OIE Standard on principles and methods of validation of diagnostic assays for infectious diseases

OIE Regional Workshop for OIE National Focal Points for Veterinary Products
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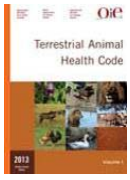
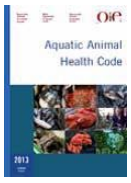
OIE standards

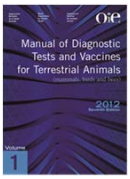
***Terrestrial Animal Health Code* – mammals, birds and bees**



***Aquatic Animal Health Code* – fish, molluscs and crustaceans**



Manual of Diagnostic Tests and Vaccines for Terrestrial Animals



Manual of Diagnostic Tests for Aquatic Animals

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***Codes* and *Manuals* available on the OIE website**

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Chapters 1.1.5. of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

- Two chapters similar on diagnostic test validation covering all the types of tests in terrestrial and aquatic animals
- Title: *Principles and methods of validation of diagnostic assays for infectious diseases*
- Provides principles and methods for diagnostic test validation
- Included for the first time in the *Terrestrial Manual* in 2000 and in the *Aquatic Manual* in 2003

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Chapters 1.1.5. of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

- Current version updated by an OIE *ad hoc* Group on validation of Diagnostic tests and adopted by the World Assembly of Delegates in 2013
- Available and downloadable on the OIE website at: http://www.oie.int/en/international-standard-setting/aquatic-manual/access-online/ http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/

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Chapters 1.1.5. of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

Seven (7) Guidelines have been developed in complement of this standard:

- Development and optimisation of antibody detection assays
- Development and optimisation of antigen detection tests
- Development and optimisation of nucleic acid detection tests
- Measurement of Uncertainty

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Chapters 1.1.5. of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

Seven (7) Guidelines have been developed in complement of this standard (contd):

- Statistical approaches to validation (including Latent Class Models)
- Selection and use of reference samples and panels
- Principles & methods for the validation of diagnostic tests for infectious diseases applicable to wildlife
- *Comparability of assays after minor changes in a validated test method* (under study)

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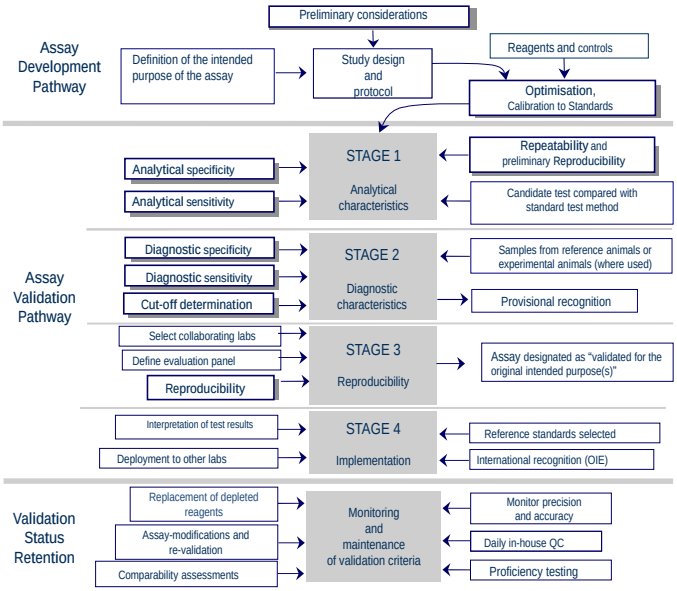
Content of the Chapters



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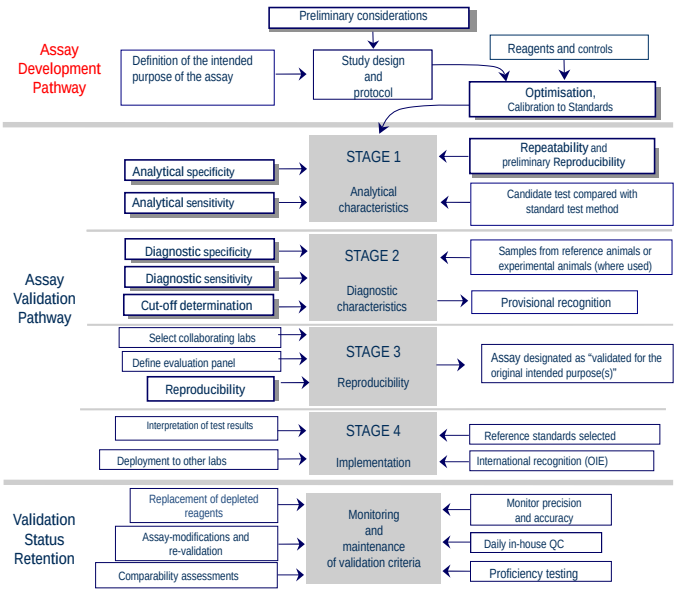

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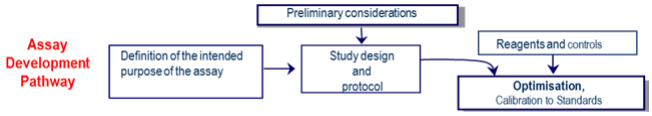
I. Assay development pathway



Definition of the intended purpose(s),
Design of the test method,
Selection of the reference materials,
Calibration, optimisation and standardisation,
Robustness,
Etc.

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I. Assay development pathway

The most common purposes are to:

- Contribute to the demonstration of freedom from infection in a defined population (country/zone/compartment/herd)
- Certify freedom from infection or presence of the agent in individual animals or products for trade/movement
- Contribute to the eradication of diseases or elimination of infection from defined populations
- Confirm diagnosis of suspect or clinical cases
- Estimate prevalence of infection or exposure to facilitate risk analysis
- Determine immune status of individual animals or populations (post-vaccination)

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I. Assay development pathway

Calibration of the assay to standards reagents:

- International and national reference standards

  OIE standards or other international reference standards. If no available, national reference standards becomes the standard of comparison

- In-house standard

  Should be calibrated against an international or national standard

- Working standard

  Calibrated against international, national or in-house standard and prepared in large quantities for routine use in each diagnostic run of the assay

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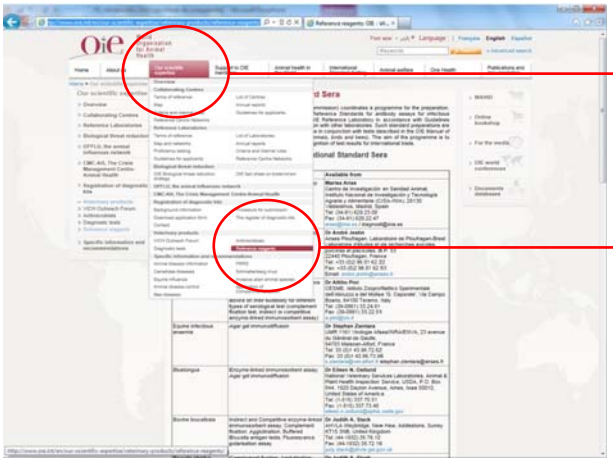
I. Assay development pathway

List of OIE approved international standard sera available on the OIE website:



http://www.oie.int/en/our-scientific-expertise/veterinary-products/reference-reagents/

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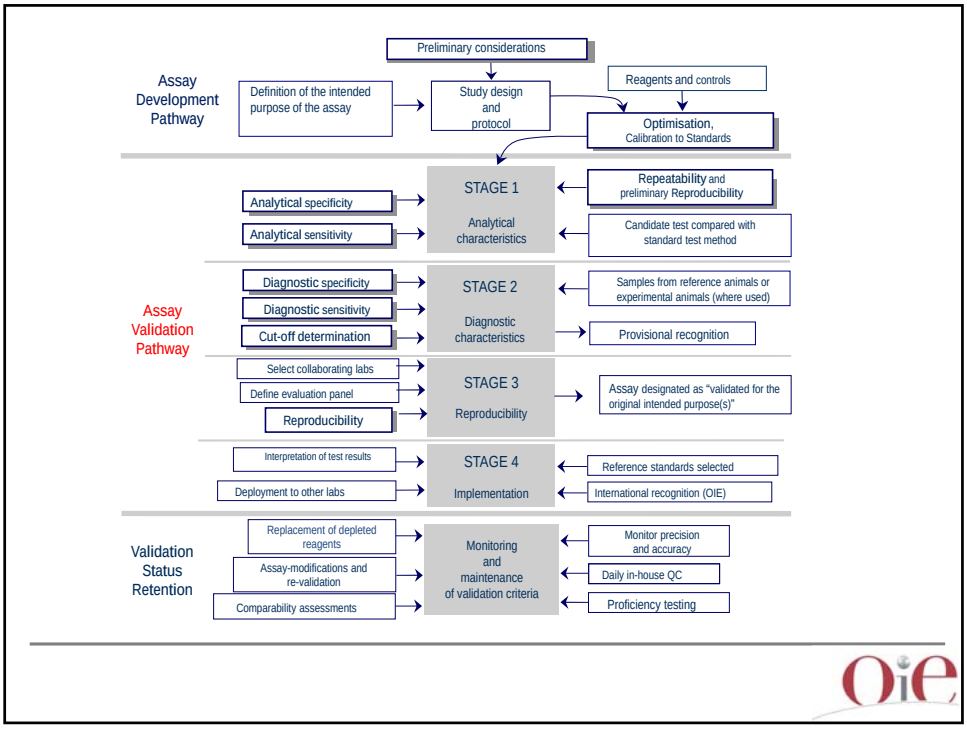

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II. Assay validation pathway

- Definition of the validation:

The validation of a diagnostic test is a **process** that determines the **fitness of this test**, which has been properly developed, optimised and standardised, for an **intended purpose and for specific specimen(s) and specie(s)**.

It is an ongoing process.

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II. Assay validation pathway

The OIE has defined a chronological validation pathway with 4 stages or steps:

- Stage 1: Analytical performance characteristics
- Stage 2: Diagnostic performance of the assay
- Stage 3: Reproducibility
- Stage 4: Programme implementation

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II. Assay validation pathway

➢ Stage 1: Analytical performance characteristics

- Analytical sensitivity: smallest detectable amount of analyte that can be measured with a defined certainty
- Analytical specificity: Degree to which the assay distinguishes between the target analyte and other components in the sample matrix
- Repeatability: Level of agreement between replicates of a sample both within and between runs of the same test method in a given laboratory

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II. Assay validation pathway

- Stage 2: Diagnostic performance of the assay
  - Selection of reference animals
  - Diagnostic specificity : Proportion of known uninfected reference animals that test negative in the assay
  - Diagnostic sensitivity : Proportion of known infected reference animals that test positive in the assay
  - Comparison with existing diagnostic test – Final Threshold determination

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II. Assay validation pathway

- Stage 3: Reproducibility
  - Definition: ability of a test method to provide consistent results when applied to aliquots of the same samples tested at different laboratories
  - Provides additional data for the estimation of the repeatability
  - Provides data on the ruggedness if the test method has been developed as a diagnostic kit.

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II. Assay validation pathway

- Stage 4: Programme implementation
  - Extensive application of the test method in different laboratories,
  - Interpretation of tests results, and
  - International recognition

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II. Assay validation pathway

- When a diagnostic test method is considered as validated?
  - Different replies depending of the test methods, of the samples available and the status of the validation

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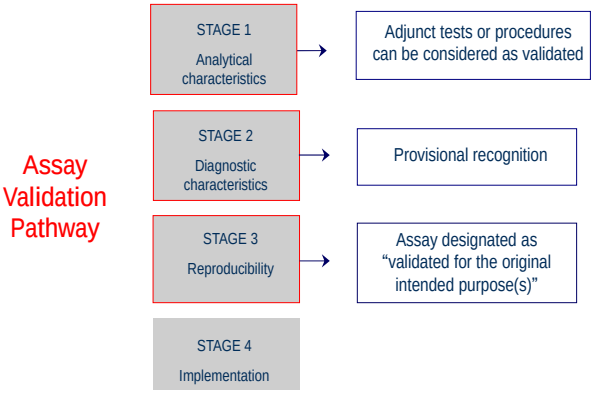
II. Assay validation pathway

➢ When a diagnostic test method is considered as validated?



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II. Assay validation pathway

➢ When a diagnostic test method is considered as validated?

STAGE 1

- **Adjunct tests or procedures**:

  Tests or procedures that are applied to an analyte that has been detected in a primary assay with the purpose to further characterise this analyte.

  Do not require the validation of the diagnostic perf.

  Example: VNT to type an isolated virus or molecular sequencing to confirm a real time PCR result.

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II. Assay validation pathway

➢ When a diagnostic test method is considered as validated?

STAGE 2

- **Provisional recognition**:

  Situation where samples from the target population are scarce and animals difficult to access (e.g. wildlife)

  Prov. recogn. consists in stage 1 completed + preliminary estimates of DSp and DSe + preliminary estimates of reproducibility

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II. Assay validation pathway

➢ When a diagnostic test method is considered as validated?

STAGE 3

- **Validated for the original intended purpose(s)**:

  A diagnostic test method that has completed the first three stages of the validation pathway can be designated as "*validated for the original intended purpose(s)*".

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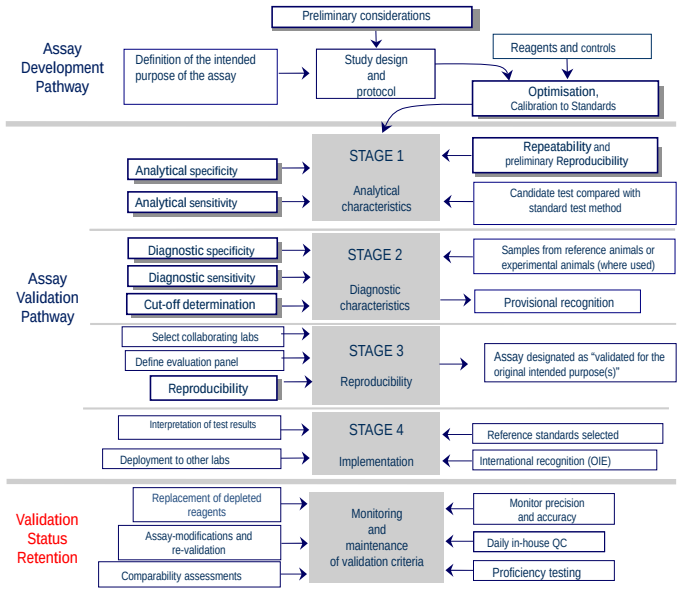

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III. Validation status retention

- Check and maintain the performance characteristics,
- Organisation of regular proficiency testing,
- Modifications (e.g. for new subtypes of existing pathogens) and enhancements (e.g. to improve assay efficiency or cost-effectiveness),
- Consideration for other purposes or other species,
- Etc.

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Verification of existing assays (in-house validation)

1. A limited verification of both ASp and ASe using available reference materials, whether they be external and/or locally acquired from the target population.

2. A limited Stage 2 validation should be considered in the context of the intended application and target population before the assay is put into routine diagnostic use.

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Support - OIE Collaborating Centres

- **ELISA and Molecular Techniques in Animal Disease Diagnosis**

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Support - OIE Collaborating Centres

- **Biotechnology-based Diagnosis of Infectious Diseases in Veterinary Medicine**

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Thank you for your attention

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