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
Maputo, Republic of Mozambique
3 – 5 December 2013

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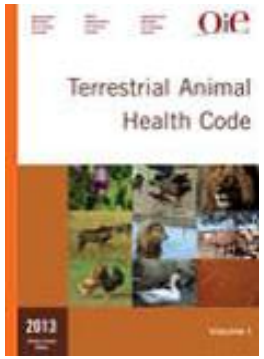
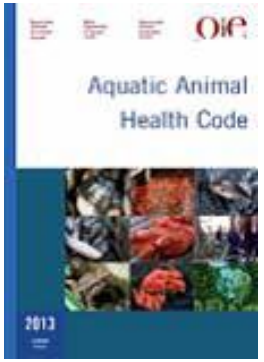
OIE Scientific and Technical Department

OIE standards

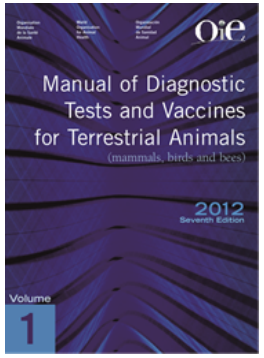
Terrestrial Animal Health Code **– mammals, birds and bees**



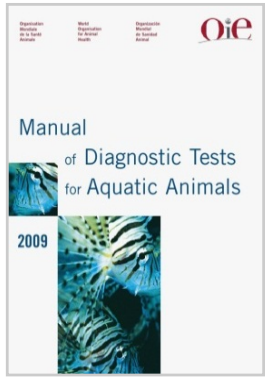
Aquatic Animal Health Code **– fish, molluscs and crustaceans**



Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

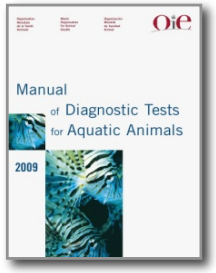


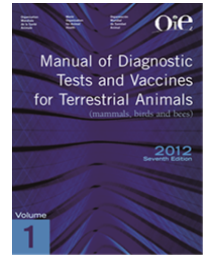
Manual of Diagnostic Tests for Aquatic Animals



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

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 and 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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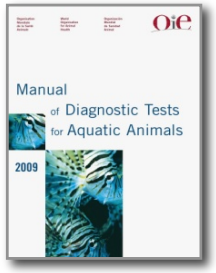
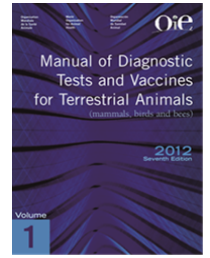




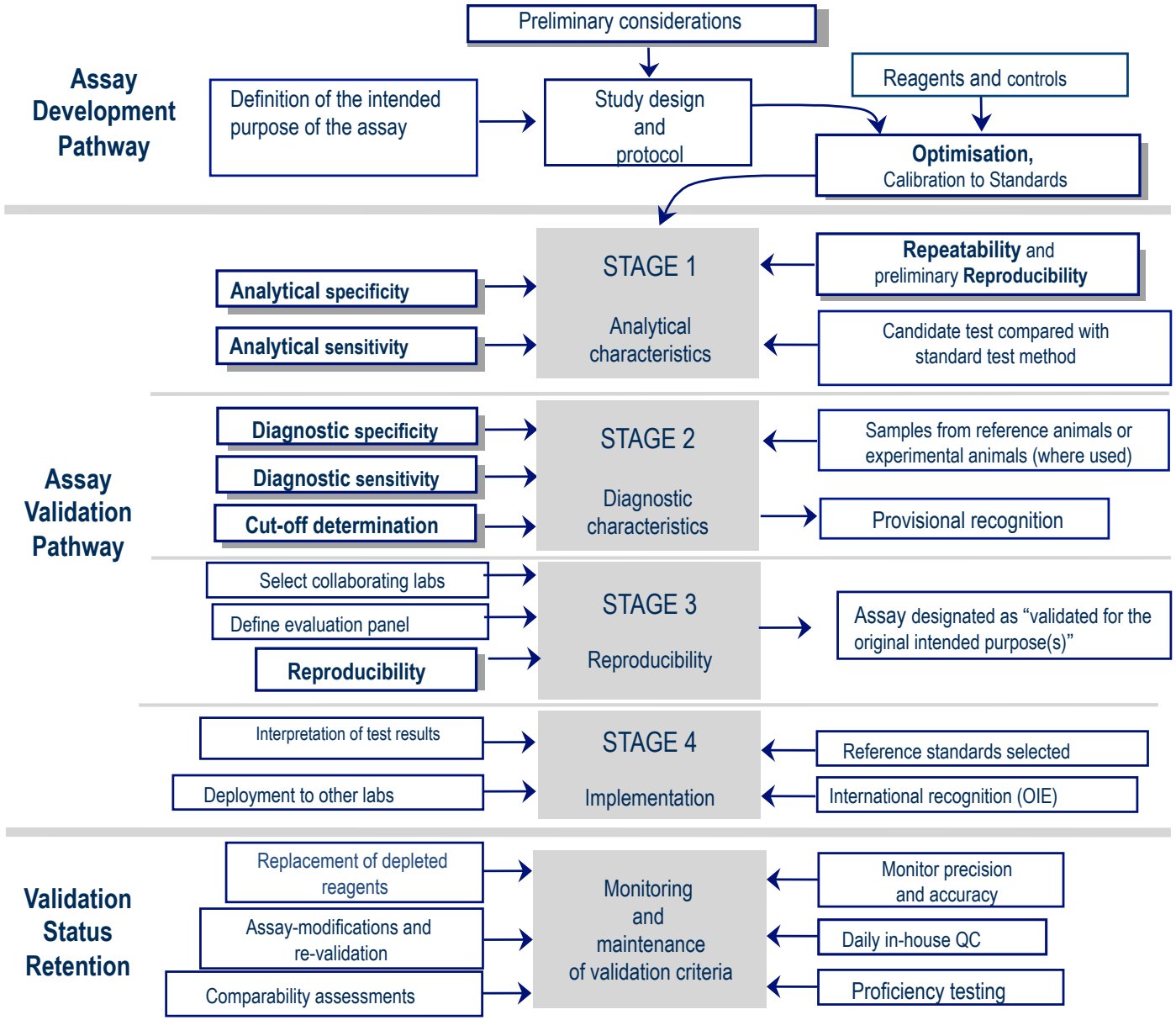
- Current version updated by an OIE ad hoc Group on validation of Diagnostic tests and adopted by the World Assembly of Delegates in 2013
- Available and downloadable on the OIE website at: http://www.oie.int/en/international-standard-setting/aquatic-manual/access-online/ http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/

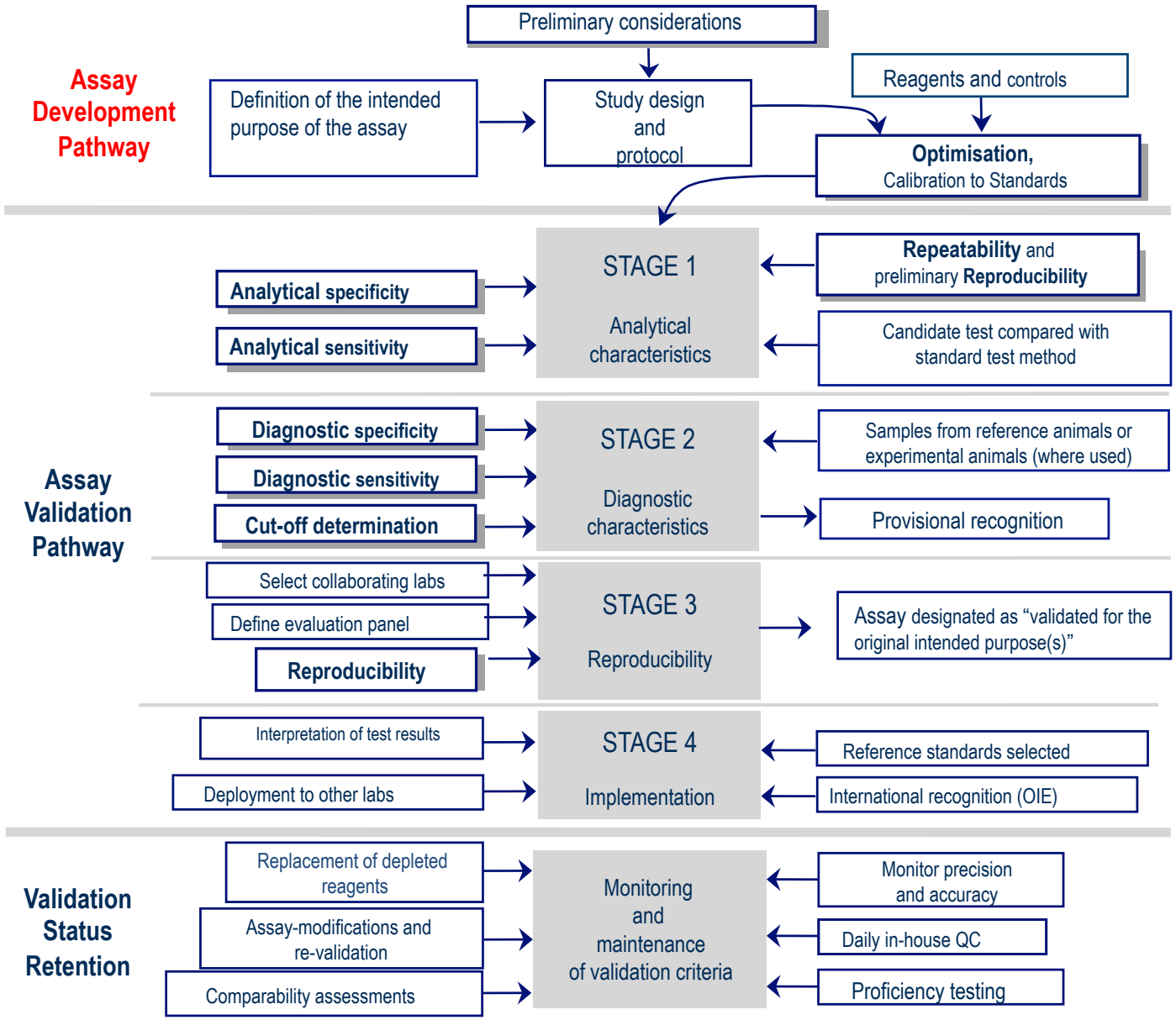
Chapters 1.1.5. of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

Seven (7) Guidelines are in development:

- 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
- Statistical approaches to validation (including Latent Class Models)
- Equivalency (Method comparability)
- Selection and use of reference panels

Content of the Chapters

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Preliminary considerations
Definition of the intended purpose of the assay
Study design and protocol
Reagents and controls
Optimisation, Calibration to Standards
Assay Validation Pathway
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Analytical characteristics
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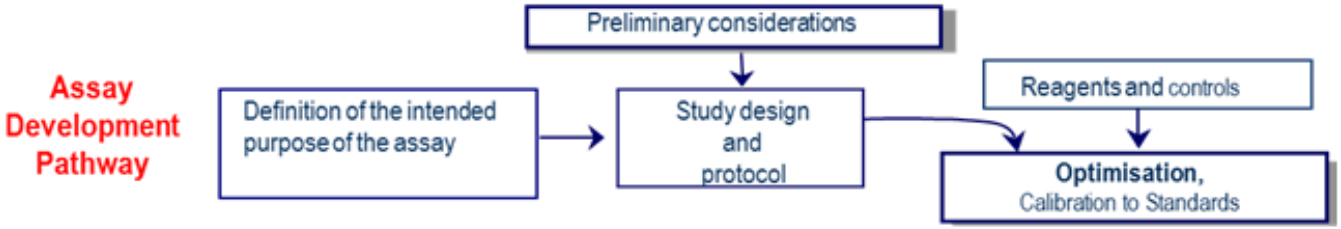
Monitor precision and accuracy
Daily in-house QC
Proficiency testing

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.

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)

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

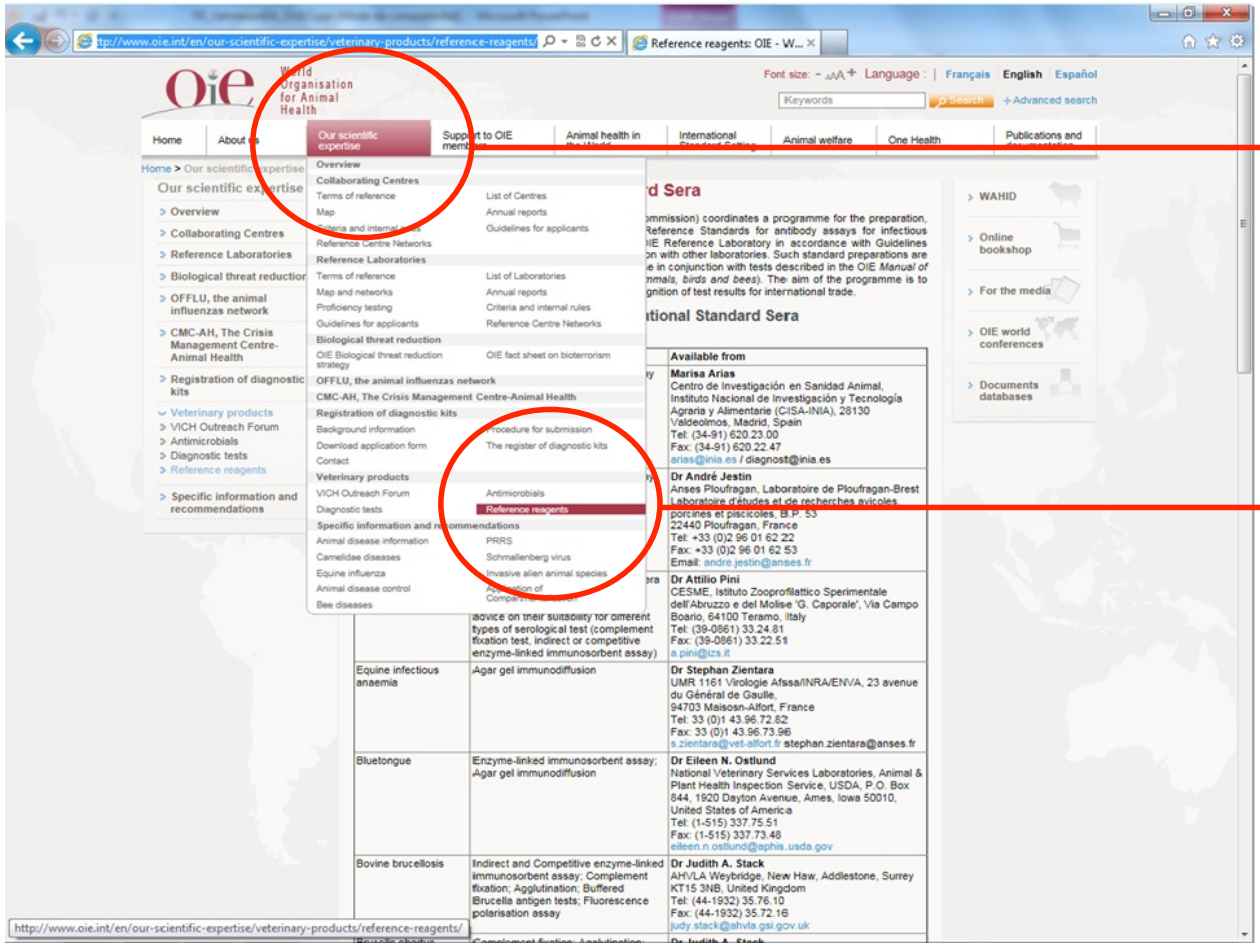
  Should be calibrated against an international or national standard

- 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

I. Assay development pathway

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

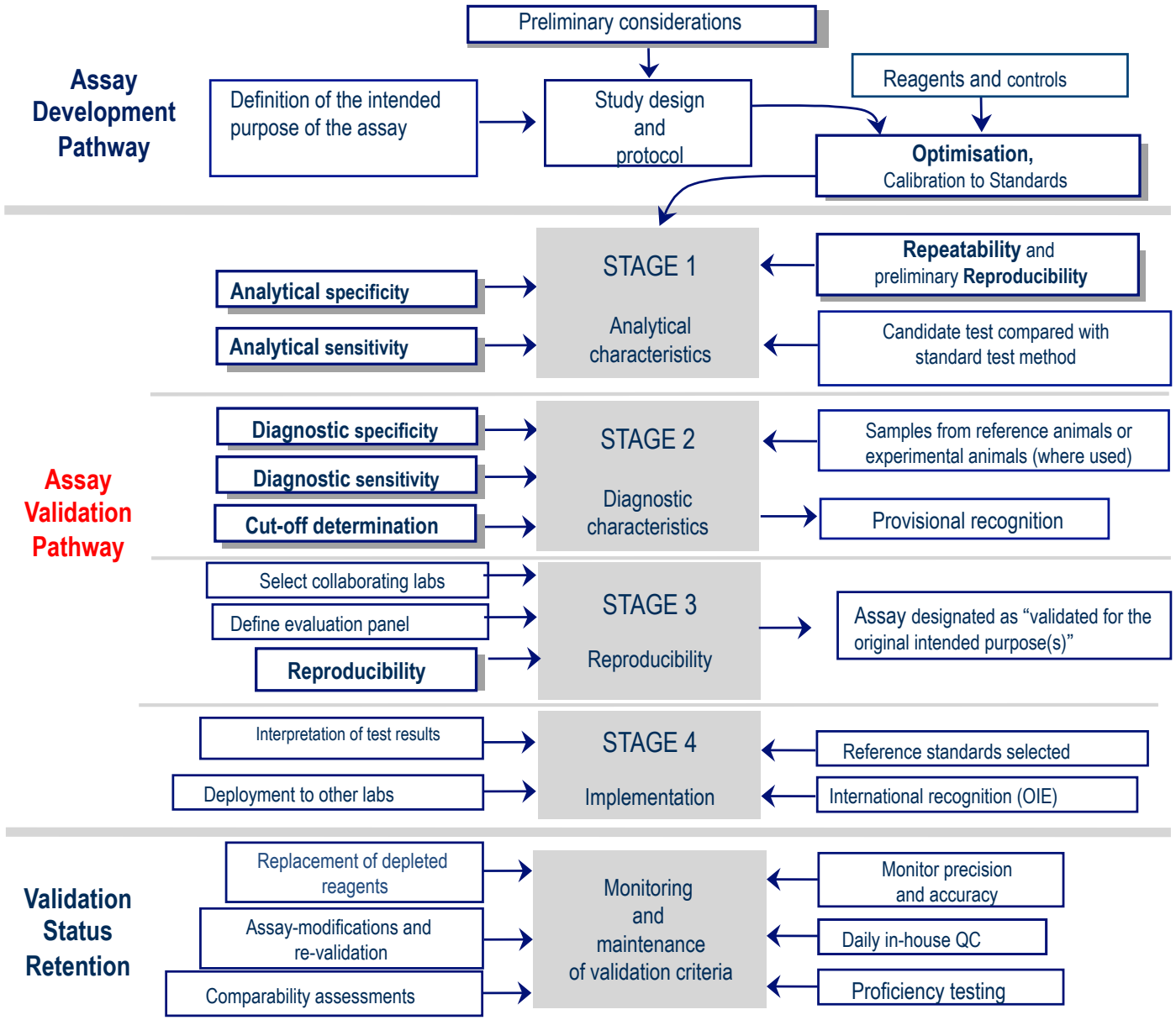


Our Scientific Expertise

Veterinary Products

- Reference Reagents

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

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

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

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

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.

II. Assay validation pathway

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

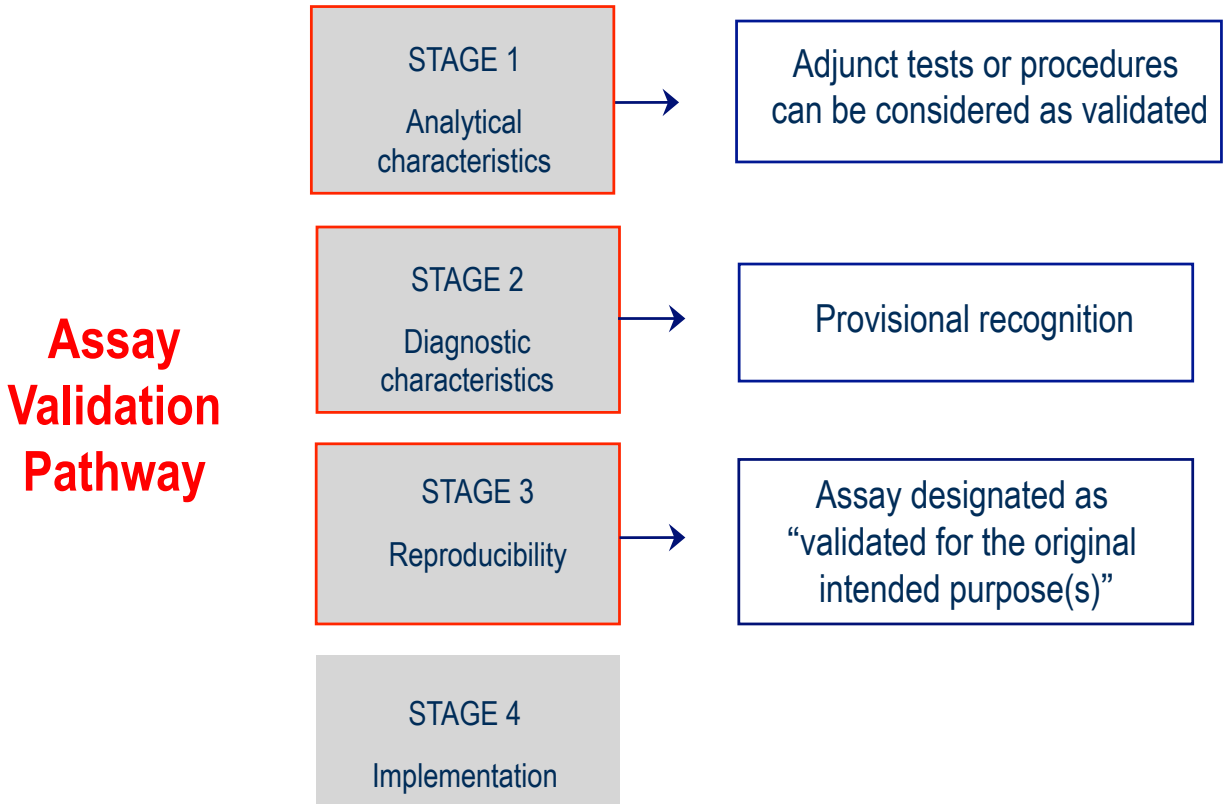
II. Assay validation pathway

- 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

II. Assay validation pathway

- When a diagnostic test method is considered as validated?



II. Assay validation pathway

- When a diagnostic test method is considered as validated?
  - **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 performance.

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

II. Assay validation pathway

- When a diagnostic test method is considered as validated?

  - **Provisional recognition**:

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

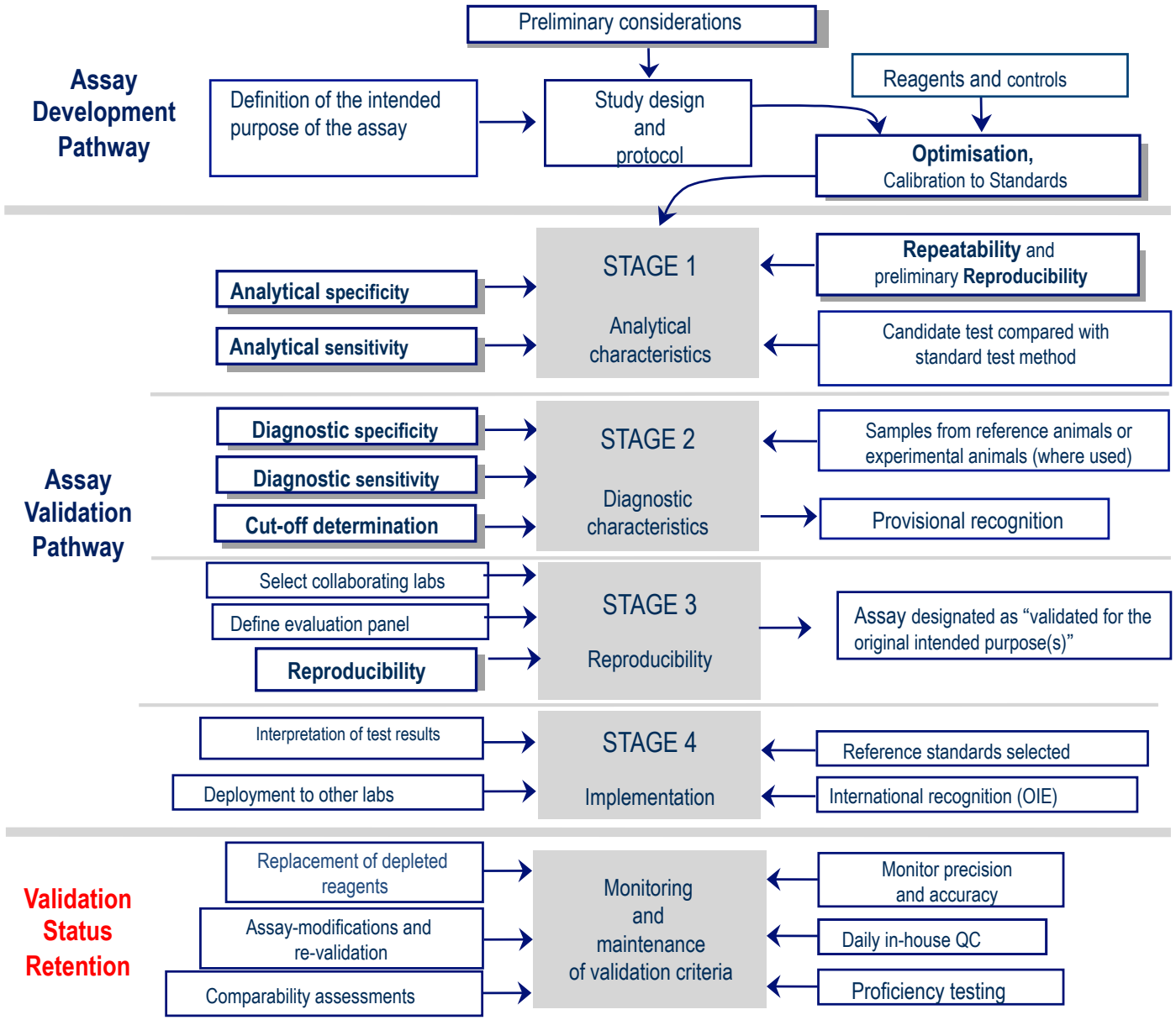
    Prov. recogn. consists in stage 1 completed + preliminary estimates of DSp and DSe + preliminary estimates of reproducibility

II. Assay validation pathway

- When a diagnostic test method is considered as validated?

  - **<u>Validated for the original intended purpose(s)</u>:**

    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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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.

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.

Support - OIE Collaborating Centres

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

FAO/IAEA Animal Production and Health Laboratory

Agriculture and Biotechnology Laboratory

IAEA Laboratories

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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

Organisation Mondiale
de la Santé Animale

World Organisation
for Animal Health

Organización Mundial
de Sanidad Animal

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