OIE Procedure for Validation and Certification of Diagnostic Assays

A FRAMEWORK FOR A HARMONISED APPROACH OF THE VALIDATION AND REGISTRATION OF VETERINARY DIAGNOSTIC ASSAYS ACROSS THE WORLD

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Introduction

• OIE Guidelines and General Principles regarding validation of veterinary diagnostic test methods

• OIE Procedure for the validation and certification of diagnostic assays

• Conclusions
OIE Guidelines and General Principles for validation of diagnostic test methods
The relevant OIE Publications

• Manual of diagnostic tests and vaccines for terrestrial animals (chapter 1.1.4/5 on “Principles and Methods of Validation of Diagnostic Assays for Infectious Diseases”)

• Manual of diagnostic tests for aquatic animals (chapter 1.1.2. identical to the chapter 1.1.4/5 of the Terrestrial Manual)

• OIE Quality Standard and Guidelines for Veterinary Laboratories: Infectious Diseases (4 Guides)
Chapter 1.1.4/5 of the OIE *Terrestrial Manual* and 1.1.2. of the *Aquatic Manual*

- New chapter resulting from the fusion of the two previous chapters on the validation.
- 7 Appendixes are in development.
- Chapter available and downloadable on the OIE website:
  - [http://www.oie.int/eng/normes/mmanual/A_summary.htm](http://www.oie.int/eng/normes/mmanual/A_summary.htm)
  - [http://www.oie.int/eng/normes/fmanual/A_summary.htm](http://www.oie.int/eng/normes/fmanual/A_summary.htm)
OIE Quality standard and Guidelines for Veterinary Laboratories

- OIE quality standard for veterinary laboratories + 4 Guides:
  1. Validation of Diagnostic Assays for Infectious Diseases
  2. Validation and Quality Control of PCR Methods used for the Diagnosis of Infectious Diseases
  3. International Reference Antibody Standards for Antibody Assays
  4. Laboratory Proficiency Testing
According to this OIE quality standard:

A test method shall be considered appropriate for routine diagnostic purposes only if it has been validated according to the principles outlined in the OIE Manual and other related OIE references.
Definition of the validation:

The validation of a diagnostic test method is a **process** that determines the **fitness of the test method**, which has been properly developed, optimised and standardised, for an **intended purpose**.

It is an ongoing process.

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**Content of the OIE Guidelines and General Principles**
The most common purposes are to:

- Demonstrate freedom from infection in a defined population (country/zona/compartment/herd)
  - ✓ Free with and/or without vaccination,
  - ✓ Historical freedom,
  - ✓ Reestablishment of freedom after outbreaks
- Certify freedom from infection or presence of the agent in individual animals or products for trade/movement
- Eradication of diseases or elimination of infection from defined populations
- Confirmatory diagnosis of suspect or clinical cases
- Estimate prevalence of infection or exposure to facilitate risk analysis
- Determine immune status of individual animals or populations
OIE validation pathway: 4 stages defined

- The validation includes estimates of the analytical and diagnostic performance characteristics of a test.

- The OIE has defined the following chronological validation pathway:
  - **Stage 1**: Analytical performance characteristics
  - **Stage 2**: Diagnostic performance of the assay
  - **Stage 3**: Reproducibility
  - **Stage 4**: Programme implementation
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.
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
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.
Content of the OIE Guidelines and General Principles

Stage 4: Programme implementation

- Extensive application of the test method in different laboratories
- Organisation of regular proficiency testing
- Monitoring the assay
- Consideration for other purposes
Study Design and Protocol

Samples from experimental animals (where used)

Samples from reference animals

Candidate test compared with Standard Test Method

Reagents and Controls

Optimization, Robustness, Calibration to Standards

STAGE 2

Diagnostic characteristics

Assay Validation Pathway

Analytical Specificity

Analytical Sensitivity

Provisional Recognition

Diagnostic Specificity

Diagnostic Sensitivity

Cut-off determination

Select collaborating Labs

Define evaluation panel

STAGE 3

Reproducibility

Ruggedness

STAGE 4

Implementation

Reference standards selected

International recognition (OIE)

Validation status retention

Replacement of depleted reagents

Assay modifications and re-validation

Equivalency assessments

Monitoring and maintenance of validation criteria

Monitor precision and accuracy

Daily in-house QC

Proficiency testing

Fitness of Assay for its Intended Purpose

Repeatability and preliminary Reproducibility

Candidate test compared with Standard Test Method

Samples from reference animals

Samples from experimental animals (where used)

Reproducibility
OIE Procedure for the validation and certification of diagnostic assays
Developed to meet the needs of OIE Member, the aim of this procedure is:

1. to certify a kit as validated fit for purpose.
2. to produce an OIE register of recognised diagnostic kits (available on the OIE web site).

All diagnostic tests for diseases, including zoonosis, caused by pathogens present in animals can be validated and certified by the OIE procedure.
OIE Procedure for validation and certification of diagnostic assays

Briefly 1/2

- Procedure based on the submission of a dossier by a kit manufacturer wishing to have the kit certified by the OIE

- Dossier, that has to be filled in, downloadable from the OIE website

- The data in the dossier are presented according to the **4 stages defined by the OIE** for the validation of a test method.
OIE Procedure for validation and certification of diagnostic assays

Briefly 2/2

- Administrative revision to check if the dossier is complete

- Scientific evaluation of the dossier by a group of 2 – 3 independent and internationally recognised experts

- If the kit goes successfully through the procedure, it is proposed by the Biological Standards Commission for inclusion in the Register to the vote of the World Assembly of Delegates

- OIE Register currently comprises 5 diagnostic kits certified (kits for Rabies, BSE/TSE, White Spot Disease, AI)
OIE Procedure for validation and certification of diagnostic assays

Outline of all the process

1. Applicant Contact
2. Dossier + Fees
3. Validation of content of the dossier
4. Appoint assessors
5. Assessment
6. Meeting of the BSC
7. Decision
8. Notification
9. Inclusion on the OIE Register

OIE Secretariat for the Procedure

Additional information

Appeals procedure

30 d

135 d
OIE Register available on the OIE Web site

Register of diagnostic kits certified by the OIE as validated fit for purpose(s)

Fit for purpose means that the kit has to be validated to such a level to show that the kit’s results can be interpreted to have a meaning in terms of diagnosis or another biological property being examined.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Name of the Diagnostic Kit</th>
<th>Name of the Manufacturer</th>
<th>Contact</th>
<th>Type of kit</th>
<th>Purpose(s) validated</th>
<th>Date and Number of registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies</td>
<td>Platelia Rabies II</td>
<td>Bio-Rad</td>
<td><a href="mailto:rahe@bio-rad.com">rahe@bio-rad.com</a></td>
<td>ELISA</td>
<td>Determination of immune status post-vaccination in individual dogs or cats (for regulation of international movement or trade), and in fox populations (for monitoring wildlife vaccination programmes)</td>
<td>May 2007 Registration Number: 200760101</td>
</tr>
<tr>
<td>Avian Influenza</td>
<td>BioChek Avian Influenza Antibody test kit</td>
<td>BioChek UK Ltd</td>
<td><a href="mailto:info@biochek.com">info@biochek.com</a></td>
<td>ELISA</td>
<td>Fit for serological diagnosis of type A avian influenza in chickens (specific to H5 in serum) and for the following purposes: 1. To demonstrate historical freedom from infection in a defined population (country/zoo, compartment/herd); 2. To demonstrate re-</td>
<td>May 2008 Registration Number: 200860203</td>
</tr>
</tbody>
</table>

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World Organisation for Animal Health
Conclusions

- Framework for a harmonised approach across the world
- Keep on improving, when relevant, the OIE Guidelines and Principles and the Procedure
- Keep on encouraging application of the OIE Standards
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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