CONCLUSIONS AND RECOMMENDATIONS

Annual Meeting

XXV Seminar on Harmonization of Registration and Control of Veterinary Medicines Americas Committee for Veterinary Medicines (CAMEVET)

November 17-19, 2021

Opening speeches

1. Participants were welcomed by Ms Ana Sgammini, CAMEVET Administrative Secretary, Dr Aida Rojas, Focal Point for Veterinary Products from Colombia, Dr Luis Barcos, OIE Regional Representative for the Americas, and Dr Alfonso Araujo, on behalf of the Colombian Agricultural Institute (ICA).

Designation of President

2. Dr Aida Rojas was formally nominated as president of the Seminar.

Plenary meeting of the official sector

3. Dr. Aida Rojas, as president, and Dr Federico Luna, member of the CAMEVET Executive Board, presented the conclusions of the meeting of the official sector. Topics discussed included the unanimous approval of the extension of the current Executive Board for one year on an exceptional basis.
4. The report of the meeting, containing a detail of the topics discussed is attached as **Annex I**.

Plenary meeting of the veterinary industry

5. Dr. Carlos Motta, representative of ASOVET Guatemala and member of the CAMEVET Executive Board, presented the topics discussed at the meeting held by the veterinary products industry sector. The importance of the adoption and acceptance of digital signatures was remarked, both for official documents and company notes, and a request was made to standardize specific documents that do not have an apostille as well as defining which require certificated signatures. In relation to labeling, the difficulty in the different countries was indicated because different criteria are applied for products labelling. The possibility of analyzing the registration fee for the next presential seminars was also proposed.
6. The report of the meeting containing a detail of the topics discussed is attached as **Annex II**.

It was resolved, by decision of the Plenary, to extend the current Executive Board positions for one year, due to the COVID-19 health situation. This implies that the

new Executive Board will be elected next year in a presential seminar. The new section to be incorporated to the CAMEVET rules is included as **Annex III.**

Secretariat Report

Ms. Ana Sgammini presented a report of the CAMEVET Secretariat, indicating that the working documents are still in progress. Detailed report is included as **Annex IV**. During the last years, a total of 8 harmonized guidelines were submitted for review and are pending for approval.

It was considered that is important that CAMEVET continues participating in VICH and other regional conferences. For that, the Executive Board will define who will be the representative of the official sector that may represent CAMEVET in the VICH extension forums.

Session I- Review of Working Documents Step IV

License extension of pharmaceutical veterinary products on minor species

Dr Christopher White, on behalf of SINDAN (Brazil), presented the progress made on the draft, currently in Status IV.

He also presented the most relevant comments received the document was circulated.

The document was approved unanimously, and is included as **Annex V**

Diagnostic Kits

Dr Byron Rippke, Focal Point of Veterinary Products from United States, presented the progress in the draft revision, currently in Status IV. In addition, presented the most relevant comments received after the document circulation.

The document was approved unanimously, and is included as **Annex VI**

Guide for the classification and inspection of veterinary products without therapeutic indication

Dr Henrique Uchio Tada, on behalf of ALANAC (Brazil), presented the progress made on the draft, currently in Status IV. It was decided to make a final circulation of the document with a 120-day deadline for comments. Based on this circulation and if there are no opposing opinions, the document will be finally proposed for approval by the next seminar.

Efficacy tests for registration Internal Antiparasitics for Ruminants and Swine

Dr Carlos Francia, representative of CAPROVE (Argentina), presented the advances in the draft revision, currently in Status III. He highlighted the comments received after having circulated the document. Since an agreement was not reached, it was decided to organize an extraordinary working group virtual meeting, in order to review the document. After that revision, draft shall be circulated again, as Status III document, with 60 days for receiving comments. The final version shall be presented at the next seminar as a final document.

Labeling Guide

Dr Tatiana Leal, Focal Point of Veterinary Products of Costa Rica, presented the progress made on the document, which is currently in Status II. Following the presentation of the results of the survey, and since no agreement was reached, it was decided to organize an extraordinary virtual meeting including all the Focal Points for Veterinary Products, as members of the working group, to review the document. Once an agreement is reached by the working group, draft will be circulated as a Status III document, with a deadline of 90 days for review and comments from all CAMEVET members.

Dr. Mc-Allister Tafur, on behalf of the Andean Community General Secretariat, offered the collaboration for the working group.

Good Manufacturing Practices for the manufacture of Veterinary Products

Dr Berta Chelle, Veterinary Products Focal Point from Uruguay, presented the progress made on the document revision, currently as Status II. Draft will be circulated again among the members of the working group for 60 days for the submission of comments. In case necessary, a virtual working group meeting will be convened to review the document, and its change into Status III document. Such draft will be circulated for 90 days for revision and comments submission by all of the CAMEVET members.

Session II – OIE and FDA presentations

Progress in the tripartite project on antimicrobial resistance, funded by the EU

Dr Maria Mesplet, Project Officer, presented the progress made in tripartite project "Working together to fight the AMR", based on "One Health" and financed by the European Union. The project is being implemented in 7 countries of the region: Argentina, Brazil, Chile, Colombia, Paraguay, Peru and Uruguay.

It was informed that one of the components of the project is based on the strengthening of the National Action Plans, and also presented the various awareness campaigns on the use of antimicrobials developed at individual countries and regionally. She also highlighted the importance of encouraging the private sector to participate in the AMR control through the creation of public-private partnerships.

She added that one of the project activities includes the creation of an e-learning platform on Antimicrobial Resistance, intended for veterinary professionals and the general public. Regarding other the activities, mentioned the development of an app for cell phones, which will allow to verify the registration of veterinary products containing antimicrobials as well as accessing technical information on such products. For that, she remarked the importance of the support to be provided by CAMEVET, especially in order to ensure its sustainability after the project finishing the end of 2023.

Report in the collection of antimicrobial use data

Dr Delfy Góchez, from the OIE Headquarters Antimicrobial Resistance and Veterinary Products Department, presented the results of the annual collection of antimicrobial use data. She highlighted the participation of the region during the 5th round of data collection, and remarked that the provision of information to this database is based on the OIE Standards. For that, she added that the OIE Codes set the need for countries to collect and monitor the quantities and use patterns of antimicrobials, as part of their national Antimicrobial Resistance surveillance programs.

Based on the 5th antimicrobial usage report published by the OIE, she remarked an increase in the number of countries providing quantitative data on antimicrobial use. It was also highlighted that, globally, 70% of countries do not use antimicrobials as growth promoters. Such value contrasts with the high rate of countries in the Americas where their usage is still authorized.

During the 2015 – 2017 period, there was a decrease in the use of antimicrobials both globally and at the regional level.

She announced that the report of the 6th round of data collection will be published in early 2022 and invited to continue collaborating and improving national systems and data provision to the OIE.

Importance of the human intestinal microbiome in the evaluation for FDA approval of drugs for consume animals

Dr Silvia Piñeiro, representing the FDA Center for Veterinary Medicine, made a presentation on the importance of the human microflora and how it is affected throughout life, for example, by the use of antibiotics.

In this regard, mention was made of the FDA159 guidance, harmonized in VICH GL36, which establishes the studies to evaluate the safety of veterinary drug residues in animals for human consumption, assessing the risk of development of antimicrobial resistance in human intestinal microorganisms.

The steps in which FDA evaluates the presence of residues in the human intestine and their activity were presented. On the other hand, a mention was made of the project with which the FDA is working on the intestine-on-chip model to study the effects of drug residues on the human intestinal microbiome and the development of antimicrobial resistance.

Session III – Working groups

Procedures for imported products

Dr Luiz Monteiro, representing SINDAN (Brazil), presented the proposal for a new topic. After the proposal, it was decided that, in order to form the working group, a Concept Note will be sent to all CAMEVET will be decided the working group creation.

Additionally, it was proposed that the document should be an extension to the already harmonized CAMEVET guide on Free Sales Certificates.

Complementary studies to the stability guide

Dr. Patricia Millares, representing CAPROVE (Argentina), presented the proposal for the new topic. The working group will be coordinated by CAPROVE and formed by the official representatives from Argentina, Colombia, Costa Rica, Cuba, Ecuador Guatemala, Mexico and Uruguay, as well as the industry representatives from AENSA (Ecuador), ALANAC (Brazil), ALFA (El Salvador), ANALAV (Mexico), APRIVET (Bolivia), APROVET (Colombia), ASOVET (Guatemala), CADIN (Nicaragua), CAPALVE (Paraguay), CLAMEVET (Argentina), CEV (Uruguay) and LABIOFAM (Cuba)

The secretariat will circulate the concept note and will contact the working group for its activities coordination.

Veterinary drug residue studies

Dr. Federico Luna, Focal Point for Veterinary Products from Argentina, presented the proposal for the new topic. The working group will be coordinated by the official sector of Argentina and formed by the official representatives from Colombia, Costa Rica Ecuador, Guatemala, Mexico, Paraguay and Uruguay, as well as the representatives from ALANAC (Brazil), APRIVET (Bolivia), ASOVET (Guatemala), CAPALVE (Paraguay), CAPROVE (Argentina), CEV (Uruguay), CIA (Costa Rica) and CLAMEVET (Argentina)

The secretariat will circulate the concept note and contact the working group in order to coordinate its activities.

CAMEVET Financial Report

Ms Ana María Sgammini, CAMEVET Administrative Secretary, presented the financial report, including the annual expenses from September 9, 2019 to the date of the meeting. The full report is included as Annex VII.

It was considered to continue discussing within the scope of the Executive Board the possibility of analyzing a new registration fee, it was highlighted that the existing balance to date covers all the expenses foreseen for the year 2022, but not for the year 2023.

A special thank was made for the collaboration and support provided by ICA Colombia in the Webinar organization, as well as the OIE Regional Representation for the Americas for sharing the use of the zoom platform.

List of acronyms used in the document

AENSA	Asociación de la Industria Ecuatoriana de Medicamentos y Nutricionales Veterinarios (Ecuador)
ALANAC	Associação dos Laboratórios Farmacêuticos Nacionais (Brazil)
ALFA	Asociación de Laboratorios Farmaceuticos (El Salvador)
AMR	Resistance to Antimicrobials
APROVET	Asociación Nacional de Laboratorios de Productos Veterinarios (Colombia)
APRIVET	Asociación de proveedores de insumos veterinarios (Bolivia)
ASOVET	Asociación de Productos Veterinarios (Guatemala)
CADIN	Cámara de Industrias de Nicaragua
CAMEVET	Americas Committee for Veterinary Medicines
CAPALVE	Cámara de Laboratorios Paraguayos de Productos Veterinarios
CAPROVE	Cámara Argentina de la Industria de Productos Veterinarios
CEV	Cámara de Especialidades Veterinarias (Uruguay)
CIA	Cámara de Insumos Agropecuarios (Costa Rica)
CLAMEVET	Cámara de Laboratorios Argentinos Medicinales Veterinarios
FDA	Food and Drugs Administration
ICA	Instituto Colombiano Agropecuario
OIE	World Organization for Animal Health
SG-CAN	Secretaria General de la Comunidad Andina
SINDAN	Sindicato Nacional da Indústria de Produtos para Saúde Animal (Brazil)
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

List of Annexes

Annex I – Minutes of the Plenary Meeting of the Official Sector
Annex II – Minutes of the Plenary Meeting of the Veterinary Industry
Annex III - CAMEVET regulations section - Extension of Executive Board positions
Annex IV – List of working documents Status
Annex V - Financial Report
Annex VI – License extension of pharmaceutical veterinary products on minor's species
Annex VII – Diagnostic Kits

Annex I

Conclusions of the Plenary Meeting of the Official Sector

On November 17th, the Focal Points of veterinary products held a general meeting of the official sector and agreed on the following conclusions:

- The extension of the current Executive Board positions for one year was unanimously approved.
- Executive Board presidency shall be defined on the basis of the decision to be taken on the host country for next CAMEVET Seminar.

Annex II

Conclusions of the Plenary Meeting of the Private Sector

On November 17th, the Associations of veterinary products held a general meeting of the private sector in order to deal with the following topics

- Bolivia: it is requested to accept the bibliography in its original language, acceptance of minimum changes in the products.
- Panama: prohibition of commercialization during registration renewal, no product may be imported while registration renewal is in process.

General: validation of notes and documents, adoption and/or acceptance of digitally signed documents.
Labeling: Difficulty in the different countries because the same criteria is not adopted in the labeling of products (technical criteria has not been unified).

Annex III

According to the health situation of COVID 19, the Plenary **decided** during the CAMEVET webinar, held from November 17 to 19, the extension **for one year** of the current Executive Board positions, namely:

Official sector:

- Argentina: Dr Federico Luna
- Brazil: Dr Marcos Vinicius de Santana Leandro Jr
- Colombia: Dr Aida Rojas
- Nicaragua: Dr Bertha Martinez

Private sector:

- Mexico ANALAV: Dr. Rogelio Cuellar
- Brazil ALANAC: Dr. Javier Carracedo
- El Salvador ALFA: Dr. Edgar Medina
- Guatemala ASOVET: Dr. Carlos Motta

Since the venue for next CAMEVET Seminar was not decided, the position of Executive Board president shall be kept as vacant, until the host country for next Seminar is decided. The Executive Board will be mandated and have the power to consult, review and decide on the venue proposals.

Annex IV

Abstract – Working documents			
Document title	**Coordination**	**E-mail**	**Observation**
Status IV			
Guide to the classification and inspection of veterinary products without therapeutic indication	Brazil (ALANAC) Dr Henrique Tada	alanac@alanac.org.br	Circulate again for 120 days
Status III			
Efficacy tests for registration of internal antiparasitics for ruminants and pigs	CAPROVE (Argentina) Dr Patricia Millares	pmillares@caprove.com.ar	A virtual meeting will be held between the working group
Status II			
GMP veterinary product manufacturing guide	Uruguay (Official) Dr Berta Chelle	vchelle@mgap.gub.uy	Continuous review within the working group
Labeling guide	Costa Rica (Official) Dr Tatiana Leal	tleal@senasa.go.cr	Continuous review within the working group
Good practices in the use of veterinary products	Guatemala (Official) Dr Maria Eugenia Paz	mariaeugeniapazvet@gmail.com	The first draft is awaited
GMP Inspection Guide for Drug Product Development – includes pharmacological, biological and Ectoparasiticides -	CAPROVE (Argentina) Dr Patricia Millares	pmillares@caprove.com.ar	The first draft is awaited
Efficacy tests for registration of internal and external antiparasitics for small animals	Argentina (Official) Dr Federico Luna	fluna@senasa.gob.ar	The first draft is awaited
Procedures for import products	SINDAN (Brazil) Dr Luiz Monteiro	luiz.monteiro@sindan.org.br	Concept Note awaited
Complementary studies to the stability guide	CAPROVE (Argentina) Dr Patricia Millares	pmillares@caprove.com.ar	Concept Note awaited
Residue studies of veterinary medicinal products	Argentina (Official) Dr Federico Luna	fluna@senasa.gob.ar	Concept Note awaited

Annex V

Financial Report - dollars

Revenue		30/12/2020 - 30/11/2021
Resources available as of December 30, 2020		USD 111.634,80
Registration for the CAMEVET Seminar 2020		USD 0,00
	Revenue Subtotal	**USD 111.634,80**
Expenses		
Fixed espenses (Salaries)		
Administrative Secretary (Ms. Ana Maria Sgammini USD 1,200/month)		USD 13.200,00
Bonus Administrative Secretary (June and December)		USD 600,00
Administrative Expenses. By use of OIE Offices (150/month) **SUSPENDED**		USD 450,00
	Fixed Expenses Subtotal	USD 14.250,00
Expenses for the CAMEVET Anual Meeting		
No expenses so far		
	Subtotal	USD 0,00
Expenses for Participation in Other Events		
No expenses so far		
	Subtotal	USD 0,00
Other Expenses		
No expenses so far		
	Subtotal	USD 0,00
Variable Expenses		
No expenses so far		
	Subtotal	USD 0,00
	Expenses Subtotal	**14.250,00 USD**
	Total balance as of November 30, 2021	**97.384,80 USD**

Financial Report – Argentine pesos

Revenue		30/12/2020 30/11/2021
Resources available as of December 30, 2020		ARS 11.808,24
Exchange of US dollars to Argentine pesos		
	Subtotal	**ARS 11.808,24**

*Includes NC Interfly for $8,272.00

Expenses

Expenses for the CAMEVET Annual Meeting

No expenses so far		
	Subtotal	ARS 0,00

Expenses for Participation in Other Events

No expenses so far		
	Subtotal	ARS 0,00

Other Expenses

No expenses so far		
	Subtotal	ARS 0,00
	Expenses Subtotal	ARS 0,00
	Total balance as of November 30, 2021	**ARS 11.808,24**

Annex VI

CAMEVET
Code: Reg-Gen 010
Approved
November 2021

GUIDE TO PROVISIONAL AND DEFINITIVE LICENSING, LICENCE EXTENSION OF PRODUCTS FOR PHARMACEUTICAL VETERINARY USE IN MINOR SPECIES OR LIMITED MARKET FOR SUCH PRODUCTS AND AUTHORIZATION FOR EXCEPTIONAL USE

CONTENTS

GUIDE TO PROVISIONAL AND DEFINITIVE LICENSING, LICENCE EXTENSION OF PRODUCTS FOR PHARMACEUTICAL VETERINARY USE IN MINOR SPECIES OR MINOR USE IN MAJOR SPECIES AND AUTHORIZATION OF EXCEPTIONAL USE FOR RARE SPECIES

1. INTRODUCTION

Considering that:

a) there is a limited number of veterinary products licensed to meet the animal health and welfare needs of the wide variety of animal species, and there is a lack of legally registered veterinary products with limited demand;

b) there is a need to encourage veterinary pharmaceutical companies to overcome the financial barriers they face in order to supply veterinary products of limited demand as soon as possible on the market;

c) veterinary products with minor use or non-frequent use, and also those of exceptional use, are an innovative option to obtain legally registered products with great potential, mainly in developing countries;

d) the need to promote the development of new veterinary products for the treatment of rare diseases or diseases limited to geographical areas, which would not be developed under current market conditions;

e) veterinary products with minor or non-frequent use, whether for use in food-producing animals, pets or wild animals, contribute to public and economic health;

f) the possibility of resistance to antimicrobials and antiparasitics for veterinary use, due to the inadequate posology, having an impact on animal health, human health, and also economic implications.

2. DEFINITIONS

2.1. Medicinal Product for Veterinary Use.

All pharmaceutical preparation that contains chemical, biological or biotechnological substances, which administration to animals, individually or collectively, directly or mixed

with food or drinking water, has the purpose of prevention, control, diagnosis, treatment or cure of diseases.

2.2. Magistral Medicine for Veterinary Use.

This is the medicinal product prepared in magistral pharmacies, according to a veterinary prescription intended exclusively for a certain animal. Except the use in animal species which products and by-products are intended for human consumption.

2.3. *Major species*

These are populations of animals of economic importance and impact on the segment of a certain veterinary product, intended for the production of food for human consumption (cattle, pigs, sheep, goats, poultry (broilers, laying hens, turkeys), productive fish (salmonids, trout, tilapia, among others) and bees and pets (dogs and cats). Each sovereign country adapts this definition depending on the economic importance of the species and their needs to encourage the development and registration of veterinary products.

2.4. *Minor species*

These are the species not classified as major species.

2.5. *Exotic animal species or Rare species*

These are very rare or scarce animal species in a certain region, such as zoo animals.

2.6. *Minor use of veterinary products*

Minor use refers to the moment when drugs are used to treat one of the major species (horses, dogs, cats, cattle, pigs, turkeys and chickens) for a disease that is rare. This is the use of a veterinary product for the treatment or prevention of diseases that occur infrequently, or in limited geographical areas or in cases where resources to provide assistance are limited, either in individual use or in populations and, therefore, it is indicated for a limited market. Minor use does not always refer to a major species; it can also be made in minor species.

2.7. *Limited market*

This is the market segment of veterinary products that is limited in size, given that it is indicated for a disease or condition that represents a minor use in major species or that occur in a minor species.

2.8. Elimination Time.

The time required between the last application of a veterinary medicinal product to an animal, under the conditions approved in the registration, and the obtainment of food products from that animal, to ensure that such products do not contain residues in quantities exceeding the maximum residue limits (MRLs) established.

2.9. Maximum Residue Limit (MRL)

This is the maximum concentration of residues legally allowed in a food product, obtained from an animal which a veterinary medicinal product has been administered to.

2.10. Rare disease:

It can be rare because it occurs only in certain areas of the country or because it affects only a small number of animals each year.

Provisional and definitive license approval exclusively -- Include conditions under which such licenses cannot be granted.

This is obtained by the company requesting the product registration for veterinary use for minor species or minor use in major species, which will have provisional approval from the Regulatory Agency of the country for the exclusive marketing of the product with that formulation and route of administration, while it collects efficacy data, and as long as its safety has been verified through a safety study. The applicant company will have the provisional license for sale for one year and may, if the Regulatory Agency of the country so allows, maintain the product sale for up to 5 years, through annual renewals, while collecting the efficacy data of the product for the definitive license granting.

2.11. *Extension of minor use or non-frequent use indication*

This is granted to the company that already has a license for a veterinary use product for major species and requests expansion for use in minor species or minor use in major species.

2.12. *Safety study*

This study evaluates the potential undesirable pharmacodynamic effects of the tested substance.

2.13. *Efficacy study*

This study demonstrates that the product for veterinary use, in the recommended posology and route of administration, administered and up to the end of its effectiveness, promotes the desired effect for the intended purpose, in the target species which the product is indicated for.

2.14. *Authorization for exceptional use for a veterinary use product*

This is granted for a product for veterinary use indicated for exotic or rare species, which could not collect sufficient data for analysis during the five years, by means of a provisional license.

3. OBJECTIVE

Develop a guide for the registration and authorization of medicinal products for veterinary use, used in low frequency or rare diseases presented in a population of certain animals.

The product classification for veterinary use will be made by the applicant company, based on the product characteristics, formulation, route of administration, posology, and indications for use. Statistical data from recognized sources or technical justification that allows classification as intended for minor species, rare species or minor use in major species can be used, and properly signed by the responsible or technical director of the company.

Prepare a guide to establish guidelines for the registration and marketing of veterinary drugs in minor species, rare species or minor use in major species.

4. CONDITIONS FOR OBTAINING THE LICENCE OR THE INCLUSION/EXTENSION OF INDICATION IN MINOR SPECIES, IN RARE SPECIES OR MINOR USE IN MAJOR SPECIES

according to the current regulations of each country involved

4.1. *In the case of a provisional or definitive license for a product* for veterinary use, the company must submit, in addition to the technical report provided for in the legislation in force, the following documents:

I - Report on the product safety study in the target species;

II - Report on the residue depletion study in the case of a product intended for animals producing food for human consumption;

III – Labelling project.

IV – Report on efficacy studies, in the case of definitive license.

V – Stability study report of the product intended for minor species, rare species or minor use in major species.

4.2. *In the case of indication extension of minor use or non-frequent use of veterinary use, the company must submit, in addition to the technical report provided for in the legislation in force, the following documents:*

I - Report on the product safety study in the new target species;

II - Report on the residue depletion study in the new target species, in the case of a product intended for animals producing food for human consumption;

III – Labelling project.

4.3. *The authorization for exceptional use of the product for veterinary use is granted for a product for veterinary use indicated for exotic or rare species, which could not collect sufficient data for analysis during the five years by means of a provisional license and will be evaluated by the Regulatory Agency of the country considering the following criteria:*

I- The use indication shall be allowed only in rare or exotic species, and not for animals producing food for human consumption;

II- Detailed opinion on the safety and efficacy of a product for veterinary use in the species and in the posology(ies) proposed in the package leaflet, issued by a specialist with knowledge in the area verified by a mini curriculum.

III- The expert opinion shall substantiate the safety and efficacy in the target species regarding the exceptional use of the product for veterinary use.

4.4. *Safety studies of the minor use or non-frequent use product conducted in the target species must contain detailed information, covering at least:* summary, place of realization, main researcher, sponsor, used product batch, product description and used reference, study objective, quality assurance statement, amendments, deviations, description of the breeding method and feeding provided to the animals, characteristics of the studied animals, origin and destination of the studied animals, experimental outline, evaluated parameters, statistical analysis, results, discussion, conclusion and bibliographic references. The company holding the product license for veterinary use must keep on file the raw data obtained in the studies, which must be available to the Regulatory Agency of the country for a period of 10 (ten) years.

4.5. *The residue depletion studies and for determining the grace period in the species of minor use or non-frequent use of the product for veterinary use must be conducted with the required formulation of the product, in the target species of minor use or non-frequent use and recommended matrices, using the highest indicated posology.*

4.6. *In studies for determining the grace period of the product for veterinary use, the MRLs established by the Codex Alimentarius or in specific legislation are accepted. In case there is no information regarding the MRLs of any active ingredient established in the Codex Alimentarius or in specific legislation and, in their absence, those internationally recognized and accepted by the Regulatory Agency of the country shall be used.* Indicate that it is the responsibility of the applicant company to conduct the relevant and necessary studies that allow establishing the MRLs.

4.7. *When changes occur to the already established MRLs, the company must adjust the grace period of the veterinary product to comply with the new MRL.*

4.8. *When there is evidence that the approved grace period is not sufficient to comply with the recommended MRL, the license holding company should adjust the grace period of the veterinary product.*

4.9. *The sample size used in the studies for determining the grace period of the product for veterinary use should follow internationally recognized or statistically justified references.*

4.10. *The calculation of the grace period of the product for veterinary use must be done by data interpolation of the curve of the residue versus time chart; the calculation by extrapolation is not allowed.*

4.11. *All data related to the non-clinical study for determining the grace period of the product for veterinary use must be submitted containing at least:* summary, experimental protocol, place of realization, used product batch, main researcher, sponsor, description of the breeding method and feeding provided to the animals, characteristics of the studied animals, origin and destination of the studied animals, experimental outline, evaluated parameters, analytical methodology and the validation results, statistical analysis, results (with the support of tables and charts), discussion, conclusion and bibliographic references. Studies should be conducted according to the principles of GCP (Good Clinical Practice). The company holding the product license for veterinary use must keep on file the raw data obtained in the studies, which must be available to the Regulatory Agency of the country for a period of 10 (ten) years.

4.12. Efficacy studies of the product for veterinary use must contain detailed information, covering at least: summary, place of realization, main researcher, sponsor, used product batch, description of the breeding method and feeding provided to the animals, characteristics of the studied animals, origin and destination of the studied animals, experimental outline, evaluated parameters, statistical analysis, results, discussion, conclusion and bibliographic references. The company holding the product license for veterinary use must keep on file the raw data obtained in the studies, which must be available to the Regulatory Agency of the country for a period of 10 (ten) years.

Note: The applicant company will have a period of up to 5 (five) years to collect sufficient data on the product use to produce the necessary information available in this paragraph.

4.13. *The technical argumentation analysis will be conducted by the country Regulatory Agency, which may request additional clarifications.*

4.14. *If the efficacy study report is not submitted or is not approved, the country Regulatory Agency may cancel the indication of the relevant target species.*

4.15. *The Regulatory Agency of the country, at any time, may cancel the Provisional License or the Definitive License if damage to the animal, human being or the environment caused by the product use is detected, or in case of its non-effectiveness.*

4.16. *The Regulatory Agency of the country, at any time, may cancel the Exceptional Use Authorization if it is detected that the product is ineffective or causes damage to the animal, the human being or the environment caused by the product use.*

4.17. *This document is not applicable to biological products for veterinary use or to kits for the diseases diagnosis.*

4.18. *Omitted cases and the doubts raised in the execution of this document shall be resolved by the Regulatory Agency of each country.*

5. LABELLING INFORMATION

5.1. The labelling of veterinary products for minor species or minor use in major species or rare species with a provisional license must state, on the package leaflet, on the label - package leaflet, on the medicinal products box - package leaflet, on the label and on the medicinal product box or packaging, just below the indications of the product, highlighting the following: *"Conditionally approved product pending a full demonstration of its complete effectiveness. Its efficacy has not been evaluated in the minor species or its minor use in a major species by the country Regulatory Agency"*. No off-label use is allowed.

In the labelling of veterinary products authorized for exceptional use in rare species, the following must appear on the package leaflet, on the label - package leaflet, on the box of medicinal products - package leaflet, on the label and on the box of medicinal products or

packaging, just below the product indications: *"The exceptional use of this product for the indicated species was authorized by the country Regulatory Agency".*

Annex VII

CAMEVET
Code: Reg-Gen 011
Approved
November 2021

GENERAL GUIDANCE FOR TEST KITS INTENDED FOR THE DIAGNOSIS OF ANIMAL DISEASES

SUBJECT: General Guidance for Test Kits Intended for the Diagnosis of Animal Diseases

I. PURPOSE

This memorandum provides guidance to support an application for regulatory approval of test kits intended for the detection of animal disease or immunological status.

II. BACKGROUND

Diagnostic test kits are intended to detect the disease or immunological status of an animal. Kits must be validated to demonstrate the fitness for intended use. The kit, regardless of format or function, must be reliable, reproducible, and scientifically sound. The formal process for evaluating these, and the diagnostic performance characteristics, is known as validation.

III. SCOPE

This document outlines an approach for validating a diagnostic test, documenting production and testing methods, and confirming the expiration dating.

IV. DEFINITIONS

A. *Reference tests.* Use one or more reference tests. Include information about the sensitivity and specificity of each reference test proposed in the protocol and in the final report. The company should do this by providing its assessment of the expected sensitivity and specificity of the reference test, using the best information available and informing the source of that information.

B. *Diagnostic Sensitivity*. Diagnostic sensitivity is the probability of obtaining a positive test result for a truly positive sample. When the results of the gold standard are accepted as correctly classifying true disease status, diagnostic sensitivity can be expressed as a percentage using the following calculation:

(true positive/(true positive + false negative)) × 100%

False negative samples are truly positive samples classified as negative by the test kit.

C. *Diagnostic Specificity*. Diagnostic specificity is the probability of obtaining a negative test result for a truly negative sample. When the results of the gold standard are accepted as correctly classifying true disease status, diagnostic specificity can be expressed as a percentage using the following calculation:

(true negative/(true negative + false positive)) × 100%

False positive samples are truly negative samples classified as positive by the test kit.

D. *Ruggedness*. Ruggedness is the measure of the capacity of the assay to remain unaffected by deliberate small variations in method parameters. It provides an indication of assay reliability under normal use.

E. *Receiver Operating Characteristic (ROC) Curve*. The ROC curve is a plot of a test's sensitivity versus its false positive rate (1-specificity) where each point on the empirical ROC curve is generated by a different potential cutoff value. A ROC curve is useful in visualizing the compromise between sensitivity and specificity for different cutoff values and for ultimately selecting a cutoff value.

F. *Repeatability*. Repeatability can be described as the variation observed in the measurements taken on a single sample by a single operator. In the context of a diagnostic test kit where a sample will be classified as positive or negative, interest lies in the ability of an operator to consistently classify a set of samples.

G. *Reproducibility*. Reproducibility can be described as the variation observed between measurements made by different operators. In the context of a diagnostic test kit where a sample will be classified as positive or negative, interest lies in the ability of the test system to produce consistent results for a set of samples when testing is conducted by different individuals, or different laboratories.

H. *Sample*. In this document 'sample' usually refers to a diagnostic specimen rather than a statistical sample of units from a population. The meaning should be clear from the context.

V. ASSAY DEVELOPMENT

The process of validating a diagnostic test kit occurs in steps which include conceptualization, development, and verification that the test kit will perform consistently.

The final report typically includes analytical criteria and sensitivity and specificity of the diagnosis for batch release and field adequacy studies.

A. *Conceptualization.* Several issues should be addressed early in the development of the diagnostic test kit:

1. The ability of the kit to detect the analyte of interest. Diagnostic analytes are typically antigens, antibodies, or genetic sequences.
2. The ability of the kit to measure the analyte in the range of concentrations expected in diagnostic test samples.
3. The type of sample and the sample processing required.
4. The potential effect of cross-reacting materials in the test preparation.

B. *Development.* During the development phase, the firm should:

1. Determine the final test kit conditions and reagent concentrations.
2. Incorporate the use of controls and methods of monitoring the performance of the test kit.
3. Determine the criteria for acceptance for reagents and controls, including serial release panel members.
4. For plate based assays, determine if there are location effects on the plate.

C. *Validation.* The firm should determine the performance characteristics, namely diagnostic sensitivity and diagnostic specificity, as well as demonstrate the ruggedness of the kit

1. *Diagnostic Sensitivity and Diagnostic Specificity.* The report should address the analysis method planned to estimate diagnostic sensitivity and diagnostic specificity. The report should specify the reference test and proposed statistical methods, particularly for those utilizing imperfect, composite, or no gold standards. For kits in which the response is determined by visual inspection, but a more objective measurement has been made, such as densitometry, the sensitivity will be estimated based on the visual classification. The visual classification should be made in the absence of knowledge of the objective measurement in these instances.
2. *Samples for Estimating Diagnostic Performance Characteristics.* Determining the true status of the sample requires testing by one or more additional tests. A reference test may exist which is the currently accepted method of designating the

status of a sample (gold standard). In some cases, a composite of multiple evaluations may be used in determining the true disease status of an animal. The reference test or tests (in the event of a composite of multiple evaluations) should be applied uniformly to all animals to determine their diagnostic status. Do not do selective retesting based on the results of the experimental kit. The selection of test specimens is instrumental for accurately estimating the diagnostic performance characteristics of the test kit. The samples used should be the same specimen type intended for use in the kit. If the label claim for the kit is for more than one specimen type (e.g., whole blood, serum, plasma) and/or more than one species, diagnostic sensitivity and specificity should be estimated for each specimen type/species combination. It is acceptable to show equivalence of performance with a limited number of samples for rare disease or rare diagnostic specimen. An adequate number of positive and negative samples of each type should be tested. The positive samples should cover the range of activity from weak positive to strong positive. Diagnostic samples don't have to be obtained from local sources to account for disease agent isolates unique to that region if strains or isolates are known to be common in different regions. The report should address the species, sample types, proposed number of samples, and the acquisition of samples, which could include any pertinent information such as geographic location, sample treatment, storage, shipping conditions, etc. The report should provide a justification for the intended sample size(s). Describe how the sample set represents the target population.

3. *Determining the Cutoff Value.* Some kits may produce a semi-quantitative test result used in conjunction with a cutoff value for determining the status (positive/negative) of the sample. The results of testing the diagnostic samples may aid in specifying the cutoff value. The ROC curve may be useful in guiding a decision regarding the most appropriate cutoff value for the intended use of the test. The final report should describe how the cutoff value was selected and include estimates of diagnostic sensitivity and diagnostic specificity for the proposed cutoff value.

4. *Ruggedness.* Evaluate ruggedness by observing the effect of changes in incubation time, incubation temperature, and other test conditions, which are not already covered by the measurement system analysis (MSA), repeatability or reproducibility testing, on the final results.

5. *Inter-laboratory comparison.* Firms are required to conduct an inter-laboratory comparison to evaluate the suitability of the test kit when used by cooperating laboratories. The laboratories should have practical experience with similar diagnostic assays.

    a. *Test Panel.* A test panel, created by the manufacturer for use in the field trial, should consist of samples spanning the expected range of reactivity. The

panel should not contain more than five negative samples. The negative samples could, but do not have to be positive for another analyte which might cross-react with the kit. The report should discuss how the reactivity of the remaining samples was determined. Every effort should be made to use samples from natural infection/exposure rather than spiked samples. It is recommended that one to two reference samples be duplicated within the panel. If the test panel cannot be created from diagnostic samples from unique, naturally infected animals, the report should discuss the rationale and provide details regarding the samples to be used in the panel.

b. *Field Study*. The panel will be sent to each of three participating laboratories, shipped in compliance with local shipping regulations. Each laboratory will test the panel members in a prelicense serial. The panel members should be randomized. Further, the individual(s) within each participating laboratory conducting the testing should be blinded to the sample status (positive/negative) as well as the number of positive and negative samples within the panel.

c. Retesting samples with discrepant results is unnecessary and should be avoided. The report must include a table displaying all test results for each sample. All raw data should be supplied to the regulatory authority for review.

d. Participating laboratories should be encouraged to determine the suitability of the test kit by testing samples submitted to their laboratory. This is especially critical for fresh samples such as whole blood and fecal samples.

VI. PRODUCT DOCUMENTATION

Manufacturing practices and production standards for test kits shall be well characterized, and as documented by the manufacturer in accordance with local regulatory requirements. The preparation of test kit components and reagents shall be well characterized and documented. The subsequent items in this section provide additional guidance but are not all-inclusive.

A. *Antibody Production*

1. Agent-specific antibody is defined as any reagent(s) which participates in, or competes with, the antigen-antibody reaction being measured by the kit.

2. May be purchased or prepared on licensed premises.

a. The product documentation must specify the identity, source (including country of origin), the acceptance criteria, and additional quality testing the firm performs on each lot. The statement, "accepted under a Certificate of Analysis" is not an acceptance criterion.

b. Purchased monoclonal antibodies must be fully characterized and specify the clone designation or reacting epitope. Changes in source must be notified to the regulatory authority. Firms are encouraged to obtain monoclonal antibodies from sources where the hybridoma is free from bacteria, fungi, mycoplasma, and extraneous viral agents.

c. Master Cell Hybridomas used in the preparation of monoclonal antibodies prepared on site by the manufacturer shall be free from bacteria, fungi, mycoplasma, and extraneous viral agents. The product documentation must specify the identity, source, the acceptance criteria, and additional quality testing the firm performs on each lot used on production.

3. Changes in propagation method, growth media, hybridoma line, or passage level may require confirmation of kit sensitivity and specificity and/or additional testing and a change to the product documentation.

4. All kits within a serial must be prepared from a same lot of antibody.

B. *Antigen Preparation, including PCR primers*

1. May be purchased or prepared on licensed premises

a. For purchased antigen, the product documentation must specify the identity, source, the acceptance criteria, and additional quality testing of each lot. The statement "accepted under a Certificate of Analysis" is not an acceptance criterion. Changes in source must be notified to the regulatory authority.

b. Master Seed Viruses (MSV) specified in the product documentation shall be tested for extraneous viable viruses, bacteria, and fungi. The MSV shall be tested for appropriate identity characteristics, as specified in the product documentation. Master Cell Stock (MCS) cultures used in the preparation or propagation of Master Seeds on official premises shall meet the applicable requirements of the regulatory authority. The product documentation must specify the identity, the acceptance criteria, and additional quality testing of each lot used on production.

2. Master Seed Bacteria (MSB) prepared on official premises specified in the product documentation shall be tested for viable extraneous bacteria and fungi and for appropriate biochemical and cultural characteristics. The product documentation must specify the identity, the acceptance criteria, and additional quality testing of each lot used on production.

3. Genetically modified (gene-deleted or recombinant) Master Seed (MS) organisms prepared on official premises shall be tested according to the requirements in section VI.C.2 or VI.C.3, as appropriate and applicable. If alternative purity, identity, or expression assays are necessary, genetically modified MS shall be tested by laboratory procedures acceptable to the regulatory authority. The product documentation must specify the identity, source, the acceptance criteria, and additional quality testing of each lot used on production.

4. Master Seeds of other microbial classes (e.g., fungi, rickettsiae, parasites) must be adequately identified and tested for purity by laboratory procedures acceptable to the regulatory authority. The filed product documentation must specify the identity, source, the acceptance criteria, and additional quality testing of each lot used on production.

5. When synthetic antigens or oligonucleotides are used in test kits, the amino acid, nucleotide sequence, or carbohydrate composition, along with any other critical structural specifications and criteria necessary to ensure quality, shall be described in the product documentation in a manner acceptable to the regulatory authority. All information submitted will be treated under warranty of confidentiality. Synthetic antigens or oligonucleotides may be purchased; the product documentation must specify the identity, source, the acceptance criteria, and additional quality testing of each lot.

6. All kits in a serial must be prepared from the same lot of agent-specific antigen, synthetic antigen, or oligonucleotide.

C. *Preparation of Standard Reagents*

Test kit components are subject to the requirements and restrictions indicated in the following chart:

Component	Produced in Official Establishment	Same Lot for Entire Serial	Source Identified and/or Formula in Product Documentation	Submit Data Before Changing	Dating of Serial
Anti-species Antibody or Conjugate	No	Yes	Yes	Yes	Yes
Agent Antigen or Antibody	No	Yes	Yes	Yes	Yes
PCR Master Mix	Yes	Yes	Yes	Yes	Yes
Sample Diluent	No	No	Yes	Yes	Yes
Controls	No	Yes	Yes	Yes	Yes
Stop Solution	No	No	Yes	Yes	No
Prepared Solid Surface	Yes	Yes	Yes	N/A	Yes

1. Describe the manufacture of the positive and negative controls used in the kit. The controls may be purchased; the filed product documentation must specify the identity, source, acceptance criteria, and additional quality testing performed on each lot. The statement "accepted under a Certificate of Analysis" is not an acceptance criterion. All kits in a single serial must be prepared from the same lot of the control.

2. The Anti-Species Antibody or Conjugate is defined as any reagent(s) used to amplify/report an antigen-antibody reaction. It includes anti-species antibody; protein-A, -G, or -L; colloidal gold; biotin; or enzyme-labeled versions of any of these. It does not need to be prepared on licensed premises, but each lot must be validated in a manner acceptable to the regulatory authority. Acceptance criteria must be specified in the product documentation. All kits in a serial must be prepared from the same lot of anti-species antibody or conjugate.

3. . The Substrate is defined as a substance which undergoes a color change or other detectable reaction when catalyzed by an enzyme-labeled kit component. It may be purchased. The product documentation must specify the source and the acceptance criteria of each lot. Changes in source must be approved by the regulatory authority. It is permissible to use more than one lot in the manufacture of a serial.

4. List all buffers included in the kit. Buffers are defined as inert liquids used to dilute test samples/other kit components, perform washes, or stop substrate reactions. Describe the source or formula for all buffers contained in the test kit. Each lot of buffer, diluent, or other liquid of non-animal origin should be stable in the final container. Methods used to stabilize the liquids, as well as a validated, maximum acceptable time interval between manufacture and stabilization to ensure lack of contamination with bacterial by-products, should be described. Stability of stop solutions composed of strong acid (e.g., 1M H_2SO_4), or other chemicals generally accepted as not supporting microbial growth, does not need to be demonstrated.

5. Changes in any of the test kit reagents relevant to test performance should be supported by data demonstrating that the changes have not altered the sensitivity and/or specificity of the test kit.

D. Preparation of the Product

1. List the preservative(s) and concentration for each component containing preservatives.

2. . When coated solid-phase components (e.g., immunoassay plates, beads, or membranes) are prepared, they must be assigned a lot identity separate from those of the coating reagent (antigen/antibody) and the uncoated solid-phase substrate. The solid-phase component type should be identified in the product documentation. Solid-phase components should be coated on licensed premises; exemptions require specific approval by the regulatory authority. Each lot of coated solid-phase component must be prepared with the same lot of coating reagent and a single lot of solid-phase substrate. All kits in a serial must be prepared using the same lot of coated solid-phase component. The formulas for reagents necessary to prepare the solid-phase components should be included. Changes in the coating method should be supported by data demonstrating the changes have not altered the sensitivity and/or specificity of the test kit.

3. List the minimum and maximum fill volumes for each final container to ensure there is enough of the component to adequately perform the test(s).

4. Describe the method used to dispose of unsatisfactory material.

E. Testing

1. In vitro Test kits are exempt from the sterility and purity tests, which should be performed for "in vivo" test kits.

2. In vitro Test kits are exempt from animal safety tests, which should be performed for "in vivo" test kits.

3. The manufacturer must perform a potency test using reference samples (serial release panel) on each assembled test kit serial. Each panel member must have an objective value for the acceptance criterion. The potency test must be performed in accordance with the instructions in the test kit insert and specified in the product documentation. Serial release testing provides confidence each serial will perform to the specificity and sensitivity standards determined at the time of licensure.

   a. The serial release panel used for the potency test must be well characterized. The panel should include examples of the following:

      (1) Negative/uninfected animals.

      (2) Strongly positive animals.
      (3) Weakly positive animals.

   b. It is acceptable for the serial release panel to be samples artificially created from antigens or antibodies, or dilutions of a single sample. However, these samples should be pre-diluted; to avoid dilution errors, a sample should not be diluted to produce multiple samples with different reactivity at the time the assay is performed. Serial release panels should be prepared in sufficient quantities and single-use aliquots to last for years (one year minimum).

   c. The serial release panel must be identified in the product documentation by lot number, recommended storage temperature, and acceptable assay ranges. The firm should submit data to show how the ranges are calculated. For example, for an ELISA test kit where results are expressed as a ratio of the optical densities of the sample to a positive control (S/P), the product documentation must specify an acceptable S/P range (including appropriate upper and lower limits) for each reference sample. For a test to be considered satisfactory, each serial release panel member

must test within the specified range. For products containing positive and/or negative controls, each positive and negative control must test within the specified range. If appropriate methods to obtain quantitative measurements are available, such as densitometry, objective criteria will be required for serial release of kits interpreted subjectively in the field.

d. All potency testing of individual serials should be done using the same panel members.

e. It will be necessary to replace members of the serial release panel as the stock depletes. The replacement sample should serve the same purpose as the sample it is replacing. Its performance should demonstrate its ability to fulfill the same role, but it need not have precisely the same reactivity as the previously approved panel member.

(1) Sufficient data should be obtained to demonstrate the replacement sample's performance in the assay. Upper and lower limits of acceptance criteria have to be defined prior to using the sample as a new member of the serial release panel.

(2) The replacement sample (e.g., positive samples not near the saturation or critical decision point of the assay) will be acceptable if the response distributions of the replacement and current member are similar. The replacement sample may also be deemed acceptable if the distributions are not similar, but it serves a similar role as the current panel member. In this case, serial release specifications may require adjustment.

(3) Weak positive replacement samples should have response values (in the assay) near the critical decision point. The acceptable result range should not cross the cutoff value between assay runs. Reactivity ranges should be established with an appropriate response range above the cutoff value.

(4) For samples at the extremes of the dynamic range, such as negative panel members, the reactivity of the replacement samples should be within the response range (e.g., all negative replacement samples should test within the negative range).

F. *Post-preparatory Steps*

1. List the number of final component containers in each kit box. Multiple variations of the kit components are acceptable.

2. Each lot of each component in the kit shall be assigned an expiration date based on the stability of the individual component. The expiration date may be indicated on the component label. The expiration date of the serial shall be calculated from the date of initiation of the first potency test but shall not exceed the expiration date of any of the components.

3. Include the kit description, list of components, recommendations, qualifications, limitations, and test interpretations for use of the kit. The description should avoid stating or implying the test kit is a quantifying assay. Information in this section is included in the insert for use for the kit. The kit should define the acceptable qualities and the potential impact for a test sample to be suitable for analysis in the test kit. All potentially infective material must be appropriately labeled. Chemical safety instructions must be included in the labeling for all hazardous materials. Disposal instructions must be given in the Outline of Production and on the package insert.

VII. CONFIRMATION OF DATING (COD)

A requirement in the US.

VIII. SHIPPING TEST KITS

A requirement in the US.