World Organisation for Animal Health

Training Seminar for National Veterinary Products Focal Points

Veterinary Products: A Vital Tool for Improving Animal Health and Welfare

05 – 07 September 2023 Lilongwe, Malawi

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WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals and VICH Guidelines

Dr Mária Szabó

Scientific Coordinator
Antimicrobial Resistance and Veterinary Products Department

Contributor : Dr Glen Gifford, Consultant, Ottawa, Canada

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TOPICS

1. Introduction (adoption mechanism)
2. The *Terrestrial Manual* in relation with the *Terrestrial Code*
3. Updates (relevant chapters and VICH GLs)
4. Acknowledgement (BSC)

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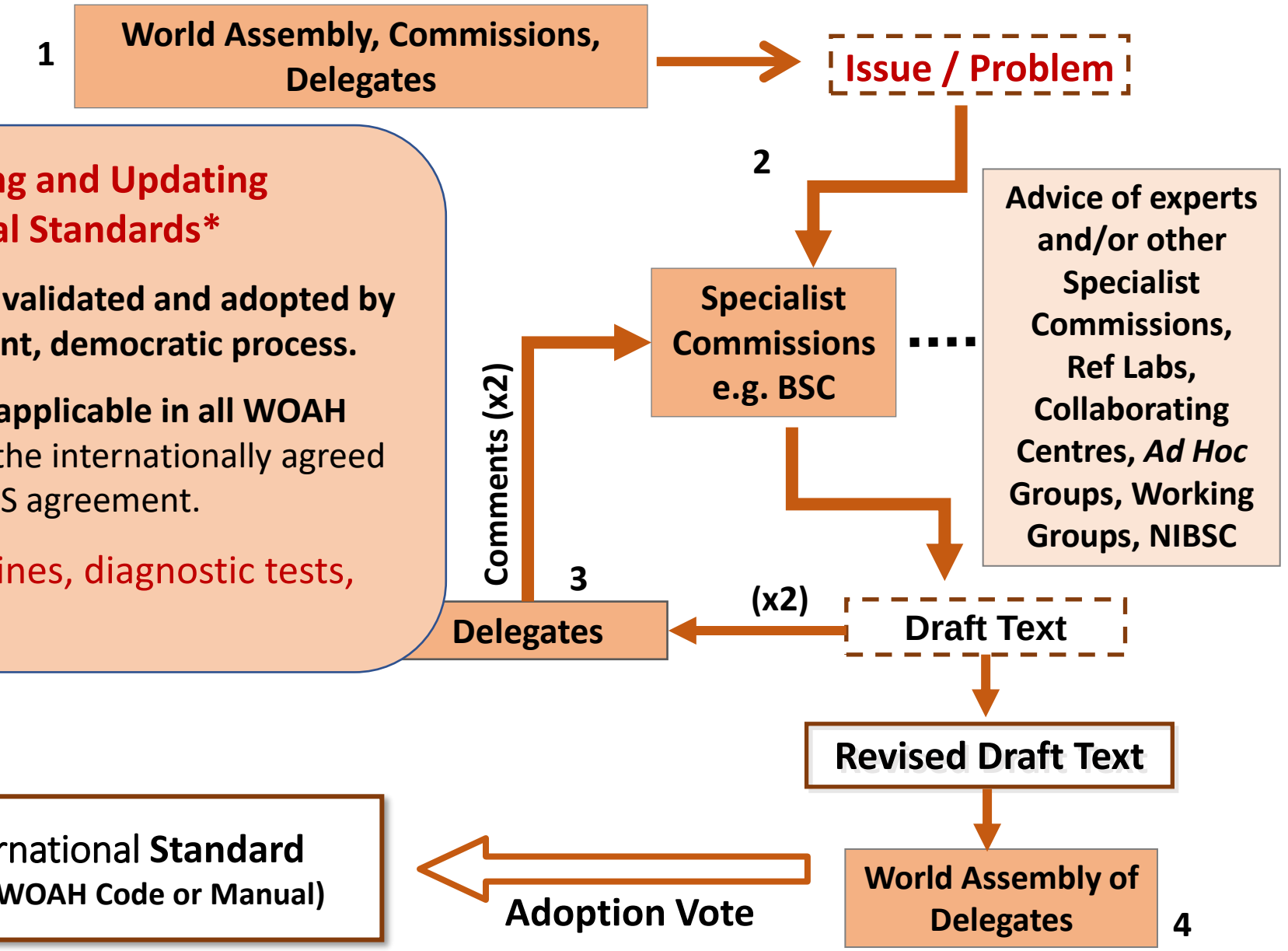
Process for Establishing and Updating WOAH International Standards*

WOAH Standards are developed, validated and adopted by Member Countries in a transparent, democratic process.

Once adopted, the standards are **applicable in all WOAH Member Countries**, and become the internationally agreed basis for trade, under the WTO SPS agreement.

* Including standards for vaccines, diagnostic tests, and reagents.



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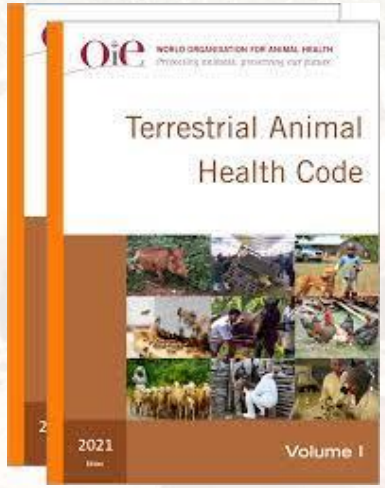
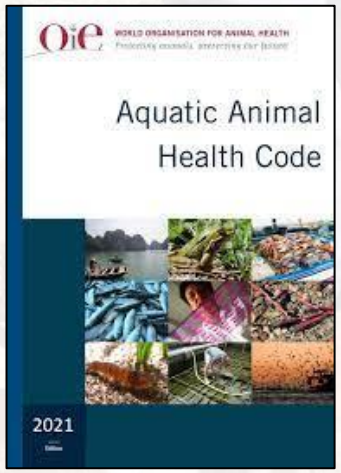
WOAH – Standard Setting

CODES

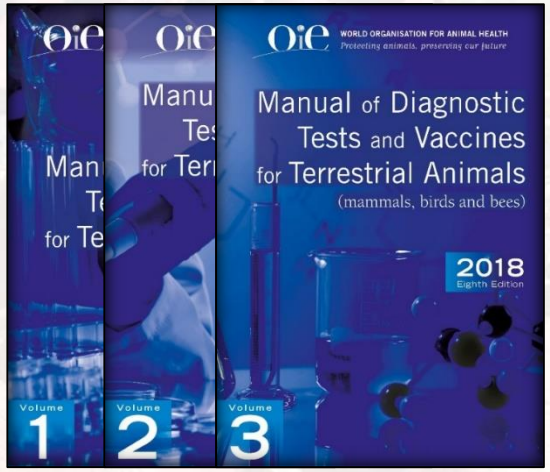
- Terrestrial
- Aquatic

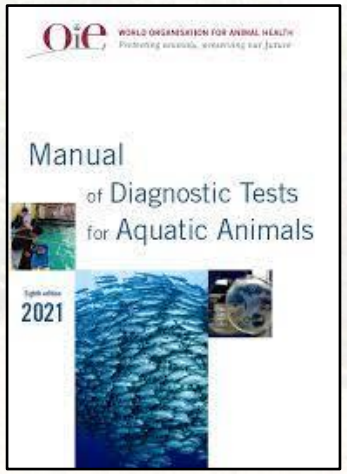




MANUALS

- Terrestrial
- Aquatic





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Relationship between Codes and Manuals

Where the ***Terrestrial Animal Health Code*** requires that tests are carried out for international movement or recommends vaccination; the ***Terrestrial Manual*** provides recommended laboratory methods and, where applicable, sets vaccine standards.

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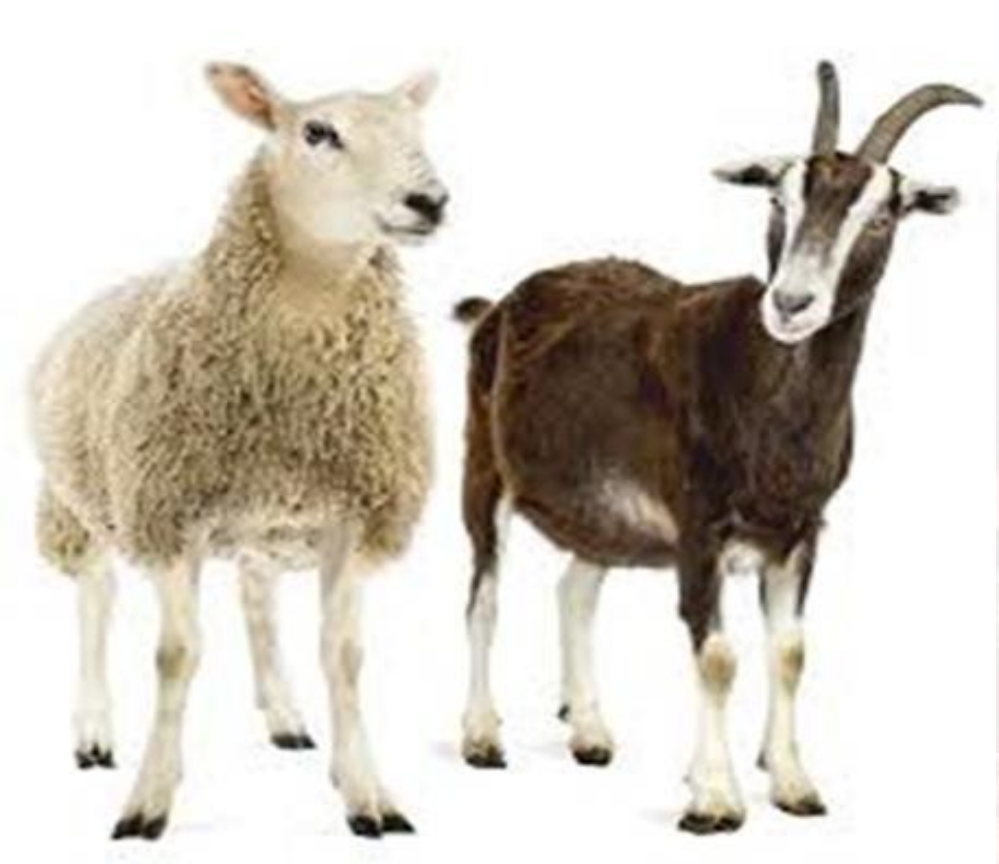

Relationship between Codes and Manuals

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WOAH *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (‘*Terrestrial Manual*’)

- All WOAH listed diseases are covered, together with additional diseases. Each chapter of the Terrestrial Manual has been written and reviewed by experts of international standing and has been approved by WOAH Members.
- The diagnostic tests and protocols referred to in the Terrestrial Animal Health Code are described in detail in the Terrestrial Manual (Chapter 1.1.6).
- The Terrestrial Manual is part of the standards recognised by the WTO.
- These publications contributed to the designation of the OIE (now WOAH) as the reference organisation for animal health by the Marrakesh Agreement establishing the WTO.

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Terrestrial Manual: Chapter 2.3.2

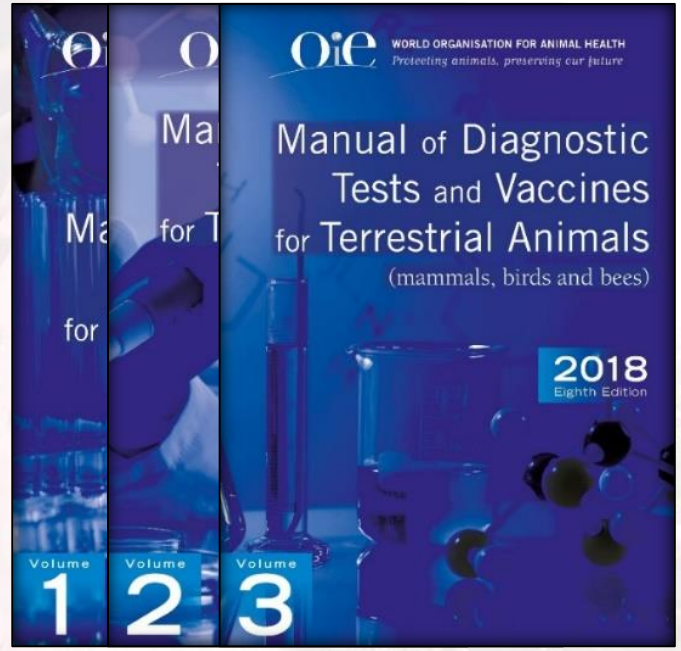
THE ROLE OF OFFICIAL BODIES IN THE REGULATION OF VETERINARY BIOLOGICALS

C. Role of International Organisations

Describes the roles, objectives and activities of WOAH (formerly OIE), WHO, FAO, VICH and national bodies.

1. The Role of the WOAH (World Organisation for Animal Health)

- Delegates, Focal Points
- Specialist Commissions, e.g., Biological Standards Commission
  - Working Groups
  - *Ad Hoc* Groups
- Reference Laboratories
- Collaborating Centres



Terrestrial Manual Online Access - WOAH - World Organisation for Animal Health

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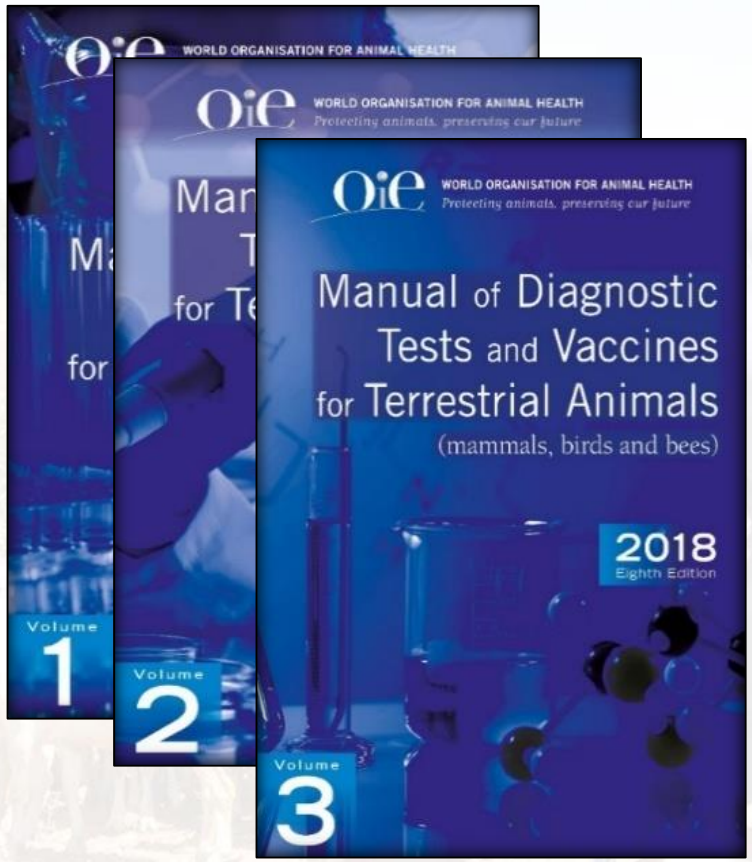

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals ('Terrestrial Manual'):

***Terrestrial Manual* Online Access** updated annually to include newly revised and adopted Chapters.

https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-manual-online-access/

Printed version, 8th edition (2018), available from WOAH Bookshop**.**
https://www.woah.org/en/ebookshop/

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Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

Online version

Access →

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Technical standards for manufacturing and quality control of veterinary vaccines

- Compilation of seven vaccine-related chapters from the *Terrestrial Code* and *Terrestrial Manual.* Published in 2019.
- Handbook intended to serve as a readily accessible technical resource for vaccine manufacturers and regulatory officials to

  Advance global awareness and implementation of the established science-based standards for the quality, safety, and efficacy of veterinary vaccines

  Maximize the quality and availability of veterinary vaccines that are required for prevention and control of animal diseases.

Available in English, French, or Spanish

Available on the Documentary Portal:

https://doc.woah.org/dyn/portal/index.xhtml?cid=3fa6cb03-c04f-4375-8b80-ae76844f71a

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Terrestrial Manual

- **INTRODUCTORY NOTE ON WOAH/OIE RECOMMENDATIONS FOR VETERINARY VACCINES/BIOLOGICALS**

  - All of the **chapters** have been **written by experts** in the respective fields and have been **subjected to an extensive process of consultation in arriving at the final texts**.

  - None of these chapters should be used in isolation. Each is designed to complement and inform the application of **Chapter 1.1.8 Principles of Veterinary Vaccine Production** in specific situations.

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Amendments to the WOAH *Terrestrial Manual*, adopted in 2022 and 2023

	1.1.6	1.1.8	2.3.4	3.8.9
Glossary Thermotolerance (2022 and 2023)	Principles and methods of validation of diagnostic Assays for infectious diseases (2023)	Principles of veterinary vaccine production (2022) • VICH GL 50, 55 and 59, noted in Section 2.2, Batch/Serial Safety Test	Minimum requirements for the production and quality control of vaccines (2022) • VICH GL 50, 55 and 59 noted in Section 2.4.1.2, Batch or Serial Safety Test	Peste des petits ruminants (infection with small ruminant morbillivirus) (2023) • 3.7.9 to 3.8.9 • 'small ruminant morbillivirus' • 2.2.4. Final product batch tests, revised and cites 1.1.8. • Table 1

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Terrestrial Manual: Part 1

- Glossary of Terms Updated : 2023
- General Standards. Introductory Chapters
- Management of veterinary diagnostic laboratories (2021)
- Collection, submission and storage of diagnostic specimens (2013)
- Transport of specimens of animal origin (2018)
- Biosafety and biosecurity: Standard for managing biological risk in the veterinary laboratory and animal facilities (2015)
- Quality management in veterinary testing laboratories (2017)
- Principles and methods of validation of diagnostic assays for infectious diseases (2013) **Updated : 2023**
- Standards for high throughput sequencing, bioinformatics and computational genomics (2016) **Principles of veterinary vaccine production (2022)**
- Tests of biological materials for sterility and freedom from contamination (2017)
- **Vaccine banks (2016) Updated : 2023**

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Amendments to the WOAH *Terrestrial Manual*, adopted in 2023

Chapter number	Title and year version adopted	Level of amendments	Major changes
1.1.6.	Principles and methods of validation of diagnostic assays for infectious diseases (2023)	Extensive	- Comprehensive revision - Added reference to point-of-care tests (POCTs) and virtual biobanks given their increasing use and importance - Improved presentation of criteria for assay development and validation - Added a table highlighting test purposes and relative importance of different performance parameters - Included a summary table on challenges and opportunities for diagnostic test validation - Added new sections on new technologies and conclusions

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Vaccine Banks

Chapter 1.1.10 VACCINE BANKS Draft revision/update…2023

D. QUANTITIES OF VACCINE REQUIRED IN A BANK

The decision as to how many doses of vaccine are required is complex, embracing questions of epidemiology, vaccinology, logistics and resources (human, technical and financial).

Factors bearing on the decision include:

i) the nature of the disease in question (serotypes, strains, pathogenesis, routes and rapidity of spread, presence and competence of vectors, etc.);

ii) the characteristics of the available vaccines (serotypes, strains, monovalent or polyvalent types of formulation), compatibility with DIVA strategies ~~vaccines~~ (DIVA: ~~detection~~ differentiation of ~~infection in vaccinated animals~~ infected from vaccinated animals), potency of the vaccines and the antigenic match between field and vaccine strains;

iii) the number, species, location and density of the animals to be protected;

iv) the types of emergency vaccination likely to be applied, and ~~whether~~ the number of doses in the vaccination ~~is with or without booster~~ regimen~~n~~;

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Terrestrial Manual : Part 2. Specific Recommendations

Section 2.1	Laboratory diagnostics
Section 2.2	Validation of diagnostic tests
Section 2.3	Veterinary vaccines
Chapter 2.3.2	The role of official bodies in the international regulation of veterinary biologicals (2018)
Chapter 2.3.4	Minimum requirements for the production and quality control of vaccines (2022)

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Terrestrial Manual : Part 1

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, twelfth edition 2023

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Terrestrial Manual: Part 2

Part 2	**Specific Recommendations**
Section 2.1.	**Laboratory diagnostics**
Chapter 2.1.1.	Laboratory methodologies for bacterial antimicrobial susceptibility testing (version adopted in May 2019)
Chapter 2.1.2.	Biotechnology advances in the diagnosis of infectious diseases (version adopted in May 2021)
Chapter 2.1.3.	Managing biorisk: examples of aligning risk management strategies with assessed biorisks (version adopted in May 2014)
Section 2.2.	**Validation of diagnostic tests**
	Introductory note on WOAH validation recommendations
Chapter 2.2.1.	Development and optimisation of antibody detection assays (version adopted in May 2014)
Chapter 2.2.2.	Development and optimisation of antigen detection assays (version adopted in May 2014)
Chapter 2.2.3.	Development and optimisation of nucleic acid detection assays (version adopted in May 2014)
Chapter 2.2.4.	Measurement uncertainty (version adopted in May 2014)
Chapter 2.2.5.	Statistical approaches to validation (version adopted in May 2014)
Chapter 2.2.6.	Selection and use of reference samples and panels (version adopted in May 2014)
Chapter 2.2.7.	Principles and methods for the validation of diagnostic tests for infectious diseases applicable to wildlife (version adopted in May 2014)
Chapter 2.2.8.	Comparability of assays after changes in a validated test method (version adopted in May 2016)
Section 2.3.	**Veterinary vaccines**
	Introductory note on WOAH recommendations for veterinary vaccines/biologicals
Chapter 2.3.1.	The application of biotechnology to the development of veterinary vaccines (version adopted in May 2010)
Chapter 2.3.2.	The role of official bodies in the international regulation of veterinary biologicals (version adopted in May 2018)
Chapter 2.3.3.	Minimum requirements for the organisation and management of a vaccine manufacturing facility (version adopted in May 2016)
Chapter 2.3.4.	Minimum requirements for the production and quality control of vaccine (version adopted in May 2022)
Chapter 2.3.5.	Minimum requirements for aseptic production in vaccine manufacture (version adopted in May 2016)

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Terrestrial Manual : Part 3. WOAH Listed Diseases and Other Diseases of Importance

Section 3.1	Multiple Species
Section 3.2	Apinae
Section 3.3	Aves
Section 3.4	Bovinae
Section 3.5	Camelidae
Section 3.6	Equidae
Section 3.7.	Leporidae
Section 3.8	Caprinae
Chapter 3.8.9	Peste des petits ruminants (infection with small ruminant morbillivirus) (2022)
Section 3.9	Suidae
Section 3.10	Other Diseases

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Biological Standards Commission:

WOAH-Approved International Standard Reagents

World Organisation for Animal Health

Biological Standards Commission Reports

Report of the Meeting of the WOAH Biological Standards Commission

Original: English (EN)

6 to 10 February 2023
Paris

Introduction and Member contribution

A meeting of the WOAH Biological Standards Commission (hereafter called 'the Commission') was held from 6 to 10 February 2023 at the WOAH Headquarters in Paris, France. During the meeting, 15 chapters from the WOAH *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) were approved for circulation for second-round Member comment and proposal for adoption at the General Session in May 2023. The Commission wished to thank the following Members for providing comments on draft texts for the *Terrestrial Manual* circulated with the Commission's September 2022 report: Australia, Belgium, Canada, China (People's Republic of), Chinese Taipei, Japan, New Zealand, Switzerland, the United States of America (USA), the United Kingdom (UK) and the 27 Member States of the European Union (EU). The Commission also wished to acknowledge the valuable advice and contributions from numerous experts of the WOAH scientific network.

Overview Members Reports Draft Chapters Links

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WOAH-Approved International Standard Reagents

- **WOAH-Approved International Standard Reagents**

- The WOAH Biological Standards Commission (BSC) coordinates a programme for the preparation, validation and distribution of WOAH-approved International Standard Reagents for diagnostic assays for infectious diseases of animals.

- The standards are prepared by a WOAH Reference Laboratory in accordance with Guidelines for antibody, antigen and polymerase chain reaction (PCR) standards drawn-up by the BSC in collaboration with other laboratories.

- The standard preparations are designated by the WOAH as primary reference standards for use in conjunction with tests described in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*mammals, birds and bees*).

- The aim of the programme is to harmonise diagnostic testing and encourage the mutual recognition of test results for international trade

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Reference Reagents

- The term '**International Standard Reagent**' is synonymous with **primary** standard.
- It represents the standard by which all others (secondary standards) are compared and calibrated.
- Secondary standards may represent national standards or working standards that are in routine use at the diagnostic laboratory level.
- The secondary standard and **not** the International Standard are to be used on a daily basis to standardise testing.
- The International Standard Reagents listed above may be obtained, in small quantities, at the corresponding address. Some laboratories may make a charge for this service.

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BSC Report Sept 2019 (extract)

10.5. PPR vaccine: SOP for thermotolerance test

The Commission received a report on the work of the PPR GEP to develop a draft testing protocol titled “Recommended procedure for PPR vaccine thermotolerance test as part of the PPR GEP”, which was prepared by the AU-PANVAC. The Commission acknowledged that this protocol would be a very useful reference that could be cited in the *Terrestrial Manual* chapter once it has been made available, preferably through publication in a peer-reviewed scientific journal.

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Thermotolerance Amendments

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Thermotolerance Amendments

Background considerations:

- Factors that can affect efficacy of vaccines:
  - Maintenance of the cold chain during storage and transport
  - Specific thermotolerance properties of vaccines (liquid vaccines tend to be less stable than lyophilized vaccines)

- The African Union Pan African Veterinary Vaccine Centre ((**AU-PANVAC)** was asked to develop a draft Standard Operating Procedure (SOP) to describe the process for testing thermotolerance of PPR vaccines.

Terrestrial Manual (2022): Added definition “thermotolerance” to Glossary and further described in Chapter 1.1.8, PRINCIPLES OF VETERINARY VACCINE PRODUCTION.

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Thermotolerance

WOAH Biological Standards Commission

Developed a revised **glossary** definition and expanded guidance for characterizing **thermotolerant** vaccine in the WOAH *Terrestrial Manual.*

> "Thermotolerant: For vaccines, the term is used to describe the ability to retain protective immunogenicity after exposure to temperatures above the storage temperature required according to the manufacturer's recommendations. Claims of thermotolerance must be supported by data."

Further information is provided in Chapter 1.1.8 PRINCIPLES OF VETERINARY VACCINE PRODUCTION. 6. Stability Tests.

Chapter 3.8.9 PESTE DES PETITS RUMINANTS (INFECTON WITH SMALL RUMINANT MORBILLIVIRUS), Section 2.3.3 contains a brief general statement about stability of lyophilised PPR vaccine.

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Chapter 1.1.8 Principles of Veterinary Vaccine Production

6. Stability tests

It is important to monitor the stability of each product through a programme to determine on-going stability.

Conditions of storage affecting the quality of the product should be taken into account as evaluated in the relevant regulatory approval, including light, temperature and the adhesive/absorptive properties of containers. All vaccines are sensitive to heat to some extent, but some are more sensitive than others. There is increasing interest in the development of vaccines that can tolerate adverse storage conditions. In this *Terrestrial Manual*, thermotolerant (see Glossary of Terms) is defined as the ability of vaccines to retain protective immunogenicity after exposure to temperatures above the storage temperature required according to the manufacturer's recommendations. Various electronic devices and heat-sensitive indicators are available to monitor cold chain temperatures. Specific thermotolerance claims should be supported by data from time–temperature studies undertaken under the relevant storage or transport conditions.

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Biological Standards Commission Reports

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BSC Report Sept 2019 (extract)

3.2. Request to delete from the *Terrestrial Manual* recommendations for conducting abnormal toxicity test (ATT) and target animal batch safety test (TABST) for veterinary vaccines

The Commission discussed a proposal from a stakeholder organisation that the OIE should revise its *Terrestrial Manual* guidance regarding animal-based batch release testing for veterinary vaccines to delete all recommendations for conducting abnormal toxicity tests (ATT) and target animal batch safety tests (TABST).

The Commission noted that *Terrestrial Manual* Chapters 1.1.8 *Principles of veterinary vaccine production* and 2.3.4 *Minimum requirements for production and quality control of vaccines* provide general guidance regarding alternatives to animal testing, in recognition of "3R" principles to refine, reduce, and replace use of animals for laboratory testing.

Corresponding amendments to eliminate animal-based batch release testing are also being incorporated into the batch release testing sections of individual disease-specific chapters to further highlight the importance of eliminating animal-based testing for batch release of veterinary vaccines whenever feasible.

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Target Animal Batch Safety Test (TABST)

In 2020, the OIE Biological Standard Commission, concluded that, rather than completely eliminating all references to the TABST, references to the TABST in the *Terrestrial Manual* should be revised to include a note that the prescribed TABST could be eliminated in situations where other quality control measures are in place.

The proposed revised texts for *Terrestrial Manual* chapters **1.1.8**, **2.3.4**, and **3.8.9** were adopted through Resolutions that were approved in the WOAH General Session in May 2021 and May 2022.

BSC implemented its decision regarding TABST by amending the TABST text in *Terrestrial Manual* chapters **1.1.8**, **2.3.4** and **3.8.9**.

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Target Animal Batch Safety Test (TABST) Amendments

World Organisation for Animal Health

Target Animal Batch Safety Test (TABST) Amendments

Background information/rationale:

- 3R principles to replace, reduce and refine use of animals In product testing and scientific research
- VICH Guidelines 50 & 55
- *European Pharmacopeia*
- EPAA (European Partnership for Alternative Approaches to Animal Testing)
- IABS (International Alliance for Biological Standardization)

Consultation:

- WOAH Collaborating Centres in France, Russia, United States of America, Japan, and Ethiopia.
- WOAH PPR Reference Laboratories in United Kingdom, France, and China.

Advice from experts:

- Some experts had noted that, due to potential variability of quality assurance systems employed by manufacturers in WOAH Member Countries, and the potential for residual toxicity of some vaccines, it would be inappropriate to completely eliminate all references to the TABST in the *Terrestrial Manual.*

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Target Animal Batch Safety Test (TABST)

Chapter 2.3.4 MINIMUM REQUIREMENTS FOR THE PRODUCTION AND QUALITY CONTROL OF VACCINES

2.4.1.2. Batch or serial safety test

i) Safety tests are not required by many regulatory authorities for the release of each batch or serial where the seed-lot system is used. Other regulatory authorities may allow waiving of target animal batch safety tests in line with VICH GL50 and 55 and waiving of laboratory animal batch safety tests in line with VICH GL59 where alternative methods exist.

ii) Where required, standard procedures are used for safety tests in mice, guinea-pigs, cats, dogs, horses, pigs, and sheep and are generally conducted using fewer animals than are used in the safety tests required for licensing. Batches or serials are considered satisfactory if local and systemic reactions to vaccination with the batch or serial to be released are in line with those described in the relevant regulatory approval dossier and product literature.

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3Rs (Objective: To refine, reduce, and replace target animal batch release testing for veterinary vaccines)

In a collaboration which started 19 May 2022, two webinars and a face-to-face workshop were organised to determine what was needed to facilitate alternative methods validation, implementation and regulatory acceptance, including global harmonisation, of non-animal-based batch release testing for veterinary vaccines.

A summary report from the 3Rs webinars and workshop, titled **3Rs Implementation in Veterinary Vaccine Batch-Release Testing: Current state-of-the-art and future opportunities,** was published in the journal 'Biologicals' in July 2023.

More information about these events is available at the following web sites:

- www.afsacollaboration.org/sciencex_event/3rs-implementation-in-veterinary-vaccine-batch-release-testing-current-state-of-the-art-and-future-opportunities/
- https://reference-standards-ottawa-2023.iabs.org/

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“If you want to go fast, go alone. If you want to go far, go together.”

-African Proverb-

Thank You !

Dr Maria Szabó
Scientific Coordinator
Antimicrobial Resistance and Veterinary Products Department
m.szabo@woah.org