Rev. Sci. Tech. Off. Int. Epiz., 2021, **40** (1), 173-188

Validation, certification and registration of veterinary diagnostic test kits by the World Organisation for Animal Health Secretariat for Registration of Diagnostic Kits

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Summary

The World Organisation for Animal Health (OIE), through its Secretariat for Registration of Diagnostic Kits (OIE SRDK), administers a 'Register of diagnostic kits certified by the OIE as validated as fit for purpose' (the OIE Register). The registration system is based on internationally accepted standards that have been endorsed by OIE Members, and are published in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* and the OIE *Manual of Diagnostic Tests for Aquatic Animals*. The OIE Register is intended to provide potential kit users and regulatory officials with a comprehensive source of information about OIE-registered kits, including a summary of their performance characteristics and overall fitness for an intended purpose. The registration procedure involves a rigorous assessment of the kit's performance, based on 11 criteria: definition of the intended purpose(s), optimisation, standardisation, repeatability, analytical sensitivity and specificity, thresholds (cut-offs), diagnostic sensitivity and specificity, reproducibility, and fitness for intended purpose(s). Information about the OIE diagnostic kit registration system, including a list of registered kits and an explanation of application procedures, is available online from the OIE.

Keywords

Aquatic Manual – Certification – Diagnostic kit – Diagnostic kit validation – Fit for purpose – *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* – *Manual of Diagnostic Tests for Aquatic Animals* – Provisional recognition – Register of diagnostic kits – Registration – *Terrestrial Manual* – Validation studies abstract – World Organisation for Animal Health.

Introduction

Diagnostic kits are widely used to detect pathogens or their associated immune responses in individual animals or herds. Potential applications include the confirmation of infection in clinically diseased animals, surveillance of infectious animal diseases to support control and eradication programmes, and certification of health status for international trade. Since the results of these diagnostic tests have important implications for the management of diseases, it is important that their fitness for use be appropriately validated for the species, specimens and systems in which they will be used.

https://doi.org/10.20506/rst.40.1.3216

Rationale for establishing the World Organisation for Animal Health diagnostic kit register

During the 71st General Session of the World Organisation for Animal Health (OIE) in 2003, OIE Members adopted Resolution XXIX, endorsing the OIE procedure for validation and certification of diagnostic assays (test methods) for infectious animal diseases (1). In line with this resolution, and to help address the needs of OIE Members to access high-quality, validated diagnostic kits, the OIE has established a 'Register of diagnostic kits certified by the OIE as validated as fit for purpose' (the OIE Register) (www.oie.int/scientific-expertise/registration-of-diagnostic-kits/the-register-of-diagnostic-kits/). The OIE Register lists recognised assays that have been rigorously assessed by a panel of experts and validated as fit for one or more specific purpose(s), based on the comprehensive technical standards published in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) and the OIE *Manual of Diagnostic Tests for Aquatic Animals* (*Aquatic Manual*) (2, 3).

The OIE Register is intended to provide potential kit users and regulatory agencies with comprehensive information about OIE-registered kits, including a summary of their performance characteristics and overall fitness for an intended purpose. Regulatory authorities of diagnostic kits in OIE Members are encouraged to adopt common technical standards consistent with those of the OIE *Terrestrial Manual* and *Aquatic Manual*, and to consider authorising or otherwise facilitating the use of OIE-registered diagnostic kits in their territories, where warranted. Manufacturers are also encouraged to take OIE standards into consideration when designing and implementing internal quality assurance protocols, and to consider submitting applications for registration of their diagnostic kits with the OIE.

Procedure for registering diagnostic kits with the World Organisation for Animal Health

Under this voluntary registration procedure, the evaluation process begins when a manufacturer submits an Application Form for the Certification of Diagnostic Kits as validated fit for specific purposes (Application Form) with supporting data (www.oie.int/scientific-expertise/registration-of-diagnostic-kits/download-application-form/). The Application Form includes a concise Performance Summary that is later formatted into a Validation Studies Abstract, which is made publicly available for registered kits. The registration procedures are explained in the Standard Operating Procedure for OIE Registration of Diagnostic Kits (4).

The reviews are conducted by a panel of experts drawn from the OIE Collaborating Centres and Reference Laboratories. The experts review the application with the aim of determining if the manufacturer's validation data satisfactorily demonstrate that the kit is fit for the stated intended purpose(s). When the review is complete, the panel of experts provide their conclusions and recommendations in a Final Review Panel Report, which is submitted to the OIE Biological Standards Commission or Aquatic Animal Health Standards Commission for endorsement, and subsequent approval by OIE Delegates at the OIE General Session. If approved, the kit is entered into the OIE Register, and the approved Validation Studies Abstract and User Manual are posted on the OIE Secretariat for Registration of Diagnostic Kits (OIE SRDK) website (www.oie.int/scientific-expertise/registration-of-diagnostic-kits/the-register-of-diagnostic-kits/).

World Organisation for Animal Health technical standards for validating diagnostic tests

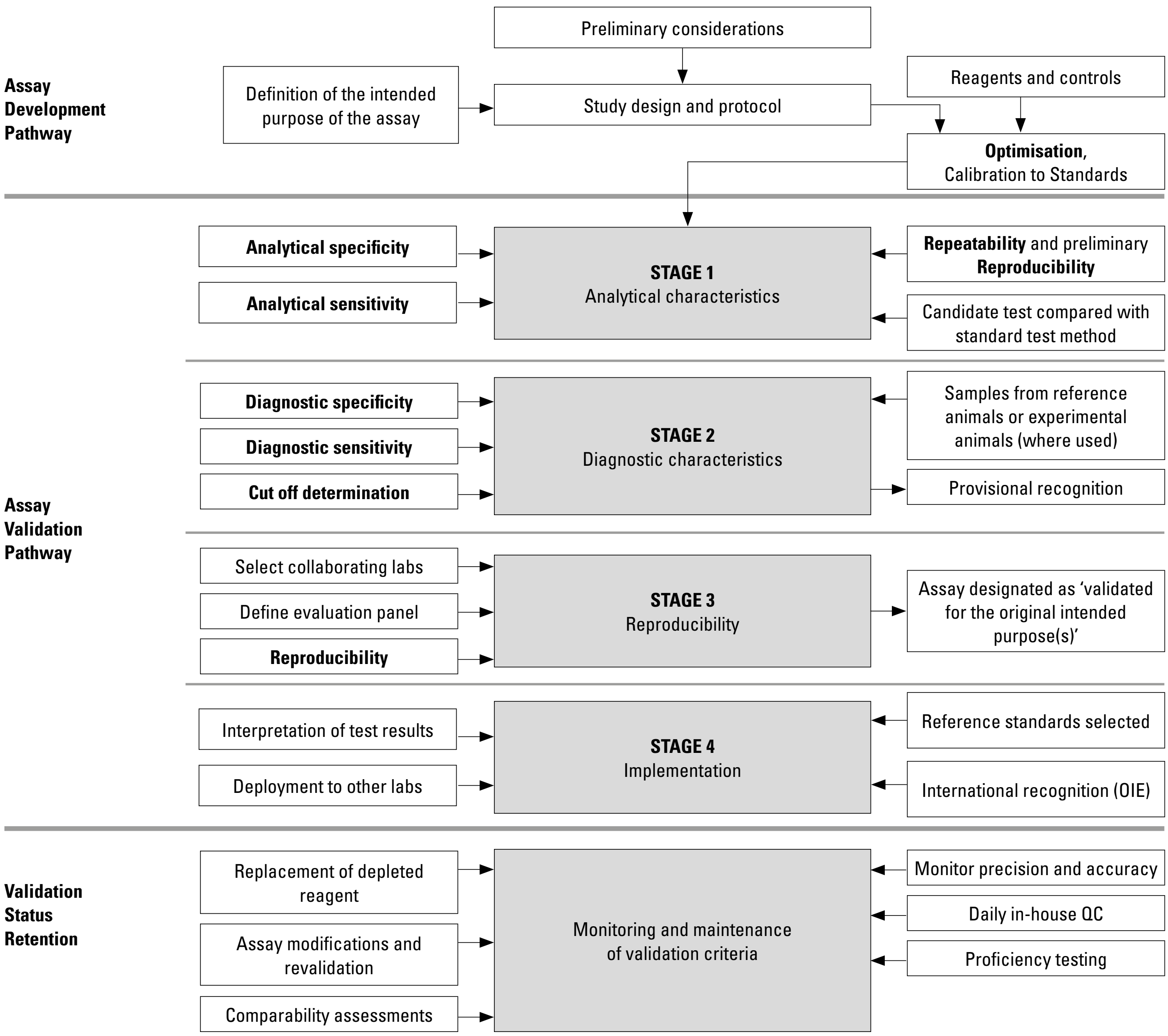
The OIE's validation procedures are based on standards described in the OIE *Terrestrial Manual*, Chapter 1.1.6., 'Principles and methods of validation of diagnostic assays for infectious diseases' (5), and in the *Aquatic Manual*, Chapter 1.1.2. of the same name (6). Additional general guidance is provided in the OIE *Terrestrial Manual*, Chapter 1.1.5., 'Quality management in veterinary testing laboratories', and Chapter 1.1.7., 'Standards for high throughput sequencing, bioinformatics and computational genomics' (7, 8).

Specific recommendations for statistical approaches to validation and the development and optimisation of specific types of diagnostic tests are presented in several chapters in the OIE *Terrestrial Manual*, Section 2.2., 'Validation of diagnostic kits' (9).

The complete pathway for assay development, assay validation, and retention of validated status is presented in Figure 1, which is an excerpt from the OIE *Terrestrial Manual*, Chapter 1.1.6. (5). The specific steps of the assay development and assay validation pathways are briefly discussed below.

Assay development pathway

The first step in assay development is to define the purpose of the assay, the target animal species, the target pathogen(s) or



OIE: World Organisation for Animal Health
QC: quality control

Fig. 1
The assay development and validation pathways, with assay validation criteria highlighted in bold typescript (5)

condition, and the sampling matrix (5). Assay development also includes optimisation, definition of the operating range of the assay (the interval of analyte concentrations or titres over which the method provides suitable accuracy and precision), standardisation, assessment of robustness, and calibration versus standard reference reagents, ideally those provided by OIE Reference Laboratories (5).

Assay validation pathway

Stage 1: Analytical performance characteristics

Analytical performance characteristics include repeatability (the level of agreement between results of replicates of a sample, both within and between runs of the same test method in a given laboratory), analytical specificity (ASp) (the ability of the assay to distinguish the target analyte from non-target analytes), and analytical sensitivity (ASe) (5). Analytical sensitivity is indicated by the limit of detection (LOD) of an assay, which is the estimated lowest amount of analyte in a specified matrix that would produce a positive result for at least a specified percentage of the time (5). A precise estimate of ASe is often not available for infectious disease assays, except in polymerase chain reaction, where it is possible to calculate the threshold number of copies of a target nucleic acid sequence that can be detected by the assay. Alternatively, it is possible to compare the LOD between the candidate test and reference test to obtain a relative estimate for ASe. For example, for serological tests, an end-point dilution analysis indicates the dilution of serum in which antibody is no longer detected. Examples of this exist in the literature (10, 11, 12).

Stage 2: Diagnostic performance of the assay

The primary diagnostic performance indicators established during validation are diagnostic sensitivity (DSe), the proportion of samples from known infected reference animals that test positive in an assay, and diagnostic specificity (DSp), the proportion of samples from known uninfected reference animals that test negative in an assay (5). In order to estimate the DSp and DSe of an assay, it is necessary to define threshold or decision limits to reduce test results to two (positive or negative) or three (positive, intermediate, or negative) categories of results (5).

Another useful indicator of diagnostic performance is the estimate of the area under the receiving operating characteristics (ROC) curve, a single numerical estimate of the global accuracy of a test, independent of cut-off values (13). It recognises that DSe and DSp at a single cut-off value do not describe the test's performance at other potential cut-off values (14). Diagnostic performance can also be indicated by the positive predictive value and negative predictive value. These are prevalence-dependent measures of the probability that, given a positive test result, the animal actually has the disease, and that, given a negative test result, the animal does not have the disease. A measure that weights both DSe and DSp and is population independent is the likelihood ratio (LR). This represents the link between the odds of the pre-test and post-test probability of disease, given a positive test result (LR of a positive test result) or negative test result (LR of a negative test result) (15).

Point estimates of DSe, DSp, LR, and area under the ROC should be calculated and reported with measures of uncertainty (such as 95% confidence intervals) (13).

One of the challenges identified in test validation is obtaining a sufficient number of samples to reliably assess an assay's diagnostic performance. The required number of samples depends on the likely values of DSe and DSp for the test and the desired confidence level for the estimates (5). Different challenges exist, depending on the samples chosen. Samples from reference animal populations may not be available in sufficient numbers to rigorously assess and characterise diagnostic performance, particularly for low-prevalence diseases, or may not be representative of the target population for the test, producing biased DSe and DSp estimates (16). Samples obtained from experimentally infected or vaccinated animals may produce less than ideal DSp and DSe estimates because multiple, serially acquired, pre- and post-exposure results from individual animals violate the requirement of independent observations (5). An additional drawback is that relatively few samples may be available from experimentally infected animals, and the dose and route of application for experimental infections may elicit a different response from that caused by natural infection.

As a result of these limitations, as well as cost constraints and animal welfare considerations associated with experimentally induced infections, it is often necessary to resort to samples from animals that have been presumptively identified as 'positive' or 'negative' by a reference test of sufficiently high accuracy. The 'gold standard model' assumes 100% DSe and 100% DSp of the reference test. However, as reference tests are rarely perfect, estimates of DSe and DSp calculated with this assumption will be flawed (5).

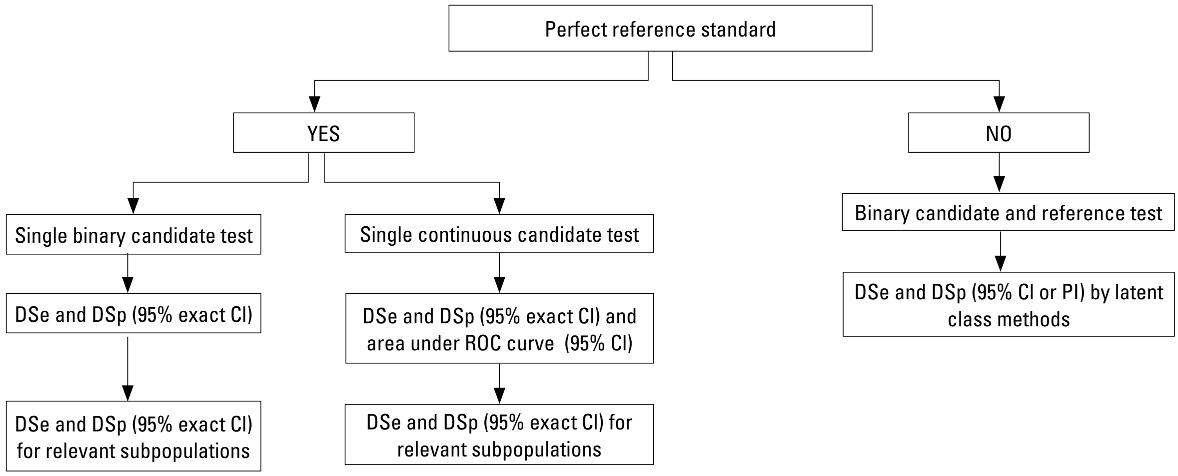
In the case of an imperfect reference test, a latent class analysis (LCA) can be performed on the joint results of the reference test and the test that is being validated, assuming that neither test is perfect (5). This analysis, via a statistical model, can be used to obtain estimates of diagnostic test performance characteristics and disease prevalence within selected populations in the absence of a gold standard. A commonly used approach in animal health is to run two tests on all samples from animals in two populations (13). A Bayesian approach can be taken by incorporating *a priori* scientific knowledge about unknown parameters, and combining this information with that contained in the likelihood based on observed data (17).

A flow chart summarising the statistical analyses that can be performed with and without a perfect reference test is presented in Figure 2 (taken from the OIE *Terrestrial Manual,* Chapter 2.2.5.) (13).

Table I presents a summary of data based on the Validation Studies Abstracts available at the OIE website for the 14 registered kits (www.oie.int/scientific-expertise/registration-of-diagnostic-kits/the-register-of-diagnostic-kits/). It includes estimates of DSe and DSp, the sample sizes used, and the source populations from which the validation samples were obtained. Thirteen of the 14 kits used reference or experimental samples and one kit used samples from naturally occurring disease in animals of unknown infection status, with a Bayesian LCA to estimate the DSe and DSp. Clear and transparently reported information is essential, as these abstracts are posted on a globally accessible OIE webpage. It is important that underlying data and information about source and target populations, case definitions and reference tests are completely described to enable readers to arrive at an informed decision as to whether a kit is fit for purpose.

Stage 3: Reproducibility and augmented repeatability estimates

Reproducibility is the ability of a test method to provide consistent results, and can be assessed through testing by at



CI: confidence interval
DSe: diagnostic sensitivity
DSp: diagnostic specificity
PI: probability interval
ROC: receiver operating characteristic

Fig. 2
Flow chart for suggested methods of statistical analysis when a single candidate test is evaluated with and without a perfect reference standard (13)

least three laboratories, using an identical protocol, reagents, controls and panel of blinded samples (5, 18). This approach also generates within-laboratory repeatability estimates through the use of replicates in individual laboratories (5).

Stage 4: Implementation

Deployment of an assay provides additional evidence of its fitness for use beyond scientific factors. In particular, it can point to practical issues (including acceptability by scientific

Table I
Summary of validation data, including source and number of samples, for diagnostic kits certified by the World Organisation for Animal Health as validated as fit for purpose [a, b]

Disease (infectious agent)	Species and specimens	Test kit name (manufacturer)	Assay type	Purpose(s)	Source of validation samples	DSe % (number of samples) [c]	DSp % (number of samples) [c]	Comments
Avian influenza (Type A avian influenza virus)	Chickens; serum	Biochek Avian Influenza Antibody Test Kit (Biochek UK Ltd)	Indirect ELISA	To demonstrate historical freedom	Not well described	100 (40)	99.2 (1,825) – 100 (302) [d]	Reference test was haemagglutinin inhibition (HI) Estimates of flock-level DSe and DSp were also provided One validation study was provided for the calculation of DSe for purposes 1, 2, 3 and 4, although in principle the samples for purpose 3 ought to be different from those for purposes 1, 2 & 4
				To demonstrate re-establishment of freedom	Not well described	100 (40)	99.2 (1,825) – 100 (302) [d]	
				To confirm suspect or clinical cases	Not well described	100 (40)	Not reported	
				To estimate prevalence	Not well described	100 (40)	99.2 (1,825) – 100 (302) [d]	
				To determine post-vaccination immune status	Experimental and field samples	85.7 (28) 2 weeks; 100 (83) 3–5 weeks	Not reported	

Notes (a) - (d) are displayed at the end of this table.

Table I (cont.) Notes (a) - (d) are displayed at the end of this table.

Disease (infectious agent)	Species and specimens	Test kit name (manufacturer)	Assay type	Purpose(s)	Source of validation samples	DSe % (number of samples)[c]	DSp % (number of samples)[c]	Comments
White spot disease (white spot syndrome virus or WSSV)	Shrimp; tissues	IQ 2000™ WSSV Detection & Prevention System (GeneReach Biotechnology Corporation)	Polymerase chain reaction (PCR)	To confirm suspect or clinical cases	Positive and negative reference samples	96.3 (300)	100 (300)	Reference test for all comparisons was nested PCR
				To estimate prevalence	Positive and negative reference samples	96.3 (300)	100 (300)	
				To certify freedom from infection	Market samples of unknown status	100 (51)	100 (49)	
White spot disease (white spot syndrome virus or WSSV)	Shrimp; tissues	IQ Plus™ WSSV Kit with POCKIT System (GeneReach Biotechnology Corporation)	Pond-side test (insulated isothermal PCR)	To confirm suspect or clinical cases To estimate prevalence To certify freedom from infection	Population with infected and non-infected, not defined IQ2000™ was used as the reference test	93.5 (400)	97 (300)	IQ2000™ was used as the reference test and agreement was 100/100 for DSe and DSp using 'undefined' shrimp from a local farm
Bovine spongiform encephalopathy- (BSE- related prion protein (PrP[Sc])	Bovines; brain	Prionics AG-Check WESTERN Kit (Prionics Ag)	Western blot (WB)	To confirm suspect or clinical cases	UK (38 positive samples) and Switzerland (190 negative samples)	100 (38)	100 (190)	Three external validation studies were performed. No clear selection of samples for a specific purpose was provided Further external validation studies were performed after 2004, including 335 positive, 24,534 negative, and 423 samples of poor quality, but no accuracy estimates were provided
				To estimate prevalence	Canada (1 positive sample and 2,036 negative samples)	100 (1)	100 (2,036)	
				To confirm a non-negative test result obtained during active surveillance	EU (300 positive samples) and NZ (1,000 negative samples)	100 (300)	100 (1,000)	
Transmissible spongiform encephalopathy (TSE) (abnormal prion protein PrP[Res])	Bovines; obex Ovines; obex Caprines; obex Cervids; lymph nodes and obex	TeSeE™ Western Blot (Bio-Rad)	Western blot	To confirm TSE-suspected positive samples To confirm prevalence To estimate prevalence	Field samples from passive or active surveillance programmes in Europe, the USA, and Canada:			The WB was validated internationally in ten external validation studies and results are summarised for DSe and DSp per species but not specifically per purpose. Agreement between the WB and other tests is also provided in tables
					Bovine	99 (315)	99.3 (282)	
					Ovine	98 (306)	100 (141)	
					Cervid	100 (272)	100 (40)	

Table I (cont.) Notes (a) - (d) are displayed at the end of this table.

Disease (infectious agent)	Species and specimens	Test kit name (manufacturer)	Assay type	Purpose(s)	Source of validation samples	DSe % (number of samples)[c]	DSp % (number of samples)[c]	Comments
Salmonellosis (*Salmonella* spp.)	Species not provided; isolates must be sampled from a pure culture	Check&Trace Salmonella (Check Points)	Multiplex LDR PCR reaction followed by detection on a diagnostic micro- array	Rapid (molecular) confirmation and serotyping of presumptive *Salmonella* spp. of 22 serotypes	Selection of regulated serotypes (n = 22)	87–100 (21–105)[d]	99.8–100 (1,614–1,697)[d]	Samples from 22 different serotypes were used to determine 'analytical' Se 96–100 and Sp 99.8–100
Salmonellosis (*Salmonella* Abortusovis)	Sheep; serum	*Salmonella* Abortusovis Test (Diatheva s.r.l)	IgG ELISA	To demonstrate historical freedom	Naturally infected and naïve sheep	97.9 (95)	98.5 (200)	Does not distinguish vaccinated from infected sheep
				To confirm suspect or clinical cases	Naturally infected and naïve sheep	99 (95)	97 (100)	
				To determine post-vaccination immune status	Vaccinates and non-vaccinates	100 (93)	100 (100)	
Bovine tuberculosis (*Mycobacterium bovis*)	Bovines; serum and plasma	IDEXX *M. bovis* Antibody Test Kit (IDEXX Laboratories)	Indirect ELISA	To detect antibody against *M. bovis* in cattle To understand prevalence and risk	Culture-positive and tuberculosis-free herds. No further information provided	64.6 (307)	98 (1,473)	Additional estimates for DSe and DSp were provided for different reference standards, e.g. single intradermal comparative cervical tuberculin test (SICCT) and gamma interferon test (IFNɣ). The applicant reported that reagents from three different lots of the ELISA were used for DSe and one lot for DSp. The impact on the accuracy of the ELISA was not discussed. Data for ASe were not provided

and regulatory communities, feasibility, and environmental impact, such as contaminated waste) or operational factors (including equipment, cost and availability, reagent stability, shelf life, storage temperatures, transport requirements, and technical skills required for use) that may impact an assay's fitness for use (5).

Validation status retention

Upon satisfactory completion of Stages 1, 2 and 3 along the validation pathway, the assay may be designated as 'validated for the original intended purpose'. However, retention of this designation depends upon continual monitoring of the assay's performance, both through assessing the results of the assay controls included with each run, and ongoing assessment of the kit's performance during routine use in the targeted population (5). The initial OIE registration is valid for five years. Renewal of registration at five-year intervals is subject to satisfactory performance throughout that time, and recommendations from a panel of experts, who are consulted before each renewal.

Table I (cont.) Notes (a) - (d) are displayed at the end of this table.

Disease (infectious agent)	Species and specimens	Test kit name (manufacturer)	Assay type	Purpose(s)	Source of validation samples	DSe % (number of samples)[c]	DSp % (number of samples)[c]	Comments
Bovine tuberculosis (*Mycobacterium bovis* and other mycobacteria belonging to the tuberculosis complex, e.g. *M. caprae*)	Cattle, buffalo, goats and provisionally sheep; whole blood	BOVIGAM® – *Mycobacterium bovis* Gamma interferon test kit for cattle; (Prionics AG)	Sandwich ELISA	To demonstrate historical freedom To demonstrate re-establishment of freedom To certify freedom from infection To eradicate infection To confirm suspect or clinical cases To estimate prevalence An ancillary test for the eradication of tuberculosis	No information provided in abstract about reference populations	Cattle 84.6 (8,879) Buffalo 81.6–91.9 (2,514) Goats 58–100 (472) Sheep 100 (4)	Cattle 97.4 (10,966) Buffalo 86.2–99.4 (608) Goats 96–100 (140) Sheep 100 (3)	The producer recommends that individual cut-offs need to be established in each country Bayesian analysis was done and resulted in a DSe of 33.9–68.8 (4,937) and DSp of 87.9–99.8 (4,937) for cattle Information is provided about comparative assessment with other tests, such as the conventional IFNɣ, skin test, etc.
Bovine tuberculosis (*Mycobacterium bovis*)	Bovines; serum	Enferplex Bovine TB antibody test (Enfer Scientific ULC)	Indirect chemiluminescent multiplex ELISA	To detect antibody against *M. bovis* in cattle serum: - to confirm clinical or suspect cases - to detect *M. bovis*-infected animals not found positive by SICCT or IFNɣ tests - to confirm inconclusive reactions in SICCT - as a positive screening test, to identify animals most likely to have visible lesions	International samples were tested using different reference tests such as culture, SICCT, CFT and IFNɣ	82–84.7 (478) (Table 4 in Validation Studies Abstract)	98.4–99.7 (4,258) 100 (161) (Table 3 in Validation Studies Abstract)	The assay has settings for a low and high cut-off resulting in high DSe and DSp estimates, and low DSe and DSp estimates, respectively. Lower and higher estimates are provided for settings in parentheses
Newcastle disease (Newcastle disease virus)	Chickens; serum	Newcastle Disease Virus antibody Test Kit ELISA (BioChek UK Ltd)	Indirect antibody detection ELISA	To demonstrate historical freedom To determine post-vaccination immune status To monitor infection or disease in unvaccinated populations To estimate prevalence	Samples for DSp were obtained from the Netherlands ($n = 79$, $n = 167$) and Germany ($n = 516$) using HI as the reference test Samples for DSe were provided from vaccinated broiler flocks ($n = 480$)	100 (480)	98.8 (762)	DSe was calculated using vaccinated broiler flocks (experimental). Data from naturally infected chickens were needed for purposes 3 and 4; 95% CI for DSe and DSp estimates were mentioned but not provided; HI was used as the reference test (Kappa for HI and ELISA was 0.992)

Table I (cont.) Notes (a) - (d) are displayed at the end of this table.

Disease (infectious agent)	Species and specimens	Test kit name (manufacturer)	Assay type	Purpose(s)	Source of validation samples	DSe % (number of samples)[c]	DSp % (number of samples)[c]	Comments
Contagious equine metritis (CEM) (*Taylorella equigenitalis*)	Horses; swabs of the reproductive tract of stallions and mares	Pourquier® IIF *Taylorella equigenitalis* (IDEXX laboratories)	Indirect immunofluorescence test	To certify freedom from infection To estimate prevalence To control infection in stallions and mares at the start of the breeding season	Three field validation studies with samples from an OIE Reference Laboratory for CEM using culture and PCR as the reference standard	100 (12) 94.7 (19) 95.4 (22)	97.2 (718) 97.6 (2,000) NA	Culture and PCR were used as reference standards. Criteria for designating an operator as 'non experienced' need to be given. Use of separate data tables for horses, and samples for both experienced and non-experienced operators, may cause confusion
					Two field validation studies performed by a 'non-experienced' operator, using culture as the reference standard	83.3 (12) 84.2 (19)	96.9 (718) 97.5 (2,000)	
Middle East respiratory syndrome (Middle East respiratory syndrome coronavirus) (MERS–CoV)	Dromedary camels; nasal swabs	BIONOTE® Rapid MERS-CoV Ag Test Kit (BioNote, Inc)	Immunochromatographic assay	Qualitative detection of MERS antigens from nasal swabs in dromedary camels for the following purposes: to detect MERS–CoV-infected herds (herd test) with acutely infected animals with high virus loads when used as a supplemental test, to estimate prevalence	No information about populations provided	93.9 (66)	99.6 (523)	Two PCRs were used as reference tests, e.g. UpE and Orf1A real-time RT–PCR
African swine fever (African swine fever virus)	Pigs and wild pigs including wild boar; blood, serum and tissues	VetMAX™ African Swine Fever Virus Detection Kit (Thermo Fischer Scientific LSI S.A.S.)	TaqMan® real-time PCR	To detect African swine fever virus in the blood, serum and tissues of pigs and wild pigs (including wild boar)	No information about populations provided for DSe and DSp estimates	100 (51 tissues)	100 (1,563 blood, serum) 100 (63 tissues)	Results from further comparative studies with established molecular tests are provided. Samples for comparison study came from European countries

a) ASe = analytical sensitivity, BSE= bovine spongiform encephalopathy, CEM = contagious equine metritis, CFT = complement fixation test, CI = confidence interval, DSe = diagnostic sensitivity, DSp = diagnostic specificity, ELISA = enzyme-linked immunosorbent assay, EU = European Union, HI = haemagglutination inhibition, IFNγ = interferon gamma release assay, IgG = immunoglobulin G, LDR PCR = ligase detection reaction–polymerase chain reaction, MERS = Middle East respiratory syndrome, MERS CoV = Middle East respiratory syndrome coronavirus, NA = not applicable, NZ = New Zealand, OIE = World Organisation for Animal Health, PCR = polymerase chain reaction, PrPRes = protease-resistant prion protein, PrPSc = scrapie isoform of the prion protein, RT–PCR = reverse transcription polymerase chain reaction, SICCT = single intradermal comparative cervical tuberculin test, TB = tuberculosis, TSE = transmissible spongiform encephalopathy, UK = United Kingdom, USA = United States of America, WB = Western blot, WSSV = white spot syndrome virus

b) This table contains only publicly available information provided by applicants in the Validation Studies Abstract for their kit, accessible at the website for the Register of diagnostic kits certified by the OIE as validated as fit for purpose (www.oie.int/scientific-expertise/registration-of-diagnostic-kits/the-register-of-diagnostic-kits/). Please note that the purposes of many of the kits, as stated in their Validation Studies Abstracts, have been summarised for this table and readers are invited to consult the full text of the purpose(s) for each kit at this website

c) Results for DSp and DSe were rounded to one decimal place

d) Where there are multiple results for DSe and DSp, e.g. using different populations and/or reference tests, the upper and lower limits are presented in the table

Current status, potential actions, and future directions for the World Organisation for Animal Health procedure for registration and certification of diagnostic kits

Current status

The OIE SRDK continually strives to maintain and expand the capacity and operational efficiency of the OIE Register, with the ultimate objective of ensuring the availability of high-quality, reliable veterinary diagnostic kits worldwide.

The OIE diagnostic kit registration procedure is a dossier-based procedure, which relies on product information and supporting performance data provided by the applicant and assessed by a panel of experts. Confirmatory laboratory evaluation or assay verification, although complementary to a dossier evaluation, is more challenging to implement and centralise, and is judged as best left to individual countries, who may prefer to perform laboratory testing that is appropriate for their particular animal health conditions and breeds. This testing could be done in national laboratories, or any other laboratory of their choice, as they see fit.

The principles and technical standards upon which the OIE diagnostic kit registration procedure is based have been widely adopted within the commercial diagnostic kit manufacturing sector. However, there has been relatively limited uptake of the OIE's formal validation and certification procedure since it was first established. As of March 2021, 14 diagnostic kits have been registered, including 12 kits for use in terrestrial animals and two kits for aquatic animals. The website of the animal health diagnostic industry association, Diagnostics for Animals (D4A), whose members account for approximately 90% of the global animal health diagnostic market, lists more than 1,640 commercially available kits (19). The D4A online database does not include information about the validation status of the listed kits, but this information can be requested from their respective manufacturers. Nevertheless, it is clear that the OIE Register currently covers only a very small percentage of commercially available kits.

The low enrolment of kits in the OIE Register, in comparison with the total number of commercially available kits, could be due to several factors. It may be that manufacturers perceive the OIE's validation requirements and administrative procedures as a 'difficult' process, primarily directed towards diagnostic tests for the highest-priority diseases. Another deterrent might be that the OIE Register and individual national registration systems tend to function autonomously, with relatively little formal communication and coordination. This is despite the fact that many countries' national registration systems for veterinary diagnostic kits are based on the same general principles as those outlined in the OIE *Terrestrial Manual* and other references, leading to a high degree of technical comparability for registered products. Since compliance with regulatory requirements constitutes a significant part of the development costs, then if OIE registration is not recognised by national authorities, there is no economic advantage for manufacturers to use the procedure.

The capacity and efficiency of the OIE Register and national diagnostic kit regulatory systems could be enhanced if there were greater coordination and work-sharing among regulatory agencies, to avoid duplicating technical reviews of applications, as well as to promote broader recognition of technical equivalency. This could also lead to cost reductions for manufacturers.

Proposed actions to increase awareness and uptake of the procedure by Members of the World Organisation for Animal Health

To promote the current OIE standards and registration procedures for diagnostic kits, and encourage OIE Members to use these resources, the following actions are being explored:

– including the topic of diagnostic kit registration in future cycles of the OIE Regional Training Seminars for National Focal Points for Veterinary Products

– strengthening cooperation, potentially through a public–private partnership, to raise awareness of available, reliable, fit-for-purpose diagnostic kits in all regions

– engaging with OIE Focal Points for Veterinary Products, to develop an understanding of national, sub-regional and regional needs for diagnostic kit registration

– considering how kits registered by the OIE could be recognised by national competent authorities, with some additional information

– exploring how the OIE procedure for registering diagnostic kits could be used as the basis for national approval processes via the global OIE network, including Headquarters, Regional Offices, Delegates and Focal Points.

Potential solutions to facilitate assessment of diagnostic performance characteristics (Stage 2 validation – diagnostic sensitivity, diagnostic specificity)

The OIE SRDK is exploring several solutions to help address the difficulties encountered in obtaining sufficient numbers of samples to estimate diagnostic kit performance characteristics (i.e. DSe, DSp and reproducibility). The lack of readily available, validated reference panels (i.e. fully characterised positive and negative reference specimens) for use in pre-registration validation studies and post-registration batch release is a challenge for all diagnostic kit manufacturers. However, it is especially problematic for the manufacturers of kits intended to diagnose emerging diseases, diseases that primarily affect minor species, and rare diseases. For these types of disease, where there may be a limited commercial market, the costs and logistical challenges of assembling the required validation panels can be prohibitive.

Similar limitations apply to validating diagnostic tests that are applied to wild animals (20). If an assay may be used for multiple species or specimens, and full validation of supplementary use(s) beyond the primary use is difficult to achieve, provisional recognition of the supplementary use(s) may be an appropriate option. Other articles in this issue discuss reference samples and virtual biobanks in more detail (21, 22).

When exploring these options, it will be essential for the documentation to conform to quality standards, such as the standards for reporting diagnostic accuracy studies (STARD) statement. The STARD statement was developed to improve the completeness and transparency of reports of diagnostic accuracy studies (23). These standards, which were updated in 2015, have been adapted to validate several different types of diagnostic tests, including diagnostic accuracy studies that use Bayesian latent class models (24). This standard provides a list of 30 essential items that should be included in every report of a diagnostic accuracy study, to assist the reader in evaluating the scientific rigour of the report.

Establish or expand existing repositories of internationally recognised reference samples/sera for validation

At present, relatively few repositories or banks of reference samples are available for validating diagnostic kits. One potential solution would be to make panels of well-characterised, validated, international standard reference samples (i.e. primary reference standards) available for shared access. These types of panels could be produced and made available on a cost-recovery basis from established reference laboratories, such as the OIE Reference Laboratories.

The need for international reference libraries of reference sera for enzyme immunoassay techniques to facilitate diagnostic test validation has long been identified (25). In 1992, a joint Food and Agriculture Organization of the United Nations (FAO) and International Atomic Energy Agency (IAEA) meeting of consultants established a consensus opinion on the use of diagnostic enzyme-linked immunosorbent assay (ELISA) techniques. The consultants' recommendations were published in a report recommending that primary reference standards for ELISA techniques should include a strong-positive, a weak-positive, and a negative standard (26).

International standard reagents for diagnostic assays for infectious diseases of animals that are approved by the OIE are already available on a limited basis from selected OIE Reference Laboratories. These standard reagents are prepared by the OIE Reference Laboratories, working in accordance with guidelines endorsed by the OIE Biological Standards Commission, and other standards, such as International Organization for Standardization (ISO) Standard 17025 (27), which describes requirements for testing and calibration laboratories, and ISO 17034 (28), which describes general requirements for the competence of reference material producers. There would be many benefits from broader access to standard reagents for validating diagnostic kits. They include:

– strengthening the overall quality and reliability of diagnostic kits used for animal disease diagnosis and surveillance
– harmonisation of diagnostic testing
– encouraging mutual recognition of the technical comparability of methods, where warranted.

All of these aims are linked to the overarching goals of protecting animal health and facilitating safe international trade in animals and animal products (and commercial trade in the diagnostic kits themselves).

Establishing inventories of reference panels for use in validating diagnostic assays would also respond directly to OIE Resolution XXIX of 2003, which endorsed the principle of validation and certification of diagnostic assays (1). Resolution XXIX stated that 'OIE Reference Laboratories should establish serum/sample reference collections to be used for validation in line with their mandates'. It would also be important to include data on population characteristics (such as age, species, sex), and the presence or absence of clinical signs, to ensure that the relevance of the reference population to the target population can be assessed.

Provisional recognition

The OIE's diagnostic kit assay development pathway (Fig. 1) includes an option for 'provisional recognition' for assays that have partially completed the validation pathway. This option is intended for assays for which it may not be feasible to provide conclusive, statistically robust data to fulfil the validation requirements beyond partial validation of their DSe, DSp and reproducibility. For provisional recognition to be granted, the proposed supplementary use would have to be satisfactorily validated through Stage 1 of the registration procedure (i.e. satisfactory demonstration of ASe, ASp and repeatability) and there must be preliminary data available to demonstrate DSe and DSp. However, the required studies, including DSe, DSp and reproducibility, have not been completed to generate conclusive, statistically robust data to fully validate the remaining steps in the assay development pathway.

Since the OIE Register is intended only to include kits that can be certified as fully validated as fit for at least one specific purpose, the OIE SRDK would ordinarily only apply this provisional recognition to supplementary uses of diagnostic kits that have been fully validated for at least one primary intended use and partially validated for other uses. For example, a diagnostic kit that has been fully validated for detection of nucleic acid, antigen or antibodies against a pathogen in specific samples from a domestic animal might also be provisionally recognised for use in detecting the same targets in alternative samples sourced from the same species or a related wild species. In these cases, there may be insufficient samples for full validation, but the assay may be useful as an ancillary/adjunct test to further characterise a diagnostic result.

Provisional recognition could also potentially be applied in special circumstances where the required validation samples are difficult to access, such as those for rare, emerging or wildlife diseases. Some regulatory authorities may decide to provisionally recognise assays that have partially met the validation requirements. This may occur when there is a reasonable expectation of satisfactory performance, based on the available validation data, and it is likely that the addition of more data over time will allow adjustment of the cut-off, or enhance confidence in the estimates. For example, Colling *et al*. (10) reported on studies to validate an ELISA antibody test for Hendra virus in horses when provisional recognition was necessary, due to difficulties in obtaining statistically sound numbers of sera from equids infected with Hendra virus.

It is important to note that provisional recognition is intended to serve as an interim or 'minor use' authorisation, and would need to be considered on a case-by-case basis. A key logistical aspect will be developing clear standards and procedures for the review and approval of supplementary data to enable a kit to proceed from 'provisional recognition' to full 'registration'. A well-defined pathway for completing each of the remaining validation steps must be established for each case.

The scope and limitations of provisional recognition for use in other species or specimens must be clearly noted in the 'Species and specimens' section of the Validation Studies Abstract and the User's Manual, to differentiate the provisionally recognised use(s) from the fully validated use(s).

Accelerated validation of kit performance when kits are required for use under emergency circumstances

An area for future consideration could be the possibility of creating an accelerated review and approval pathway for kits that need to be validated under emergency circumstances. During disease outbreaks, it may be difficult to obtain sufficient quantities of the required validation samples within a short time frame. Decisions on the implementation of this type of accelerated procedure would need to be made in a transparent manner, with input from stakeholders, to ensure that there is a consensus regarding the designation of emergencies and prioritisation of reviews.

Future directions for the World Organisation for Animal Health Register of diagnostic kits

To sustain and expand the OIE Register's contribution to global quality control of veterinary diagnostic kits, it is important to continue collective efforts to increase uptake of the registration system by diagnostic kit manufacturers. It is also essential to promote the OIE Register among regulatory agency officials as an appropriate forum for cooperation, work-sharing for quality control, and registration of diagnostic kits. To achieve success, it is essential to ensure that the registration system's validation processes and certification clearly add value to those kits that have met the registration requirement, and to provide a worthwhile return on investments by the OIE, its Reference Centres, the diagnostic kit manufacturing sector, and Veterinary Services of Members.

For optimum uptake and utility to meet the current and future needs of manufacturers, Veterinary Services, and diagnostic kit users, as well as to ensure sustainability, efficiency and adaptability, the OIE diagnostic kit registration system must continue to be based on the transparent implementation of internationally accepted technical standards. The OIE must therefore continue to work with its network of experts from Reference Laboratories and Collaborating Centres, as well as stakeholders in the diagnostic kit manufacturing sector and Veterinary Services, to identify the strengths of the OIE diagnostic kit registration procedure and the obstacles that have limited its adoption.

The ultimate goal is to facilitate OIE Members' access to quality, fit-for-purpose diagnostic tools by implementing a sustainable, efficient system for validating and certifying veterinary diagnostic kits, based on science-based principles and standards that are continuously updated to reflect technological advances. Success in achieving this goal will depend on continued progress towards adopting common technical standards and the convergence of quality assurance and validation procedures, with the goals of establishing technical comparability, avoiding unnecessary duplication, and streamlining or simplifying registration procedures. ■

Validation, certification et enregistrement des kits de diagnostic vétérinaire par le Secrétariat pour l'enregistrement des kits de diagnostic de l'Organisation mondiale de la santé animale

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Résumé

L'Organisation mondiale de la santé animale (OIE), par l'intérmediaire de son Secrétariat pour l'enregistrement des kits de diagnostic (OIE SRDK), gère un « Registre des kits de diagnostic certifiés par l'OIE comme ayant été validés aptes à l'emploi(s) prévu(s) » (en abrégé, le Registre OIE). Le système d'enregistrement repose sur des normes reconnues à l'échelle internationale, qui ont été adoptées par les Membres de l'OIE et publiées dans le *Manuel des tests de diagnostic et des vaccins pour les animaux terrestres* et le *Manuel des tests de diagnostic pour les animaux aquatiques* de l'OIE. Le Registre de l'OIE a pour objet de fournir aux utilisateurs potentiels des kits et aux agents responsables de la réglementation une source complète d'informations sur les kits enregistrés par l'OIE, y compris une synthèse des caractéristiques de performance de ces tests et de leur aptitude globale à l'emploi qui leur a été assigné. La procédure d'enregistrement d'un kit passe par une évaluation rigoureuse de ses performances à partir de 11 critères : définition du ou des objectif(s) prévu(s), optimisation, normalisation, répétabilité, sensibilité et spécificité analytiques, seuils (valeurs limites), sensibilité et spécificité diagnostiques, reproductibilité, et adéquation avec le ou les objectif(s) prévu(s). Les informations sur le système d'enregistrement des kits de diagnostic de l'OIE sont disponibles en ligne sur le site de l'OIE, y compris la liste des kits enregistrés et une explication des procédures de soumission des demandes d'enregistrement.

Mots-clés

Aptitude à l'emploi – Certification – Enregistrement – Kit de diagnostic – *Manuel aquatique* – *Manuel des tests de diagnostic et des vaccins pour les animaux terrestres* – *Manuel des tests de diagnostic pour les animaux aquatiques* – *Manuel terrestre* – Organisation mondiale de la santé animale – Reconnaissance provisoire – Registre des kits de diagnostic – Résumé des études de validation – Validation d'un kit de diagnostic.

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Validación, certificación y registro de kits de diagnóstico veterinario por la Secretaría de la Organización Mundial de Sanidad Animal

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Resumen
La Organización Mundial de Sanidad Animal (OIE), por medio de su Secretaría de Registro de Kits de Diagnóstico (OIE SRDK, por sus siglas en inglés), administra un «Registro de kits de diagnóstico certificados por la OIE y validados aptos para una finalidad definida» (el Registro de la OIE). Este sistema de registro se basa en normas internacionalmente aceptadas, que los Miembros de la OIE han suscrito y que están publicadas en el *Manual de Pruebas de Diagnóstico y de las Vacunas para los Animales Terrestres* y el *Manual de las Pruebas de Diagnóstico para los Animales Acuáticos* de la OIE. El Registro de la OIE está pensado para ofrecer a los eventuales usuarios de los kits, así como a los funcionarios de organismos de reglamentación, información completa sobre los kits registrados por la OIE, lo que incluye una síntesis de sus características de rendimiento y su nivel general de aptitud para un propósito determinado. El procedimiento de registro implica una rigurosa evaluación del rendimiento del kit en función de 11 criterios: definición del/de los propósito/s, optimización, estandarización, repetibilidad, sensibilidad y especificidad analíticas, umbrales (puntos de corte), sensibilidad y especificidad de diagnóstico, reproducibilidad y idoneidad para el/los propósito/s. En el sitio web de la OIE se puede obtener información en línea sobre este sistema de registro, incluida una lista de los kits registrados y explicaciones sobre los procedimientos de solicitud.

Palabras clave
Certificación – Kits de diagnóstico – Idoneidad para un propósito – *Manual Acuático* – *Manual de las Pruebas de Diagnóstico y de las Vacunas para los Animales Terrestres* – *Manual de Pruebas de Diagnóstico para los Animales Acuáticos* – *Manual Terrestre* – Organización Mundial de Sanidad Animal – Reconocimiento provisional – Registro – Registro de kits de diagnóstico – Reseña de estudios de validación – Validación de kits de diagnóstico.

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