CONCLUSIONS AND RECOMMENDATIONS

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

October 1 – 5, 2018
Quito, Ecuador

Opening speeches

The participants were welcomed by Agr. Eng. Eddie Pesántez Benítez, Undersecretary for Livestock of the Ministry of Agriculture and Livestock, Dr. Martín Santiago Minassian, Technical Assistant of the OIE Regional Representation for the Americas, and Agr. Eng. Patricio Almeida, Executive Director of Agrocalidad.

Appointment of the President and Vice-President

Dr. Verónica Loza, Focal Point for Veterinary Products of Ecuador, was formally designated president of the Seminar.

Plenary meeting of the official sector

Dr. McAllister Tafur Garzón from SG CAN and on behalf of the official sector of Colombia presented the conclusions of the meeting held by the official sector, indicating the topics dealt with. This included free sales and "Expert only" veterinary products certificates, resistance to antimicrobials, and the enforcement of new regulations by Ecuador. Other issues discussed included Good Manufacturing Practices and the need for training in this field.
The report of the meeting, listing the topics proposed, is included as Annex I.

Plenary meeting of the veterinary industry

Dr. Mercedes Etcheverry, representative of CEV, presented the topics discussed at the meeting held by the veterinary products industry sector. Dr. Etcheverry indicated the various difficulties identified and posed in relation to the registration of veterinary products, and agreed with the importance of the joint participation of the industry and the official sector in the resolution of issues in the framework of CAMEVET.
The report of the meeting, with a list of the topics proposed, is included as Annex II.

Session I – CAMEVET relations

Procedures for the participation of CAMEVET in the proposals for creation and modification of OIE Standards

Dr. Minassian presented the structure of the OIE, described the standards setting process, and presented the results of the 86th.OIE General Session OIE held in May 2018.

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Dr. Minassian briefly reviewed Technical Item Nº 1, entitled *"Implementation of OIE Rules by the OIE Members Countries: current situation and specific needs for strengthening capabilities".* He added that the OIE is using this as a basis to develop an Observatory to follow-up the implementation of its standards, increase transparency, and identify the limitations and difficulties faced by member Countries. He also noted that this work model could be useful to CAMEVET.

In addition, went on to present the procedure for the registration of OIE-validated and certified diagnostic tests, listing the advantages of such registration.

Lastly, he noted that the last General Session led to the adoption of modified Chapters, including 17 Chapters of the Terrestrial Animal Health Code (plus 9 new Chapters added), 16 Chapters of the Aquatic Animal Health Code (and the addition of a new Chapter), 29 Chapters of the Terrestrial Manual, and 6 Chapters of the Aquatic Manual.

In relation to the proposals to modify the Terrestrial Animal Health Code, Dr. Minassian noted the importance of the Secretariat´s support in disseminating the reports of the OIE´s Specialized Commissions to enable the National Focal Points and veterinary products industry Associations to prepare and send comments through their national OIE Delegates.

CAMEVET participation in the OIE- VICH Outreach Forum

Dr. Bárbara Ágate Borges Cordeiro, representing the official sector of Brazil, presented the results of her participation representing the Committee. She noted that the activities of CAMEVET were presented, including the harmonized documents, as well as the results of the survey on the implementation of VICH guides in CAMEVET participant countries.

Dr. Cordeiro described the participation in discussion forums that dealt with regional strategies and collaborative systems, the implementation of the existing VICH pharmacovigilance guidelines, and the anthelminthics efficacy assessment.

She also noted that a lengthy debate was held concerning the actual scope of the VICH Outreach Forum.

Dr. Cordeiro described the topics discussed by the Expert Working Groups, and highlighted the participation of Argentina in the group that discussed residue withdrawal studies in apiculture and the group that dealt with combined products, and the participation of CAMEVET in stability studies for climate zones 3 and 4. She also noted the possibility of participating in the Expert Work Groups.

Lastly, highlighted the relevance of the participation of the official sector and the industry sector that form part of CAMEVET in the activities of the VICH Outreach Forum.

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Session II – Working Documents

Guide for the implementation of Pharmacovigilance system

Dr. Gabriel Ardiles Andía, representative of ALAVET (Chile), presented the progress made in the discussion of the document, which is currently in Status IV, and mentioned the most relevant comments received after its circulation.

Following this presentation, and considering the number of comments received, it was agreed to circulate the document one last time, allowing a period of 60 days following distribution for receiving comments, while the document remains in Status IV.

Aquaculture Veterinary Products

Dr. Gabriel Ardiles Andía, representing Dr. Fernando Zambrano Canelo, Focal Point for Veterinary Products of Chile, presented the steps in the progress made in the working document, which is currently in Status IV. Following the presentation, which included the comments received, the document was approved unanimously, and is included as an Annex IV.

Instructions for filling CAMEVET forms for the registration of pharmacological and biological products.

Dr. Carlos Francia, from CAPROVE, on behalf of the coordinator of the work group, Dr. Federico Luna, Focal Point for Veterinary Products of Argentina, presented the progress made in the document, currently in Status IV. Following the presentation, which included the comments received, the document was approved unanimously and is included as an Annex V.

Falsified of veterinary product rights

Dr. Eduardo Ríos, from the Corral Rosales legal firm, presented an overview of the most common property right violations relating to veterinary products detected in Ecuador. Among others, he noted intellectual property infringements, including forgeries, and regulatory infringements which comprise the use of unregistered and smuggled products.

General guidance for test kits intended for the diagnosis of animal diseases

Speaking on behalf of Dr. Brian Rippke, of the USA Center for Veterinary Biologics, Dr. Geetha B. Sinivas presented a summary of the contents of the Working Document, currently in Status III.

Based on the comments made, consensus was reached to forward the document to Status IV. The document will be circulated for a last time, allowing a period of 60 days for the reception of comments. If no comments are received, the document will be proposed for approval at the following Seminar.

Test guideline for the immunogenicity control of inactivated bovine vaccines containing bovine viral diarrhea virus

Participants were informed of the impossibility to present the progress made in this working document, currently in Status III. Consequently, the document will remain in its current status and will be presented at the next Seminar.

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Minor Species and Uses

Dr. Christopher White, of SINDAN, presented the progress made in the Working Document, which is currently in Status III, including the comments received.

Since the deadline for receiving comments on the first draft in Status III is November 10, the reception of comments will remain open.

The final draft including all the comments received will be circulated again, for the reception of comments and approval proposal at the following Seminar, as Status IV.

Manufacturing and Quality Control Guide for advanced cell therapy products

Dr. Bárbara Ágate Borges Cordeiro, on behalf of the official sector of Brazil, presented the progress made in the Working Document, currently in Status III, including the comments received. The document will advance to Status IV, and consequently will be circulated one last time, remaining open to comments, and will be proposed for approval at the next Seminar.

Revision of the harmonized document on labeling of veterinary products

Dr. Benigno Alpízar Montero, Focal Point for Veterinary Products of Costa Rica, presented through a videoconference the progress made by the Working Group in the revision of the harmonized document on veterinary products labelling, currently in Status III. This document revision was coordinated by the official sector of Costa Rica, with the contribution of all the official sector representatives, and was circulated to all the members of CAMEVET.

Based on that discussion, it was agreed that the document shall be circulated for 60 days in order to advance in its approval in case no comments are receive.

Revision of the harmonized guide for the development of stability studies for veterinary pharmaceuticals

Dr. Milena Aguirre, of CAPROVE, presented the document with the modifications made as a result of its last circulation, in Status III. The document will be circulated again allowing a 60-day period for comments, in Status IV.

Good Manufacturing Practices for Veterinary Products

Dr. Berta Chelle, Focal Point for Veterinary Products of Uruguay, spoke on behalf of the coordinator of the working group, Dr. Benigno Alpízar Montero, presenting the progress made in the revision of the working document, currently in Status III.

Since the deadline for receiving comments is October 10, a proposal was made to extend the period for receiving comments for a further sixty days as from that date.

In view of the complex nature of the document, it was agreed to organize a videoconference to conduct a detailed revision of all its items. This videoconference will be organized by the Secretariat.

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

Speaking on behalf of Dr. Henrique Uchio Tada, of ALANAC, Dr. Fernando Marcussi presented the progress made in the discussion and preparation of the document, including the comments received. Since the document is open to comments until November 6, 2018, it will remain in Status III.

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Session III – Revision of working documents

Status of implementation of CAMEVET harmonized documents in Member countries. Priorities list for review and update.

Miss. Ana María Sgammini, Secretary of CAMEVET, presented the results of the review of priorities for the revision of CAMEVET harmonized documents.

The documents agreed as having priority for revision are listed below, followed by the members of the Working Groups formed:

Guide for inspection of GMP for the manufacture of pharmacological products (including Ectoparasiticides).

The Working Group will be coordinated by CAPROVE (Argentina), and made up by the official representatives of Brazil, Ecuador, the United States, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Paraguay, Peru and Uruguay, with the participation of CADIN (Nicaragua), ALANAC (Brazil), CLAMEVET (Argentina), INFARVET (Mexico), ANALAV (Mexico), CIG (Guatemala), AENSA (Ecuador), ASOVET (Guatemala), ASIFAN (Costa Rica), CIA (Costa Rica), FENALCO (Colombia), CAPALVE (Paraguay), CEV (Uruguay), and ADIPRAVE (Uruguay).

Good practices for the use of veterinary products

The Working Group will be coordinated by Guatemala and made up by the official representatives of Brazil, El Salvador, United States, Guatemala, Honduras, Mexico, Nicaragua and Uruguay, with the participation of CADIN (Nicaragua), ALANAC (Brazil), CLAMEVET (Argentina), INFARVET (Mexico), ANALAV (Mexico), CIG (Guatemala), AENSA (Ecuador), CEV (Uruguay), CIA (Costa Rica), ASIFAN (Costa Rica), and ADIPRAVE (Uruguay).

Efficacy tests for the registration of internal antiparasitics for ruminants and swine.

The Working Group will be coordinated by CAPROVE (Argentina), and made up by the official representatives of Mexico and Uruguay, with the participation of INFARVET (Mexico), ANALAV (Mexico), CIG (Guatemala), ASOVET (Guatemala), AENSA (Ecuador), LABIOFAM (Cuba), FENALCO (Colombia), ALANAC (Brazil), CEV (Uruguay), ADIPRAVE (Uruguay) and CLAMEVET (Argentina).

Glossary of terms

It was decided that the harmonized document adopted on the XVII Seminar shall be circulated by the Secretariat to all of the CAMEVET members for the reception of suggestion of terms to be included.

Classification of products as Innovative, Generic, Similar and New

Dr. Carlos Rufrano, representative of CLAMEVET and member of the Executive Board, presented a draft document that contains definitions and requirements relating to product categories. The document presented will advance to Status III, and consequently will be circulated to the members of CAMEVET and open for the reception of comments for a period of 90 days.

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Session IV – Settlement of conflicts that require an open discussion by the Official Sector and Industry Sector.

Discussion round table

The proposals received by the Executive Board of the topics that require discussion and the search of common solutions were presented. Topics proposed led to a fruitful discussion as well as the proposal of alternatives for solving the situations posed.

CAMEVET members were reminded that the Secretariat will receive proposals of topics that require an open discussion by the official and industry sectors. Proposed topics will be received up to three months prior to the beginning of the Seminars, and the parties involved will be informed accordingly. The Executive Board will review the proposed topics and decide which shall be included based on their relevance.

Session V –Training in CAMEVET

Regional Seminar on Antimicrobial Resistance

Seminar included an one day meeting organized by the OIE, which covered topics related to antimicrobial resistance. Presented topics included a technical presentation, as well as the OIE standards and guidelines and antimicrobial use data collection, the participation of other international and regional Organizations, as well as the collaboration from the veterinary products producers Associations. Additionally, included the presentation of the Alliance for the Responsible Usage of Antimicrobials, as well the advancement in the implementation of National Action Plans.

The meeting was considered as a source of high level scientific information. Also, allowed knowing the global and regional actions on the field as well as collaborative actions, oriented to reducing antimicrobial resistance. It was agreed to include a similar meeting in next Seminar agenda.

Good Manufacturing Practices Training Course.

The Seminar included a training in Good Manufacturing Practices for Veterinary Products delivered by Pharm. Natalia Guelfi.

Session VI – Operative aspects of CAMEVET

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

Dr. Carlos Rufrano presented the document prepared by the latter, which aims to update the current procedure and simplify the processing of the Committee´s documents.
This document will be distributed to the Members of CAMEVET for comments, and the Executive Board will be responsible for the preparation of the final version and its submission for approval at the next Seminar.

Approval of venues proposed for the forthcoming Seminars

The representative of the official sector of Jamaica informed that shall make the required consultations in order to head next Seminar in his country.

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Dr. McAllister Tafur Garzón from SG CAN and on behalf of the official sector of Colombia proposed his country as the venue for the Seminar to be held in the year 2020.

Both proposals were unanimously approved.

Financial Report of CAMEVET

Mrs. Ana María Sgammini, Administrative Secretary of CAMEVET, presented the financial report, including annual expenses and incomes generated during the present Seminar, as well as the expenses prevision for the following period. Report is included as Annex VI.

A salary increase of the Administrative Secretary to USD 1200, including an annual prize with the value of a monthly salary was proposed and accepted.

The proposal for assigning funds for countries organizing Seminars was discussed

Special note was made of the financial contribution made by CAMEVET to the Focal Points that requested funding, namely Belize, Bolivia, Cuba, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua and Peru.

The Executive Board informed that it will analyze actions to be carried out to ensure the participation of the Focal Points in the Seminars, especially in the event that they as speakers.

Special reference was made to the work carried out by the Secretariat as well as the local organizers.

Conclusions and recommendations. Reading and approval of the final document.
The document containing the conclusions and recommendations was read and was approved by the Plenary Meeting after the inclusion of suggested modifications.

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List of acronyms used in the document

ADIPRAVE	Agrochemical and Veterinary Product Industry Association (Uruguay)
AENSA	Association of the Ecuadorian Industry of Veterinary Drugs and Nutrition
ALANAC	Association of National Pharmaceutical Laboratories (Brazil)
ALANAV	National Association of Veterinary Laboratories (Mexico)
ALAVET	Association of Veterinary Product Laboratory Trade Unions (Chile)
ANDIA	National Association of Distributors of Agricultural Supplies and Machinery (Panama)
APROVET	National Association of Veterinary Product Laboratories (Colombia)
ASIFAN	National Industry Pharmaceutical Association (Costa Rica)
ASOVET	Veterinary Product Association (Guatemala)
CADIN	Chamber of Industry of Nicaragua
CAMEVET	Americas Committee for Veterinary Medicines
CAPALVE	Chamber of Paraguayan Veterinary Product Laboratories
CAPROVE	Argentine Veterinary Product Industry Chamber
CEV	Chamber of Veterinary Specialties
CEVEPA	Chamber of Veterinary Specialties of Paraguay
CIA	Chamber of Agricultural Inputs (Costa Rica)
CIG	Chamber of Industry of Guatemala
CLAMEVET	Chamber of Argentine Veterinary Medicine Laboratories
FENALCO	National Federation of Merchants (Colombia)
INFARVET / CANIFARMA	Veterinary Pharmaceutical Industry / Industria Farmacéutica Veterinaria (Mexico)
LABIOFAM	LABIOFAM Business Group (Cuba)
OIE	World Organization for Animal Health / Organización Mundial de Sanidad Animal
SG-CAN	Andean Community General Secretariat
SINDAN	National Syndicate of the Animal Health Products Industry (Brazil)
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

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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- Balance 2017 2018
Annex IV – Considerations for regulation of aquaculture vaccines in the Americas
Annex V – Guide for the Preparation of the CAMEVET Form for Biological Products and Preparation of CAMEVET Pharmacological Products Registration Form

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Annex I

Conclusions of the Plenary Meeting of the Official Sector

Quito, October 2, 2018

Report of the meeting of official sector representatives present at CAMEVET

Written by: McAllister Tafur Garzón SG CAN/(Colombia), Ofelia Flores (Mexico), and Emigdio Lemes (Cuba).

Under the framework of the 2018 XXIV CAMEVET SEMINAR, and with the support of AGROCALIDAD - the Ecuadorean Animal Health and Veterinary Product registration authority, the representatives of the veterinary product registration authorities of ten (10) countries from the Americas met on October 1, 2018. As representative of the OIE, Dr. Martín Minassian welcomed the veterinary product registration officers and thanked AGROCALIDAD for its hospitality.
Ms. Rita Pamela Ruales, Engineer, Coordinator of the Registry of Agriculture and Livestock Supplies, and Dr. Verónica Sofía Loza, Director of the Livestock Supplies Registry, thanked the representatives from the various countries for their presence. Subsequently, the participants were introduced individually and Dr. Loza invited each one to present the main topics and issues of concern, which included the following salient issues:

Products susceptible of registration and determination of the criterion to that end.

- Certificates of Free Sale: Some countries expressed their concern over the heterogeneity of conditions and the occasional voids in the wording of certificates of free sale. Nevertheless, it was reminded that CAMEVET has a harmonized type form for preparing Certificates of Free Sale, and the countries were encouraged to use the document referred to wherever possible.
- Export Certificates and registration of veterinary products: Ecuador expressed its concern regarding export certificates. In this regard, some countries indicated that these certificates are drawn up in line with the requirements of the sanitary authority of the country of destination, when in actual fact the products involved are not registered in the country of origin. Other countries stated that, despite not being registered, the manufacture of those products is expressly authorized to that end by the competent authority. It was also noted that CAMEVET has a harmonized type certificate for this purpose.
- Antimicrobial resistance: Various countries expressed their concern regarding antimicrobial resistance given the risk it poses to animal health, public health and the environment. They highlighted the fact that international agencies such as the OIE, FAO and WHO have established global risk management directives, and stressed that these must be instrumented in the countries of the Americas, and that sustained training actions will be essential to that end. The need to know the restriction and prohibition measures that have been implemented by certain countries in relation to antimicrobial products was emphasized as highly important in order to have a unified vision of the risks

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and their management, considering that we must act under the One Health concept. In this regard, it was concluded that the official members of CAMEVET must channel concerns regarding antimicrobial resistance in the Americas in a coordinated manner through the country Delegates, who are responsible for raising the issue at the OIE meeting, and driving the development of the strategies envisaged by the OIE to that end – with the support of the Veterinary Product Focal Points.

- **Import requests for products that do not comply with the harmonized requirements established in the rules:** The countries expressed that import requests covering veterinary products not registered in the importing country remain a concern, as well as the detection of labels that do not meet the conditions established by the country of destination. In this regard, it was reiterated that, in these cases, the risk management step required is clear since the entry of such products cannot be authorized, and that it is necessary to strengthen the information of requirements for importing veterinary products, and apply the corresponding control steps envisaged by the Competent Authorities.
- **Good Manufacturing Practices (GMP) for veterinary medicines:** The Group of participants from the official sector highlighted the importance of moving forward in the harmonization of GMPs, using the reference documents on the matter as a basis (including Report 32 of the World Health Organization), and emphasizing the need to request training from the OIE in the form of workshops and seminars, and virtual tools to facilitate the participation of the countries.
- **Resolution 003 of AGROCALIDAD**: In particular, Ecuador requested the opinion of the countries regarding the enforcement of Resolution 003 of AGROCALIDAD which concerns the authorization of veterinary product manufacturers for exporting to that country. Some countries said they would use the seminar to present their concerns in this regard to the representatives of AGROCALIDAD.

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Annex II

Conclusions of the Meeting of Industry

Excessive time span for registration and renewal proceedings in: **Costa Rica, Dominican Republic, El Salvador, Honduras and Panama**. In the latter three countries the situation is worsened by the marketing, import and export prohibition imposed on products whose application is in process.

EL SALVADOR: Primary standards continue to be requested for renewals and for processing new registrations. However, drug mixtures that comprise active ingredients with renowned use are considered innovative products.

NICARAGUA: Although there is no written regulation to this effect, an additional payment is required annually by way of renewal/authentication of registered products. Additionally, manufacturing laboratories must register their different activities with the IPSA, while all other countries require a single registration per manufacturing laboratory that covers the entire activity.

GUATEMALA: This country requires legal documents to be signed in blue ink. Since this is not an official requirement, it is difficult for it to be adopted by all the countries. It should be noted that processing times have improved in the last year.

HONDURAS: The Apostille or consular legalization is required for quali-quantitative formulas, as well as an affidavit, power to authorize the proceeding per product for each proceeding, in addition to the Free Sale Certificate (CLV) indicated in the Central American Technical Regulation (RTCA). Another situation that has arisen is that, although the RTCA allows the use of a sticker only for the registration number, Honduras does not accept this.

MEXICO: This country is requiring the registration number to be placed below the brand in labels, complicating a harmonized labeling procedure.

URUGUAY: A certificate of authorization to operate for the plant is being requested for each product renewal proceeding as an additional requirement.

COLOMBIA: The requirements of all the authorities are requested in this event. Additionally, the harmonization of the Andean Community (CAN) regulation is not clear, and must be clarified by the official sector.

BRAZIL: institutions need more staff in order to process regulatory proceedings more expeditiously. Regulatory instruction #30 published recently regarding the official analysis of each batch of veterinary medicines prior to marketing poses an excessive requirement, given the effectiveness of the GMP to which manufacturing laboratories are already subject.

ARGENTINA: a request is made to flexibilize the regulation that allows the manufacture of Veterinary and Human medicines at a same plant.

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ECUADOR: The resolution concerning the authorization of manufacturing plants contained in Manual 003, Annexes 2 and 3, contains excessive requirements and does not recognize GMPs issued by the official entities of every country. Additionally, whenever government officers change, the registration rules change at discretion. Ecuador does not recognize GMP certificates issued by the other countries. The application proceeding contained in Annex 2 and 3 is complicated in terms of the documentation requested by the official sector.
Quality analysis rule 17025 exceeds the actual analysis capacity in the region.
Another problem relating to moist food products (canned) is that they are included under Agroquality rule 003, which does not apply implicitly to these products.

- A request is made to allocate a portion ($150) of the CAMEVET seminar registration fee to the organizers of the seminar.
- Technical data sheets must be updated so that documents can be referenced by all countries.
- The authorities of the countries of Central America are urged to harmonize the implementation of the RTCA, given the evidence in several countries of requirements that are not regulated.

We believe that the official sector and Industry must work jointly

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Annex III

Account in argentine pesos

Income		29/12/2017 - 31/10/2018
Total until December 29, 2017		ARS 792,62
Exchange of US dollars to Argentine pesos		ARS 102.780,00
	Subtotal	**ARS 103.572,62**
Expenses		
Expenses for the CAMEVET Annual Meeting		
Expenses for the purchase of airline tickets (Ms. Ana Sgammini)		ARS 49.285,69
Expenses for the purchase of airline tickets financing(Dra. Bertha Martinez)		ARS 49.272,26
	Subtotal	ARS 98.557,95
Expenses by other events		
Expenses for the purchase of airline tickets – Vich		ARS 0,00
	Subtotal	ARS 0,00
Other expenses		
Miscellaneous (Translation ESP / ENG Conclusions CAMEVET Seminar)		ARS 4.800,00
	Subtotal	ARS 4.800,00
	Subtotal of Expenses	ARS 103.357,95
	Total October 31, 2018	**ARS 214,67**

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Account in Dollars

Income		29/12/2017 - 31/10/2018
Resources available as of December 29, 2017		USD 130.775,00
Registration to the CAMEVET Seminar 2018		USD 49.250,00
	Subtotal	**USD 180.025,00**
Expenses		
Fixed expenses (Salaries)		
Administrative Assistant (Srta. Ana Maria Sgammini USD 1.000/9 months + 1200/1 month)		USD 10.200,00
Administrative Expenditures For use of the OIE Offices (150/month)		USD 1.500,00
	Subtotal	USD 11.700,00
Expenses for the CAMEVET Annual Meeting		
Financing to Focal Points for CAMEVET Annual Meeting		USD 15.269,00
Financing to Speakers for CAMEVET Annual Meeting		USD 1.154,00
CAMEVET Staff Expenses		USD 2.267,20
Material purchases for the CAMEVET Annual Meeting		USD 100,00
	Subtotal	USD 18.790,20
Expenses by other events		
Participation in meetings of the VICH Outbreach Meetings		USD 0,00
OIE Conference Regional Commission for the Americas		USD 0,00
	Subtotal	USD 0,00
Others expenses		
Internet of CAMEVET		USD 0,00
Realization of CAMEVET Payment receipts		USD 0,00
	Subtotal	USD 0,00
Variable expenses		
Change from Dollars to Argentine Pesos		USD 2.750,00
	Subtotal	USD 2.750,00
	Subtotal of Expenses	**33.240,20 USD**
	Total October 31, 2018	**146.784,80 USD**

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Annex IV

CAMEVET
Cod:
STEP IV
October 2018

CONSIDERATIONS FOR REGULATION OF AQUACULTURE VACCINES IN THE AMÉRICAS

AMERICAS COMMITTEE ON VETERINARY MEDICINES (CAMEVET)
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I. Introduction

Aquaculture is an economically important activity for several countries in the Americas. There is considerable potential for future expansion and diversification; however, potential losses due to viral and bacterial infectious diseases are a major concern. Some of these diseases can be prevented by vaccination. Aquaculture producers, therefore, require timely access to safe and efficacious vaccines and other animal health products, to help protect aquatic animal health and welfare, and to reduce the financial risks from diseases.

This overview document outlines some recommended approaches for standardizing the regulatory controls, technical standards, documentation, and regulatory approval processes for vaccines and related veterinary biologics that are intended for use in aquaculture. It provides general background information and recommendations, with the objective of facilitating the pre-licensing review and approval processes, as well as avoiding duplication of post-licensing regulatory oversight for regulatory agencies of CAMEVET member countries.

II. General regulatory considerations

In many countries, the government agencies that regulate animal health products for terrestrial animals generally also have the necessary enabling legislation and delegated authority to implement regulatory controls for the manufacturing, importation, and distribution of vaccines and other animal health products for diagnosis, treatment, prevention, and control of infectious diseases in aquatic animals. However, the agencies that are responsible for regulating terrestrial animal health products may not have implemented specific regulations or technical standards for regulating aquaculture products. Nevertheless, many of the key elements of the regulatory frameworks, technical standards, and quality assurance systems that have been developed and implemented for terrestrial animal vaccines can be readily applied or adapted for regulation of aquatic animal vaccines.

In the following document, the terms "aquatic animal vaccine" and “aquaculture vaccine” are intended to refer to products that are comprised of naturally occurring or synthetic biological substances, or a mixture of biological substances, that are manufactured, sold or represented for use in prevention or control of a specific infectious disease in aquatic animals, and which act primarily through stimulation of an acquired immune response. Terms such as "licensing", “permitting”, "registration", or “marketing authorization” may be used synonymously to mean regulatory approval or permission to manufacture, import, distribute, release or use a veterinary vaccine within a jurisdiction. These regulatory approvals may be granted through issuance of licences, permits, or other documents. Various restrictions or conditions may be applied, and should be clearly stated on the regulatory approval document.

In some countries, there may be a perceived overlap or gap in regulatory authorities for regulating aquaculture vaccines because the existing animal health legislative authorities for regulating vaccines for terrestrial animals may not explicitly include authorities for regulating aquaculture vaccines, or a different regulatory agency may be responsible for implementing the controls for aquatic animals and their products. Another factor to consider is that the enabling legislation and regulatory agencies covering aquaculture may be situated in a different Ministry,

such as the Department of Health, Agriculture, Environment, or Fisheries. This may necessitate a Memorandum of Understanding or other arrangement to delineate the division of regulatory responsibilities between agencies.

The technical and jurisdictional challenges for regulation of aquaculture vaccines may be further complicated by the fact that aquaculture may comprise a relatively small segment of the agriculture sector in a country, and there may be no licensed domestic manufacturers of aquaculture vaccines, so all aquaculture vaccines are imported. Consequently, it may not feasible for each individual country's regulatory agency to invest in developing a regulatory infrastructure, and maintaining the necessary specialized technical expertise that would be required to autonomously develop and implement the necessary science-based regulatory controls for the aquaculture vaccine sector.

III. Technical considerations for regulation of vaccines for use in aquatic animals

In general, the principles and approaches that are employed for regulation of veterinary vaccines for terrestrial animals can be adapted to regulation of vaccines for aquatic species. However, due to differences in immunological responses and aquaculture health management practices, as well as differences in manufacturing and testing procedures, some modifications may be required for regulation of aquaculture vaccines.

Vaccination is relatively widely used for commercially raised fin fish species, such as Atlantic salmon, catfish, and tilapia to stimulate an active humoral and cellular immune response. However, the roles of the innate and acquired immune system in disease resistance for fin fish are less well characterized than in terrestrial species. Crustaceans such as crayfish, lobsters, and shrimp, and molluscs such as clams, scallops, oysters, and mussels have a much less well developed immune system that is primarily based on innate immune responses, therefore conventional vaccines that are intended to elicit an acquired humoral or cellular immune response may not be efficacious for crustaceans and molluscs, unless they activate the innate immune responses.

In comparison with the relatively advanced state of knowledge of the pathogenesis of diseases affecting avian and mammalian domestic species, considerably less is known about the pathogenesis of infectious diseases of aquatic animals (which frequently involve emerging pathogens), and the corresponding protective immune response mechanisms. As a result, well-characterized, validated, predictive *in vitro* tests for assessing vaccine potency or immune responses may not be readily available for use in pre-licensing immunogenicity/efficacy studies or post-licensing batch release potency tests. Consequently, manufacturers and regulatory agencies tend to rely on vaccination-challenge tests to evaluate potency of each serial (batch) of vaccine, using a method of calculating relative percent protection (RPP) or relative percent survival (RPS) which involves comparing the level of protection or survival of vaccinated fish to that of unvaccinated controls.

Vaccination-challenge studies are used to demonstrate efficacy, and they are also currently frequently used as a serial (batch) release potency test. Due to animal welfare concerns, there is

a trend toward replacement of the vaccination-challenge batch release potency tests with *in vitro* antigen detection tests or *in vivo* tests to compare the serologic immune responses in fish vaccinated with a production serial versus the serologic responses in fish vaccinated with a reference serial by comparing pre-vaccination and post-vaccination antibody levels. In the batch release potency tests, the relative potency could be assessed by comparing the potency of a production serial with a reference standard that has been shown to be efficacious in vaccination-challenge tests.

In efforts to reduce the use of aquatic animals for batch release safety tests, the initial stages of *in vivo* batch release potency tests can also serve as a batch release safety test, based on a lack of adverse reactions in vaccinates during the interval between vaccination and challenge.

From an animal welfare refinement perspective, if an *in vivo* vaccination-challenge test must be used for batch release, the challenge dose should be adjusted so it reliably elicits a detectable level of disease in unvaccinated controls, and little or no clinical disease or mortality in vaccinates.

Vaccination-challenge tests require highly specialized aquatic facilities for maintenance of fish, segregation of treatment groups, biocontainment, and decontamination of effluent. Since there is a potential for inadvertent release of aquatic pathogens in effluent, the vaccination-challenge tests present a potential biosafety risk. Consequently, it may not be feasible for individual manufacturers or lead regulatory agencies to maintain aquaculture testing facilities for confirmatory testing. As an alternative, manufacturers may elect to arrange for contract approved laboratories with specialized expertise to conduct pre-licensing testing, validation *of in vitro* potency tests, and post-licensing batch release safety and efficacy tests. For similar reasons, rather than conducting confirmatory batch release testing in government laboratories or 3rd party laboratories, it may be more expedient for regulatory agencies to supplement their pre-licensing review of data with an onsite evaluation of manufacturing and testing procedures, and periodic audit the manufacturer's batch release testing procedures during facility inspections.

Table 1 lists some of the factors and parameters that must be considered when regulating vaccines intended for use in aquaculture facilities.

IV. Coordination of regulatory oversight for manufacturing and Importation of veterinary vaccines

When implementing pre-licensing evaluations, post-licensing regulatory controls, and confirmatory testing for imported products, it may be preferable and more expedient for regulatory officials to take into consideration the regulatory oversight and preceding decisions of other regulatory agencies which may have more familiarity with specific aquaculture vaccines, and to defer some of the direct regulatory oversight to a lead regulatory agency where the manufacturer is located.

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The regulatory agency of the country where the manufacturing facility is located is often best positioned to serve as the lead regulatory agency, with primary responsibility for oversight of the manufacturing and testing procedures for the licensed aquaculture vaccines that are produced in the facility. For regulation of imported veterinary vaccines, the responsibility for regulatory oversight may be shared between the regulatory agency in the country where an aquaculture vaccine is manufactured and the regulatory agency in the destination country. The two regulatory agencies would generally function autonomously, however the destination country's regulatory agency may elect to take the preceding regulatory decisions and ongoing regulatory oversight of the lead regulatory agency into consideration when reviewing licensing applications and post-licensing documentation for imported vaccines, and determining the appropriate level of post-licensing regulatory oversight for a specific product.

This type of collaborative approach, where regulatory agencies of importing countries consider the decisions and regulatory controls of other agencies when establishing import conditions and other post-licensing regulatory controls, would help minimize duplication of pre-licensing evaluations, post-licensing regulatory controls, and confirmatory testing, especially considering the similarity of the controlled conditions of fish breeding in ponds and lakes.

Whenever possible within the scope of their regulatory authorities, individual regulatory agencies should strive to adopt common documentation and technical standards, and consider the preceding approvals in other jurisdictions when reviewing licensing submissions. In doing so, the individual regulatory agencies could maintain overall regulatory authority, and retain varying levels of regulatory oversight for review and approval of pre-licensing submissions, post-licensing batch release, and approval of major changes in manufacturing and testing procedures, but could defer to preceding assessments, testing, and regulatory controls of other agencies, when warranted.

Similarly, to avoid duplication of regulatory oversight for importing countries, the scope, depth, and frequency of manufacturer facility inspections could be modified if a lead regulatory agency or a competent authority from another importing country is conducting periodic, comprehensive, in-depth facility inspections, and the inspection results are available to other regulatory agencies through the regulated manufacturer.

It may be useful for regulated companies to authorize communications and exchange of confidential product review information among regulatory agencies, for the purpose of facilitating the review and approval of supporting documentation, and to avoid duplication of regulatory oversight. This authorization could be done through a broad-based *Memorandum of Understanding* between regulatory agencies to authorize sharing confidential information on all facilities and products that they both regulate. Alternatively, a more limited type of product-specific authorization could be achieved through a letter from a manufacturer authorizing two regulatory agencies to share confidential information and decision documents pertaining to a specific product or a group of products.

V. General guidance

A. General criteria for product acceptability

1. The product must be properly characterized in relation to the purity of the seed, safe, potent and efficacious when used in the target species, according to the label directions.
2. Each biologically active component must be relevant to the infectious aquatic animal disease conditions and aquatic animal genetics in the country or region where the product will be used.
3. The product must be manufactured and tested by qualified personnel approved by the competent authority, in facilities that are acceptable to the responsible regulatory agencies.

B. Potential reasons to refuse permission to manufacture or import an aquaculture vaccine

1. Product manufactured in countries where specific transboundary diseases affecting aquatic or terrestrial animals post a risk for contamination of the regulated vaccine, when the manufacturer does not comply with the appropriate biosafety regulations.
2. Product manufactured with components originating from countries where transboundary diseases affecting aquatic or terrestrial animals pose a risk for contamination of the regulated vaccine.
3. Product for the prevention or diagnosis of aquatic animal diseases which are under regulatory control or eradication program, or considered foreign to the country or region. Some exceptions may be granted, i.e., for restricted use of vaccines in government control and eradication programs, if deemed in the best interest of the success of the control or eradication program.
4. Live attenuated vaccine with an unacceptable level of residual virulence, which could present a disease risk to unvaccinated animals of the target species, or in-contact aquatic animals.
5. Product which has not been demonstrated to be satisfactorily efficacious in the target species.
6. Product that is deemed to be contrary to the best interests of public health, animal health, environmental protection, or aquatic animal health control or survey programs.

VI. Recommended documents and forms for licensing submissions

The process for licensing aquatic animal vaccines manufactured within a country generally involves a phased, in-depth review of documents by the lead regulatory agency in the country where the vaccine is manufactured. For imported products, which have been previously reviewed and approved by a competent regulatory agency, a complete licensing submission is generally submitted, which includes all key documentation which was submitted to the lead regulatory agency, as well as any key correspondence pertaining to the review and approval by the lead agency. However, the regulatory agency in the destination country may deem it appropriate to take into consideration the preceding decisions and ongoing regulatory oversight of other competent authorities when reviewing licensing submissions, and may, therefore, decide to waive or modify some data review procedures, pre-licensing testing requirements, or post-licensing regulatory controls.

In some circumstances, such as when it is necessary to authorize restricted importation or provisional marketing authorization to facilitate importation or release of a specific serial (batch) of a vaccine for emergency or research use, the manufacturer and importer may be permitted to file an abbreviated licensing submission which provides summary information (i.e. production outline, batch release test results, material of animal origin documentation, labelling). The application for restricted use should cite any previous review and approval in another jurisdiction, including conditional approval. It may need to be supported by other documents or attestations such as an Establishment Licence, *Product Licence, Certificate of Licensing and Inspection, Export Certificate, or Certificate of Free Sale* pertaining to the individual serial (batch) to be imported, and the method of analysis.

VII. General requirements for products manufactured for domestic distribution and export

Vaccine manufacturers are primarily subject to controls under regulations that are administered by the regulatory agency (competent authority) in the country or region where the product is manufactured. This regulatory agency would ordinarily serve as the lead agency responsible for regulating the manufacturing facility and its products. The regulatory agency of importing countries would serve a secondary role, and may delegate some responsibilities to the lead regulatory agency (e.g., pre-licensing master seed testing, pre-licensing serial testing, post-licensing batch release testing, and in-depth facility inspections).

For products manufactured and distributed within a country, a phased review may be carried out, where the initial phase of the new product licensing submission may contain only preliminary data. A *Permit to Release Veterinary Biologics* (or similar regulatory authorization), is required for the use of experimental products or unapproved products in field studies outside of biocontainment facilities, or if experimental aquatic animals are intended for entry into the food chain. An assessment by the regulatory agency may also be required for products derived from GMOs or when novel micro-organisms or biotechnology-derived products are used.

In addition to a complete product file, the licensing of vaccine manufactured by a domestic veterinary vaccine manufacturer requires the satisfactory inspection and licensing of the manufacturing facilities, data of the master seeds and approval of pre-licensing serials.

Products that are licensed (approved) for distribution within a country would ordinarily also be eligible for export, provided they meet the requirements of the importing country's regulatory agency. However, some products may be manufactured for export only. In the licensing submission, the manufacturer should specify whether the product will be manufactured "for domestic distribution and export" or "for export only", as the document requirements and regulatory approval processes would be different for these two types of approvals.

Regulatory agencies of importing countries may take any pertinent regulatory decisions and post-licensing regulatory controls of the lead regulatory agency into consideration when determining the appropriate level of regulatory oversight for a specific imported product.

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If approval is granted, various post-licensing restrictions and conditions may be applied. These restrictions and conditions should be clearly listed on a *Veterinary Biologics Establishment Licence, Veterinary Biologics Product Licence, Import Permit, Permit to Release Veterinary Biologics, Marketing Authorization,* or corresponding document, and explained in supplemental correspondence as required.

VIII. Special requirements for products manufactured for export only

For products manufactured "for export only", the manufacturer is required to submit the production outline, special outlines, and product labelling, as well as supporting data to demonstrate the safety of the product, the purity of the master seeds and the master cell stocks. The manufacturer must provide documentation to demonstrate approval by the regulatory agency in the destination country (e.g., approval letter, copies of approved label, copy of Marketing Authorization or Import Permit) or a statement of intention to license, in the country of destination.

In some instances, a product which is licensed "for export only" may be similar, or identical to a product manufactured for domestic sale, except it may have different quality control specifications or different label claims (i.e., languages, intended species, directions for use, precaution statements) to conform to the importing country's regulatory requirements. In other cases, it may be a vaccine for use in a species that is not farmed in the country, or a vaccine against an agent that is not present in a country. In the latter case, there would need to be appropriate biocontainment measures (1), and introduction of a potentially virulent vaccine seed organism into the manufacturing facility may be restricted or prohibited. Similarly, there may be restrictions or prohibitions on vaccination-challenge testing.

IX. Facilities, equipment, and personnel

All vaccines intended for distribution and use within a country, or for export to other countries, must be manufactured in a facility that has been approved by the lead regulatory agency in the country where the manufacturing facility is located.

The approval of a new vaccine manufacturing facility involves a review of the facility, personnel, manufacturing and quality control/quality assurance documents, and a pre-licensing inspection of all premises where manufacturing, testing, preservation, packaging, labelling, storage and distribution of veterinary vaccines are performed, in compliance with Good Manufacturing Practices that must being certified

Appropriate quality management programs, quality control programs, laboratory biosafety programs, and preventive control plans must be in employed. The document requirements for aquaculture vaccine facilities and personnel should be the same as for terrestrial animal vaccine manufacturers.

X. Manufacturing and testing protocols

Manufacturers should prepare and submit copies of a production outline and related special outlines, in a format acceptable to the regulatory agency. These descriptions of the

manufacturing and testing methods should be sufficiently detailed to enable regulatory evaluators to assess the appropriateness of the manufacturing and testing methods to demonstrate that the product manufacturing methods conforms to the quality standards established for production of the pre-licensing serials.

The production outline may refer to one or more special outlines, or it may cite internationally accepted regulatory requirements and technical standards such as the United States Department of Agriculture *Title 9 Code of Federal Regulations (9 CFR)*, the *European Pharmacopoeia*, or the World Organisation for Animal Health (OIE) *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* and *Manual of Diagnostic Tests for Aquatic Animals,* as well as applicable standards of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), among others.

Once the production outline and special outlines are approved and stamped as satisfactory, one copy of each will be retained on file with the regulatory agency, and one copy will be returned to the manufacturer.

In the interest of standardizing the quality assurance procedures for veterinary vaccines, it would be helpful if manufacturers and regulatory agencies could work toward development and implementation of common technical standards for manufacturing and testing veterinary vaccines, such as the principles and procedures that are outlined in the CAMEVET Guideline *for Good Manufacturing Practices for Veterinary Products,* or other technical references that may be developed in the future.
In exceptional and justified cases, additional confirmatory testing may be required to meet the requirements of the manufacturer's domestic regulatory agency or the destination country's regulatory agency. This testing must be done by a laboratory acceptable to the regulatory agencies, which could include a contract testing laboratory.
Veterinary vaccines may be manufactured and tested in whole or in part in a contractor's facility that has been previously approved by the lead regulatory agency for the manufacture of veterinary vaccines. In this case, the manufacturer presenting the licensing submission must provide a flow chart indicating the source(s) of all antigens and/or other components. The manufacturer presenting the licensing submission is also responsible for ensuring that all relevant and up-to-date production outlines and special outlines are provided to the lead regulatory agency, as well as the destination country regulatory agency if required as a condition of importation.

XI. Master seeds, master cell stocks, and pre-licensing serials
The following information is required:

1. Master cell stock data: Identity (species, cell type) karyology, freedom from extraneous agents and the corresponding certificates
2. Master seed data: Identity (genus, species, biotype); purity, freedom from extraneous agents; passage number; back passage studies of modified live vaccines; genetic characterization for the master seed, if the product is biotechnology-derived.

3. Manufacturers must submit summary test results to verify serial-to-serial consistency of consecutively produced serials, e.g., three consecutive batches with a minimum size of 10% or 50% of commercial batches, at the discretion of each regulatory agency. These data demonstrate the manufacturer's ability to consistently manufacture serials that meet the established production outline specifications for a pre-licensing reference serial that has been shown to be safe and immunogenic when used according to label recommendations in the target species. Summary test results for consecutively produced pre-licensing serials serve to demonstrate the uniformity of the serials, as an indicator of the manufacturer's ability to meet the established quality criteria and minimize batch-to-batch variability.

XII. Materials of animal origin documentation

In order to protect animals and the public from transmissible spongiform encephalopathies (TSEs) and from other infectious animal diseases, all materials of animal origin used in the production of veterinary vaccines must be sourced from countries and animals that are acceptable to the lead regulatory agency, as well as the regulatory agencies of the destination country. The manufacturer of the product must require suppliers of raw materials of animal origin, additional documentation to demonstrate the conformity of these materials with the regulations in force in the country of origin and destination, which will be presented to the official authorities at the time of submitting the license in the country of destination.

XIII. Pre-licensing safety and efficacy testing, and post-licensing serial (batch) release testing

Pre-licensing efficacy and safety testing of vaccines for fin fish should be done in the target species, using fish of the minimum recommended size, which are vaccinated with a prototype vaccine in a manner that is representative of the anticipated field use.

For demonstrating efficacy, the prototype vaccine would ordinarily be formulated to the minimum acceptable potency, so that it may be used as a reference serial in post-licensing batch release tests.

For evaluating target aquatic animal safety, preliminary studies are ordinarily conducted in biocontainment facilities, and larger numbers are subsequently tested in field safety tests.

The serologic immunogenicity studies to measure antibody responses, or vaccination-challenge efficacy studies to measure clinical protection should be conducted in parallel with the proposed post-licensing batch release tests (*in vivo* or *in vitro*). These parallel tests serve to establish the correlation between the proposed batch release potency test and the protective dose, when the product is tested in vaccination-challenge studies involving a prototype vaccine that will serve as a reference serial.

Studies supporting efficacy and safety must be conducted with serials that are representative of the final product, as described in the submitted production outline. In general, efficacy studies should be conducted with a vaccine containing the minimum allowable potency, and safety studies should be conducted with a vaccine at meets or exceeds the maximum allowable potency, as stated in the approved production outline.

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In the interest of reducing the use of fish for batch release testing, if an *in vivo* test is used, the first phase of the potency test (in the days after vaccination, but before the challenge), can serve as a batch release safety test.

Once consistency of manufacturing has been demonstrated, if a reliable *in vitro* batch release potency test is available (based serologic antibody responses in vaccinated fish, or a measure of antigen in the vaccine), the *in vivo* vaccination-challenge potency test may be discontinued and replaced by an alternative test such as a post-vaccination serum antibody assay, or a quantitative *in vitro* antigen assay.

Individual animal data for all the animals used in the studies are required; however, these data may be presented in summary tables. Copies of individual records and test reports may be required by the lead regulatory agency or destination country regulatory agency, to supplement the information in summary test reports.

XIV. Labelling

Labelling for vaccines intended for use in aquaculture should conform to the harmonized standard requirements that have been established for other types of vaccines.

XV. Summary test reports for serial (batch) release

In vitro testing should be utilized for post-licensing serial release testing, wherever feasible. If animal testing is employed, the 3R principles of reducing, refining, and replacing animal testing should be followed.

Any required batch release test results should be submitted to the regulatory agency on a standardized *Manufacturer's Serial Release Test Report* that is acceptable to the lead regulatory agency, and the regulatory agency of the destination countries. Test references on serial release test result forms should cite the current production outline and special outline, as filed with the responsible regulatory agencies.
Manufacturers must retain production and testing records for all serials of products that are manufactured or tested within the facility, for at least one year after the expiry date of the batch.

All serials destined for export must be initially released by a company quality assurance official, prior to distribution within the country or export. Regulatory officials of importing countries may allow importation of any released serial of a licensed product, without further restrictions, or they may approve importation of each serial individually, after review and approval of the manufacturer's batch release test results.

XVI. Environmental assessment

For any novel or biotechnology-derived product that is intended for release into the environment, the manufacturer cloud be required to assess the environmental impact of the environmental release, by the competent regulatory agency or complementary committee. Since these summary documents are intended for public release, the documents should be prepared in a format that does not disclose any confidential business information. If necessary, a more

detailed version for internal reference may be prepared for the regulatory agencies, with request for confidentiality

XVII. Manufacturer and importer inspections

Regulated products should be shipped directly from the manufacturer or a regulated regional distributor to the designated importer(s) in the importing country. This helps maintain the cold chain, and minimize the transit time between the manufacturer and importer. Veterinary vaccines should be managed in compliance with good storage, transportation, and distribution practices.

The inspection of the manufacturer and importer facilities can be scheduled shortly after the reviewer has concluded the review of the licensing documentation. The manufacturing facility inspection should be scheduled in consultation with the regulated manufacturer, to ensure that pertinent manufacturing and testing activities will be ongoing, and that the appropriate personnel will be available during the inspection, as well as to provide time for the regulated party to assemble any required documentation, such as test results or facility drawing. It also ensures that any key documentation will be available for examination, and helps minimize any disruptions for the manufacturer or importer.

The inspections serve as an onsite evaluation of the manufacturing and testing procedures, as a supplement to the descriptions of the facilities and materials and methods, and personnel that are provided in the licensing submission. The inspections/onsite evaluations are also an opportunity to further discuss and explain the regulatory system and requirements, establish contact with key corporate regulatory personnel, and answer any questions.

XVIII. Adverse reaction monitoring

Prior to licensing or authorizing restricted importation of a vaccine from another country, the regulatory authority in the destination country may request pharmacovigilance data from the manufacturer in the country of origin. This allows the destination country's officials to review the performance of the vaccine in the originating country, during the time since the product was originally licensed in the country of origin to provide supplemental safety information. This information could be utilized by the regulatory authority to make decisions regarding any special label precautions, conditions, or restrictions that should be implemented as a prerequisite for licensing or importation.

XIX. Post-licensing regulatory oversight

The monitoring will be managed in accordance with the legislation in force in each licensing country.

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XX. Table 1. Parameters to consider when regulating vaccines for use in aquatic species

Aquaculture system water temperature	Cold water (salmon, trout) versus warm water (catfish, carp, tilapia). Since water temperatures can influence pharmacokinetics of clearance of residues, withdrawal times and duration of efficacy for some vaccines may be determined in degree-days, rather than calendar days.
Species	Fin fish (i.e., trout, salmon, tilapia, catfish, carp) – innate and acquired immunity. Crustaceans (i.e., crayfish, shrimp) – innate immunity. Molluscs (clams, mussels) – innate immunity.
Water salinity	Fresh water pond, fresh water tanks, marine salt water net pens.
Federal disease control program, surveillance	Diseases may be reportable or notifiable.
Pathogen	Virus, bacteria, protozoa, fungus, endoparasite, ectoparasite.
Epidemiology of disease	Endemic/emerging/epidemic Wild fish may be reservoir, or susceptible to transmission from farmed fish. Human health risk - food borne disease risk for some zoonotic diseases.
Target species	Major use, major species versus minor use, minor species.
Intended use of species	Commercial food production, sport fishing, or ornamental.
Minimum size of fish to be vaccinated	Usually 10-30 gram for salmon. May also vaccinate later in production cycle, or mature broodstock as a booster or according to the protocol proposed and justified by the interested party or the holder of the license.
Dose, quantity of vaccine	Range from 25 uL (0.025 mL) to 100 uL (0.1 mL) for injectable vaccines or according to the protocol proposed and justified by the interested party or the holder of the license.
Route of administration	Immersion (dip), intraperitoneal, intramuscular, oral (in feed).

XXI. Reference: Containment standards for facilities handling aquatic pathogens

1. Containment Standards for Facilities Handling Aquatic Animal Pathogens – First Edition URL: http://www.inspection.gc.ca/animals/aquatic-animals/imports/pathogens/facilities/eng/1377962925061/1377963021283

Annex V

Version:

Effective Date:

TITLE: Guide for the Preparation of the CAMEVET Form for Biological Products

Objective: Establish detailed guidelines and instructions for the Preparation of CAMEVET FORM002 for biological products for veterinary use. This document is a guide, and may not envisage the specific requirements of certain countries. Similarly, it may contain excessive detail compared with the information required by certain countries.
This document does not establish new requirements and does not modify the registration forms.

CONTENTS:

1. SCOPE

This procedure applies to the Preparation of the CAMEVET Form for Biologicals in general.

2. SPHERE OF ENFORCEMENT

CAMEVET member countries.

3. DEFINITIONS/ ABBREVIATIONS

For purposes of definitions, the following documents approved by Camevet will be used: Codes GLO001 Proceeding VI of October 2011 and subsequent updates, ROT002 Proceeding I of October 2010 and subsequent updates.

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4. REFERENCES/ BIBLIOGRAPHY

Code	Name
BOV 1	Guide for Potency and Efficacy Test for bovine vaccines whose formulation contains Bovine Herpesvirus (BOHV-1), the causal agent of infectious bovine rhinotracheitis (IBR)
BPM 001	Good Manufacturing Practices (GMP) Standard
BPM 003	GMP Inspection Guide for the Manufacture of Biologicals
BPU 001	Good Usage Practices for Veterinary Products
CERT 001	CAMEVET Specimen Free Sale Certificate
CERT 002	Export Authorization Certificate
FORM 002	Application for Registration of Biologicals
FORM 003	Registration Form for Immunogens of Subunits obtained through Biotechnology
GLO 001	Glossary
NOM	Technical Data Nomenclator
RES 2	Guide for calculating withdrawal period in edible tissue
RES 3	Guide for validation of analytical methods for determining residues in animal origin biological matrixes
ROT 001	Veterinary products Labeling standard
ROT 002	Synonymia

5. INSTRUCTIONS

The different fields contained in CAMEVET Form 002 and instructions for completing them are listed below:

1.- Product Trade Name:

- Indicate the trade name of the product proposed for registration before the competent agency. The trade name must include alphabetical characters and may include alphanumerical characters, only numerical characters, or a combination of these.
- In the case of imported products, the name as it will be registered in the country of destination and as it is described in the Free Sale Certificate, Export Certificate or equivalent document issued by the competent authorities of the country of origin must be included.
- The label cannot contain the generic name alone (drug + dose); it must be accompanied by the brand. This may be the name of the company that is the holder of the registration or any other name associated with the marketed line.

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2. – CLASSIFICATION - GENERIC NAME (for official use exclusively)

- Do not fill in this section. To be completed by the control body.

3.- APPLICANT ESTABLISHMENT: OWNER / LEGAL REPRESENTATIVE

3.1- Name: .....

- Indicate the name of the applicant establishment duly registered with the NATIONAL REGISTRY.

3.2- Domicile (Street – City – Country): .....

- Indicate the domicile declared in the registration before the competent agency.

3.3- Official Authorization Number: .....

- Complete the data relating to the official registry authorization number of the entity that owns the product (this is not the company registration number).

3.4- Technical Director: .....

- Indicate first and last name of the Technical Director declared in the corresponding registry.

3.4.1- Profession: .....

  - Indicate the profession of the Technical Director declared in the corresponding registry. In most countries, for biological products the Technical Director must have a degree in Veterinary Medicine.

3.4.2- Professional ID Nº (Professional Registration or License).

  - Indicate the registry or license number corresponding to the profession of the Technical Director.

4.- MANUFACTURING ESTABLISHMENT (for products manufactured in the country)

4.1- Name: .....

4.2- Address (Street – City – Country): .....

4.3- Official Authorization Number: .....

4.4- Technical Director: .....

4.4.1- Profession: .....

4.4.2- Professional ID Nº (Registration or License):.....

- This section must be completed in a similar manner to section 3, but with the data relating to the manufacturing establishment (instead of the applicant establishment).
- Do not mistake for registration number of the outsourcer / toll manufacturer.

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- Third party manufacturers or toll manufacturers that are duly registered must be included here.

5.- FRACTIONATING ESTABLISHMENT (for products manufactured in the country)

5.1- Name: .....

5.2 - Address (Street – City – Country): .....

5.3 - Official Authorization Number:.....

5.4- Technical Director: .....

5.4.1- Profession: .....

5.4.2- Professional ID Nº (Registration or License): .....

- Where applicable, items 5.1 to 5.4 must be filled in as done in section 3, but with the data of the fractionating establishment instead of those of the manufacturing establishment.
- This section must reflect the data referred to in the Free Sale Certificate.

6.- MANUFACTURING ESTABLISHMENT AT PLACE OF ORIGIN (for imported products)

6.1 - Name: .....

6.2 - Address (Street – City – Country): .....

6.3 - Official Authorization Number: .....

6.4 - Technical Director: .....

6.4.1 - Profession: .....

6.4.2 - License/Registration Nº: .....

- Where applicable (fractionated products), items 6.1 to 6.4 must be completed in similar manner to section 3, indicating the data of the manufacturer at the place of origin (instead of the data of the applicant).
- Data provided here must coincide fully with the data contained in the legal documents attached to the registration application (see Section 7).

7.- LEGAL DOCUMENTS

This documentation varies according to each country. What follows is a guide that covers the majority of cases:

7.1.- Manufacturing agreement/s.

- In the case of local or foreign products not manufactured by the applicant, the contract executed between the applicant and the product manufacturer must be submitted.

7.2.- Representation Agreement with the Manufacturer in the place of origin.

- In the case of imported products, evidence must be furnished of the assignment of marketing rights granted by the owner of the product in the country of origin.

7.3.- Manufacturing Establishment Authorization Certificate.

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- In the case of imported products, the authorization certificate of the facility where the product is manufactured issued by the competent authorities of the country of origin must be furnished.

7.4.- For imported products the following must be submitted: Registration and Free Sale Certificate (CAMEVET specimen) or equivalent documentation, issued by the competent authorities of the country of origin, or Manufacturing Authorization (Export Certificate) and reasons for not marketing the product in the country of origin.

NOTE: Originals or a true copy certified by notary public must be submitted of all the legal documentation listed above. Documentation issued by countries other than the country where the application will be submitted must bear the following:

- Apostille or consular certificate
- Translation to the local language by a certified translator (where necessary).

8.- DEFINITION OF BIOLOGICAL LINE:

Vaccine antigens: identify the agent and indicate whether it is a live attenuated, inactivated, recombinant product, subunits, or any other technical designation relating to the biotechnology or genetic engineering used to obtain it.
Serum: specify immunoglobulins and agents or species (in the case of serpents) for which the serum has been manufactured.

- In the case of immunoglobulins, information on the species of origin and the species in which they have been developed should be included.

9.- PHARMACEUTICAL FORM

Indicate the pharmaceutical form of the finished product (powder, pill, capsule, solution, suspension, emulsion, etc.) and types of presentation and content in which the product will be sold (Ex: lyophilized powder for injectable suspension).

If the product is not presented in its final pharmaceutical form, for example: “powder for reconstituting”, “lyophilized powder for injectable suspension” “lyophilized pill for reconstituting”, etc., the final pharmaceutical form must be indicated.

10. - QUALITATIVE AND QUANTITATIVE FORMULA – BIOLOGICAL AND CHEMICAL CONSTITUTION

10.1 Antigen: identification, quantity per dose (titer, antigenic mass, protein or other)

10.2 Serums: concentration in IU

10.3 Inactivants; preserving agents; stabilizers; emulsifiers, adjuvants or other substances.

10.4 Diluent: chemical constitution.

- The qualitative and quantitative formula must include all the product ingredients or antigens and excipients or adjuvants in line with the internationally recognized pharmacopeia or references.
This must include designation, identification of strain or serum/s, titer per dose or per mL where applicable, or quantity in µg/doses or per mL, or concentration in IU or other unit. In

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the case of inactivated products, the antigen titer or content must be indicated expressed in the corresponding units per dose or per mL before inactivation.
- Excipients, adjuvants, preserving agents, stabilizers, emulsifiers or other substances must be described with the excipients. The regular common designation or chemical designation of the substance, or the name and CAS (*Chemical Abstract Service*) number, must be indicated. The indication "vehicle q.s.p." will not be accepted as part of the excipients. The vehicle must be described according to the instructions described above.
- The main function of the active ingredients and of the excipient in the formula must be included. The qualitative and quantitative formula in the registration application must be presented in the following format:

	Name	Quantity/dose	% in formula	Function
Active ingredients	Ingredient 1			Antigen
	Ingredient 2			Antigen
Excipients	Excipient 1			Stabilizer
	Excipient 2			Adjuvant (aqueous phase)
	Excipient 3			Adjuvant (oily phase)

If the products contain diluents, information on their composition must be included pursuant to the above table, and the available presentations.

11. – SPECIFICATIONS AND CONTROL METHODS FOR THE INGREDIENTS IN THE FORMULATION

11.1 Origin and characterization of the strain and the control test of the seed strain – parent, working and production strain.

11.2 Quality controls on adjuvants and inactivants.

- **Describe the origin (method for obtaining it where applicable), specifications and analytical methods that must be used in the qualitative and quantitative evaluation of the raw materials, including active principles, adjuvants and inactivants used to manufacture the product.**
- **The reference used as a basis must be provided (Pharmacopeia / in-house rule).**

12. – SPECIFICATIONS AND CONTROL METHODS USED FOR CULTURE MEDIUMS, SUBSTRATES AND OTHER BIOLOGICAL MATERIAL USED

- **Describe the origin (method used to obtain it where applicable), specifications and analytical methods that must be used in the qualitative and quantitative evaluation of the materials of biological origin (cell lines, serum, enzymes, etc.) used to manufacture the product.**
- **The reference used as a basis must be provided (Pharmacopeia / in-house rule).**

Depending on the legislation in force in each country, for biologicals that use raw material of animal origin, statements and/or certifications must be included to attest that they have been manufactured pursuant to the recommendations of the official agency to minimize the risks of transmission of agents of transmissible spongiform encephalopathies.

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13. – METHODOLOGY FOR MANUFACTURING THE PRODUCT

13.1 Describe the manufacturing process in summary form. Describe all the necessary steps in the registration form. Include a flow diagram describing the steps in the production process and controls applied until product release.

13.2 In-process product control methods.

Describe:

- Production method.
    - Active ingredient
    - Bulk preparation
    - Filling of biological product
- In-process controls
    - Working seed(s)
    - Embryonated eggs (where applicable)

Active ingredient

- Include the methodology used to produce the immunological product, showing each step of the process from the raw material (active substance production) to the final product (mixing and filling of the product in primary packaging).
- Controls carried out on the working or production seed: purity, identity, absence of extraneous agents, etc. and other applicable controls.
- Controls carried out on working or production cell banks: purity, identity, absence of extraneous agents, etc., and other applicable controls.
- Description of relevant processes and related controls: purification, inactivation, etc.
    - Inactivation method: Describe the method used for inactivation of the products, product and the procedures used for the control of inactivation of the antigen, when appropriate
    - Method of antigenic modification: include antigenic modification procedures for the agents used in the production of the vaccine. Any modification or manipulation made in the agent to improve the immune response should be included, when appropriate.
- Include summary information and supporting documents relating to the uniformity of the production process.

In the case of biotechnological products, the information requested varies according to each country and has not been harmonized. The information most frequently requested is listed below:

- For products obtained through recombination (recombinant or vector vaccines), full data must be included: gene, origin, isolation strategy, and sequence; in the case of plasmids: molecular characterization must be included (if sequences have been included or taken from the *GenBank* the corresponding identification must be included). Information on vector construction is essential and must include origin, and function of promotor, replicator, amplifier and regulator, and data on insertion, deletion or cloning.
- In case cloning is used, include the host cell or microorganism without the vector, origin, characteristics (phenotypic and genotypic), and culture mediums. Information must be provided on the gene and nucleotide sequence analysis of the cloned gene, adjacent regions and expression vector structure. Information must be provided on host-vector characterization, expression control and promotion.

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- In all cases, insertion, deletion or cloning must be demonstrated using a validated methodology, and genetic stability must be shown using the highest passage used in production.
- In the case of vaccines produced using microorganisms submitted to genetic manipulation, full data must be provided for the gene, origin and sequence; in the case of plasmids, full molecular characterization must be included (if the sequences have been included or taken from the *GenBank,* the corresponding identification must be included). The insertion or deletion must be supported by strain genetic stability studies.

14. – FINISHED PRODUCT CONTROL METHOD

14.1 Sterility and purity control

14.1.1 Biological tests

a) Identity: full information must be provided for the identity test to identify the agent contained in the product.
b) Other trials in animals.

14.1.2 Microbiological tests

a) Bacterial and fungal sterility. These must be suitable microbiological tests to demonstrate product sterility, just when it's needed. Molecular tests will not be accepted unless they have been accepted internationally and validated for quality control.
b) Mycoplasma (except in inactivated vaccines when it has been demonstrated that the inactivating agent inactivates Mycoplasma). This must be done using reference microbiological tests, just when it's needed. Molecular tests will not be accepted unless they have been accepted internationally and validated for quality control.
c) *Salmonella*, using the recommended microbiological tests, just when it's needed in biological products non sterilized (live vaccines). Molecular tests will not be accepted unless they have been accepted internationally and validated for quality control.
d) Absence of extraneous agents, carried out according to international recommendations and in suitable substrates, just when it's needed.

14.1.3 Physical and chemical tests

- Appearance / Aspect
- Residual humidity (for lyophilized products)
- Existence of vacuum (for lyophilized products)
- Stability in the emulsion (for inactivated emulsions)

14.2 Innocuousness control

14.2.1 Test type and species

14.3 Inactivation control: only applicable to inactivated products

14.4 Batch immunological efficacy and potency control

14.4.1 Type of Method and species (vg. Titrations, serologic tests, *in vitro* test like antigenic mass)

14.5 Adjuvant, stabilizer and diluent control.

14.5.1 Chemical methods

- Identity, valuation and pH

14.5.2 Physical and chemical methods

- Appearance and volume

14.5.3 Biological methods

Other elements to be included

- Finished product specifications must be included in this section.
- Finished product specifications must be compatible with finished product quality control certificates for the parameters evaluated.
- Describe the control methods used to demonstrate product quality.
    - In the case of standardized methods (contained in recognized Pharmacopeia, CFR), it will suffice to cite the method appropriately.
    - In the case of in-house rules, a copy of these must be provided in an annex.

15.- FORM OF PRESENTATION AND CONTENT

- Describe all the commercial presentations in which the product will be released on the market. This description must include the following minimum information:
    - Number of doses per container
    - Number of containers per package. If the product is separated into two of more fractions (ex: lyophilizate and diluent), the number of containers of each fraction must be indicated.

16.- SPECIFICATION AND CONTROL OF CONTAINERS

16.1 Container characteristics

16.2 Tamper-proof system

16.3 Container quality control

- Specifications must be provided for the container, including the material that is in contact with the product.
- Describe the tamper-proof system used for the product, i.e. features visible to the consumer that indicate if the container has been opened prior to purchase.
- Describe packaging quality control
    - When standardized methods are used (recognized Pharmacopeia, CFR) it will suffice to cite the method appropriately.
    - In the case of internal standards, a copy of these must be attached.

17.- STABILITY STUDIES

Attach stability studies for the product that justify the indicated validity period.

- Stability studies for three product batches must be attached to justify the proposed validity of the product.

If the product will be marketed in more than one presentation, studies must be carried out for all the commercial presentations, unless the same material is in contact with the product in each presentation and the container has similar geometrical form. In this case, the stability study submitted may be carried out on the smallest container size, as this poses the greatest challenge for the product.

18.- VALIDITY PERIOD (Expiry date)

- Mention the validity period justified by the stability studies included in the previous section.

19. – EFFICACY AND SAFETY TESTS

Bibliographic references and clinical tests, where applicable.

- Tests must meet CAMEVET rules.
- Where there are no applicable CAMEVET rules, work carried out by the company (applicant) will be accepted when it is compliant with suitable international standards relating to Good Clinical Practices and Animal Welfare.
- Complete papers will be submitted in an annex, and must include: abstract, introduction, materials and methods, results, discussion and conclusion, and references where applicable.
- Preferably, studies must be submitted in the language of the country where the product is intended to be registered. Studies will be accepted in Spanish, Portuguese or English when the respective summary and conclusions have been duly translated into the local language.

The regulatory authority may request a full translation into the local language when deemed necessary.

20. - INDICATIONS FOR USE AND MARKETING CATEGORY

20.1. Principal and/or supplementary indications.

20.2. Target animal species.

- Describe the indications for use of the product that relate to the prevention and/or treatment of animal diseases.
- Indicate the animal species to be treated using the product.
- Indicate the categories of the animal species for which the product is indicated. These may be:
  - Age categories (“not older than 2 weeks”, or “1 day old”)
  - Production categories (broiler chickens, dairy cows)
  - Physiological categories (pregnant dogs)

21. - ADMINISTRATION ROUTE AND FORM OF ADMINISTRATION or USE OF THE PRODUCT

Parenteral, oral, dermal, pulverization, scarification, ocular, nasal or other routes.

- Indicate the route of administration or application of the product (oral, SC, IM, EV, etc.)

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- Where necessary, for products administered orally, indicate if the product must be mixed with food or diluted in drinking water.

22. – PRODUCTS FOR EXTEMPORANEOUS PREPARATION

22.1 Preparation of the product for proper use

22.2 Indicate the validity period of the reconstituted product as supported by stability studies.

- If the product is not in ready-to-use form, the procedures required for its suitable preparation prior to use must be indicated. This must be reflected in the product label.
- Submission of the stability study carried out on the reconstituted product is mandatory, unless an indication is provided that the product must be used immediately after reconstitution.

23. - DOSING

23.1 Indicate product dose(s) for preventive or curative application per live weight for each species and age.

- The dose must be indicated in terms of doses or volume of the biological product. Include the product dose per species and category for which the product is indicated.
- If the product must be administered in drinking water, via eye or nasal drop, include the following indication: “each animal must receive one dose of the product”.

23.2 Recommended administration program.

- If a vaccination plan applies, this must be indicated in this point. The vaccination plan or program must be supported by the corresponding studies carried out with the product.
- The frequency of interval must be indicated in days or weeks as applicable, in line with the manufacturer´s recommendation based on the corresponding efficacy studies.
- Minimum age for administration must be indicated.
- Indicate the suitable time for product administration; for example: last trimester of pregnancy, six weeks prior to peak laying period, etc.

23.3 Time needed to confer immunity, and duration of immunity.

- Indicate the term needed for the development of effective protection in the vaccinated animal based on the corresponding studies.
- Indicate the period of protection against the indicated disease conferred by the product following vaccination, according to the instructions provided in the vaccination plan. Duration of immunity must be supported by the corresponding studies.
- Any necessary revaccinations must be indicated in line with the duration of immunity or, alternately, based on the epidemiological status of the region and the criterion of the acting Veterinary professional.

24. - POSSIBLE SIDE EFFECTS (Local and/or general), PHARMACOLOGICAL INCOMPATIBILITIES AND ANTAGONISMS

24.1. Contraindications and limitations for use (cases in which product administration may lead to harmful effects).

24.2. Precautions to be taken before, during or after administration.

- List any contraindications: cases in which use of the product should be avoided (for example: hypersensitivity)
- Indicate side effects or adverse effects detected in safety studies or in pharmacovigilance reports for the product (if any). It is recommended to inform the degree of severity and estimated frequency of these effects, where applicable. Include any data on limitations or contraindications in this section. For example: “do not administrate in breeding animals”, “do not administrate in pregnant females”, “do not no use in birds during the laying period”, or others as may apply. The corresponding supporting technical data or bibliography must be provided.
- Indicate whether the product is compatible or not with other products. If no specific studies are available, include the indication: “do not use with other pharmacological, biological or medicated food products”.
- If compatible products exist (i.e. products that can be administered simultaneously), provide supporting studies.
- Indicate any known pharmacological antagonisms. Describe any known interaction or antagonism specifically in this section.
- Indicate any known antidotes or specific treatment, emergency procedure or symptomatic treatment where applicable.
- Inform on the risks of using the product in specific physiological stages (for example, use in pregnant and lactating females)
- Indicate the precautions to be taken to ensure suitable administration of the product (calibration of administration equipment, asepsis, etc).

25. – GENERAL PRECAUTIONS

Maximum and minimum temperature limits for proper storage.

Describe suitable storage and transport conditions, and provide instructions for product destruction and disposal of any packaging that may constitute a risk to Public Health, animals and/or the environment.

- Indicate the temperature interval at which the product must be stored.
- Indicate the general storage precautions. The legend: “Keep in original container in a dry place away from sunlight” is usually sufficient.
- Include the legend: “Keep out of reach of children”.
- Indicate any special storage precautions that may be required.
- Where necessary, describe transport rules that must be observed in the country where the product intends to be registered.
- Describe the suitable method for eliminating empty packaging and any unused product. For example, it may be necessary to disinfect prior to eliminating any unused product/packaging, in which case the disinfection procedure must be described in detail.
- Any method described for destruction of waste must be in full accord with local regulations.
- Risk to Public Health and to the environment: in the case of products that contain agents with zoonotic potential, all relevant information relating to public health and the environment must be included to minimize the risk of contamination.

26. – LABELS AND LEAFLETS – DRAFT PRINTED LABEL

- Include draft printed matter, which must be in line with CAMEVET Rule ROT001 governing veterinary product labels.

27. - SCIENTIFIC PUBLICATIONS AND/OR PAPERS

Scientific publications and/or papers relating to the product must be attached.

- Depending on the language of the original work, a translation of the summary and conclusions of these papers into the corresponding official language must be provided. Mention bibliography that supports the registration of the product, including any bibliography read and/or taken into consideration for the preparation of the product, and experimental and scientific tests related to the active ingredient(s).
- Bibliography must be presented in the following format: Name of author, (year of publication); Name of publication; issue and volume in which it is published; page number.
- Each bibliographical reference must be properly identified as a separate entry.
- Full works must be attached to the application as an annex.

28. - REMARKS

29. - AUTHORIZED SIGNATURES

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Version:

Effective Date:

TITLE: Preparation of CAMEVET Pharmacological Products Registration Form

Objective: Establish detailed guidelines and instructions for the Preparation of CAMEVET FORM001 for the registration of veterinary pharmacological products. This document is a guideline. There could be omission of specific requirements for a specific country. On the same line, ther could be excessive details for some other countries

This document does not establish new requirements and does not modify the inscription forms.

CONTENTS:

1. SCOPE

This procedure applies to the Preparation of the CAMEVET Form for Veterinary Pharmacological Products in general.

2. SCOPE OF ENFORCEMENT

CAMEVET Member Countries

3. DEFINITIONS/ ACRONYMS

The definitions contained in the following CAMEVET approved documents will be used as a reference: Document Codes GLO001 Proceeding VI of October 2011 and subsequent updates, ROT002 Proceeding I of October 2010 and subsequent updates.

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REFERENCES/ BIBLIOGRAPHY

Code	Name
AI 001	Efficacy Tests for the Registration of Internal Antiparasitics for Ruminants and Swine
BPM 001	Good Manufacturing Practices (GMP) Standard
BPM 002	GMP Inspection Guide for the manufacture of Pharmacological products
BPM 004	GMP Inspection Guide for the manufacture of Pharmacological products (including ectoparasiticides)
BPU 001	Good Usage Practices for Veterinary Products
CERT 001	CAMEVET Specimen Free Sale Certificate
CERT 002	Export Authorization Certificate
ECT 001	Manufacture of Ectoparasiticides
EST 001	Guide for the Preparation of Stability Studies for Veterinary Pharmaceuticals
GLO 001	Glossary
NOM	Technical Data Nomenclator
RES 1	Technical guide for carrying out veterinary pharmacological agent residue metabolism and kinetic studies in animals for food production
RES 2	Guide for calculating withdrawal period in edible tissue
RES 3	Guide for validation of analytical methods for determining residues in animal origin biological matrixes
ROT 001	Veterinary products Labeling standard
ROT 002	Synonymia

6. INSTRUCTIONS

The different fields contained in CAMEVET Form 001 and instructions for completing them are listed below:

1.- Product Trade Name:

- Indicate the trade name of the product proposed for registration by the competent agency.
- The trade name must include alphabetical characters and may include alphanumerical characters, only numerical characters, or a combination of these.

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- In the case of imported products, the name as it will be registered in the country of destination and as it is described in the Free Sale Certificate, Export Certificate or equivalent document issued by the competent authorities of the country of origin must be included.
- The label cannot contain the generic name alone (drug + dose); it must be accompanied by the brand.

2. – CLASSIFICATION - GENERIC NAME (for official use exclusively)

- Do not fill in this section. To be completed by the control body.

3.- APPLICANT ESTABLISHMENT: OWNER / LEGAL REPRESENTATIVE

3.1- Name: .....

- Indicate the name of the applicant establishment duly registered with the regulatory authorities.

3.2- Address (Street – City – Country): .....

- Indicate the address declared in the registry before the competent agency.

3.3- Official Authorization Number: .....

- Complete data relating to the official registry authorization number of the entity that owns the product (this is not the company registration number).

3.4- Technical Director: .....

- Indicate first and last name of the Technical Director declared in the corresponding registry.

3.4.1- Profession: .....

  - Indicate the profession of the Technical Director declared in the corresponding registry.

3.4.2- Professional ID Nº (Professional Registration or License).

  - Indicate the registry or license number corresponding to the profession of the Technical Director

4.- MANUFACTURING ESTABLISHMENT (for products manufactured in the country)

4.1- Name: .....

4.2- Address (Street – City – Country): .....

4.3- Official Authorization Number: .....

4.4- Technical Director: .....

4.4.1- Profession: .....

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4.4.2- Professional ID Nº (Registration or License): .....

- This section must be completed in a similar manner to section 3, but with the data relating to the manufacturing establishment (instead of the applicant establishment).
- Do not mistake for registration number of the outsourcer / toll manufacturer.
- Third party manufacturers or toll manufacturers that are duly registered must be included here.

5.- FRACTIONATING ESTABLISHMENT (for products manufactured in the country)

5.1- Name: .....

5.2 - Address (Street – City – Country): .....

5.3 - Official Authorization Number:.....

5.4- Technical Director: .....

5.4.1- Profession: .....

5.4.2- Professional ID Nº (Registration or License): .....

- Where applicable, items 5.1 to 5.4 must be filled in as done in section 3, but with the data of the fractionating establishment instead of those of the manufacturing establishment.
- This section must reflect the data referred to in the Free Sale Certificate.

6.- MANUFACTURING ESTABLISHMENT AT PLACE OF ORIGIN (for imported products)

6.1 - Name: .....

6.2 - Address (Street – City – Country): .....

6.3 - Official Authorization Number: .....

6.4 – Technical Director: .....

6.4.1 - Profession: .....

6.4.2 – License/Registration Nº: .....

- Where applicable (fractionated products), items 6.1 to 6.4 must be completed in similar manner to section 3, indicating the data of the manufacturer at the place of origin (instead of the data of the applicant).
- Data provided here must coincide fully with the data contained in the legal documents attached to the registration application (see Section 7).

7.- LEGAL DOCUMENTS

These requirements could be different in different countries. However this guideline is applicable in most of the countries,

7.1.- Manufacturing contract/s

- In the case of local or foreign products not manufactured by the applicant, the contract executed between the applicant and the product manufacturer must be submitted.

7.2.- Representation Agreement with the Manufacturer in the place of origin.

- In the case of imported products, evidence must be furnished of the assignment of marketing rights granted by the owner of the product in the country of origin.

7.3.- Manufacturing Establishment Authorization Certificate.

- In the case of imported products, the authorization certificate of the facility where the product is manufactured issued by the competent national authorities of the country of origin must be furnished.

7.4.- For imported products the following must be submitted: Registration and Free Sale Certificate (CAMEVET specimen) or equivalent documentation, issued by the competent authorities of the country of origin, or Manufacturing Authorization (Export Certificate) and reasons for not marketing the product in the country of origin.

NOTE: Originals or a true copy certified by notary public must be submitted of all the legal documentation listed above. Documentation issued by countries other than the country where the application will be submitted must bear the following:

- Apostille or consular certificate
- Translation to the local language by a certified translator (where necessary).

8. – PHARMACEUTICAL FORM

- Indicate the pharmaceutical form of the finished product. Common examples include (the following is not an exhaustive list):
    - Solids
        - Powder
        - Pill
        - Capsule
        - Block
    - Liquids
        - Solutions
        - Emulsions
        - Suspensions
    - Semi – solids
        - Paste
        - Cream
        - Ointment
        - Gel
- Standard terminology established in international pharmacopeia or references must be used. For example:
    - Solids: powders, capsules, tablets, globules, and others.
    - Liquids: oral solutions, parenteral solutions, ophthalmic solutions, emulsions, suspensions.
    - Semisolids: gels, creams, ointments and pastes.
    - Gases: volatile anesthetics.
- If the product is not presented in its final pharmaceutical form, for example: “powder for reconstitution”, the final pharmaceutical form must be included.
- Indication must be provided here of whether or not the product is sterile.

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9. – COMPLETE QUALITATIVE AND QUANTITATIVE FORMULA

The common designations recommended by recognized International Agencies must be used when they are available; otherwise, regular common designations or chemical denominations must be presented.

Components must be indicated in percentages: w/w, v/v, v/w, w/v and/or in I.U. or U, with the corresponding weight or volume.

- The qualitative and quantitative formula must include all the active ingredients and excipients in the product per the International Common Denomination (ICD) or internationally recognized pharmacopeias or references. If the active ingredient is not included in a pharmacopeia, the regular common denomination or chemical designation of the substance, or CAS (*Chemical Abstract Service)* name and number, must be used. Components must be indicated in percentage form.
- For liquids, weight in volume is the preferred formula, indicating the concentration of each component in the formula per 100 ml of product.
- For solids, the preferred formula is generally weight in weight, indicating the concentration of each component in the formula per 100 g of product. In the case of pills or tablets, reference may be made to dosing unit, i.e. the weight of each component per pill or tablet.
- When the active ingredient is expressed as a salt or hydrate, the equivalent value in base or anhydrous form must be included. In these cases, the content of active ingredient may be expressed in two forms:

Ampicillin (as sodium salt)……500.00 mg

or

Ampicillin, Sodium salt (equivalent to 500 mg base ampicillin)……531.45 mg

- In the case of imported products, the formula must be identical to the formula indicated in the free sale certificate issued by the authorities of the country of origin.
    - In the case of powdered products that require a diluent for reconstitution, the qualitative and quantitative formula of the diluent must be included.
    - The indication “vehicle q.s.” will not be accepted as part of the excipients. The vehicle must be described in detail. In the case of capsules, their composition must be included.
    - The main function of the active ingredient(s) and excipient(s) in the formula must be included. The qualitative and quantitative formula in the registration application must be presented in following format (some functions have been included by way of example).

	Name	**Quantity**	**% in formula**	**Function**
Active ingredients	Active ingredient 1			Antibacterial
	Active ingredient 2			Antifungal
	Active ingredient 3			Anti-inflammatory

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Excipients	Excipient 1			Stabilizer
	Excipient 2			Moisturizing agent
	Excipient 3			Preservative
	Excipient 4			Vehicle

10. – SPECIFICATIONS AND CONTROL METHODS FOR THE INGREDIENTS IN THE FORMULATION

- Identify each raw material unambiguously. Preferably, indicate the corresponding CAS number.
- Describe specifications for each raw material.
- Describe the analytical methods to be used in the qualitative and quantitative assessment of active ingredients used to manufacture the product.
- The reference used as a basis for specifications and control methods must be provided (Pharmacopeia / internal Standard). If an internal standard is used, a copy of the relevant standard operating procedure must be provided.
- Information may be collected from procedures and specifications currently in force (Controlled Copy) in the Laboratory Quality Control area.

11. – PRODUCT MANUFACTURING METHODOLOGY

11.1. Provide a summary description of the product´s manufacturing process.

- Provide a brief description of the product´s manufacturing process. It is recommended to provide a production flow diagram
- Describe in-process controls and methodology.
- Volumes used in the production process, pilot batch size, and maximum size of production cycle batch must be indicated.

12. – FINISHED PRODUCT SPECIFICATIONS AND CONTROL METHODS

Indicate and describe the specifications and methods that must be used in the qualitative and quantitative assessment of the components in the finished product formulation.

12.1.- Biological Methods.

- Bacterial endotoxins or pyrogens: for sterile solutions, the first test must be "*in vivo*" and the second "*in vitro*". This is mandatory for intravenous products, encouraged for other injectable products, and those required in reference pharmacopeias.

12.2.- Microbiological methods.

- Sterility: this must be conducted for sterile products and must use reference strains for test validation.

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- Microbial limit: this must be carried out for non-sterile products, and must investigate the presence of meso-aerobic microorganisms, pathogens, fungi and yeasts. For oral, intra-mammary, intra-ruminal bolus and other products requested in the reference pharmacopeia.

- Potency (for antibiotics) Potency assay of some antibiotics is done usin microbiologic methods. These methods have to be included in this item.

12.3.- Chemical methods.

- Titrations used for identity determination or assay.

12.4.- Physical methods.

Appearance (all products)

Weight (solid or semisolid products)

Volume (liquid-aerosol products)

Density

Viscosity (suspensions, emulsions and semisolids)

Any other method required by reference pharmacopeia to guarantee product quality.

12.5.- Physical and chemical methods

- Active pharmaceutical ingredient identity: use a validated method to identify the active drug substance(s). (Applicable to all kind of products)
- Assay of active pharmaceutical ingredient(s). (Applicable to all kind of products)
- Any other method required by reference pharmacopeia to guarantee product quality, like pH, dissolution; loss on drying, volatile substances, heavy metals, degradation substances.

In this item it has to be included

- **Describe finished product specifications.**
- Describe control methods used to show product quality:
    - In the case of standardized methods (recognized Pharmacopeia, CFR), it will suffice to cite the method properly.
    - In the case of internal standards, a copy of these must be attached.

13.- PRESENTATION AND CONTENTS

- Describe all the commercial presentations in which the product will be launched on the market. This description must include as a minimum:
    - Number of doses per container.
    - Number of containers per package.

14.- PACKAGING SPECIFICATION AND CONTROL

14.1 Packaging description

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- Specifications must be provided for primary and secondary packaging, including the material that is in contact with the product.

14.2 Tamper-free system

- Describe the tamper-free system used for the product, i.e. features visible to the consumer that indicate if the container has been opened prior to purchase.

14.3 Packaging quality control

- Description of packaging quality control must be provided:
    - When standardized methods are used them (recognized Pharmacopeia, CFR) it will suffice to cite the method properly.
    - In the case of internal standards, a copy of these must be attached.

15.- STABILITY STUDIES

Attach stability studies and galenic formulation for the product, like photostability, resistance to low temperatures and frozen and other ones done during the development of the product, that justify the indicated validity period.

- Stability studies that are fully in line with the CAMEVET Stability Guide (EST 001) corresponding to three product batches must be attached to justify the proposed validity of the product.
- When the product dossier is submitted, it will suffice to attach one accelerated stability study and the initial determinations for the natural stability study, with a commitment to submit the full results once the study has concluded. It is not necessary to present the complete study at the start of the dossier, since as the dossier is evaluated the time elapses and more data is obtained. At the time of registration, the validity granted would be that corresponding to the available results. Then, if the study continues, the extension may be requested.

16.- VALIDITY PERIOD (Expiry date)

- Mention the validity period justified by the stability studies included in the previous section.

17.- EFFICACY TESTS

Bibliographic references and clinical efficacy tests, where applicable.

- Submit a list of tests carried out by the applicant that demonstrate the efficacy of the product to be registered.
- Tests must meet CAMEVET rules.
- Where there are no applicable CAMEVET rules, work carried out by the company (applicant) will be accepted when it is compliant with suitable international standards relating to Good Clinical Practices and Animal Welfare.
- Include antimicrobial susceptibility studies carried out "*in vitro*" or "*in vivo*" or, in the case of bioequivalent products, include the supporting study.
- Complete studies must be attached.
- Preferably, studies must be submitted in the language of the country where the products is intended to be registered. Studies will be accepted in Spanish, Portuguese or English when the respective summary and conclusions are duly translated into the local language.

- When deemed necessary, the regulatory authority may request a full translation into the local language.

18. - INDICATIONS FOR USE AND MARKETING CATEGORY

18.1.- Principal and/or supplementary indications.

- Describe indications for use of the product that relate to the prevention and/or treatment of animal diseases. Name the pathological entities for which the product can bring relief or cure.

18.2.- For antimicrobial and antiparasitic products, specify susceptible etiologic agents.

- In the case of antimicrobials and antiparasitics, specify the etiologic agents for which the product has proven efficacy and for which it will be indicated.

18.3.- Target animal species and categories, specific use in facilities, equipment, or other uses.

- Indicate the animal species that will be treated with the product.
- Indicate the categories of the species for which the product is indicated. These may be:
  - Age categories (not older than two weeks, 1 day of age)
  - Production categories (broiler chickens, dairy cows)
  - Physiological categories (pregnant dogs)

18.4.- Category (conditions for sale): over the counter (OTC), prescription, etc.

- Indicate the conditions under which the product must be sold. This classification must be in full agreement with the prevailing law of the destination country.

19. – ADMINISTRATION ROUTE AND FORM OF ADMINISTRATION or USE OF THE PRODUCT

Parenteral, oral, on facilities, equipment, instruments, other.

- Indicate the route of administration or application of the product (oral, SC, IM, IV, etc.)
- Where necessary, for products administered orally, indicate if the product must be mixed with food or diluted in drinking water.

20. – PRODUCTS FOR EXTEMPORANEOUS PREPARATION

20.1 Preparation of the product for proper use (Premixes, solutions, pre-emulsions, suspensions, or other).

- If the product is not in ready-to-use form, the procedures required for its suitable preparation prior to use must be indicated. This must be reflected in the product label.

20.2 Indicate the validity period of the reconstituted product as supported by stability studies.

20.3 When a product is intended for administration in food rations or in drinking water, its stability, compatibility and/or time of effective storage in mixed form or as a solution must be indicated.

- Submission of the stability study for the reconstituted product is mandatory, unless an indication is provided that the product must be used immediately after reconstitution.

21. - DOSING

Indicate the quantity or quantities of the active ingredient(s) expressed in units of weight, volume and/or IU per Kg. live weight per the indication for use for the different species and ages.

21.1.- Indicate product dose(s) according to the indication for use per live weight for each species and age.

- Indicate active ingredient dosing scheme in terms of mg/kg live weight.
- Indicate product doses in mg (powder), units (pills or tablets), or volume (liquids) as applicable according to the pharmaceutical form. Preferably, units should always be expressed in terms of the live weight of the animals to be treated: mg/kg, mL/kg, pills/tablets/kg.
- In some cases, the product dose will be fixed for a given animal or a given category or weight range; for example: 2 ml for foals; 4 mL for mares; 6 mL for stallions.
- If the product must be administered in drinking water or in feed, the dose must be indicated in terms of this.
- The product dose for each species and category for which the product is indicated must be included.
- The dose must be supported by bibliography or dose determination studies.
- Preventive or therapeutic doses must be supported by the corresponding studies. If studies have not been conducted, reasons must be provided for dose selection, with bibliographic references to support these recommended doses.

21.2.- Interval between doses.

- Indicate the time interval between product administrations. This must be supported by the corresponding bibliography and data on product bioavailability.

21.3.- Duration of treatment.

- Indicate the number of days the product must be administrated and the corresponding technical justification.

22.- SAFETY STUDIES

22.1. – PRODUCT PHARMACOKINETICS - BIOAVAILABILITY

Active ingredient(s) and/or metabolite(s) absorption, distribution and elimination routes.

- Include a summary of the pharmacokinetic profile and parameters considering the active ingredient and its metabolites, with the following information: absorption, distribution, metabolism and excretion. Bibliographical references will be accepted for widely known products; for new products and formulations, product bioavailability must be provided.

- The information provides has to include the basic pharmacokinetic parameters (Cmax , Tmax AUC).

22.2. – PRODUCT PHARMACODYNAMICS (SUMMARY)

- Describe the mechanism of action of the product. A description must be provided of the mode of action of the pharmacological product according to the dose, route and form of administration.

In the case of products with more than one active ingredient, each of these must contribute to the final effect of the product. For example: a product can be an association in which each active ingredient acts independently, or it may be synergic, so that a joint synergic effect is produced. Bibliography is accepted.

22.3. – POSSIBLE SIDE EFFECTS (Local and/or general), PHARMACOLOGICAL INCOMPATIBILITIES AND ANTAGONISMS

22.3.1.- Contraindications and limitations for use (cases in which product administration may lead to harmful effects).

-If there is data available on limitations or contraindications, it must be included in this section. For example: “do not administrate in breeding animals”, “do not administrate to pregnant females”, “do not use in chicken during the laying period”, or other indications that may apply. This information must have supporting technical or bibliographical material. If data on interactions or antagonisms with other drugs is available, these effects must be specifically described in this section. If no specific studies are available, the following caption must be included: “do not use simultaneously with other pharmacological or biological products or medicated feed”.
-Instructions must be provided to ensure effective use of the product in the target species, including any precaution to be taken by those handling the product.

- List any contraindications: cases in which use of the product should be avoided (for example: hypersensitivity).
- Indicate side effects or adverse effects detected in safety studies or in pharmacovigilance reports for the product (if any). It is recommended to inform the degree of severity and estimated frequency of these effects, where applicable.
- Indicate whether the product is compatible or not with other products.
- If compatible products exist (i.e. products that can be administered simultaneously), provide supporting studies.
- Indicate any known pharmacological antagonisms.
- Inform on the risks of using the product in specific physiological stages (for example, use in pregnant and lactating females).

22.3.2.- Precautions to be taken before, during or after administration.

- Indicate the precautions to be taken to ensure suitable administration of the product (calibration of administration equipment, asepsis, etc.).
- List any measures that must be taken before, during and after administration (Ex: shake before use).
- Describe how to use the product efficiently and safely for the target animals and precautions for the handlers, if any.

Additionally, if there is information available, data must be provided regarding use in animals at different stages of growth, physiology, reproduction, pregnancy, lactation, and in animals of different breeds, genetic lines, or any other.

22.4. – INTOXICATION AND OVERDOSE IN ANIMALS

22.4.1 Safety and innocuousness margin in target species

- Indicate the safety margin of the product, taking into account the safety of its active ingredients.
- This result must be obtained from toxicity studies carried out on the active ingredients. This section may be justified with pertinent bibliography.
- In the case of ectoparasiticides, it is recommended to provide a calculation of the LD50 for the formulation using the WHO procedure.
- Include the results of safety studies with one dose (overdosing) and repeated doses. These studies have to be done with the product in target species, using the indications intended for the product.

22.4.2 Symptoms, behavior in an emergency, and antidotes.

- Describe symptoms to look out for in the case of intoxication with the product.
- Indicate the availability of any antidotes or specific treatments, emergency procedures, or symptomatic treatment, where applicable.

22.5. – INTOXICATION IN HUMANS

22.5.1 Toxicological category

- Where applicable (ectoparasiticides), indicate the toxicology category established by the WHO for the active ingredient and the formulated product.

Criteria for generic classification per active ingredient for ectoparasiticides

Ectoparasiticides	**Example molecule**	**Generic classification**
Organophosphates	Chlorfenvinphos	Very dangerous (Ib)
Carbamates	Propoxur	Moderately dangerous (II)
Pyrethrins and pyrethroids	Cypermethrin	Moderately dangerous (II)
Formamidines	Amitraz	Moderately dangerous (II)
Macrocyclic lactones	Spinosyn (Spinosad)	Scarcely dangerous (III)
Chloronicotinyl-nitroguanidine by-products	Imidacloprid	Moderately dangerous (II)
Chitin inhibitors	Benzoyl-phenyl urea	Scarcely dangerous (III)
Phenylpyrazole by-products	Fipronil	Moderately dangerous (II)

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Juvenile hormone analogs	Methoprene	Unlikely to present acute toxicity (U)
Semicarbazones	Metaflumizone	Unlikely to present acute toxicity (U)

Criteria for classification of pesticides based on their formulation:

The final classification of any product should be established according to its formulation, i.e. classification based on toxicity data obtained from tests carried out and provided by the manufacturer. However, often this information is not available, or studies have not been carried out. In this case, when such results are not available, and where the Competent National Authority deems it appropriate, the classification may be based on proportional calculations using LD_{50} values for the technical ingredient(s) as a reference, according to the following formula:

$$\frac{\text{LD50 active ingredient x 100}}{\text{\% active ingredient in the formula}}$$

If the formula has more than one active ingredient (including solvents, moisturizing agents or others) that may increase the toxic properties of the product, the classification must be according to the toxicity of the agents in the mixture. LD50 obtained have to be compared with the doses included in WHO documents, in order to establish the toxicological category of the product.

22.5.2 Information must be provided on treatment, antidote, and reference toxicology centers in the country.

- Describe symptoms in case of intoxication with the product.
- Mention toxicology centers in the country that may be resorted to by users, and contact details.

22.6. – UNWANTED BIOLOGICAL EFFECTS

Indicate whether the active ingredient(s) produce any of the adverse effects listed below when the product is used according to indications, and provide any useful scientific bibliography where applicable.

Only include information in this section if the active ingredient causes unwanted biological effects when the product is used as indicated. Provide a summary of observed reactions to administration of the pharmacological product. The legend: “no reaction observed” may be included only when studies have been carried out to prove this. When no studies have been carried out to support this, the legend: “no known reaction” may be included if there is published scientific evidence to support this. The legend: “no information available” must be used when there is no available scientific information and no studies have been carried out.

22.6.1.- Carcinogenesis

22.6.2.- Teratogenesis:

22.6.3.- Mutagenesis:

22.6.4.- Resistance to pathogens:

22.6.5.- Blood dyscrasia:

22.6.6.- Neurotoxicity:

22.6.7.- Hypersensibility:

22.6.8.- Reproductive toxicity:

22.6.9.- Toxicity on normal intestinal flora:

- Indicate whether the active ingredient(s) produce any of the effects referred to in section 22.6.
- For new active ingredients for which there is little or insufficient available information, toxicology studies must be furnished to support the statements made.
- It is generally recognized that all active ingredients can cause hypersensitivity reactions.
- It is generally established that all antimicrobials and antiparasitics can cause the development of resistant strains.
- It is generally recognized that all antimicrobials can cause modifications in normal intestinal flora.

22.7. - CONTROLS ON DRUG RESIDUES

ONLY FOR PHARMACOLOGICAL PRODUCTS DESTINED FOR USE IN ANIMALS WHOSE PRODUCTS AND BYPRODUCTS ARE DESTINED FOR HUMAN CONSUMPTION AND WHICH CONTAIN ACTIVE INGREDIENTS FOR WHICH AN MRL HAS BEEN ESTABLISHED PER THE CODEX. PHARMACOLOGICAL PRODUCTS FOR OTHER ANIMAL SPECIES ARE EXEMPTED FROM THE REQUIREMENT TO PROVIDE THIS INFORMATION.

22.7.1.- Data regarding Acceptable Daily Intake (ADI)

- Inform the ADI value for the active ingredient(s) according to the International Codex Alimentarius, national regulations, or values published by reference international agencies, such as EMA or FDA.

22.7.2.- Maximum Residue Limit (MRL) in tissue (muscle, liver, kidney, fat), milk, eggs and honey.

- Inform MRL values for the active ingredient(s) according to the international Codex Alimentarius, national regulations, or values published by reference international agencies, such as EMA or FDA.

22.7.3.- Time between the last treatment and animal slaughter for human consumption.

- Propose the restriction period, withdrawal period or safety period that must be observed to ensure that meat obtained from treated animals is safe for consumers, without exceeding the MRL established for the active ingredient.
- The proposed withdrawal period for residues must be justified by residue studies carried out in full accord with CAMEVET guides RES001 and RES003.
- The proposed withdrawal period for residues must be calculated in full accord with CAMEVET guide RES002

22.7.4.- Time from the last treatment administration to the destination of milk, eggs or honey for human consumption (with or without prior processing).

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- Propose the restricted use period, withdrawal or safety period that must be observed to ensure that the products obtained from treated animals are safe for consumers, without exceeding the MRL established for the active ingredient.
- The proposed safety period for residues must be supported by residue studies carried out in full accord with CAMEVET guides RES001 and RES003, or with guides issued by other reference international agencies.
- The proposed safety period for residues must be calculated in full accord with CAMEVET guide RES002.

23. – GENERAL PRECAUTIONS

Minimum and maximum temperature limits for proper storage.

Provide instructions for suitable storage, transport and destruction of the product, and method for eliminating packaging that may constitute a risk to the Public Health, animal health and the environment.

- Indicate the temperature interval at which the product must be stored.
- Indicate the general storage precautions. The legend: “Keep in original container in a dry place away from sunlight” is usually sufficient.
- Include the legend: “Keep out of reach of children”.
- Indicate any special storage precautions that may be required.
- Where necessary, describe transport rules that must be observed in the country where the product intends to be registered.
- Describe the suitable method for eliminating empty packaging and any unused product. For example, it may be necessary to conduct disinfection prior to eliminating any unused product/packaging, in which case the disinfection procedure must be described in detail.
- Any method described for destruction of waste must be in full accord with local regulations.

24. – CAUSES THAT MAY HAVE AN IMPACT ON PRODUCT QUALITY

Exposure to rainfall, cold, heat, light, humidity, dissociation, reduction or loss of activity of the active ingredient(s), compression during stowage or in warehouses.

- Mention any damage that could be caused to the product by exposure to light, heat and/or humidity.
- This item relates to any stability tests carried out and mentioned previously.
- The information provided here must be in line with any related information presented previously.

25. – LABELS AND LEAFLETS – DRAFT PRINTED LABEL

- Include draft printed matter, which must be in line with CAMEVET Rule ROT001 governing veterinary product labels.

26. – SCIENTIFIC PUBLICATIONS AND/OR PAPERS

Scientific publications and/or papers relating to the product must be attached.

A translation of the summary and conclusions of these papers into the corresponding official language must be provided.

- Mention bibliography that supports the registration of the product, including any bibliography read and/or taken into consideration for the preparation of the product, and experimental and scientific tests related to the active ingredient(s).
- Bibliography must be presented in the following format: Name of author, (year of publication); Name of publication; issue and volume in which it is published; page number.
- Each bibliographical reference must be properly identified as a separate entry.
- Summaries must be in the Spanish language.
- Full works must be attached to the application.

27. - REMARKS

28. – AUTHORIZED SIGNATURES

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