
    - whole blood and DBS at relevant temperatures
  - Limit of quantification
  - Specificity in uninfected individuals
  - Robustness

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Scientific validation milestones

- 12 month
  - Stability of standard curve and QC material
  - Sensitivity in relevant subtypes
  - Transfer of protocol to alternate instrument

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Main challenges so far

- Tracking down old documentation
- Incomplete records
- Making time

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Conclusion

- Meeting the NPAAC documentation requirements depends on planning and co-operation
  - Designate an in-house IVD review team
  - Determine milestones
    - Assign person responsible and due date
  - Re-purpose existing documents where possible
  - Create forms to aid record-keeping

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