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Development of a Framework for International Certification by OIE of Diagnostic Tests Validated as Fit for Purpose

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SUMMARY

Historically, the OIE has focussed on test methods applicable to trade and the international movement of animals and animal products. With its expanding role as the World Organization for Animal Health, the OIE has recognized the need to evaluate test methods relative to specific diagnostic applications other than trade. In collaboration with its international partners, the OIE solicited input from experts through consultants meetings on the development of guidelines for validation and certification of diagnostic assays for infectious animal diseases. Recommendations from the first meeting were formally adopted and have subsequently been acted upon by the OIE. A validation template has been developed that specifically requires a test to be fit or suited for its intended purpose (e.g. as a screening or a confirmatory test). This is a key criterion for validation. The template incorporates four distinct stages of validation, each of which has bearing on the evaluation of fitness for purpose. The OIE has just recently created a registry for diagnostic tests that fulfil these validation requirements. Assay developers are invited to submit validation dossiers to the OIE for evaluation by a panel of experts. Recognizing that validation is an incremental process, tests methods achieving at least the first stages of validation may be provisionally accepted. To provide additional confidence in assay performance, the OIE, through its network of Reference Laboratories, has embarked on the development of evaluation panels. These panels would contain specially selected test samples that would assist in verifying fitness for purpose.

BACKGROUND

The OIE's *Terrestrial Animal Health Code* [1] describes international trade standards for terrestrial animals and their products. Within these standards, reference is made to 'prescribed' tests methods. These are the assays required by the *Code* for the testing of animals before they are moved internationally. Prescribed tests may be found in the OIE's *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* [2]. The *Manual* is the international standard for diagnostic assays and is recognized as such in the SPS Agreement of the WTO. Therefore, the *Code* and the *Manual* are companion standards, so much so, that the disease chapters in the *Manual* are organised in the same fashion as in the *Code* for ease of cross-reference. In addition to prescribed tests, the *Manual* also describes 'alternative' tests. These assays are suitable for the diagnosis of disease within a local setting, and can be used in the import/export of animals but only after bilateral agreement. A compendium of both prescribed and alternative tests, organised by disease, may be found in the *Manual* under the heading 'List of Tests for International Trade'.

The OIE's Biological Standards Commission, which is an elected body, oversees the production of the *Manual* and is responsible for establishing or approving test methods for the diagnosis of disease in mammals, birds and bees. As indicated above, application to international trade has been at the centre of the approval process. In addition to the many disease-specific chapters, the *Manual* begins with ten

introductory chapters that cover a broad range of subject areas of general interest to infectious disease diagnostic laboratories. Two of these introductory chapters deal specifically with test method development and validation. The original chapter covers immunologic assays [3] and a more recent addition targets genomic assays [4]. Both chapters summarise the essential principles of assay development and validation that have been described in more detail by Jacobson [5]. These introductory chapters are intended to provide the scientific basis for validating assays as well as background information and guidance toward achieving a validated assay.

The OIE *Standard for Management and Technical Requirements for Laboratories Conducting Tests for Infectious Animal Diseases* [6] is a specific interpretation of the more generally stated requirements of the ISO/IEC 17025:1999 international quality standard for testing laboratories. The OIE Quality Standard clearly states that test methods and related procedures must be appropriate for specific diagnostic applications in order for the test results to be of any relevance. In other words, the assay must be 'fit for purpose'. The Quality Standard further states that in order for a test method to be considered appropriate, it must be properly validated and that this validation must respect the principles outlined in the validation chapters of the *Manual*.

The test methods currently described in the *Manual* are considered to be standard methods. Many of these test methods are 'classic' in that they have been used in diagnostic laboratories for many decades and their performance characteristics, including limitations, are well known. These assays, while still useful, will remain *status quo* in terms of reagents and format until replaced with newer technologies. The introduction of new test methods into the *Manual* has for the most part been initiated by test developers in national research establishments involved in regulatory diagnostic services. Prior to the addition of any new test method to a chapter, the developers are requested by the Biological Standards Commission to submit validation data for review. However, both the submission requirements and the peer review process have been rather informal. Based on reviewer's comments, the Commission would then consider the addition of the method to the chapter and, if appropriate, its recommendation to the International Committee of the OIE for adoption as a prescribed or alternative test for trade. The above process has precluded submissions directly from the commercial sector.

In its role as the World Organisation for Animal Health, the OIE's scope of activities has broadened considerably over the past decade. In great part, this has been driven by the global impact of diseases such as bovine spongiform encephalopathy, foot and mouth disease and highly pathogenic avian influenza. So too, the need for appropriate test methods has expanded beyond trade applications alone. Although the *Manual* sets out the general principles of test validation, it was felt by the OIE and its international partners that there was a need for a more prescriptive framework for test developers to follow in the validation process. It was also recognised that the design of the validation studies should reflect the intended application of the assay.

FIRST CONSULTANTS MEETING

The Joint Division of the Food and Agriculture Organization of the United Nations (FAO) and of the International Atomic Energy Agency (IAEA) in Vienna, Austria manages a large programme on 'Nuclear and Related Techniques in Food and Agriculture'. Animal health is a key component of the Animal Production and Health Sub-programme and the IAEA's Seibersdorf Laboratory is an OIE Collaborating Centre for ELISA and Molecular Techniques in Animal Disease Diagnosis. The Joint Division hosted two expert consultants meetings on the subject of 'OIE Guidelines for Validation and Certification of Diagnostic Assays for Infectious Animal Diseases'.

The first consultants' meeting was convened in Vienna in November, 2002. In attendance were programme experts from international organizations, including FAO, IAEA, OIE, WHO and PAHO. In addition, diagnostic experts from the UK, Canada, the USA, Australia, Denmark, and Sweden were invited. Three principle subject areas were addressed in detail:

1. Diagnostic test applications in animal health
2. Validation and performance characteristics
3. Assay recognition or certification

Given that animal disease management is required for economic, public health and environmental reasons, that risk assessment is a key component of this management and that risk assessment is highly dependent on the appropriate evaluation of animals and their products, it was agreed that fitness for purpose was integral to assay development and validation. These purposes or applications could be classified into six broad categories:

1. Demonstration of population 'freedom' from infection (prevalence apparently zero)*
   a. 'free' with vaccination
   b. historical 'freedom'
   c. re-establishment of 'freedom' post-outbreak
   * i.e. apparent 'freedom', recognising that absolute proof of freedom from infection in populations is not possible
2. Demonstration of freedom from infection or agent in individual animals or products for trade purposes
3. Eradication of infection from defined populations
4. Confirmatory diagnosis of clinical cases
5. Estimation of prevalence of infection to facilitate risk analysis (surveys, classification of herd health status, implementation of disease control measures)
6. Determination of immune status in individual animals or populations (post-vaccination)

It was agreed that the key data required to evaluate an assay comprised the following parameters:

1. Test type (detection of antibodies, infectious agents or their components)
2. Analytical sensitivity and specificity
3. Diagnostic sensitivity and specificity
4. Repeatability (within laboratory)
5. Reproducibility (between laboratories)
6. Quality assurance capability
7. Throughput capacity in the laboratory
8. Turn-around-time of test
9. Technical sophistication (skills and equipment needed)
10. Interpretation skill required

In addition to these assay performance characteristics, factors such as the epidemiological parameters of the disease and the host population, sampling strategy and the structure and capability of the field veterinary services all have an impact on the deployment and application of a given test and must be taken into consideration when designing a disease control or testing programme.

With respect to a process for recognition or certification of assays, the participants proposed the following guidelines:

1. Assay developers should apply standard template requirements towards validation of a new test.
2. Total validation package should be evaluated by other laboratories (they should not have been involved in the original validation).
3. Evaluating laboratories must have established records in working with assays for the disease in question (at least one OIE Reference Laboratory if possible).
4. The template, with supporting documents, should be submitted to the OIE for evaluation.
5. The OIE should accept the assay after a positive and independent peer review of results. The OIE should provide an independent opinion on the purpose(s) for which the assay is deemed to be fit at the time of the OIE evaluation. Any subsequent changes need re-evaluation and demonstration of equivalency or improvement.

Based on the above, the consultants' group drafted the following recommendations to the OIE:

1. The OIE should adopt a process for evaluation of diagnostic tests for specific purposes (based on the list above).
2. A standard validation template should be created to provide guidance to assay developers and to facilitate third party evaluation.
3. The template should support incremental stages of validation
4. A registration process and a registry of certified test methods should be created and managed by the OIE
5. OIE Reference Laboratories should establish characterised serum/sample collections to provide analytical references, evaluation panels and proficiency panels in support of the validation process

A complete report of the first consultants meeting was submitted to the OIE and was reviewed by the Biological Standards Commission at their biannual meeting in Paris in January, 2003.

OIE RESOLUTION

At the 71st General Session of the OIE in Paris in May, 2003, the International Committee adopted Resolution XXIX which states that:

1. Fitness for purpose should be used as a criterion for validation
2. The Director General make provisions to establish a registry for assays with levels of validation specified
3. OIE Reference Laboratories should be intimately involved with validation efforts
4. OIE Reference Laboratories should establish serum/sample reference collections to be used for validation in line with their mandates
5. The Director General be given the mandate to review, in close consultation with the Standards Commission, the procedures involved in the timely approval of assays. This may entail the creation of a specific Ad hoc group comprising relevant experts to evaluate any submissions received
6. The Director General be authorised to recover if necessary, any costs incurred in the process of validating such assays

The above resolution gave the Director General of the OIE a clear mandate to proceed with the establishment of a new process for the evaluation and certification of diagnostic tests.

SECOND CONSULTANTS MEETING

The second consultants' meeting was convened by both the Joint FAO/IAEA Division and the OIE in Vienna in December, 2003. The same experts were invited that participated in the first meeting. In addition, experts in the validation of assays in the absence of gold standards were invited from Denmark and Belgium. As the OIE resolution no longer places restrictions on who may submit validation dossiers, major stakeholders from the commercial sector were also invited. Three principle tasks were assigned to working groups selected from amongst the participants:

1. Finalise a prototype validation template
2. Propose an operating procedure for dossier submission
3. Develop guidelines for evaluation panels

A detailed prototype template was presented by the working group tasked with this assignment. The prototype was agreed by all of the participants. The key components of the prototype are listed below:

1. Background Information
   a. Test method (functional description)

b. Intended purpose(s) of test
c. Applicant
d. Scientific contact
e. Accreditation status of developing laboratory
f. Intellectual property considerations

2. Test Method
   a. Protocol (detailed description of method and reagents)
   b. Kit configuration (if commercial)
3. Validation – Stage I (Analytical)
   a. Calibration data
   b. Repeatability
   c. Analytical specificity
   d. Analytical sensitivity
4. Validation – Stage II (Diagnostic)
   a. Reference animals (description)
   b. Threshold (cut-off) determination
   c. Diagnostic performance estimates
      i. Conventional estimates of diagnostic specificity and sensitivity using defined reference animals
      ii. Mathematical estimates of diagnostic specificity and sensitivity using 'no gold standard' models
      iii. Comparison between currently used test(s) and proposed new test
5. Validation – Stage III (Reproducibility)
   a. Laboratory selection criteria
   b. Evaluation panel (description)
   c. Reproducibility analysis
6. Validation – Stage IV (Current use)
   a. Laboratories currently using test method
   b. Assay application (purpose)
   c. International reference reagents (availability of calibration reagents)
   d. Inter-laboratory testing programmes (involving assay)
   e. International recognition (list of agencies/organizations endorsing as an 'official' test method)

The second working group developed proposed guidelines for an operating procedure for submission of dossiers for potential inclusion in the OIE registry. The principle essential features of this operating protocol included:

1. Purpose and aims of registry
2. Eligibility of submitters
3. Review panel selection and composition
4. Administrative responsibilities (OIE)
5. Guiding principles for review procedure
6. Conflict resolution
7. Registration as fit for purpose
8. Change control (affecting assay performance once registered)
9. Registration maintenance and renewal
10. Registration of current 'standard' methods
11. Registration fee structure

12. Glossary of terms and definitions (to assist developers and reviewers)

The third working group developed proposed recommendations for creation and use of evaluation panels. This latter task is somewhat multipurpose as evaluation panels potentially have more than one application in the assessment of both the test method and the laboratories using them. This working group made the following recommendations related to the following:

1. Purpose and aims of evaluation panels
2. Confirmation of fitness for purpose assertions (as an adjunct to validation dossier)
3. Other applications (proficiency testing, serial release testing, etc,)
4. Composition and characterisation of evaluation panels (disease specific)
5. Responsibility for preparation and application (OIE Reference Laboratories)
6. Cost recovery of development and application of panels
7. Reporting and consequence of results

A complete report of the second consultants meeting was submitted to the OIE and was reviewed by the Biological Standards Commission at their biannual meeting in Paris in January, 2004.

CURRENT STATUS

Over the period from 2004 to the present, a web version of the validation template as described above and application instructions have been developed and published on the OIE website (www.oie.int) and the registry is now open for submissions. A secretariat has been appointed within the OIE and a set of operating procedures established for the processing of applications. The process will be overseen by the Standards Commission and it will appoint expert reviewers to assess validation dossiers. It is recognised that the template is designed around the validation of serological assays; however the same principles apply to other methods such as antigen detection and molecular methods. The template and procedures will be kept under review and will be updated and improved as necessary as in light of comments received from external sources.

Successful applicants will be allowed to use the OIE recognition as evidence of the validity of their test method for the stated purpose(s), and the register itself will be maintained on the OIE website. Tests on the register will be subject to periodic review and re-approval of their status.

Work has begun on the development of guidelines for the creation and application of evaluation panels. These guidelines will be distributed to OIE Reference Laboratories as part of their expanded role in the validation process.

Additional work is planned on the development of a template and guidelines for reviewers. This will ensure a uniform quality of review for all submissions. At the same time, the glossary of terms that currently accompanies the OIE Quality Standard will be reviewed and expanded to assist both test developers and reviewers. The glossary will be expanded to include more comprehensive epidemiological terms, new terms unique to molecular methods, as well as descriptive terms related to fitness for purpose.

The Standards Commission is also developing links with statisticians and epidemiologists with special expertise in the application of latent class and extension of Bayesian theory to new models. This will add a valuable dimension to the design of test evaluation studies.

The OIE Registry and the supporting templates and guidelines have been developed to provide a formal mechanism for the certification and recognition of test methods as fit for purpose. However, all laboratories involved test development or the application of diagnostic test methods are encouraged to use these templates and guidelines whether or not they intend to seek formal OIE recognition. In doing so, the quality of infectious diagnosis will be enhanced worldwide.

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