CONCLUSIONS AND RECOMMENDATIONS

XXV Seminar on Harmonization of Registration and Control of Veterinary Medicines
Americas Committee for Veterinary Medicines
(CAMEVET)
&
OIE Workshop on the Database on Antimicrobial Agents
Intended for Use in Animals in theAmericas

September 23-27, 2019
Montego Bay, Jamaica

Opening speeches

Participants were welcomed by Mr. Floyd Green, Minister of State in the Ministry of Industry, Commerce, Agriculture and Fisheries, Mr. Demon Spence, Minister of Industry, Commerce, Agriculture and Fisheries, Dr. Osbil Watson, Chief Veterinary Officer and Delegate before the OIE for Jamaica, Dr. Catya Martinez, Technical Assistant of the OIE Subregional Representation for Central America, the Dr Linnette Peters, Director of the Veterinary Public Health Unit of the Ministry of Health and Welfare and Dr. Gloria Alarcon, OIE Focal Point for Veterinary Products of Paraguay, representing the CAMEVET Executive Board.

Designation of President and Vice-President

Dr. Kevin Walker, Focal Point for Veterinary Products of Jamaica, was formally designated as president of the Seminar.

Plenary meeting of the oficial sector

Dr. Federico Luna, OIE Focal Point for Veterinary Products of Argentina, presented the conclusions of the meeting of the official sector. Among the topics discussed, Dr. Luna referred to the request made by the Official Sector of Canada to change the name of CAMEVET Seminars to *Annual meeting and Seminar*. The request was approved unanimously.

Onother issue discussed was the need to improve the visualization of harmonized documents available on the website of the OIE Regional Representation for the Americas.

The report of the meeting containing a detail of the topics discussed is attached as Annex I.

Plenary meeting of the veterinary industry

Dr. Carlos Rufrano, representative of CLAMEVET Argentina and member of the Executive Board of CAMEVET, presented the topics discussed at the meeting held by the veterinary products industry sector. Dr. Rufrano highlighted the importance of the term of validity of certificates and of the period prior to their expiry, during which renewal should be applied for, and the related requirements. Additionally, topics were established, shuch as marketing prohibition during renewal of registration and the improvement of renewal time spans.

The detail of the topics discussed is attached as Annex II.

Discussion round table

The proposed topics received by the Secretariat of CAMEVET that require discussion and the search for common solutions were presented. The topics proposed led to a fruitful discussion and to the proposal of alternatives for solving the situations presented.

CAMEVET members were informed that the Secretariat will receive proposals of topics that require an open discussion by the official and industry sectors. Proposals shall be received up to three months prior to the start of the Seminars, and the parties involved shall be informed accordingly.

Session I – CAMEVET Relations

Procedures for the participation of CAMEVET in proposals for the creation and modification of OIE Standards. Rules currently under review.

Dr. Martinez referred briefly to the structure of the OIE and the necessary steps for the approval and/or modification of OIE standards. Additionally, the resolutions of the 87th. General Session held in May 2019 were informed.

It was noted that the approval of Resolution N° 36 of the 86th. OIE General Session seeks to enhance the participation of Member Countries in the standard development process, in particular, through an effective coordination of the multiple interested sectors at a national and regional level.

Dr. Martinez went on to present the two new resolutions approved at the 87th. OIE General Session held in May 2019, namely: Resolution N° 14 "OIE's Engagement in the One Health Global Effort to Control Antimicrobial Resistance", and Resolution N° 31 "Register of diagnostic kits validated and certified by the OIE", both having relevance for the sector represented at the seminar.

Lastly, it was informed that the General Session adopted the modifications to 11 Chapters of the Terrestrial Animal Health Code, 11 Chapters of the Terrestrial Manual, updated 10 Annexes of the Aquatic Animal Health Code and 3 Annexes of the Aquatic Manual.

Regarding participation in the OIE standards development process, member countries were encouraged to take part, since these documents are available to the general public and it is important for delegates and focal points to disseminate them in their countries to enable the timely submission of comments, proposed modifications, and proposals for new chapters in the Terrestrial Animal and Aquatic Animal Health Codes and in the respective Manuals.

Participation of CAMEVET in the OIE-VICH Outreach Forum

Dr. Virginia Quiñones, representing the official sector of the Dominican Republic, presented the results of her participation representing the Committee at the 11th VICH Outreach Forum.

Dr. Quiñones referred to the participation in discussion forums relating to studies for establishing withdrawal periods, the proposal of topics such as pharmacovigilance, stability and efficacy for veterinary medicines, and the importance of increasing awareness of how those studies can improve public and animal health.

It was also noted that the VICH has requested CAMEVET to submit proposals from Member countries concerning needs and expectations for the forthcoming meetings of the forum.

CAMEVET strategy at VICH

Miss. Ana Sgammini, representing the Secretariat of CAMEVET, presented the strategy the Committee will adopt at the following VICH meetings.

It was noted that the strategy presented was developed in previous years but has has not been applied to date.

The importance of working jointly with the VICH to broaden the range of harmonized technical documents was highlighted. In this regard, the importance was noted of analysing which guides are considered most important by the Commitee, so that these are analysed at the CAMEVET Seminar.

It was considered relevant to propose to VICH a list of CAMEVET harmonized documents to be considered as working drafts.

Lastly, it was informed that the next VICH Meeting will be held in Tokyo, Japan, on November 19 and 20. Dr. Virginia Quiñones was chosen by the Executive Board to CAMEVET at that forum.

Summary of CAMEVET Harmonized Documents

Ms. Ana Sgammini presented a summary of the Working Documents that have been harmonized since the start of the Committee.

Since the creation of CAMEVET, a total of 32 documents have been approved; these are available on the web page of the OIE Regional Representation for the Americas.

Additionally, to improve the visibility of the documents available on the web page, it was decided to classify them according to the code assigned to each one. These codes identify documents as pertaining to operative, quality and regulatory matters.

At present, there are seven documents under review and seven documents pending review. It was decided to include documents relating to Good Manufacturing Practices, Inspection Guides for Biologicals, and Manufacture of Ectoparasiticides in the Guide of Good Manufacturing Practices for Veterinary Products, currently under review.

Procedures for the identification, study, follow-up, approval and adoption of CAMEVET harmonized documents.

Ms. Ana Sgammini presented the new procedure for establishing Work Groups.

In relation to processing Status I, it was decided that the concept note will be presented at the Plenary Meeting for the latter to decide regarding the approval or not of the topic.

It was noted that the corresponding procedure is currently available in the Spanish language, and, following the conclusion of the seminar, it shall be translated to Portuguese by arrangement of the SINDAN, and to English by Belize, and circulated as a final document.

The need to improve communication relating to the reception of comments was also noted. It was agreed that any comments made by countries shall be copied to the coordinator of the Work Group, requesting acknowledgement of receipt. A request was also made to implement a new methodology for the delivery of comments. Additionally, reference was made to the time frames established for the submission of documents, noting that in many cases it is difficult to complete an initial draft in the 120-day period assigned.

Proposal: 4th. Strategic Plan 2020-2025

Ms. Sgammini presented the proposal of a new Strategic Plan developed by the Secretariat and circulated to the members of the Executive Board.

It was noted that the Strategic Plan shall be effective for 4 years, starting on January 1 of the year 2020 and ending on December 31, 2024.

The plan includes five objectives and five actions that shall be carried out to accomplish each of those objectives. In connection with the first objective, which relates to the internalization of the Work Groups, a request was made to implement an indicator, via a survey, to check progress achieved in the internalization of each CAMEVET Harmonized Document.

The document shall be circulated in the three languages. Belize shall be responsible for having it translated into English, while SINDAN shall have it translated into Portuguese. Is attached as Annex IV

Session II – Working Documents

Guide for the implementation of the Pharmacovigilance system

Dr. Gabriel Ardiles Andía, representative of ALAVET (Chile), presented the progress made on the document, which is currently in Status IV. He also presented the most relevant comments received after having circulated the document.

Following this presentation, the document was approved unanimously, and is included as Annex V.

Stability of veterinary medicines

Dr. Andrea Fraga, of CAPROVE Argentina, presented the progress made on the document under review, which is currently in Status IV. Following the presentation, which included the comments received, the document was approved unanimously, and is included as Annex VI.

Good manufacturing practices at cell processing plant

Dr. Michele spoke on behalf of the official sector of Brazil and of Dr. Barbara Cordeiro, coordinator of the Work Group, and presented the progress made on the document currently under review and in Status IV. Following the presentation, which included the comments received, the document was approved unanimously, and is included as Annex VII.

Extension of authorisation for products for pharmaceutical veterinary use in minor species

Dr. Christopher White presented the progress made on the document currently under review and in Status IV. Following the presentation, which included the comments received.

It was agreed that the document would be circulated one more time, providing a term of 60 days for receiving comments.

Guide for the registration of Diagnostic Kits for diseases

Dr. Geetha B. Sinivas, speaking on behalf of Dr. Byron Rippke, of the United States Center for Veterinary Biologics, presented a summary of the contents of the Work Document, which is currently in Status IV.

It was agreed that the document would be circulated one more time, providing a term of 60 days for receiving comments.

Classification of products as Innovative, Generic and New

Dr. Carlos Rufrano, representative of CLAMEVET and member of the Executive Board, presented the document that contains the definitions and requirements for product categories, currently in Status IV, which included the comments received.

It was agreed that the document would be circulated one more time, providing a term of 60 days for receiving comments.

Labeling Guide

Dr. Tatiana Leal, representing the official Sector of Costa Rica in replacement of the coordinator of the Work Group, presented the progress made in the development of the Work Document, which is currently in Status IV, including the comments received. The Work Document shall be circulated again.

Special reference was made the need to approved the document in the next Seminar

Keep this card in your wallet or purse Good Manufacturing Practices for the manufacture of Veterinary Products

Dr. Tatiana Leal, representing the official Sector of Costa Rica and speaking on behalf of the coordinator of the Work Group, Dr. Benigno Alpízar Montero, presented the progress made in the review of the work document, currently in Status III.

In view of the level of complexity of the document, it was agreed to circulate it again, providing a term of 60 days for receiving comments, remaining in Status III.

It was informed that Costa Rica has decided not to continue as coordinator of the Work Group, but shall remain a member of the group. Consequently, Dr. Berta Chelle, OIE Focal Point for Veterinary Products of Uruguay, took over as coordinator of the work group. Additionally, representatives from the official and private sectors of El Salvador (ALFA) have joined the Work Group.

Guide for the classification and inspection of veterinary products with no therapeutic indication

Dr. Henrique Uchio Tada, from ALANAC, presented the progress made in the discussion of the document, including the comments received. The document, which is currently in Status IV, shall be circulated to all CAMEVET members.

Internal Antiparasitics for Ruminants and Swine

Dr. Silvana D'Onofrio, representing CAPROVE and acting as coordinator of the Work Group, presented the progress made on the document, which is currently in Status II.

The Document shall be circulated among the members of the Work Group for subsequent comment.

Review of the Glossary of terms

Ms. Ana Sgammini presented the results obtained after having circulated the Document among the Spanish speaking countries for suggestions of terms to be included. The document will be circulated again with the comments received, and shall be circulated as a final document in the three languages. Belize will be responsible for the translation into English, while SINDAN will be responsible for the translation into Portuguese.

Session III – Training in CAMEVET

OIE Workshop on the database of antimicrobial agents destined for animal use in the Americas.

The CAMEVET Seminar included an event organised by the OIE, which began on the Thursday, with the participation of Dr. Osbil Watson, Chief Veterinary Officer and Delegate before the OIE for Jamaica, Dr. Catya Martínez, Technical Assistant of the OIE Subregional Representation for Central America, Dr. Delfy Góchez and Dr. Morgan Jeannin, from the OIE Department of Antimicrobial Resistance and Veterinary Products.

Topics discussed included a focus on the countries of the Americas in the 3rd. Annual Report of the OIE, data collection concerning antimicrobial agents used in animals, the importance of a national follow-up of quantities and patterns of use of antimicrobial agents in animals, and common errors detected at country level upon sending the report on the use of antimicrobials. The event also included presentations by the Official Representatives of Costa Rica, Brazil and Dominican Republic relating to the use of antimicrobials in those countries.

Additionally, a closed session was held for the Official Representatives to provide training in the identification of data sources, calculation of kilogrammes of active ingredient and of animal biomass.

This event was deemed to have contributed high-level scientific information. It also provided a forum for sharing knowledge concerning global and regional actions and options for collaborating toward the reduction of resistance to antimicrobials.

Training course in Good Manufacturing Practices.

The Seminar included training in Good Manufacturing Practices for the manufacture of Veterinary Products, provided by pharmaceutical chemist Natalia Guelfi.

The workshop covered topics such as the importance of veterinary product qualification, calibration and validation, and audits as part of Good Manufacturing Practices.

Session IV – Operative aspects of CAMEVET

Approval of proposed venues for the forthcoming Seminars

The representative of the official sector of Nicaragua, Dr. Bertha Martinez, proposed her country as the venue for the following Seminar to be held in the year 2020.

Dr. Aida Rojas, representing the official sector of Colombia, proposed her country as the venue for the Seminar to be held in the year 2021.

Both proposals were approved unanimously.

Financial report of CAMEVET

Ms. Ana María Sgammini, Administrative Secretary of CAMEVET, presented the financial report, including annual expenses and income received during the present Seminar, and the expense forecast for the following period. This report is included as an annex.

During this presentation, the budget appropriation of USD 17,000.00 for financing was approved, which shall be allocated to applicants in accordance with the regulations.

It was noted that CAMEVET provided economic assistance to the Focal Points that requested it, including the Focal Points of Belize, Bolivia, Cuba, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Nicaragua, Panama and Peru.

Election of members of the Executive Board

In accordance with the new regulation of CAMEVET, official representatives and active members were chosen to cover the vacancies on the Executive Board.

The following members were chosen from the Official Sector:

- Dr. Federico Luna, National Focal Point for Veterinary Products of Argentina
- Dr. Claudina Loza, National Focal Point for Veterinary Products of Bolivia
- Dr. Luna Lisboa, National Focal Point for Veterinary Products of Brazil
- Dr. Aida Rojas, National Focal Point for Veterinary Products of Colombia

The Official Sector representatives shall serve on the Board for a period of two years, according to the Regulation.

The following were elected from among the Active Members:

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

The active members elected as representatives shall serve for a period of two years, according to the Regulation.

The Executive Board shall be presided by Dr. Bertha Martinez, National Focal Point for Veterinary Products of Nicaragua, venue of the next seminar.

Additionally, Dr. Virginia Quiñones, Focal Point for Veterinary Products of the Dominican Republic and CAMEVET representative before the VICH, shall be invited to take part in the regular meetings.

Work Groups

A new Work Group was formed for the Guide on small animal Internal Antiparasitics.

This Work Group shall be coordinated by official sector of Argentina and made up by the official representatives of Colombia, El Salvador and Uruguay, with the participation of ALANAC (Brazil), ALAVET (Chile), ASOVET (Guatemala), CADIN (Nicaragua), CAPROVE (Argentina), CLAMEVET (Argentina).

Additionally, it was announced that official sector of Belize, Ecuador and El Salvador, with the participation of ABIQUIF (Brazil) and ALFA (El Salvador) shall join the Work Groups that correspond to the Inspection Guide relating to GMP for the manufacture of Pharmaceuticals (including Ectoparasitics).

ABIQUIF (Brazil) shall join the Work Groups that correspond to the Efficacy tests for the registration of internal antiparasitics for ruminants and swine.

Conclusions and recommendations. Reading and approval of the final document.

After being read, and having made certain suggested modifications, the document containing the conclusions and recommendations was approved by the Plenary Meeting.

List of acronyms used in the document

ABIQUIFI	Brazilian Association of Pharmaceutical Supplies Industry (Brazil)
ALANAC	Association of National Pharmaceutical Laboratories (Brazil)
ALANAV	National Association of Veterinary Laboratories (Mexico)
ALAVET	Association of Veterinary Product Laboratory Trade Unions (Chile)
ALFA	Association of Pharmaceutical Laboratories (El Salvador)

ASIFAN	National Industry Pharmaceutical Association (Costa Rica)
CADIN	Chamber of Industry of Nicaragua
CAMEVET	Americas Committee for Veterinary Medicines
CAPROVE	Argentine Veterinary Product Industry Chamber (Argentina)
CLAMEVET	Chamber of Argentine Veterinary Medicine Laboratories (Argentina)
GMP	Good Manufacturing Practices
OIE	World Organization for Animal Health
SINDAN	National Syndicate of the Animal Health Products Industry (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 - Financial Report
Annex IV – Procedure for the creation of Working Groups (Only Spanish)
Annex V – Guide for the implementation of the Pharmacovigilance system
Annex VI - Stability of veterinary medicinal products
Annex VII - Good manufacturing practices in cell processing establishment

ANNEX I

Conclusions of the Plenary Meeting of the Official Sector

On September 23th, the Focal Points of veterinary products will hold a general meeting of the official sector in order to deal with the following topics:

Venue of the next CAMEVET Seminar: Dr. Berta Martinez, Focal Point of Nicaragua, ratifies her country as the next venue for the Seminar.

Election of new members of the executive board: The focal points of Argentina Dr. Federico Luna, Bolivia Dr. Claudina Loza, Brazil Dr. Luna Lisboa and Colombia Dr. Aida Rojas were unanimously elected. Dr. Berta Martinez will integrate the table as President of CAMEVET and Dr. Virginia Quinones as representative before the VICH.

Finalized, the Focal Point of Canada Dr. Surinder Saini, manifests the need to change the name of the "Seminar" by the one of "Annual Meeting", since of this form the sanitary authorities of each country will give greater importance to the participation of the focal points.

ANNEX II

Panama

- Prohibition of commercialization during the renovation of registrations, does not allow import of product while the renovation of the registration is in process.

- Change of registration number after renovation.

Honduras

- Retention of products with sticker, in customs, although the RTCA accepts it.

- Request for Primary Standards.

- Extended times of renewal and prohibition of commercialization until concluding the procedure.

- Request secondary packaging printed on new products, printing techniques not accepted .

Guatemala

- Change of registration numbers after renovation.

- Free sale certificates that say "in process of renewal" are not accepted.

El Salvador

- Renovation times have improved, but they take a long time.

Costa Rica

- Very long times for registrations.

- Postponement of new registrations to review renovation.

Problem of registration in Costa Rica - delay

Points for improvement

- - It is proposed that an extension of the registration be issued in the face of such a delay.
- - Difficulty in the different countries because the same criterion is not adopted in the labelling of products (technical criterion has not been unified). It should be noted that the labeling and registration topic was discussed after the negative experiences that the industries go through at the time of registering products (Costs).
- - It is requested that the insert be allowed to place everything special for each country and that it be obligated to put on a label or primary packaging only what is indispensable.
- - Certificates time of validity
- - Original documents and / or copies unify criteria (searched in these forums).
- - Period prior to expiration, to submit renewal and requirements.
- - Permission to import or trade if renewal is in process.

- - Validity of Free sale certificates and GMP
- - BPM Certificate Validity Period in each country, are different years. It is requested to unify criteria
- - Apostilled and/or consularized documents
- - Languages accepted for the Bibliography.
- - Presentation of printing arts in pdf instead of originals. in many cases with the changes that request the countries do not have originals until product approval is obtained. this is as a result of not having unified labeling criteria.
- - Approval of the labeling document (costs)
- - Products already registered and current renewal, must be re-registered as new product.

ANNEX III
Financial Report

Ingresos	28/12/2018 - 2/9/2019
Recursos disponibles al 29 de diciembre de año 2018	USD 143.515,80
Inscripción al Seminario CAMEVET 2019	USD 1.750,00
Subtotal de Ingresos	**USD 145.265,80**

Egresos	
Gastos fijos (Salarios)	
Asistente Administrativa (Srta. Ana Maria Sgammini USD 1.200/8 mes + aguinaldo)	USD 10.200,00
Gastos Admin. Por uso de las Oficinas de la OIE (150/mes)	USD 1.200,00
Subtotal Gastos Fijos	USD 11.400,00

Gastos de Participación en Otros Eventos	
Participación en reuniones del VICH Outbreach Meetings	USD 1.490,00
OIE Conference Regional Commission for the Americas	USD 0,00
Subtotal	USD 1.490,00

Otros Gastos	
Internet (Dominio de CAMEVET)	USD 10,00
Pago de confección de recibos CAMEVET	USD 0,00
Subtotal	USD 10,00

Gastos Variables	
Cambio de Dólares a Pesos Argentinos	USD 3.950,00
Subtotal	USD 3.950,00

Subtotal de Gastos	**16.850,00 USD**

Saldo total al 2 de septiembre de 2019	**128.415,80 USD**

Ingresos	**28/12/2018- 2/9/2019**
Recursos disponibles al 28 de diciembre de año 2018	ARS 214,67
Cambio dolares americanos a pesos argentinos	ARS 174.835,00

	Subtotal	**ARS 175.049,67**
Egresos		
Gastos para la Reunión Anual de CAMEVET		
Gastos por compra de tiquetes aéreos (Sta. Ana Sgammini)		ARS 70.970,00
	Subtotal	ARS 70.970,00
Gastos de Participación en Otros Eventos		
Gastos por compra de tiquetes aéreos – Vich		ARS 91.653,78
Gastos tramite Visa Sudafrica		ARS 10.800,00
	Subtotal	ARS 102.453,78
Otros Gastos		
Miscelaneos (Traduccion ESP/ENG de Conclusiones Seminario CAMEVET)		ARS 0,00
	Subtotal	ARS 0,00
	Subtotal de Gastos	ARS 173.423,78
	Saldo total al 2 de septiembre de 2019	**ARS 1.625,89**

ANNEX IV
(Only Spanish)

PROCEDEMIENTOS PARA LA IDENTIFICACION, ESTUDIO, SEGUIMIENTO, APROBACION Y ADOPCION DE DOCUMENTOS ARMONIZADOS DE CAMEVET

INTRODUCCION

En el transcurso del trabajo de armonización que se ha venido desarrollando con el liderazgo de la Representación Regional de la OIE de las Américas y la participación del sector Oficial de los Registros de Medicamentos Veterinarios de los países y de la Industria se han presentado, discutido y aprobado documentos, los cuales deben ser correctamente identificados.

Asimismo, es imprescindible que se cuente con un mecanismo de circulación de documentos, definiendo claramente los pasos que deben darse para llegar a la armonización, estableciendo plazos de tiempo para cada paso.

De este modo, se dispondrá de un sistema que permita a los interesados conocer la etapa en que se encuentra el proceso, quedando bien definido cuando éste ya ha concluido y, en definitiva, se agilizará la armonización regulatoria.

OBJETIVOS

El presente procedimiento tiene como objetivos

a. Identificar las diferentes etapas en la elaboración de documentos CAMEVET;
b. Establecer los plazos requeridos para la circulación y recepción de comentarios previos a la aprobación de los mismos.
c. Establecer el sistema de identificación de los documentos

ALCANCE

Están alcanzados por el presente procedimiento el trabajo de todos los grupos que se formen para tratar un tema y los documentos que produzcan los mencionados grupos de trabajo.

TÉRMINOS Y DEFINICIONES

Grupo de trabajo: Grupo formado por Representantes del sector oficial o privado que manifiestan interés para trabajar sobre un determinado tema

Coordinador del Grupo de trabajo: Representante del sector oficial o privado que asume la responsabilidad de coordinar las acciones del grupo de trabajo con el fin de asegurar que se cumplan con las pautas de este procedimiento.

Nota de concepto (Concept paper): documento que plantea un posible tema de análisis y justifica la necesidad del mismo

PROCEDIMIENTO

1. **Tramite I**: Presentación de la nota de concepto y aprobación del enunciado del tema.

1.1. Los miembros de CAMEVET podrán sugerir a la Asamblea o a la Mesa Ejecutiva los temas que consideren que deben ser incluidos en la agenda de trabajo de CAMEVET para su estudio

1.2. Para la sugerencia de un nuevo tema se deberá presentar a la Mesa Ejecutiva una nota de concepto que contendrá como mínimo:

- Título: el título deberá expresar claramente la temática del problema a evaluar
- Reseña: se deberá contar con una breve reseña que explique la finalidad y objetivos del tema propuesto.

1.3. La Asamblea analizará los temas sugeridos. Los temas serán sometidos a votación, requiriéndose una mayoría simple para su aprobación.

1.4. Para los temas aprobados, se formara un Grupo de Trabajo integrado por un Coordinador y los representantes de todas aquellas instituciones oficiales o privadas que deseen participar en el estudio del tema.

1.5. Los temas aprobados y con Grupo de Trabajo conformado ingresaran a la Secretaria en status de **Tramite I.**

2. **Tramite II:** El Grupo de Trabajo deberá presentar el primer Proyecto de trabajo dentro de los 180 días de finalizado el Seminario en el cual se aprobara el tema. Cumplido este requisito el documento ingresara en status de **Tramite II**

2.1. Habiendo finalizado el plazo establecido y de no ser presentado el Proyecto, el tema quedara excluido del programa del próximo Seminario. Este Proyecto podrá ser incorporado si es nuevamente presentado y aprobado por el Plenario.

3. **Trámite III:** Los proyectos de guía técnica o de otros documentos por los cuales el CAMEVET establezca una posición regional que sean consensuados en el grupo de trabajo serán remitidos a la Secretaría, en formato CAMEVET y en los tres idiomas oficiales (Español, Inglés y Portugués). Los documentos que cumplan con estos requisitos ingresan al status de Tramite III y serán presentados en el siguiente Seminario, bajo un formato de power point, pre-establecido donde se expondrán las principales características del Proyecto.

3.1. Las traducciones estarán bajo la responsabilidad de la coordinación del Grupo de Trabajo.

3.2. Cumplidos estos requisitos los documentos ingresan en el estatus de Trámite III

3.3. Los documentos en **Trámite III** se distribuirán a través de la Secretaria a todos los miembros del CAMEVET para la recepción de comentarios. El plazo para la recepción de comentarios será de 120 días luego de la distribución del mismo.

3.4. Cumplidos los 120 días la coordinación distribuirá dentro del Grupo de Trabajo los comentarios recibidos y este evaluara su incorporación, o no, al documento final. En el caso de que las sugerencias no sean incorporadas al documento el Grupo de Trabajo deberá explicar los motivos de la exclusión.

3.5. El Coordinador del grupo de trabajo fijará el plazo necesario para la correcta evaluación de los comentarios y comunicará a la Mesa Ejecutiva la fecha en la que se concluirá esta evaluación. Asimismo, deberá mantener informada a la Mesa Ejecutiva de los avances del grupo, remitiendo un estado de situación cada 90 días.

3.6. En el caso en que un documento en trámite III no recibiera comentarios, se considera que todos aquellos que no enviaron están de acuerdo y el documento pasa automáticamente a ala etapa siguiente.

4. Trámite IV: El documento final que incluye los comentarios ingresará al status de **Tramite IV** y tendrá una 2º circulación, de 90 días, entre todos los miembros de CAMEVET, para su conocimiento y eventual aprobación durante la Asamblea.

4.1. En el caso de que el documento no sea aprobado en la Asamblea, se mantendrá en Trámite IV y, la Asamblea, decidirá si se realiza una nueva circulación de 90 días o si se descarta el proyecto.

4.2. Todos aquellos documentos en que durante el período entre un seminario y el siguiente no hubieran tenido avances o modificaciones dentro de los parámetros establecidos en este procedimiento serán dados de baja de la agenda del CAMEVET.

5. Trámite V: Los documentos que cumplan con todos los requisitos mencionados ingresan al status de Tramite V y serán presentados en el siguiente Seminario, bajo un formato de power point, pre-establecido donde se expondrá el historial resumido de los comentarios recibidos.. Estos documentos estarán en condiciones de ser sometidos a aprobación por parte del Plenario. Los documentos aprobados durante la Asamblea ingresaran al status de **Tramite VI.**

5.1. Estos documentos armonizados serán publicados por la Secretaría en la página web del CAMEVET entre los documentos armonizados dentro de los 60 días a partir de su aprobación.

6. Trámite VI: Todos los documentos aprobados podrán ser revisados o actualizados a partir de una solicitud con justificación científica y será sometida a la Mesa Ejecutiva y luego al Plenario de Camevet, los documentos en revisión ingresaran al status de **Tramite VI**, siguiendo los mismos pasos como si estuvieran en trámite III.

7. Identificación: Los documentos CAMEVET, tanto borradores como armonizados, serán identificados en el ángulo superior derecho de la carátula (Anexo 1) con las siguientes líneas: CAMEVET

XXX 001
Trámite (I al VI)
Fecha: (mes y año)

7.1. XXX es una codificación que otorgará la Secretaría, identificando al grupo de trabajo. Por ejemplo, BPM se refiere a Buenas Prácticas de Manufactura.

7.2. El número de tres dígitos posterior al código que identifica el grupo de trabajo se utilizará para identificar distintos documentos producidos por el mismo grupo.

8. Presentaciones: Todas las presentaciones que se realicen a la Asamblea se harán en formato power point, pre-establecido, que será provisto por la Secretaría.

8.1. Aquellas en las que se describan proyectos, se limitarán a reseñar las principales características de los mismos

8.2. Las destinadas a presentar documentos en trámite III o trámite IV, incluirán los comentarios recibidos y la decisión de aceptación o rechazo de los mismos. Los rechazos deberán ser justificados.

RESPONSABILIDADES

Coordinador del Grupo de Trabajo

- Recibir e incorporar los comentarios que se vayan realizando durante el desarrollo del Grupo de Trabajo notificando a la Secretaria de la evolución del mismo.
- Cumplir con los plazos de elaboración de proyectos
- Informar los avances del grupo de trabajo a la Mesa Ejecutiva cada 90 días
- Justificar los rechazos a comentarios
- Presentar los documentos en Trámite III en los tres idiomas oficiales del CAMEVET

Secretaría del CAMEVET

- Realizar seguimiento de la evolución del trabajo de los grupos.
- Distribuir los documentos a comentarios a los miembros de CAMEVET
- Realizar seguimiento de los plazos de elaboración de proyectos y de comentarios
- Publicar los documentos armonizados dentro de los 60 días de su aprobación

REFERENCIAS

- 24º Manual de Procedimiento (2015) – Codex Alimentarius Internacional
- VICH/96/002 Revision 12 October 2015 FINAL ORGANISATIONAL CHARTER OF VICH

ANEXOS

- Anexo 1: Modelo de carátula
- Anexo 2: Flujograma de aprobación de documentos

ANEXO 1 Modelo de carátula

Encabezado:

logo CAMEVET

CAMEVET
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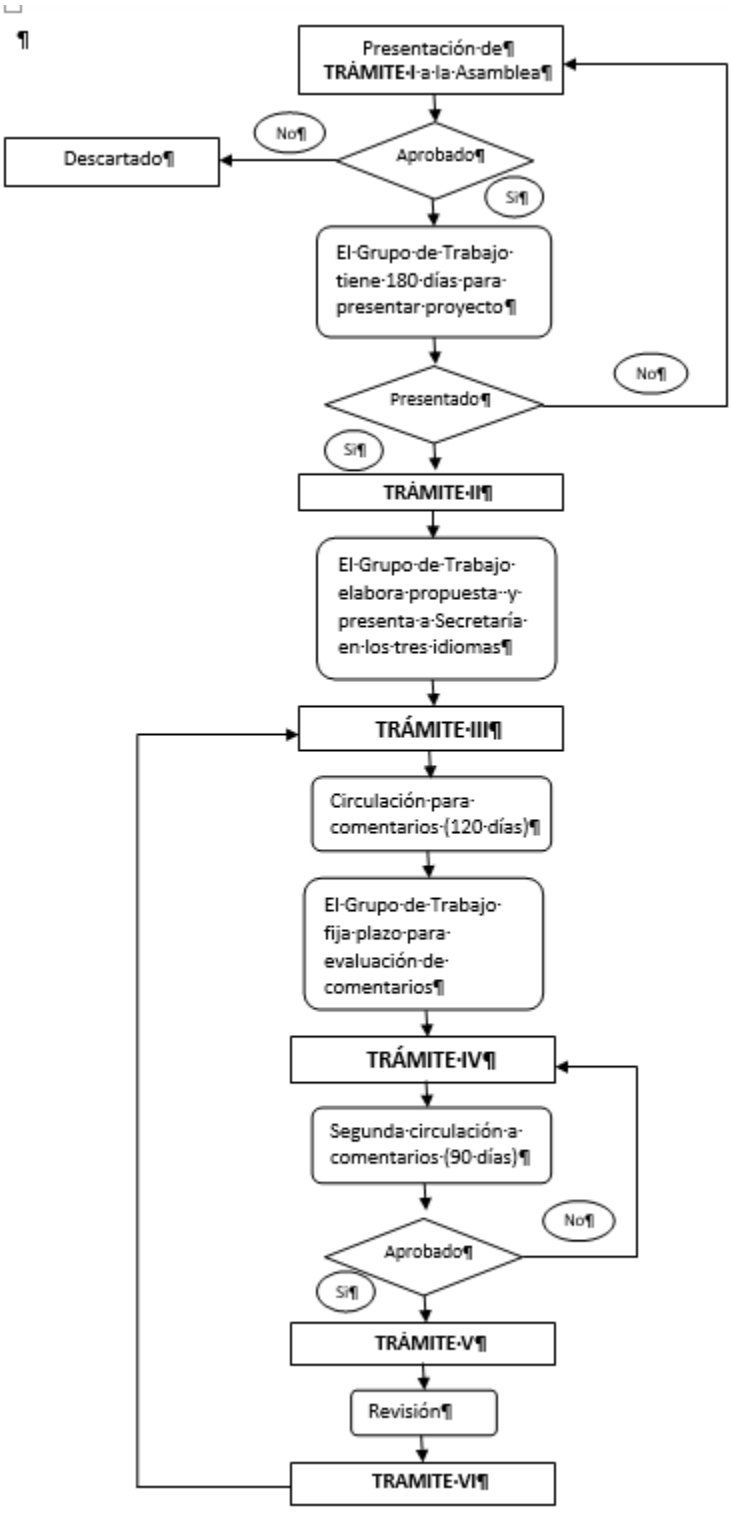
Fecha: (mes y año)

TÍTULO DEL DOCUMENTO

Pie de página:

ANEXO 2 Flujograma



COMITE DE LAS AMÉRICAS DE MEDICAMENTOS VETERINARIOS (CAMEVET)
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ANNEX V

CAMEVET
Code: Reg - Farm 001
PROCEDURE: IV
September 2019

PHARMACOVIGILANCE IMPLEMENTATION SYSTEM GUIDELINE FOR VETERINARY MEDICINES

Index

PHARMACOVIGILANCE IMPLEMENTATION SYSTEM GUIDELINE FOR VETERINARY MEDICINES

1. INTRODUCTION

Pharmaceutical companies carry out clinical and preclinical tests prior to commercialize a veterinary medicine, which allows proving their products efficacy, for the proposed use and with a better risk/benefit relation for animals, environment, worker and final consumer. All of these must be assessed by governmental regulatory authorities for each country within a sanitary registration routine process. However, clinical and preclinical test results come from a limited number of animals, and often not all variables encountered in the post-commercilization stage are considered, for instance, interactions with medicine administered in parallel, use in diverse breed, body conditions and age ranges, safety condition, among other variables. Even more, the limited number of animals included in preregistration tests, reduce the possibility of detection of less frequently reported or slowly developing adverse reactions.

Based on the above mentioned facts, it becomes necessary to implement a pharmacovigilance system for veterinary medicine, with an objective to identify adverse reactions in the post-commercialization stage, and in this way to continue to assess the veterinary medicine risk/benefit relation and safety/efficacy profile.

2. DEFINITIONS

2.1 Adverse Effects (EA):

Un-intentional damaging effects that may occur following consumption of a veterinary medicine on following or not the use recommendations indicated in the labels. It includes secondary damaging effects on animals (adverse reactions), as well as possible inefficacy of a medicine or adverse effects on the humans after the product exposure, final consumer and environment.

2.2 Serious Adverse Reaction (AR):

It provokes death, endangers life, produces significant incapacity or disability that may transform into a congenital malformation or birth defect, or may trigger permanent or prolonged symptoms in treated animals. The adverse reaction that results in euthanasia is also considered a serious AR, even if by itself, has not generated death. For animals managed and treated as a herd, only an increase in the incidence of serious adverse events that exceed the levels usually expected in that particular group are considered a serious adverse event.

2.3 Notification:

An action through which an authority and/or person in charge is informed about a patient, person or environment that has developed an adverse effect supposedly originated by a veterinary medicine. Consists of a format duly completed by the notifying officer in order to confirm causality, and it can be sended by any way the local competent authority defines.

2.4 Off label use:

Utilization of a medicine different to the one authorized in labels intentional or not, including different dosage, intended species, use indications, administration form, among others.

2.5 Competent Authority: CA

Authority with professional proficiency in the area of Pharmacovigilance.

2.6 Unexpected adverse effect: **(UAE)**

Any adverse effect unknown up to date and, therefore, veterinary labels does not describe its nature, seriousness and consequences.

2.7 Periodic Safety Report (PSR):

A report of the adverse effects that have been notified to the CO during a specific and predefined period that provides an assessment of the benefit / risk balance of a veterinary medicine, which is sent periodically to the CA by the CO in order to provide an update of the safety and efficacy data of the veterinary medicine.

2.8 Commercialization Owner (CO):

Depending on each countries legislation, it is a natural or legal person, authorized to carry out primary commercialization of a veterinary medicine in a determined country.

2.9 Pharmacovigilance Accountable Professional (PVAP):

is a professional accountable on behalf of the CO, to coordinate and implement all activities related to Pharmacovigilance according to current regulations and is the valid interlocutor with the competent authority.

3. PHARMACOVIGILANCE OBJECTIVES AND SCOPE:

Pharmacovigilance objectives are:

1. To detect unknown adverse effects and interactions.
2. To detect any increase in the frequency of a known adverse effect.
3. To identify risk factors and possible mechanisms, which trigger adverse effects.
4. To permanently assess the veterinary medicine risk/benefit relation and safety/efficacy profile.

Pharmacovigilance scope:

1. Adverse reactions under authorized use conditions, i.e., observing the label recommendations.
2. Adverse reactions associated to off label use.
3. Alleged inefficacy of a veterinary medicine registered in a determined country
4. Alleged insufficiency of the established control periods.

5. Adverse effects in people handling veterinary medicine.

6. Adverse effects manifested in the environment due to veterinary medicine use and/or its final disposal.

7. Infectious agents transmission by contaminated veterinary medicine.

It is recommended to implement the pharmacovigilance systems gradually in the country and according to the type of products applied.

4. NOTIFICATION SYSTEMS:

a) Private persons or citizens, cattle farmers or animal owners

They can notify about an AE, although they are not obliged to report or to fill any specific form.

In the event that there is a suspicion of an AE, a person can report by any means to the medicine Commercialization Owner (CO), to a veterinary doctor, to the technical director of the company where the product is available or directly to the competent authority.

b) **Veterinary Doctors:**

Veterinary Doctors should inform every AE suspicion they come to know in their routine clinical practice by observing a set of signs or symptoms, which cause suspicion about an eventual association with the administration of a veterinary medicine.

They shall notify any suspicious AE information they receive from private persons, cattle farmers or animal owners.

Regardless of the information source, veterinary doctors should notify the Commercialization Owner of the suspicious veterinary medicine, or to the Competent Authority by using the Green notification form, which must be sent to the CO of the suspect veterinary drug and / or directly to the competent authority, as defined by each country.

In the event that an AE appears in more than one animal species, a separate notification for each species is recomended, but it must indicate that both notifications are related. This also applies whenever the AE occurs in animals and in humans.

Whenever an AE appears in a non-treated animal that was exposed to a treated one, even though they are different species, a single notification must be submitted related to the animal affected by AE. In this case, the animal that received treatment with the veterinary medicine must be identified clearly. Further, information about the route of administration shall reflect the way in which the animal was exposed, i.e. orally (if the contact was by licking or by mutual grooming) or by cutaneous way (if there was skin contact between the animals).

Whenever AE appears in the descendants, it will be informed as follows:

- Spontaneous abortion or fetal death: notification should consider only the mother.

- Whenever the AE is shown only in progeny (example: malformations) but the father is not affected: notification should only consider descendants. The number of affected litter descendants and the quantity of treated adults should be notified in order to know the proportion of affected animals. The latter is particularly important whenever there is inefficacy suspicion.

- In the event that AE is observed both in the mother and the progeny (fetus intrauterine exposure): there should be one notification both for the mother and the progeny. Animal details notified should be the mother´s and the quantity of treated animal should be one (1): reported clinical signs should consider the mother and progeny.

To proceed with notification, suspicion must fulfill the following four minimum requirements:

- Notifying party identity: name, initials and contact information. It can be an individual, cattle farmer, owner or veterinary doctor.

- Affected party identification: (who or what has shown the AE): animal (specie, sex, age) humans (name or initials, sex, age) or environment (location).

- To identify at least one veterinary medicine suspicious of causing AE (example: name of the product, number of sanitary registration, commercialization owner or serial number, among others).

- AE Description

To have a valid notification, a great effort should be done to get complete and required information.

In cases of incomplete notifications, mainly in cases of serious or unexpected AE, there must be a follow up in order to get additional information from the initial notifying party or from other available documents or sources (results of laboratory analysis)

Additionally, veterinary doctors' responsibilities are the following:

- To respect the truthfulness of the data received whenever registration of AE takes place.

- To protect confidentiality of data, which may lead to the identification of the person, in order to respect the privacy. In exception of the competent authority and/ or CO, so that it is possible for them to obtain additional information.

- To safeguard AE clinical documentation in order to complete or follow up cases.

- To collaborate with the Pharmacovigilance accountable professional PVAP at the Commercialization Owner CO, by providing any requested information in order to notify afterwards the Competent Authority CA

- To collaborate with the CA by providing all requested information to expand or complete AE information

- To keep himself updated about safety and efficacy data on prescribed or consumed medicine.

c) **Technical directors at retail stores (TDRS)**

TDRS are obliged to notify all AE they come to know, from individuals, cattle farmers or animal owners by filling out the Green notification form which must be forwarded to the CO for the suspicious veterinary medicine or directly to the Agriculture and Cattle Farmer Department (ACFD)

To proceed with a notification, those four minimum requirements detailed in previous section (b) must be fulfilled.

d) **Commercialization Owners** (import companies and domestic production laboratories)

Whenever the CO receives information about an AE suspicion, it should confirm previous data and, if necessary, contact the notifying person to obtain more or to complete information. In addition, he should contact the notifier and ask for supplementary background data, such as laboratory test results, necropsy in case of death and follow up history of cases.

In all cases where the CA receives a notification of suspicion of AE, it must be sent to the CO; who must have the capacity to avoid duplication of information received from the same source (notifier) through different channels.

i. **Individual Notification:**

The COs who receive information related to an AE suspicion, should report it to ACFD by filling out a yellow notification form **no later** than 15 working days after receiving the notification, in cases of:

- Serious AR suspicion in animals (both expected and unexpected) that have occurred in the country.
- AE suspicion in humans exposed to veterinary medicine that have occurred in the country.
- AE suspicion in the environment and a possible transmission of infective agents that have occurred in the country.

AE suspicion should be considered after the drug consumption according to the approved use and the off label use.

All of these AE, are classified as “expeditious or serious”

The yellow form must be filled out, and sent to the CA.

When no information is available, it should be indicated “unknown” or “it does not apply” in the corresponding items.

In cases of a serious AR suspicion in animals (expected and unexpected), that have occurred in the country, and at the same time there is suspicion of quality failure of the veterinary medicine, it must be reported no later than 72 hours since the time of reception of the notification.

Suspected serious adverse reactions, occurring in third countries, should be included in the periodic safety report.

ii. Periodic Safety Report

The AEs not included in the previous paragraph (i) are considered as “not expeditious or not serious”, and there is no obligation to report them individually, however, they must be reported to the CA in a Periodic Safety Report (PSR).

Regarding reports of events occurring in third countries, such as suspicions of unexpected serious AR, suspicion of AE in humans or in the environment and the possible transmission of infectious agents, they should also be included in the periodic safety report.

The Purpose of PSR is to provide an update on the safety and efficacy information to the world veterinary community. Even when there is no AE reported in a period, the CO must prepare and present the PSR.

The safety information must be gathered, analyzed, and assessed by the CO to define whether additional tests or changes in valid label are required.

Each PSR is defined by a data block point (DBP), matching the report closing date. At this point, all PV information known by the CO must be gathered and analyzed.

To initiate a PSR

- Starting from the sanitary registration date or the International Registration Date, as it is suitable.
- For administrative effects, the last day of each month must be considered.

Submission frequency

o Every six months, starting from the registration date up to effective commercialization date.

o Every six months, 2 years after effective commercialization in the country.

o Annually, during two consecutive years

o Every three years, starting from the last yearly report.

CA will define for every case the PSR modification frequency, for instance, whenever registration is changed including a new target species, dosage, use instruction, consumption forms, new excipient lacking a safety profile or whenever a closer continuous monitoring requirement about the product safety emerges.

PSR Cycle:

- It should start the following day after the previous PSR data block point. There cannot be any uncovered day by the PSR nor data overlapping.

Delivery date:

o Up to 60 days following DBP.

PSR Scope:

- PSR should cover all species, indications and commercialized presentations, either as originally registered or added in subsequent changes.
- It should include those AE reported within the country and in third countries.

PSR content:

1. Veterinary Doctor's information.

- Generic and commercial name
- Pharmaceutical form
- Sanitary Registration number
- Registration date
- PSR correlative number
- PSR formulation date
- PSR covered period
- First effective commercialization date
- PVAP's name and signature
- Number of countries in which the product has been approved

2. CO's name and address

3. Regulatory measures update or actions taken from the CA in any country of the world due to safety reasons, since the last report, such as registration denial, general or for a specific indication; registration or market withdrawal; registration renewal denial, registration change, risk management plan imposed by the CA, inter alia.

4. Presentation's estimate

- Sales volume: for the reported period, both domestically and in third countries, expressed as:
  - Vaccines: dose quantity or volume in case the vaccine indicates different doses according to type of animal.
  - Liquids: liters
  - Powder: kilograms
  - Tablets: Tablet quantity
  - Collars: collars quantity
  - Paste: kilograms

- Pipette: Pipette quantity

- Treated animal estimate: Even though each CA must define it, it is recommended that the PSR includes the estimated number of treated animals and incidence. regardless of the AE appearance, in some cases the number of treated animals (for each authorized target species) corresponds to the number of sold dose, however in other cases the standard treatment period should be taken into account or the worst scenario (maximum recommended dose and longest treatment period) considering a standard weigth for each target species.

Species and subcategory	Standard average weigth (kg)
Equine	550
Canine	20
Cat	5
Bovine	550
Veal	150
Unweaned Calf	50
Sows/Boars	160
Pigs (fats)	60
Piglet	25
Ovine	60
Lambs	10
Chicks broilers	1
Laying Hens	2
Turkeys	10
Rabbits	1,5

* for those species and subcategories in which a standard average weight is not included, the CO must define and report the average weight that will be used to perform the calculations, having to use the same data consecutively.

For drugs intended for several species or subspecies, the OC should make a general estimation of the proportion of animals treated per species or subspecies; in order to calculate the incidence as detailed below.

5. AE Incidence

- Spontaneous AE general percentage incidence (A, B, O including O1. See definition in point 5: CAUSE ANALYSIS) after indicated and off label use, for all authorized target species, in relation to the sold volume. Those AE detected in post registration safety tests should be excluded.

- Percentage of lack of effectiveness incidence, after recommended use, in relation to volume sold.

- Proportion of animals with AE: in general and for each target authorized species.

- Proportion of animals that have EA: in general and for each target animal species authorized and commercialized.

- Quantity of animals with AE (A,B,O including O1) during the period/Dosages quantity sold during the period.

- Incidence
  - Quantity of animals affected by AE (A,B, O including O1) during the period/estimated quantity of treated animals during the period x 100.
  - An Incidence Estimation for each reported country shall be prepared.

6. Data Check

- All individual AE reported during the period, highlighting main findings and AE types (foreseen, unforeseen, serious and not serious).
- Reported AE in animals (including for inefficacy and off label use)
- AE reported in humans
- Other Pharmacovigilance areas: environment, vigilance period, infectious agent transmission
- Presentation, analysis and assessment of new safety data, which change known data in terms of frequency and severity.
- Charts summarizing main findings will endorse analysis.

7. Ordinary Reports

- If the CA determines it, to attach data from other sources, like post registration analysis, AE published data, users experience studies; those should be reviewed and discussed.
- To attach bibliographic list of published scientific articles that report AE for the same PSR period, and a brief discussion of results.

8. Other information

- AE due to medical prescription, treatment mistakes (name change or veterinary medicine with similar appearance), misuse and/or abuse.

9. Safety General Assessment

- Summary of all AE contained in the report.
- A critical analysis on presented data and a critical assessment on the risk/benefit relation, particularly about frequency changes of known AE, occurrence of unexpected AE, interaction with other drugs, inefficacy and AE in humans
- An assessment must indicate whether:
  - Safety information remains in line with accrued experience up to the date and the label.

- There are new safety and efficacy data, which may advise to start post-registration tests and incorporate label changes.
- To specify any recommended action and its justification.

10. Important information after DBP.

- Summary of all AE contained in the report.
- Any information received after the DBP should be included if relevant and may cause modifications to the general evaluation informed in the previous point.

11. List of cases

- It must contain all AE occurred throughout the world and spontaneously reported to CO or to CA.
- It should contain all individual cases classified as A, B , O, O1 and N.
- To report all measures taken by the CA or by the CO
- Standard information must contain:
  - Treatment/vaccination date
  - Use indication
  - Off label use
  - AE date
  - Quantity of treated animals
  - Target species
  - Age (s)
  - Quantity of animals which reacted
  - Quantity of death animals
  - Other accompanying drugs administered (Commercial names and active substances)
  - Case description and symptoms
  - Symbols list
  - Allocated causality assessment
- For AE in humans, the following should be included:
  - Patient identification
  - Occupation

- Exposure date
- AE date
- Exposure type
- Type of reactions and symptoms
- Reaction result
- Conclusion

Shorten PSR:

A shorten PSR is submitted whenever the veterinary medicine has not been commercialized in any country of the world, and when no AE has been reported in any additional post registration tests.

PSR content must include:

Generic and commercial name, pharmaceutical type, Sanitary Registration No.; Sanitary Registration No. date; PSR correlative Number, PSR covered period, non-commercialized and un-existing AE statement (in animals or in humans) for which risk/benefit balance remains unchanged, commercialization estimated date, CO's name and address, PVAP's name and signature.

In addition, CO are accountable for the following:

- To keep detailed registration of all AE that have been notified.
- To have a PVAP permanently available.
- Avoid sharing with clients any PV data, which has not been communicated beforehand or in parallel to the CA
- To monitor International references about AE caused by an active principle that is a component of a drug for which he is the authorized commercialization owner CO.
- To report to veterinary doctors on new data regarding safety or efficacy whenever CA ponders as required. The report content should have the CA agreement beforehand.
- To report immediately to the CA about urgent restrictions adopted due to PV.

5. CAUSE ANALYSIS

Regardless of the AE notification source, CO must assess or relationship between the veterinary medicine consumption and the notified AE appearance. Conclusions from causality assessment should be included in yellow format or PSR, depending on an expeditious or non-expeditious AE respectively.
The analysis of causality is an individual analysis for a given notification, which does not intend to study the risk potential of the drug globally or the importance of the risk induced by the drug in the population.

In order to determine causality, the following aspects must be considered:

- Manifestation of a temporary association (including non-exposure and re-exposure) or association in treated and affected anatomical exposure.

- Pharmacological or immunological explanation, blood levels, active principle previous knowledge.

- Manifestation of pathological phenomena or clinical features.

- Exclusion of other potential causes.

- Reported case complete and reliable data

- Quantitative measurement on the veterinary medicine impact to the AE development (dosage-effect relation).

Cause analysis is performed throughout ABON methodology, which studies five categories:

Category A: Probable

- There is a reasonable temporary association between the veterinary medicine administration and the AE occurrence and period.

- The clinical phenomenon description should be consistent with the AE, or at least credible according to the known veterinary medicine pharmacology and toxicology.

- There is no other credible AE development explanation.

Category B: Possible

- Veterinary medicine causality is one of many possibilities or it is a plausible cause, but available information does not comply with Category A's inclusion principle.

Category O: Non-classifiable

- Available data is not reliable or sufficient to determine causality.

Category O1: Non Conclusive

- Association cannot be dismissed, however, there are factors preventing the allocation of a determined causality.

Category N: Unlikely

- Cases with enough information to establish beyond any reasonable doubt that there is AE alternate explanation and which is unrelated to veterinary medicine.

6. SIGNALS DETECTION

The causality assessment carried out by the CO must be evaluated by the CA.

When the causality analysis results determine an AE pattern associated to the medicine utilization, depending on the conditions under which AE have appeared and seriousness, CA might introduce corrective actions aimed to improve veterinary medicine risk/benefit relation.

Information about a possible cause relation between an AE and a veterinary medicine, unknown or insufficiently documented, constitutes a signal. Whenever there is a suspicion of a signal either from CO or from CA, causal relation and any AE aspects that could be relevant, must be assessed.

AE ordinary review and analysis by CO and CA may contribute to detect potential signals, such as:

o AE increase in a short period of time.

o An increase in the frequency of clinical sign(s).

o Whenever a new clinical sign stands out.

o Public health or animal sanitary impact suspicion.

When the CA or the CO detects any of the following situations, the CO must start an investigation:

o AE reaching an incidence level higher than basal (i.e. 1:10.000).

o Serious or unexpected AE appearing in 3 different sites in a week or there is a serious and unexpected AE incidence increase.

o Whenever there are more than 3 AE in farm animals with above normal mortality rate, and within the first 3 months of a new product commercialization.

o A suspicion about the vigilance periods is insufficient to confirm the residue levels lower than the maximum residue level.

When a signal that might affect the benefit / risk balance of the medicine is detected, there must be a formal communication between the CO and the CA or vice versa, depending on which entity identifies it.

When the above occurs, the signals must be validated by the CO and the CA; and in this case the assessment of the benefit / risk balance can be modified by the following actions:

o To increase benefit: including more information for medicine use improvement.

o To reduce risk: counter-indicate usage under certain circumstances, changing dosage, adding special usage precautions, etc.

In an enunciative and non-restrictive way, CA may take the following regulating measures:

- To include contraindications, usage warnings or precautions on the labels.

- To make changes in authorized usage conditions (use indications, dosage, time schedule, target species, vigilance, among others).

• Agreement to carry out post-registration studies by the CO, in case it is essential to obtain additional and relevant information.

• Increase in the periodicity on sending the PSR in order to evaluate the results of the actions taken.

• Based on the benefit / risk assessment of the medicine, temporary suspension and / or immobilization of the veterinary drug registration, until the safety / efficacy issues have been resolved.

• Cancellation of veterinary drug registry.

7. COMMUNICATION

The purpose is to keep veterinary doctors, suppliers technical directors (wholesale and retail) cattle farmers, animal owners and general public informed about any significant change in the information about any medicine (technical specification and graphic label), registration suspension or removal due to PV, in addition to any confirmed concern or suspicion which requires vigilance.

A communication must include the following aspects:

- The right message must be sent to the right group and at the right time.
- The appropriate terms should be used, having in mind diverse target groups.
- Communication should be clear, brief, and unbiased, without any commercial or promotional information.
- A contact person or place to receive any additional information request should be identified.
- Before a regulatory measure is taken, a communication should be delivered, except whenever there is an urgent prohibition due to safety reasons.
- CO or CA prepares communication, upon co-ordination and agreement from both parties regarding content, distribution plan, target group and implementation deadline.
- Distribution of a communication is carried out through different setups, like:

o Press Release

o CA web page

o CO web page

o Annual PV bulletin from CA

o Other digital media

Direct communication with Veterinary Doctors (VDDC)

By general rule, relevant new or emerging information must be communicated first to veterinary doctors, before the rest of target groups, So that they can be better prepared and clarify any doubts from cattle farmers, animal owners or public in general.

The previous paragraph refers to the need to take actions or either to adapt their clinical practice.

VDDC does not provide answers to veterinary doctors' requirements, or educational material for routine risk minimization activities.

When there is more than one CO with registered products manufactured under the same active principle, a single and consistent message should be issued.

A VDDC shall be distributed in situations when an immediate action is needed or a change in current uses of a veterinary medicine is required:

- A significant change in a veterinary medicine usage condition, due to a usage restriction indication, a new counter-indication, or a dosage change recommended due to safety reasons.
- A restriction in a veterinary medicine availability, that may cause potential effects in animals, humans or environment.
- Suspension, withdrawal or cancellation of a registration due to safety reasons.

Other situations whenever a VDDC must be considered are the following:

- New warnings, drug interactions or special usage precautions.
- New information that identifies a previous unknown risk or a frequency or seriousness change.
- Substantial knowledge that a veterinary medicine does not conform the registered efficacy.
- New recommendations to prevent or treat AE or to avoid medication misuse or mistakes, associated to a veterinary medicine.
- Ongoing assessment of a significant potential risk, for which all available data are insufficient to take regulatory action (in this case VDDC should encourage close monitoring about the risk in question; also encourage report making and delivery of information about ways to minimize this risk).

CA can distribute or request the distribution of a VDDC, in any situation when it may be necessary to keep address the safety and efficacy of a veterinary medicine.

8. PHARMACOVIGILANCE SYSTEM DETAILED DESCRIPTION

CO shall have a suitable and documented PV system and the required infrastructure to compile and notify AE occurring in any country where the veterinary medicine is marketed. The PV system should ensure close supervision of veterinary medicines so that appropriate corrective measures are applied when required.

CO shall have a PV professional in charge, of suitable profession, which must be informed to the CA and who will be accountable for the following:

- To set up and maintain a PV system.
- To carry out a continuous and periodic PV system assessment.
- To warrant an accurate AE registration.
- To inform to CA about any AE suspicion.
- To elaborate and submit Periodic Safety Reports PSR.
- To assess and allocate causality.
- To warrant a prompt, timely and correct answer to any information request from CA.
- Provide any information to de CA that may be of interest to evaluate the risk/benefit relation.
- To supervise data base, quality control system, contractual agreements in PV and internal audits matters.
- To be aware of the continuous process that is carried out for the detection of signals and its validation.
- To provide training to the company staff in PV related issues, as well as the staff of exclusive distributors if applicable.

It is preferable, although not obligatory, to appoint a Professional who will be accountable for all PV system matters (PVAP), and there should be a documented procedure to follow in the absence of the profesional.

PVAP must be properly qualified and with accredited experience in all PV's matters to perform his duties; and a professional with similar qualifications should be available to substitute him whenever he needs to take a leave of absence.

Some or all PVAP duties may be transferable to a hired person or institution; however the CO should have the overall responsibility.

CO shall provide to CA a detail description of the implemented system, including monitoring of various functions and training of various parties for proper functioning of the Pharmacovigilance system content:

1) Information of the PVAP

- Name, Profession and contact information
- Summary of his Curriculum Vitae, with special emphasis on his education and PV background
- Short description of his position and delegation of his duties
- PVAP's Substitute background information

- List of PV duties delegated to another professional

2) PV system organization

- Description of functional duties and responsibilities for all units involved in PV
- Organization chart showing the PVAP position within the organization and relationship with head office, branches and outsourcing companies.
- Summary of PV activities performed by each organization unit.
- Flow chart of AE notification activities, relating the manner in which AE and PSR are compiled, processed and notified.
- PV activities and data base location.

3) Standardized functional procedures.

- Available procedures list
- PVAP activities and back up procedure in his absence.
- AE collection, management, quality control, coding, classifying, assessment and notification.
- Data base management and utilization
- PV system internal audit
- Training
- Data storage

4) Data bases

- List of main available data bases, functional description and status validation.

5) PV areas subcontracts

- Contracts description, task and duties identification.

6) Training

- Training, documenting and registering system's short description.

7) Documents

- PV document files brief location description.

8) Quality assurance system

- Implemented system brief description.
- Quality internal audits

9) Support documentation

9. BIBLIOGRAPHY

VICH GL24: Veterinary medicine pharmacovigilance. Adversed events reports management.

Standard 2001/82/CE: Determines a community code for veterinary medicine.

European Community Volume 98: Pharmacovigilance guideline for veterinary medicine.

SENASA Argentina: Pharmacovigilance system notification form

YELLOW NOTIFICATION FORM

NATIONAL PHARMACOVIGILANCE SYSTEM

CA name
CA Address

CA Phone No. : **CA E-mail:**
CA Web Page:

CONFIDENTIAL

For exclusive use of CA

Reference Number:

1. ADVERSE EFFECT IDENTIFICATION(AE)

Safety Problem	**Inefficacy**	**Vigilance Period**	**Environmental**
In Animals			
In Humans			

2. NOTIFYING PARTY DATA

Full Name:	
Name of Commercialization Owner:	
Address:	
Telephone Number:	
E-mail:	

3. NOTIFICATION DATA

Adverse Effect reception data (mm/dd/yy):

Type of Report: Initial

Follow-up report – if this option is selected, indicate:
Date of Initial Notification (mm/dd/yy):
Initial Notification Reference N° :

Type of Notifier: Veterinary Doctor
Doctor
Other (specify):

Name of the animal owner:
Pharmaceutical

4. VETERINARY DOCTOR/HUMAN DOCTOR/PHARMACEUTICAL DATA	**5. ANIMAL OWNER/PATIENT DATA**
Name:	Name:
Address:	Address:
Telephone N°:	Telephone N°:

6. ANIMAL (S) DATA

N° of Treated animals: N° of animals with symptoms: N° of dead animals:

Species: Breed/productive activity:

Reference (s) of animal (s) with symptoms:

Sex/Physiological Status: Female Male Pregnant Castrated Lactating Unknown
Other:

Weight (kilograms): **Age:**

Health status when treatment was prescribed: Good Acceptable Bad Critical Unknown

Reason for Treatment (preventive against an initial illness or diagnosis):

7. PRODUCT DATA

Commercial/generic name:

Sanitary Registration Nº: **Pharmaceutical Presentation:** **Concentration:**

Serial N°: **Validity Date (mm/dd/yy):**

Description of real storage conditions:

Treatment details:

Dosage/Frequency:

Route and place of treatment consumption:

Starting of treatment (mm/dd/yy): **Final treatment (mm/dd/yy) and duration:**

Accountable person for the medicine consumption: Veterinary Doctor owner of the animal, Other,
(Specify)

Consumption according to approved label**:** Yes Unknown
No (specify):

Action taken after appearance of adverse effect: Interruption of treatment Reduction of dose
Other (specify):

Does the AE stopped when treatment was taken? Yes No Does not apply

Does AE re-appeared when treatment is started? Yes No Does not apply

8. ADVERSE EFFECT DATA (EA)

Date of appearance of AE(mm/dd/yy): **Date AE ended (mm/dd/yy):**

Describe Sequence of events, including route of the product administration, clinical signs, location where AE reaction occurred, seriousness, laboratory tests conducted and its results, autopsy results, and other factors that could have contributed. Include details of treatment prescribed.

Or was the AE treated? No Unknown

Yes (Describe):

Chronological tracking of the AE:

	Euthanasia	Dead	Under treatment	Alive with sequelae	Recovered	Unknown
Quantity of animals						
dates (mm/dd/yy)						

9. CRITERIA OF VETERINARY IN CHARGE OF TREATMENT

According to the Veterinary Doctor, to what degree the product has caused AE:

Probable Unlikely Without any Veterinary Doctor care

10. EXPOSURE TO PREVIOUS REACTIONS OF VETERINARY MEDICINE

Was there any previous history of exposure to the product?

No Unknown Yes (specify a date (mm/dd/yy) if known):

Has there been a reaction to this medicine?

No Unknown

Yes (Specify):

Has there been any reaction to ANOTHER medicine?

No Unknown

Yes (Specify):

11. DATA ABOUT ALLEGED AE IN HUMANS

Data about patient:

Sex: Date of birth (mm/dd/yy) Occupation (relation with exposure):

Veterinary Medicine exposure date (mm/dd/yy):

Date of appearance of alleged AE (mm/dd/yy):

Type and duration of exposure AE details (including symptoms), consequences and results:

12. PRODUCT CAUSALITY ASSESSMENT

Classification: A(Probable) B(Possible) O (Non- classifiable) O1 (Non conclusive) N (Unlikely)

Justification of classification:

13. DATA ON PRODUCT(S) CONSUMMED SIMULTANEOUSLY **(whenever more than 2 medicine are taken simultaneously, duplicate this form)**		
	1	**2**
Commercial/Generic name		
Pharmaceutical presentation and concentration (e.g.: 100 mg tablets)		
Sanitary Registration No.		
Batch No.		
Validity date (mm/dd/yy)		
Storage real conditions		
Route and place of consumption		
Dose/ Frequency (dosage)		
Treatment Duration / Exposure Starting Date (mm/dd/yy): Final Date (mm/dd/yy):		
Who prescribed the medicine? (veterinary doctor, owner, other)		
Was the medicine prescribed according to the approved label use?	Yes Unknown No (Specify):	Yes Unknown No (specify):
	Treatment Suspension Dose Reduction Other (specify):	Treatment Suspension Dose Reduction Other (specify):
Does the adverse reactions disappeared when the treatment stopped?	Yes No Does not apply Unknown	Yes No Does not apply Unknown
Does the reaction re-appears after treatment re-starts ?	Yes No Does not apply Unknown	Yes No Does not apply Unknown

14. NOTIFYING PARTY SIGNATURE

AE notification date (mm/dd/yy):

Location (City):

Name of Notifying party:

Signature*: _____
*Only in case this formulary is delivered Printed.

Contact (telephone Number) (in case is different from the number indicated in page 1)

GREEN NOTIFICATION FORM

NATIONAL PHARMACOVIGILANCE SYSTEM

CA name

CA address

CA Phone No.: **CA e-mail**

CA web page:

CONFIDENTIAL

For exclusive use of CA

Reference Number:

ADVERSE EFFECT (AE) IDENTIFICATION	**NOTIFYING PARTY DATA**	**NAME AND ADDRESS OF ACCOUNTABLE PERSON OF INVOLVED ANIMALS.**
- Safety Problem: In animals In human **- Inefficacy** **- Vigilance period problem** **- Environmental problem**	Role: ☑ Veterinary ID N° : ☐ Technical Director at retail store ☐ Other Name: Address: Telephone E-mail :	

PATIENT(S) DESCRIPTION

Species	Breed	Sex	Status	Age	Weight	Reason for Treatment
		Female Male Unknown	Castrated Pregnant Other (specify)			

VETERINARY MEDICINE WAS ADMINISTERED BEFORE THE ALLEGED ADVERSE EFFECT APPEARANCE **(***whenever more than 3 medicine were prescribed simultaneously, duplicate this form)*			
	1	**2**	**3**
Veterinary medicine commercial name			
Pharmaceutical presentation and concentration (e.g.: 100 mg tablets)			
Sanitary Registration Number			
Serial Number			
Route and place of consumption			
Dose / Frequency (dosage)			
Treatment /Exposure Starting date (mm/dd/yy): Final Date (mm/dd/yy):	**/ /** **/ /**	**/ /** **/ /**	**/ /** **/ /**
Who prescribed the medicine? (veterinary, owner, other)			
Do you believe the AE is caused by the medicine?	Yes / No	Yes / No	Yes / No
Has the relevant laboratory been informed?	Yes / No	Yes / No	Yes / No

ALLEGED ADVERSE EFFECT DATE (mm/dd/yy) **/ /**	**Time passed between medicine administration and AE in minutes, hours or days**	**AE duration in minutes, hours or days**
	N° of treated animals	**N° of animals with symptoms**	**N° of dead animals**

REACTION DESCRIPTION *(Safety problems in animals / alleged inefficacy expected / Vigilance period problems / Environmental Problems) Please, specify:*

Also indicate whether the AE has been treated. How and which medication was used and what result(s) was obtained?

OTHER RELEVANT INFORMATION (e.g.: Completed or ongoing tests, relation of necrosis. Attach documents in timely manner).

ADVERSE EVENTS IN HUMANS (If AE occurred in human beings, please complete the following information)

- Contact with treated animal ☐
- Oral intake ☐
- External exposure ☐
- Ocular exposure ☐
- Injection exposure ☐ Finger ☐ hand ☐ joint ☐ other ☐
- Other ☐ specify:
- Received Dose:

NOTIFYING PARTY SIGNATURE

Date (mm/dd/yy): / /

I hereby declare the above information is true.

Full name:

Signature* : _____

- Only if this form is handed in

Contact (telefone No.) (only if is different from the number indicated in the first page):

ANNEX VI

CAMEVET
Cod: Reg - Est 001
REVIEW / APPROVAL
September 2019

GUIDE FOR THE DEVELOPMENT OF STABILITY STUDIES OF VETERINARY MEDICINES.

GUIDE FOR THE DEVELOPMENT OF STABILITY STUDIES OF VETERINARY MEDICINES

1. INTRODUCTION

The scope in stability studies is to supply evidence about quality alterations in a substance or pharmaceutical product along time, influenced by environmental factors such as temperatura, humidity, or light exposure and to establish the validity period of product in the chosen packing material and its storage conditions, as well as to define re-test periods for these substances or products.

This document about requirements in "stability studies for veterinary medicines registration for all CAMEVET countries" is an agreement of minimal requirements with enough flexibility to use different focus for diverse products as long as they are supported by well-known scientific references .

For its implementation in the level of demand were taken into consideration:

1.1. Reports from different countries.
1.2. Stability testing of new veterinary drug sustances and medical products recommended for implementation at step 7 of the VICH Steering Comitee
1.3. The current report for Public Health Mercosur.
1.4. EMEA/CVMP/846/99 (Issued by the Veterinary Products Committee of the EU)
1.5. It was also taken into consideration the particular problems derived from veterinary pharmaceutical industry in Latin America and the Caribbean Region.

2. OBJETIVE AND SCOPE:

Set standards to perform stability studies of veterinary medicines in order to determine its shelf life.
Biological products are not included.

These studies could be required at registration time and in the following situations:

2.1. Shelf life changes, expiry or validity.
2.2. In the renewal when the original study didn't fit in the present regulations.
2.3. Change or addition of new primary packaging materials, as long as regulatory authority considered it suitable.
2.4. Qualitative or quantitative modification of excipients, as long as regulatory authority considered it suitable, .
2.5. Modification of the manufacture process, as long as regultory authority considered it suitable.
2.5. New manufacturing site, when considered necessary by the health authority.
2.6. Changes in active drug specifications, when considered suitable.

3. TERMS AND DEFINITIONS

3.1 Accelerated stability studies: These studies are designed to increase the rate of chemical degradation or physical modification of veterinary pharmaceutical products, using forced conditions of storage, in order to predict the tentative shelf life at commercial storage conditions. Results of accelerated stability studies are not always predictive of physical changes. The validity period so defined by prediction upon these accelerated tests, must be confirmed afterwards by the long-term stability tests.

3.2 Long-term stability studies: These are studies done under certain storage conditions for veterinary pharmaceuticals products according to the climatic zone of the market that is targeted, in a period not less than the period proposed (or approved) for shelf life. In this kind of study, physical, chemical, biological and microbiological characteristics of veterinary pharmaceutical products are evaluated, in order to determine the definitive shelf life.

3.3. Climatic zones: They are the four zones in which the world is divided based on the prevalent annual climatic conditions

Stability study program must consider the climatic zones in which the veterinarian pharmaceutical product will be used.

Climatic zone	**Definition**
I	Warm
II	Subtropical with possible high humidity
III	Hot and dry
IV	Hot and wet

World Health Organization, published in the guidelines "stability studies of pharmaceutical products containing known drugs in conventional dosage forms" Technical Report No. 863. Annex 5, 1996

4. SYMBOLS AND MEASUREMENT UNITS

a. % RH: Relative Humidity
b. °C: Celsius degrees

5. PROCEDURES:

5.1 Stability Studies

In general terms it is considered that the main objectives of stability studies are:

DEFINITION	STUDY TYPE	USE
Select properly (from the perspective of stability) formulations, and packaging and container closure systems of veterinary pharmaceutical products. Establish the proper conditions to store the product. Evaluate effect of temperature excursions out of recommended conditions	Accelerated	Product Development
Determine shelf life and storage conditions	Accelerated and long term or Long term only	Registration dossier. Once finished, long-term stability tests

		must be presented to regulatory authority for evaluation.
Support the shelf life stated or authorized	Long term and/or on going *	Registration renewal (when required)
Verify that the changes that have been introduced in the formulation or manufacturing process or manufacturing site affected or not product stability, when considered necessary by the competent authority.	Accelerated and long term or Long term only	Modification of the approval conditions that could affect stability

*On-going stability, in-use stability and stability of reconstituted product are not within the scope of this guideline. Specific documents will be prepared for those tests.

5.2 Accelerated stability studies

5.2.1. Test conditions will be determined by pharmaceutical form of product.

5.2.2. Accelerated stability studies on veterinary pharmaceutical products submitted in semipermeables container-closure systems, must consider temperature and humidity as catalytic factors of degradation.
Consequently, when the veterinary pharmaceutical product was packaged in impermeable containers, stability studies could be conducted under any condition of relative humidity.

5.2.3. The conditions of accelerated stability study are:

1. Medicinal products intended for storage at room temperature

Climatic zone	Definition	
I	Warm	40º ± 2 °C / 75 % ± 5% HR 6 months
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

2. Medicinal products intended for storage under refrigeration

Climatic zone	Definition	
I	Warm	25º ± 2 °C / 60 % ± 5% HR 6 months
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

5.2.4 When there are significant changes in the accelerated stability study, additional tests can be performed under intermediate conditions. These changes must be sustained. As examples of significant changes it could be mentioned: an active drug content decrease of more than 5 % related to the inicial value, or not compliance with

acceptance criteria for potency in biological or immunological methods; a rise in degradation products level exceeding specifications, not compliance with dissolution test specifications, decrease or rise in pH value or other parametres out of specifications limits; failure of physical parameters such as apperance, color.

5.3. Long-term stability study

5.3.1 The conditions of the study must be: storage with temperature and relative humidity controlled according to climatic zone of the target market of the product.

1. Medicinal products intended for storage at room temperature

Climatic zone	**Definition**	**Storage conditions**
I	Warm	21º C±2ºC - 45%± 5% HR
II	Subtropical with possible high humidity	25º C±2ºC - 60% ± 5%HR
III	Hot and dry	30º C±2ºC - 35% ± 5%HR
IV	Hot and wet	30ºC±2ºC - 65% ± 5%HR

2. Medicinal products intended for storage under refrigeration

Climatic zone	**Definition**	**Storage conditions**
I	Warm	5º ± 3 °C
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

3. Medicinal products intended for storage in a freezer

Climatic zone	**Definition**	**Storage conditions**
I	Warm	-20º ± 5 °C
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

World Health Organization, published in the guidelines "stability studies of active pharmaceutical ingredients and finished products" Technical Report No. 953. Annex 2, 2009

Different conditions to the established can be used when tecnhically justified. These changes must be reflected in the product label.

The sponsor have to submit to the regulatory authorities the long term stability study supporting the approved validity period when it was finished,

5.4 Labeling (Storage Conditions Indications)

After concluded the stability studies, one of the following recommendations must be included in the packaging (label or secondary packaging)

Conditions under which stability study was carried out	Labeling Recommendations	Additional statements, if relevant
25°C/60% RH (long-term) 40°C/75% RH (Accelerated)	Do not store above 25ºC	Do not expose to refrigerating temperatures. Do not freeze
25°C/60% RH (long term) 30°C/65% (intermediate conditions)		
30°C/65% RH (long-term) 40°C/75% RH (Accelerated)	Do not store above 30ºC	Do not expose to refrigerating temperatures. Do not freeze
5°C ± 3 °C	Store refrigerated (between 2 ° C and 8 ° C)	Do not freeze
-20°C ± 5°C (*)	Store frozen (between -25ºC and -15ºC)	-

Reference: WHO Technical Report Series, Nº953, 2009 – Annex 2 – Stability testing of active pharmaceutical ingredients and finished pharmaceutical products.
Appendix 3 Recommended labelling statements
(*) Ultra-frozen products, intended to be stored at temperatures lower than -25ºC, are out of the scope of this guideline

Any other different temperature range could be accepted, at the registry owner request, according to the regulatory authority approval, as long as it was defined within the range indicated in the chart above.

Labeling statements out of the above mentioned ranges, must be duly justified by an specific stability test, which approval will depend on evaluation of the regulatory authority

It should always be included, as appropriate, any additional information such as:
Protect from light, keep in a dry place, protect from freezing, discard the remaining product after opening (for multidose containers if no in-use stability test was available), discard the remaining product after dilution/reconstitution (if no reconstituted stability test was available).

5.5 Study design

5.5.1. Storage conditions, study duration, sampling times and batch conditions chart.

	Accelerated stability studies*	**Stability study of long-term**
Study Duration	Not less than 6 months	Not less than the shelf life proposed
Sampling times	At least 0, 3 and 6 months	At least every 6 months during the first 2 years (0, 6, 12, 18, 24 months).And for every additional year, at least every 12 months (36, 48, 60 months).

		Accelerated stability studies*	Stability study of long-term
Batch size and number	For registration, for changes in formula, manufacturing site or procedure	At least 3 batches. Size: Industrial or representative.	At least 3 batches (they could be the same used in accelerated stability) Size: Industrial or representative.
	Shelf life checking or extension	Accelerated tests are not valid	At least 3 batches Size: Industrial

* Minimal requirements for initial registration consist of complete accelerated stability test up to at least 6 months. With this study, a 2 years provisory validity period is granted. With long-term stability finished, its conclusion will define the definitive validity period of product.

5.5.2 Minimum parameters to be assessed must be all that have been stated in final product quality specifications in the registration dossier. It must be considered the following: chemical (Ex.quantification), microbiological (Ex. Sterility), physical (Ex. Particle size), among other stability indicators. Degradation products must be previously evaluated and quantified when they had therapeutic or toxicological relevance.

5.5.3 For products with more than one active substance quantification of the least stable of them should be done at all time points. The rest of active substances may be just quantified at initial and final testing times.

5.5.4 Sterility testing or other microbiological tests should be done, when necessary, at least at the beginning and at the end of the study.

5.5.5 Analytical methods used in the tests have to distinguish quantitatively the active substance from its degradation products. Preferentially chromatographic methods shall be used, but other methods could be accepted if technically justified. Methods not described in pharmacopeias must be validated. Methods from pharmacopeias must be verified.

5.5.6 Manufacturing process for stability tests batches, shall be representative of industrial proceedings and must supply the same quality product and fulfill the same commercial final product specifications

5.5.7 For products demanding reconstitution before using, an additional stability test in the reconstituted condition must be performed. It must support the validity period after reconstitution proposed. If product use is immediate and complete, there is no need of an extra stability study, indicating this condition on product labels. Additionally, chemical and/or microbiological stability shall be performed on solvent/diluent, if suitable, along the same shelf-life proposed for product.

5.6 Containers into which the study is conducted

Studies must be developed in the same packaging in which product will be marketed. For products whose final packaging was of big size, the study may be developed in a container of less capacity as long as this container featured the same material, geometric characteristics and closure system of the marketed one.

For products that are marketed in several sizes into containers of the same material, stability study will be conducted at least in the smaller container since this is the one with the worst conditions in terms of container surface/product content rate.

If there were two or more packages of different materials the tests should be performed on each packaging material, unless delivery of technical tests of the packaging material showing the worst risk of deterioration of the product, and therefore the study should be conducted on this worst case container.

5.7 Stability study report

It must contain:

5.7.1 Title.
5.7.2 Product name (or identification code, in development stages)
5.7.3 Identification of the facilities/institution where the study was conducted
5.7.4 Identifications of the facilities where the product was manufactured
5.7.5 Name and signature of the person in charge of the study
5.7.6 General conditions of the study. (Manufacturing date, batch type and size, primary packaging, type of study and duration, batch number, storage conditions).

Example:

Batch N°	Manufacturing date	Batch type and size	Primary packaging	Study		Study duration
AA50107	01/10/2007	Representative/ 30 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
			PET	LT	25° ± 2°C / 60% ± 5% HR	36 months
AB00207	15/10/2007	Industrial/ 300 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
				LT	25° ± 2°C / 60% ± 5% HR	36 months
AB00307	20/11/2007	Industrial/ 300 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
				LT	25° ± 2°C / 60% ± 5% HR	36 meses

References: Acc, accelerated study; LT, Long Term Study

5.7.7 Complete qualitative and quantitative product composition.
5.7.8 Justification of the chosen tracer compound, if suitable.
5.7.9 Type of material and primary container specifications, including closure system.
5.7.10 Data chart indicating active drug concentration versus time.
5.7.11 Specifications, analytical methods and analytical standard reference used. Documents supporting analytical standards origin may be requested.
5.7.12 According to the references supporting the proposed methodology, validation may be required .
5.7.13 Math calculations, statistical analysis and graphics used to determine shelf life.
5.7.14 Study conclusions: they must include clearly the storage conditions and shelf life proposed, signed by professional person responsible for the tests.

5.7.15 Instrumental records of the different tests performed are not part of the report but may be required by regulatory authorities. They must be performed in equipment that record the analysis date. Instrumental records, environmental conditions records, and batch records of the stability test prducts must exist as supporting documents of the study.

6. ANNEX

6.1 Annex 1. Guideline for evaluation parameters in stability tests

7. REFERENCES

7.1. MERCOSUR/GMC/Res.Nº 53/96 (issued by the Mercosur group of Public Health. Is the current document in the Mercosur to Human Health)
7.2. EMEA/CVMP/846/99 (issued by the Committee for veterinary medicinal products in the EU)
7.3. Stability Testing of New Veterinary Drug Substances and Medical Products
7.4. Recommends for Implementation at step 7 of the VICH Steering Committee
7.5. Stability reports submitted by different countries in the CAMEVET
7.6. Stability document of Brazil
7.7. World Health Organization, published in the guidelines "stability studies of active pharmaceutical ingredients and finished products" Technical Report No. 953.

8. AUTHORS:

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Revision team 2019:
Argentina (Official sector: SENASA – Private sector: CAPROVE – CLAMEVET)
Brasil (Private sector: ALANAC – SINDAN)
Chile (Official sector: SAG – Private sector: ANVET)
Colombia (Private sector: APROVET – FENALCO)
Costa Rica (Private sector: CIA)
Guatemala (Official sector: MAGA – Private sector: ASOVET – CIG)
México (Official sector: SENASICA/SAGARPA – Private sector: ANALAV – INFARVET)
Nicaragua (Private sector: CADIN)
Panamá (Official sector: MIDA)
Paraguay (Private sector: CAPALVE)
Uruguay (Official sector: MGAP/DILAVE – Private sector: CEV)

EST001 – Stability on veterinary medicines
ANNEX 1

GUIDELINE FOR EVALUATION PARAMETERS ON STABILITY TESTS

This guideline intends to mention a list of possible parameters to be considered in stability studies according to the pharmaceutical form of the veterinary medicine.
This list was prepared as a suggestion or guideline for stability protocol but it must not be taken as mandatory or excluding.
The product developers must choose, considering their knowledge of product and professional experience, the most accurate parameters to prove stability in the intended formulation for registration purposes.

Microbiological parameters, for any pharmaceutical form, when considered suitable, could be tested at initial and final time.

When photostability testing was considered necessary, a specific study should be designed. This test may be avoided when containers prove to be protective from deleterean effects of light on product.

- **Tablets, Coated tablets and dragees:**
  - concentration of active drug per unit,
  - organoleptic features,
  - friability,
  - disintegration,
  - dissolution
  - humidity (when appropriate).

- **Capsules:**
  - concentration of active drug per unit,
  - organoleptic features of capsule and of content,
  - dissolution
  - humidity (when appropriate).

- **Emulsions:**
  - concentration of active drug,
  - organoleptic features.
  - When appropriate:
    - viscosity,
    - microbial limits,
    - preservatives efficacy test (for multidose containers) and/or preservatives assay,
    - sterility

- **Solutions and suspensions:**
  - concentration of active drug,
  - organoleptic features,
  - pH (for acqueous base products).
  - When appropriate:

        - resuspensibility (in suspensions),
        - microbial limits (for acqueous or oil based products),
        - preservatives efficacy test (for multidose containers) and/or preservatives assay,
        - sterility.

- **Powders for oral solution/suspension:**
    - concentration of active drug,
    - organoleptic features,
    - humidity.
    - When appropriate:
        - microbial limits.
    - When reconstituted according to label instructions, parameters to be tested along recommended validity period are:
        - Concentration of active drug,
        - organoleptic features
        - pH (for acqueous solutions or suspensions);
        - When appropriate:
            - preservatives efficacy test (for multidose containers) and/or preservatives assay.

- **Solutions for injection, powders for solutions/suspensions for injection and lyophilized powders:**
    - concentration of active drug,
    - organoleptic features,
    - pH (for acqueous solutions/suspensions),
    - sterility.
    - When appropriate:
        - humidity (for powders),
        - preservatives efficacy test (for multidose containers) and/or preservatives assay
    - If product is to be reconstituted, prepare it following label instructions and parameters to be tested are:
        - concentration of active drug,
        - organoleptic features
        - pH (for acqueous solutions or suspensions).

- **Aerosols y nebulizers:**
    - concentration of active drug
    - organoleptic features.
    - Ratio propelent/concentrate. Net content.
    - When appropriate:
        - dosis homogeneity,
        - particle size (for suspensions).
        - microbial limits.

- **Creams, gels, pastes and ointments:**
    - concentration of active drug,
    - organoleptic features,
    - homogeneity,
    - viscosity.

- When appropriate:
  - pH (for acqueous base products),
  - microbial limits,
  - preservatives efficacy test (for multidose containers) and/or preservatives assay,
  - sterility.

- **Suppositories and ovules:**
  - Concentration of active drug per unit,
  - melting temperature,
  - organoleptic features.
  - When appropriate:
    - dissolution test
    - liquefaction/fussion time.

ANNEX VII

CAMEVET
Code: Cal - BPM 005
APPROVED
September 2019

GUIDE FOR MANUFACTURE AND QUALITY CONTROL OF ADVANCED CELL THERAPY PRODUCTS

Table of Contents

GUIDE FOR MANUFACTURE AND QUALITY CONTROL OF ADVANCED CELL THERAPY PRODUCTS

1. INTRODUCTION

In veterinary medicine, the number of commercial laboratories that offer therapies based on autologous or allogenic mesenchymal stem cells and their derivatives has been growing considerably.

For the purpose of this guide, the products originating from the manipulation of these cells and their derivatives will be called advanced therapy products.

Clinical studies show that cell therapy have efficient and safe results in the treatment of diseases in animals, among which is the chronic kidney disease (Lee et al., 2017), neurological disorders (Zhang et al., 2005; Marconi et al., 2013), medullary lesion (Jung et al., 2009; Kim et al., 2016), hip dysplasia, osteoarthritis (Diekman et al., 2013; Davatchi et al., 2016) and corneal ulcers (Yao et al., 2012; Di et al., 2017).

The stem cells, in these cases, have immune-mediation, anti-inflammatory and tissue regeneration functions.

To ensure the safety and quality of the advanced therapy products provided for therapeutic use in animals, it is necessary to specify minimum technical-health requirements for the functioning of the laboratories that manipulate stem cells.

1. OBJECTIVES

The purpose of this guide is to provide technical guidance for the manufacture and quality control of advanced cell therapy products.

For the purpose of this guide, advanced therapy products are biological products constituted by animal cells or their non-chemically defined derivatives, with the purpose of obtaining therapeutic, preventive or diagnostic properties through their main mode of action of metabolic, pharmacological and/or immunological nature, for autologous or allogenic use in animals, provided that tissues/cells:

I –have been subjected to minimum manipulation and act with a function different from that performed in the donor tissue; or

II – have been subjected to extensive manipulation;

The provisions of this guide do not apply to any type of cells or tissues that are genetically manipulated.

3. DEFINITIONS

3.1 Packing: process by which the cells, advanced therapy products and biological samples are placed in packages for transportation or storage purposes, aimed to protect the material, people and the

environment.

3.2 Biological samples: blood, cells, fragments of tissues, smears, lavage, among others, from donors or recipients and that will be used to conduct laboratory tests or quality control tests;

3.3 Autologous cells: these are cells that are collected and administered to the same animal; the donor and recipient is the same individual;

3.4 Allogenic cells: these are cells that are collected from one donor animal and used in another recipient animal of the same species: the donor and recipient are not the same individual;

3.5 Stem cells: these are cells able to divide indefinitely and differentiate into distinct types of specialized cells, not only morphologically, but also functionally.

3.6 Batch of advanced therapy product: specific quantity of the final product, originated from a single donor, which is intended to have uniform qualities, within specific limits, produced according to a single processing protocol during the same processing cycle;

3.7 Minimum manipulation: it is the processing of cells that does not involve cell cultivation;

3.8 Extensive manipulation: it is the processing of cells that involves cell cultivation;

3.9 Autologous use: the implantation, transplant, infusion or transfer of cells back to the animal from which the cells were recovered;

4.0 Allogenic use: the implantation, transplant, infusion or transfer of cells from a donor animal to another recipient animal of the same species;

4. THE QUALITY CONTROL OF ADVANCED THERAPY PRODUCTS

The advanced therapy products can only be released for therapeutic use only after the observation of the predefined determinants or criteria related to the selection of the donor, quality controls of the production process and the finished products specified below:

I – For processes considered minimally manipulated:

a) count of the total number of cells;

b) cell viability test;

c) microbiological tests for fungi and bacteria research.

When it is proved that it is not possible to carry out one or more tests described in the item I, they may be dispensed.

II – For processes considered as extensive manipulation:

a) count of the total number of cells;

b) cell viability test;

c) immunophenotyping appropriate for the cell therapy product and quantification of the cell populations present;

d) dosing of endotoxins;

c) microbiological tests for fungi, bacteria and mycoplasma research.

f) karyotyping test;

g) confluence analysis:

The karyotyping test must be conducted in case the production process requires a number of passes greater than 4;

The confluence analysis must be conducted before each pass and before freezing.

The certificate of release for each batch of advanced therapy product must contain the identification code of the donor in addition to what is required by the applicable effective legislation.

5. THE PHYSICAL INFRASTRUCTURE

The physical infrastructure of the establishment that manipulates advanced therapy products must consist of, at least, environments for the execution of the following activities:

I – administrative;

II – receiving of biological material;

III – processing of advanced therapy products;

IV – storage of advanced therapy products; and

V – quality control.

The ISO 5 "operational" condition should be maintained in the area around of cells and Advanced Therapy Products, as well as materials and reagents that will come into direct contact with cells and Advanced Therapy Products, whenever exposed to the environment or when removing aliquots or samples for quality control or diagnosis.

6. THE LABORATORY SCREENING OF THE DONOR

6.1 Preliminary donor assessment:

The cell donations must mandatorily be preceded by the blood test with results within the reference ranges.The performance of the laboratory screening tests is not mandatory for autologous use, provided the therapy does not cause the potentiation of a previously existing disease.

The laboratory tests must be conducted on each cell donation, for autologous or allogenic use, regardless of the results of the previous donations.

During each collection of biological tissue, blood or serum samples must be collected to conduct laboratory tests to:

- Detect the main infectious diseases of concern each donor species:

I – Canine Species: canine distemper, parvovirus and leishmaniasis;

II – Feline Species: feline immunodeficiency virus (FiV), feline leukemia virus (FelV), toxoplasmosis and coronavirus;

III – Equine Species: Infectious equine anemia; and

For other animal species, the regulatory agency must establish the tests to be conducted.

- Detect endemic diseases in the region where the donor lives;

For allogenic transplants, only animals with results in compliance with the aforementioned laboratory tests can be the donors.

6.2 Requirements for processing donor samples

The performance of serological tests must not be allowed in the pool of blood samples of donor animals.

The use of pool of blood samples of donor animals is allowed for nucleic acid tests (NAT), according to

the recommendation of the manufacturer of the diagnosis kit used.

In case of the performance of the NAT tests in pool, the group of samples with positive result must be dismembered and their samples tested individually to identify the infectious agents in question or dispose of all the materials originated from those donors involved in the pool.

6.3 The following are exclusion criteria of the cell donation candidate for allogenic or autologous use:

I – Nonconformity results of the laboratory screening tests;

II – the presence and history of malignant neoplastic disease; and

III – clinical condition that places the donor's health at risk;

In the allogenic treatment, in case the laboratory tests results are inconclusive, the donor must be excluded.

In the autologous treatment, in case the laboratory tests results are inconclusive, the risk-benefit of the application must be evaluated.

7. THE PACKING, LABELING AND TRANSPORTATION OF BIOLOGICAL SAMPLE

The labeling of products must be as determined by the effective legislation applicable in addition to containing:

I - donor identification;

II – in case of autologous transplant, the information "Only for autologous use" and the data of the recipient.

The identification of the donor must necessarily be written on the label, and the information contained in item II can be contained in the package insert.

For cryopreserved products, the date of manufacture must be considered as the day of freezing.

For products used "fresh", the date of manufacture must be considered the day of removal of the cultivation cells and preparation for shipment.

The establishment must define and validate the temperature conditions of the biological materials and biological samples during transport in order to preserve the integrity and stability of the

transported material.

8. THE FINAL AND TEMPORARY PROVISIONS

Any Quality Control documentation related to the records of a batch, including the documentation of the donor, must be kept for one year after the expiry date of the batch.

The applicable determinations of the effective legislation related to Good Manufacturing Practices must be observed.

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