CONCLUSIONS AND RECOMMENDATIONS

XXIII Seminar on Harmonization of Registration and Control of Veterinary Medicines
Americas Committee for Veterinary Medicines
(CAMEVET)
November 6-10, 2017
Asunción del Paraguay, Paraguay

Opening speeches
The participants were welcomed by Dr. Manuel Adrián Barboza González, General Director of Technical Services of the National Animal Quality and Health Service (SENACSA), Dr. Martín Santiago Minassian, Technical Assistant of the Regional Representation of the OIE for the Americas, Dr. Rolando Juan Alarcón Ríos, President of CAPALVE, and Dr. Alejandro Vazquez, Vice-president of CEVEPA.

Appointment of the President and Vice-President
Dr. Gloria Alarcón, Focal Point for Veterinary Products of Paraguay, formally took office as President of the Seminar.

Plenary meeting of the official sector
Dr. Maria Eugenia Paz Díaz, Focal Point for Veterinary Products of Guatemala, presented the conclusions of the meeting held by the official sector. Dr. Paz Díaz highlighted the need to promote the participation of National Focal Points, to which end the support of the Delegates is required. She added that it is also necessary for Focal Points to participate in the activities of CAMEVET and of the OIE.

The report of the meeting of the official sector is included as Annex I.

Plenary meeting of the veterinary industry
Dr. Carlos Rufrano, representative of CLAMEVET, presented the topics discussed at the meeting held by the veterinary products industry sector. These included the comment regarding the preparation of the new CAMEVET regulation, and various difficulties presented in relation to the registration of veterinary products. Dr. Rufrano agreed that is it necessary to support the participation of representatives from the official sector at the Seminar.

The report of the meeting of the veterinary industry is included under Annex II.

Session I – CAMEVET relations

Procedures for the participation of CAMEVET in proposals relating to the creation and modification of OIE Standards. Rules currently under review.
Dr. Minassian presented the structure of the OIE, described the procedure for establishing rules, and presented the results of the of the 85th. General Session of the OIE held in May 2017.

Dr. Minassian presented the Resolution adopted in relation with Technical Item Nº 1, *"Global action to alleviate the threat of antimicrobial resistance: progress and opportunities for future activities under the 'One Health' initiative*", under which the Member Countries undertook to continue supporting the activities of the OIE, including –among others- the collection of data relating to the use of antimicrobials and the implementation of the existing OIE rules and standards on the matter; and to support the Global Action Plan (GAP) to combat Antimicrobial Resistance.

Dr. Minassian went on to present the procedure for the registration of OIE-validated and certified diagnostic tests, and listed the advantages of their registration.

Lastly, he noted that the last meeting of the Code Commission revised the modifications to Chapters 6.7 (Harmonization of national programs for surveillance and follow-up of resistance to antimicrobial agents), and 6.8 (Follow-up of antimicrobial agent use patterns and quantities in animals destined for food) of the Terrestrial Animal Health Code.

In relation to these proposals to modify the Terrestrial Animal Health Code, it was agreed that the Secretariat will support the dissemination of this report to enable National Focal Points and veterinary product industry Associations to prepare and send comments.

Dr. Minassian noted that comments must be presented solely through OIE Delegates before the established deadline.

State of implementation of CAMAVET harmonized documents in member countries

Dr. Minassian presented the state of implementation and application of documents harmonized under the framework of CAMEVET. He noted the data collection work carried out by the Secretariat, despite difficulties in obtaining responses from Focal Points.

Based on the discussion that arose in terms of differences between the implementation of documents harmonized under the framework of CAMEVET and their use as technical guides, it was proposed that the Executive Board revise the harmonized documents that require updating, and prepare a list of priorities.

This list of priorities will be presented at the next Seminar with a view to organizing work groups to revise and update the documents identified.

Revision of the harmonized document on Good Manufacturing Practices

In view of the scarce progress achieved by the work group formed at the XXII Seminar for the revision of the Rule on Good Manufacturing Practices for Veterinary Products, the proposal to extend this work group under the coordination of the official sector of Costa Roca was accepted.

The work group will continue revising the document and will present its proposals at the following Seminar. The Official Sector of Bolivia is included into this Working Group

Participation of CAMEVET at the VICH Outreach Forum

Dr. Enrique Argento, former Secretary of CAMEVET, informed on the organization of the last meeting of the Executive Committee and the VIII VICH Outreach Forum, organized in Buenos Aires, Argentina, in February 2017.

He highlighted the participation of CAMEVET and of the countries representing the Americas in this Outreach Forum. He also informed of the participation of Brazil in the VICH as observer.

Dr. Argento described the topics discussed, and highlighted the topics that received support from CAMEVET. These included the expansion of climatic zones in stability tests, and formulations based on combined active principles.

Due to the unavailability of the proposed CAMEVET representative to attend the next meeting of the VICH Outreach Forum, Dr. Barbara Ágate Borges Cordeiro was proposed to take their place. Dr. Cordeiro will participate in the Forum representing Brazil on behalf of CAMEVET

Presentation of the Training Course. Presentation of content, format, and platform.

Dr. Maria Esther Pasco Gosme spoke on behalf of Dr. Liliana Revolledo to present the detailed proposed training project drawn up for CAMEVET.

Based on the discussion relating to project methodology, content and costs, it was decided to continue with the project. To this end, it was proposed to form a group to analyze the proposal, with particular focus on the participation of universities, cost of implementation, and funding options.

The Training Commission was established with the participation of the official sectors of Guatemala, Ecuador and the Dominican Republic, and of CLAMEVET (Argentina), INFARVET (Mexico), and CEV (Uruguay). The group will be coordinated by INFARVET.

The Training Commission will report on its progress to the Executive Board, and the latter will present proposals to the General Assembly of CAMEVET for their adoption.

Joint Technical Committee PG345/FEEDLATINA/STDF – Interaction with the official sector in relation to animal feed

Mr. Gustavo Blanco (Agricultural Engineer), representing the Mixed Technical Committee, made a presentation of the Project, describing its beginnings and proceedings up to the obtainment of financial support from the STDF.

Mr. Blanco described the activities carried out under the Project, which comprised the harmonization of registration requirements for animal feed, and the provision of training courses using distance education tools.

Lastly, he added that these activities have improved the capacities and performance of the official and industrial sectors of the participating countries.

Session II – Working Documents

Good manufacturing practices at cell-processing establishments
Dr. Barbara Ágate Borges Cordeiro, Focal Point for Veterinary Products for Brazil, presented the topic, which is currently in status I draft.

Dr. Cordeiro described the type of therapeutic products obtained using the methods referred to, their clinical applications, and the procedures required to obtain and process them. She described the need to work on the preparation of a technical document containing guidelines.

The proposal of the topic was accepted, and upgraded to status II.

The work group that will prepare the first draft was established under the coordination of the official sector of Brazil, with the participation of the official sector of Uruguay, and of ALANAC and SINDAN (Brazil), ADIPRAVE and CEV (Uruguay), and INFARVET (Mexico).

Registration of homeopathic products
Dr. Mario Renck Real, representing SINDAN, commented that the document -which is currently in status III draft- only received proposals for minor changes from the official sector of Costa Rica. Considering that the Status III document was circulated previously a number of times, without receiving comments, it was decided to approve the document without requiring a second distribution.

The harmonized document is included as an Annex.III

Guide for the implementation of a Pharmacovigilance system
Dr. Gabriel Ardiles Andía, representative of ALAVET (Chile), presented the progress achieved by the work group, with the comments received after the circulation of the document, which is currently in draft Status III.

Since the work group was unable to prepare the document including the comments received in time for a second circulation prior to the Seminar (as required for Status IV), the document will be circulated as soon as it is available, and is deemed to be in Status IV.

Aquaculture Veterinary Products
Dr. Fernando Zambrano Canelo, Focal Point for Veterinary Products of Chile, presented the working document, currently in status III, with the comments received and added to the text.

Based on this presentation, and there being no comments, it was decided to move the document to status IV for circulation, providing a term of 60 (sixty) days to receive comments, for approval at the following Seminar.

Instructions for filling CAMEVET forms for the registration of pharmacological and biological products.
Dr. Carlos Rufrano, representing the coordinator of the working group, Dr. Federico Luna Focal Point for Veterinary Products of Argentina, presented the progress made on the related document,

and informed on the difficulty to incorporate comments to the working document, currently in status III.

Based on the above, the document will move on to status IV, for final circulation.

Guide for registration of diagnostic Kits for diseases
Dr. Emigdio Lemes Anaya, Focal Point for Veterinary Products of Cuba, presented the progress achieved in the preparation of the Working Document, currently in status II.

Based on the request by Dr. Lemes Anaya to update the members of the Work Group, coordinated by the official sector of the United States of America, the participation was confirmed of the official sector of Cuba, Canada and Guatemala, in addition to the participation of CLAMEVET (Argentina), INFARVET (Mexico), SINDAN and ALANAC (Brazil). Official sector from Mexico will be consulted on the interest to continue in the Working Group

The document will consequently move on to status III.

Resistance to antiparasitic drugs
Dr. Alexandra Luna Orta, representative of INFARVET, introduced Dr. Noé Soberanes Céspedes, who described the basis for the preparation of the document, which is currently in status II.

The document seeks to standardize applicable methodologies for determining the resistance to antiparasitic drugs indicated for helminths, bovine ticks, and horn fly.

Based on the discussion relating to the advisability of making progress with this document, the continuity of the work group was confirmed, which will be joined by the official sectors of Brazil, Costa Rica and Panama. ALANAC (Brazil) and AFIRPROVA (Dominican Republic)

The document was moved on to status III, and will be circulated for comments from the countries.

Potency test guide for vaccines containing Bovine Viral Diarrhea Virus (BVDV).
Dr. Andrea Pécora, from the INTA (Argentina), presented the basis for preparing the working document, currently in status II.

Dr. Pécora described the contents of the document, which aims to serve as a guide with a unified criterion for assessing the potency of BVDV vaccines.

Based on the presentation, the document was moved on to status III.

Guide for bioequivalence studies
Dr. César Díaz, representative of CAPROVE (Argentina), presented the progress made and comments received in connection with the working document, currently in status IV.

Based on this presentation, the document was approved. The document is included as an Annex IV

Revision of the harmonized document on labeling of veterinary products
Dr. César Díaz, representative of CAPROVE (Argentina), presented the progress made in the revision of the harmonized document on labeling of veterinary products.

In view of the low level of response received, it was agreed to circulate the document again and maintain the current status III. Given the importance of this topic a Working Group was created. Group shall be coordinated by Costa Rica and formed by of all the representatives of the official sector.

Revision of the harmonized guide for the preparation of stability studies for veterinary pharmaceuticals
Dr. Andrea Fraga and Dr. Milena Aguirre, representing CAPROVE, presented the basis for the revision of the harmonized document, currently in status II.

Based on the discussion, it was agreed to circulate the document again and maintain status III.

Distribution, Storage and Transport Guide (Working Document in special process)
Based on the decision made in the previous Seminar to make the final circulation of the document to receive comments, under a status equivalent to status IV, and considering that no comments were received following its circulation, the document is adopted.

The document is included as an Annex V

Guide for the classification and inspection of veterinary products with out therapeutic indication
Based on the request to continue with the development of the working document, in process status II, a Working Group coordinated by ALANAC (Brazil) and formed for the official sector of Bolivia, Brazil and Chile, CADIN (Nicaragua), INFARVET (Mexico), CAPROVE y CLAMEVET (Argentina), ASOVET (Guatemala), ASIFAN (Costa Rica), APROVET (Colombia), AFIRPROVA (Dominican Republic) y ANDIA (Panama).

Session III – Operative aspects of CAMEVET

Inclusion of topics of common interest for the official and industrial sectors in Seminars
Agreement was reached on the need to include a forum for solving conflicts at the next seminars agenda. To this end, the Secretariat will receive proposed topics that require open discussion by the official and industrial sectors. These proposals will be requested by the Secretariat and will be received up to three months prior to the start of each Seminar, keeping informed the involved parties of the conflict. The Executive Board will analyze the topics proposed and will decide which to include based on their relevance.

Update of the CAMEVET Regulation
Dr. Minassian presented the participants with the final version of the CAMEVET Regulation, and described its salient items.

This document was prepared by the Executive Board and circulated to all the Members of CAMEVET, and the proposed modifications were incorporated. Based on this, the Regulation was

sent to the Delegates of the OIE member countries in the Americas, and no comments were received.

Based on the above, CAMEVET will continue to operate under the new Regulation.

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

Dr. Minassian presented the general aspects of the document prepared by the Executive Board, in order to update the current procedure and simplify the processing of documents prepared by the Committee.

This document will be distributed among the members of CAMEVET for the reception of comments; and the Executive Board will be responsible for its final drafting and submission for approval at the following Seminar.

Storage of draft working document files

At the request of various members of CAMEVET, the Secretariat will procure the development of an on-line file for draft working documents at their various stages in order to facilitate their query.

Election of members of the Executive Board

Pursuant to the new CAMEVET Regulation, official representatives and members were elected to the Executive Board.

The following representatives from the Official Sector were elected:
Dr. Gloria Alarcon, National Focal Point for Veterinary Products for Paraguay
Dr. Berta Chelle, National Focal Point for Veterinary Products for Uruguay
Dr. Benigno Alpizar, National Focal Point for Veterinary Products for Costa Rica
Dr. Fernando Zambrano, National Focal Point for Veterinary Products for Chile
Official Sector representatives will serve for a term of two years, according to the Regulation.

The following people were elected representing the supporting Members:
Dr. Mercedes Etcheverry, authorized representative of CEV, of Uruguay
Mrs. Edith Gamarra, authorized representative of CAPALVE, of Paraguay
Dr. Carlos Rufrano, authorized representative of CLAMEVET, of Argentina
Dr. Ricardo Hoigjelle, authorized representative of CADIN, of Nicaragua
Representatives of members of CAMAVET will serve for a term of two year, as per the Regulation.

The Executive Board will be chaired by Dr. Hipatia Nogales, National Focal Point for Veterinary Products of Ecuador and next Seminar hasting country.

Approval of proposed locations for the following Seminars

The representative of the official sector of Ecuador proposed that country as the seat of the next Seminar.

The representative of the official sector of Jamaica proposed that country as the seat of the Seminar to be held in 2019.

The two proposals were approved unanimously.

Financial Report of CAMEVET

Miss. Ana María Sgammini, Administrative Secretary of CAMEVET, presented the financial report, including the annual expenses and income generated during the present Seminar, in addition to the expense forecast for the following period. This report is included as an Annex VI.

The financial contribution that CAMEVET made to the Focal Points that requested funding, such as Bolivia, Costa Rica, Cuba, Ecuador, Guatemala and Honduras, was highlighted.
The Secretariat were thanked for their good work as well as the local organizers.

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

The document that contains the conclusions and recommendations of the Seminar was read. Following certain suggested changes, the document was approved by the plenary meeting.

List of acronyms used in the document

ADIPRAVE	Asociación de las Industrias de Productos Agroquímicos y Veterinarios (Uruguay)
AFIRPROVA	Asociación de fabricantes, importadores y representantes de productos veterinarios y afines, inc. (Rep. Dominicana)
ALANAC	Asociación de Laboratorios Farmacéuticos Nacionales / Associação dos Laboratórios Farmacêuticos Nacionais (Brasil)
ALAVET	Asociación Gremial de Laboratorios de Productos Veterinarios (Chile)
ANDIA	Asociación Nacional de distribuidores de insumos agropecuarios y maquinarias (Panamá)
APROVET	Asociación Nacional de Laboratorios de Productos Veterinarios (Colombia)
ASIFAN	Asociación Farmacéutica de la Industria Nacional
ASOVET	Asociación de Productos Veterinarios (Guatemala)
CADIN	Cámara de Industrias de Nicaragua
CAMEVET	Comité de las Américas de Medicamentos Veterinarios
CAPALVE	Cámara de Laboratorios Paraguayos de Productos Veterinarios
CAPROVE	Cámara Argentina de la Industria de Productos Veterinarios
CEV	Cámara de Especialidades Veterinarias (URUGUAY)
CEVEPA	Cámara de Especialidades Veterinarias del Paraguay
CLAMEVET	Cámara de Laboratorios Argentinos Medicinales Veterinarios
INFARVET / CANIFARMA	Industria Farmacéutica Veterinaria (México)
INTA	Instituto Nacional de Tecnología Agropecuaria (Argentina)
OIE	Organización Mundial de Sanidad Animal
SENACSA	Servicio Nacional de Calidad y Salud Animal (Paraguay)
SINDAN	Sindicato Nacional da Industria de Produtos para Saúde Animal
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

List Annexes:

Annex I: Minute Plenary meeting of the official sector
Annex II: Minute Plenary meeting of the private sector.
Annex III: Balance 2016-2017
Annex IV: Registration of homeopathic
Annex V: Guide for bioequivalence studies
Annex VI: Distribution, storage and transport guide

Annex I

CONCLUSIONS OF THE PLENARY MEETING OF THE OFFICIAL SECTOR

The **Plenary Meeting of the Official Sector** was held on Monday, November 6, 2017, at 16:00 hs. at the hotel that is the Seat of the Seminar.

Items discussed.

1.- Concern of the Executive Board: The Executive Board expressed its concern over the withdrawal of one official sector representative and the withdrawal of one representative of the industry sector.

2.- The Executive Board expressed its concern over the **lack of participation of the official sector.** There were only **16 participant countries**; despite the **support provided this year by CAMEVET** for **7** focal points for veterinary medicines, not all of them were able to attend the Seminar (as was the case of Belize).

3.- The **time** required to obtain authorization for the corresponding permits is greater than one month; additionally, in some cases the authorization must be issued by the President of the republic or country.

4.- The **OIE Delegates** are requested to consider including in their **annual budgets** the participation at the CAMEVET Seminar.

5.- We must seek a strategy to enable the participation of the focal point for veterinary medicines, by including relevant topics, such as **Antimicrobial Resistance**.

6.- Each year we note **greater** participation of the industry sector, and a decline of the official sector participation.

7.- The topics that present the greatest difficulties for complying with sanitary registration requirements for veterinary medicines include the Free Sale Certificate, and Labeling

8.- We need Training and Regulations covering veterinary products manufactured using biotechnology.

9.- We must show **greater commitment** with the revision and discussion of the different **technical documents.** This requires greater participation and the technical opinion of each of the focal points for veterinary medicines.

Annex II

Conclusions of the Meeting of the Industry Sector

The Meeting of the representatives of the industry sector was held according to plan.
The meeting was coordinated by the Industry Sector representatives on the Executive Board of CAMEVET (Ms. Edith Gamarra (Engineer), Dr. Mercedes Etcheverry, and Dr. Carlos Rufrano).
Ms. Edith Gamarra welcomed the participants and opened the floor to debate.

The representative of INFARVET (Mexico) informed of the visits carried out by the Sanitary Authority of Guatemala to Mexican biologicals laboratories, and informed that Certificates are only issued subject to the approval of audits. She consulted whether this mechanism was followed in other countries.

The representative of Costa Rica informed that El Salvador requests Primary Standards for active ingredients as a requirement for registration. Various other countries reported that they are subject to the same request.

A request was made to approve the modifications to the RTCA (Central American Technical Regulation).

It was informed that in Colombia pharmaceutical forms are being manufactured pursuant to WHO Report 37 and 45, whose technical requirements are very strict, and the companies in the sector find it very difficult to comply with them.

The Brazilian private sector informed that the Sanitary Authorities of that country request Stability Studies for animal feed, additives and/or products indicated for administration in feed mixes.

Information was requested regarding the status of the use of Formaldehyde for disinfection of premises.

New Regulation in Ecuador:
Concern was expressed by the entire industry over the scope of the new regulation in force in Ecuador (Resolutions 002 and 003).

Training Project:
A report was presented of the project proposed by Dr. Liliana Revolledo, and put to the consideration of the attendees, with the comments and conclusions on the matter made by the representatives of the industry sector on the Executive Board.
Additionally, it was informed that the Project will be presented during the Seminar.
It was agreed that it is in the best interest of the industry sector for this training to be offered by an internationally recognized university, and for it to include a distance education platform.
The representative of Mexico offered to contact the Autonomous University of Mexico (Universidad Autónoma de México) on behalf of CAMEVET as an option for this training.

It was informed that there are significant differences in criteria among the bodies responsible for registration from one country to another and even within countries; consequently, it was requested to study how CAMEVET can contribute to the unification of these criteria.

Seat of the next Seminar

To date, there has been no proposal for the seat of the next CAMEVET Seminar.

It was noted that the organization of the Seminar requires intense work and implies a significant financial effort.

It was proposed that CAMEVET should make a financial contribution to the country that is the seat of the Seminar. This contribution could represent 50% of the income obtained from registration fees each year, and would help to fund the event.

Annex III

Dollars

Income		31/10/2017 - 30/11/2017
Resources available as of October 31		USD 103.391,00
Registration to the CAMEVET Seminar 2017		USD 42.075,00
	Income Subtotal	**USD 145.466,00**
Expenses		
Fixed expenses (Salaries)		
Administrative Assistant (Ms. Ana Maria Sgammini)		USD 1.000,00
Administrative Expenditures For use of the OIE Offices		USD 150,00
	Income Subtotal	**USD 1.150,00**
Expenses for the CAMEVET Annual Meeting		
Financing to Focal Points for CAMEVET Annual Meeting		USD 10.168,00
CAMEVET Staff Expenses		USD 1.173,00
	Subtotal	**USD 11.341,00**
Variable expends		
Change from Dollars to Argentine Pesos		USD 700,00
Refund of registration payment XXIII Seminar Carlos Rufrano (Speaker)		USD 350,00
	Subtotal	**USD 1.050,00**
	Subtotal of Expenses	**USD 13.541,00**
	Total Income minus Expenses until November 2017	**USD 131.925,00**

Pesos argentinos

Income	**31/10/2017 - 30/11/2017**
Total Income minus Expenses until November 2017	ARS 1.242,62
Exchange of US dollars to Argentine pesos	ARS 12.460,00
Subtotal	**ARS 13.702,62**

Expenses

Expenses for the CAMEVET Annual Meeting

Expenses for the purchase of airline tickets financing (Dr. Argento)	ARS 10.560,00
Subtotal	**ARS 10.560,00**

Other expenses

Miscellaneous (Translation ESP / ENG Conclusions CAMEVET Seminar 2016)	ARS 2.350,00
Subtotal	**ARS 2.350,00**
Subtotal of Expenses	**ARS 12.910,00**
Total Income minus Expenses until November 2017	**ARS 792,62**

Annex III

CAMEVET
PROCEDURE IV
REVIEW DATE in BRAZIL:
HOMEOPATHIC COMMISSION - SINDAN
June 26, 2017

GUIDE TO REGISTER HOMEOPATHIC VETERINARY PRODUCTS

SÃO PAULO, BRAZIL
June 2017

GUIDE TO REGISTER HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS

1. OBJECTIVE AND SCOPE:

Establish the conditions and requirements under which the registration of homeopathic veterinary products will be granted for marketing. The present document applies to all individual or legal entities dedicated to the production, contract production or import of homeopathic veterinary products.

2. DEFINITIONS. For the purpose of this document, the following were adopted:

- ✓ **GOOD MANUFACTURING PRACTICES.** Set of technical procedures and standards intended to guarantee the quality of homeopathic veterinary medicinal products.
- ✓ **HOMEOPATHIC STRAIN OR PARENT DYE.** It is the whole primary preparation using raw materials of animal, plant, mineral or synthetic origin, used as a starting point for homeopathic preparations.
- ✓ **TAG OR LABEL.** It is the printed information, under any system, which must be on packages, for any type of material.
- ✓ **EXCIPIENT OR INERT INGREDIENT.** It is the compound or mixture of compounds that has no pharmacological action in the concentrations present in a dosage form.
- ✓ **OFFICIAL HOMEOPATHIC PHARMACOPOEIAS.** All the Official Homeopathic Pharmacopoeias of the member countries of CAMEVET as well as of the European Union, Germany, France, England, India or others that the official bodies of the Registration target countries consider relevant to use.
- ✓ **DOSAGE FORM.** Physical form of a pharmaceutical preparation, the purpose of which is to facilitate the administration and dosage of a drug.
- ✓ **PACKAGE INSERT.** It is the complementary information to that expressed on the label or package of the product.
- ✓ **BATCH.** Quantity of a product produced in a single manufacturing cycle. The essential characteristic of the batch is its homogeneity and identification through numbers, letters or the combination of both.
- ✓ **HOMEOPATHIC VETERINARY PRODUCT.** It is the pharmaceutical preparation obtained from homeopathic strains or parent dyes, according to the preparation rules described in the official homeopathic pharmacopoeias.
- ✓ **BIOTHERAPICS** – these are pharmaceutical preparations obtained from chemically undefined biological products, such as: microbial cultures, secretions, tissues, organs, products of microbial origin, helminths,

arthropods, hemoparasites, larval stages, cysts, eggs and embryonic stages of animals, etc...

These preparations can be of *pathological origin* (nosodes) or non-pathological origin (sarcodes) and must be elaborated according to the chosen official Homeopathic Pharmacopoeia.

- ✓ **REFERENCE COUNTRIES.** Reference countries are the Members States of the OIE – World Organization for Animal Health and the others indicated by the official body of the registration target country.
- ✓ **ACTIVE INGREDIENT.** It is the starting point for the preparation of the homeopathic product, which may be a drug, pharmacon, parent dye and derived dosage form.
- ✓ **THERAPEUTIC INDICATION.** These are therapeutic indications and/or recommendations based on the various properties that a homeopathic product may have: to prevent diseases, promote the balance of the animal or herd, improve the individual or collective zootechnical performance or restore the health of an animal or herd through a specific pathological process, which justifies its therapeutic use.
- ✓ **ISOPATHY.** Therapeutic technique that is based on the Law of the Identical (*Aequalia Aequalibus Curantur*), whose use does not require pathogenetic experimentation.
- ✓ **DILUTION.** It is the reduction of the active ingredient concentration by the addition of a suitable inert ingredient.
- ✓ **DYNAMIZATION.** It is the process characterized by successions applied to dilutions or triturations when the active ingredient of the homeopathic drug in preparation is solid.
- ✓ **STRENGTH.** It is the quantitative indication of the number of dynamizations received by an active ingredient or homeopathic drug.
- ✓ **INNOCUITY –** it is the characteristic that ensures that the active ingredient does not produce harmful effect to the animal receiving it.

3. GENERAL PROVISIONS OF THE REGISTRATION.

The Registration applications of homeopathic veterinary product should be sent to the Competent National Authority (NCA) and must satisfy the requirements of this Guide and the specific legislation of each country.

- ✓ All duly qualified legal Establishments may produce, market and register homeopathic veterinary products provided that they comply with the items described below.
- ✓ All individual or legal entities interested in marketing and registering homeopathic veterinary products that are produced in another country should present to the official body the Registration application for each product separately, with the following information and attachments:

4. GENERAL REQUIREMENTS

For IMPORTER, the technical documents must be officially translated such as the official certifications, in the language of the country where they are to be registered.
The general requirements are:

4.1 Use the Registration to exercise activities of: Manufacturer, Contract Producer or Importer of homeopathic products for veterinary use, granted by the National Competent Authority (NCA).
4.2 Present Registration application (Annex 1) signed by the interested party, the technical documents must be signed by the respective professional responsible (Veterinary Doctor).
4.3 Document that confirms the legal and technical representation granted by the owner to the individual or legal entity according to the legislation of each country to process the registration and market the product(s).
4.4 For imported products:
4.4.1 Certificate of Free Sale issued in the country of origin by the NCA with all its consular transactions. This certificate should contain the following:
4.4.1.1 Composition of the product, which identifies each homeopathic parent dye or strain with the respective botanical, zoological, chemical or biological nomenclatures in Latin, followed by the dilution and dynamization scale, according to the official homeopathic pharmacopoeia used, the excipients, inert ingredients and quantities used.
4.4.1.2 Dosage Form
4.4.1.3 Registration Owner
4.4.1.4 Name of Manufacturer
4.4.1.5 Registration number and expiry date

4.4.2 Certificate of Good Manufacturing Practices or equivalent document of the country of origin of the producing establishment.

4.5 Attach the Report or Technical Report that describes:
4.5.1 The obtainment method and information on quality control of the homeopathic parent dye or strain. The quality and quantity of active ingredients used according the preparation method of the homeopathic strains or parent dyes. Correlate the quality standard or grade described in the monographs of the accepted homeopathic pharmacopoeias for each active ingredient of the registration target product;
4.5.2 In the case of an active ingredient not included in the officially accepted Homeopathic Pharmacopoeias, the quality control methods used should be described.
4.5.3 In the case of Excipients or Inert Ingredients, their quality must be shown and traceability ensured.
4.5.4 For homeopathic veterinary products that contain Biotherapics, the Report should include a description of the measures adopted to guarantee the elimination of any pathogenic agent in the dynamization effectively used on the product.

4.6 Present document that describes the manufacturing process according to the dosage form, indicating the dilution method, dynamization scale and pharmacopoeia used.

4.7 Present document that describes the specifications and results of the quality control: microbiological, physical-chemical and others described by the monographs of the official homeopathic pharmacopoeias used for the finished product, as appropriate. In case the administration route of the homeopathic veterinary product is parenteral, the sterility and apyrogenicity tests conducted by a qualified laboratory should be included.

4.8 Present the Stability Study Report of the product and, if necessary, its different dosage forms that establish the expiry date and storage conditions. The report must include the following:
4.8.1 Full Description of the product subject to registration.
4.8.2 Specifications: physical, chemical and microbiological.
4.8.3 Parameters Evaluated: physical, chemical or microbiological, according to the dosage form.
4.8.4 Study Duration: as minimum, the intended expiry date to be given to the product or the duration described in the Accelerated Stability studies required by each country.
4.8.5 Package: the studies should be developed in the same primary packaging in which the product is to be marketed. Indicate the specifications of the primary packages.
4.8.6 When a product has packages of different weights or volumes, the Stability Study will be conducted for each one. For products with commercial presentation greater than one (1) kilogram or one (1) liter, the Stability Studies may be conducted on presentations of smaller sizes, in packages that have the same characteristics and specifications as those in which the products are to be marketed.
4.8.7 Sampling Times: at time zero (0) and a time for each year of the product's shelf life. The last analysis should be conducted at the limit of the shelf life to be requested, except that described in item D regarding the Accelerated Stability studies.
4.8.8 Full description of the results obtained performed by a specialized company recognized by the NCA of the country where the Registration is to be made, with the final conclusions.

Any change in the primary packaging materials determines the execution of a new stability study and presentation of the respective report.

4.9 Present the sketches of the product labels with Tag, Box and Package Insert (if included).

4.10 In case the homeopathic product to be registered is not elaborated by the applicant but is manufactured in the country, attach copy of the Manufacturing

Agreement and the Quality Control signed with a homeopathic product manufacturer registered at the NCA and also present at the NCA the effective Good Manufacturing Practices certificate or equivalent document.

5. SPECIFIC REQUIREMENTS

5.1 PROOF OF THE THERAPEUTIC INDICATION OF HOMEOPATHIC VETERINARY INGREDIENTS OF NON-BIOLOGICAL STRAINS AND NOT INCLUDED IN THE PHARMACOPOEIA:

Present the justification and defense of the strains or combination of strains in their respective dilutions, supported in scientific documentation like: *monographs, medical articles, homeopathic therapeutic treatments, pathogenetic experimentation studies, natural or experimental toxicological studies, scientific articles, published clinical cases or corresponding document* that indicates the possible homeopathic use of the said strain or parent dye.

5.2 PROOF OF THE THERAPEUTIC INDICATION OF HOMEOPATHIC VETERINARY PRODUCTS OF BIOLOGICAL STRAINS:

5.2.1 That the homeopathic strains or parent dyes are expressed in any of the effective official homeopathic pharmacopoeia in the Reference Countries.
5.2.2 Certificate issued by the health authority of at least one (1) Reference Country, which states that the product is authorized in that country.
5.2.3 That observes and proves the compliance with the quality requirements demanded to ensure the elimination of eventual pathogenic agents, especially in the dynamization used.
5.2.4 Certificate of observation of the Good Manufacturing Practices of the manufacturing laboratory, issued by the competent health authority or similar document that contains the authorization for its production.

5.3 THERAPEUTIC PROOF OF HOMEOPATHIC VETERINARY PRODUCTS OF NON-PHARMACOPOEIC BIOLOGICAL STRAINS - BIOTHERAPICS:

For evaluation purposes of the therapeutic use, a scientifically solid justification should be considered with the defense of the strains or combination of strains in their respective dilutions. The use should be based on scientific documentation:

A) Monograph of the strain(s) not included in the pharmacopoeia(s), the strain(s) should be authorized in the composition of a homeopathic drug of at least one reference country. For evaluation purposes of the homeopathic strain, the information on the description of the raw material, preparation method of the parent dye and its specifications, as well as the certificate of quality control should be attached, or,

B) Report of the homeopathic use of the strain based on the pathogenetic experimentation studies or document of one of the health authorities or organizations accredited by these, of the reference countries, which certifies the use or the possible homeopathic use of said strain, or,

C) Document that justifies that the introduction of said strain in the composition of a homeopathic veterinary product is the result of a TECHNOLOGICAL INNOVATION, whose use is based on the therapeutic principle of Isopathy or Homeopathy and not from the pathogenetic experimentation or other type of applicable indication.

The dynamization used in the finished homeopathic product, of the said innovative strain, should have a document, for registration purposes, which confirms the absence of microbiological growth of any kind.

6. LABELING. The final arts of the label, box and package insert of the homeopathic veterinary products should comply with the specific legislations of each registration target country.

7. REFERENCES

- ✓ Council Regulation (EEC) No. 2377/90. Laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.
- ✓ CPMP Committee for proprietary medicinal products. European Medicines Agency. 2003. Guideline on stability testing: stability testing of existing active substances and related finished products.
- ✓ Directive 2009/9/CE of the Commission (February 10, 2009). Which modifies Directive 2001/82/CE of the European Parliament and the Council through which a community code on veterinary drugs is established.
- ✓ Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary products.
- ✓ Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products.
- ✓ Irish medicines board. 2008. Guide to the registration of homeopathic veterinary medicinal products.
- ✓ MAPA Ministry of Agriculture, Livestock and Supply. *Secretaria de Defesa Agropecuária* [Secretariat of Farming Defense]. 2001. Service Instruction No. 001/CPV. Coordination of veterinary product inspection.
- ✓ ANVISA. Brazilian Homeopathic Pharmacopoeia 3rd edition.
- ✓ MAPA. Brazil. Official Circular 002 DFIP/DAS of 03/28/2013
- ✓ MAPA. Brazil. Official Circular 003 DFIP/DAS of 04/10/2013
- ✓ MAPA. Brazil. Normative Instruction 46 of 10/06/2011
- ✓ Regulation (EU) No. 37/2010 of the Commission. Related to the pharmacologically active substances and their classification in relation to the maximum limits of residues in food products of animal origin.

- ✓ Regulation (CE) No. 470/2009 of the European Parliament and the Council (May 6, 2009). Whereby community procedures are established to lay down the MRL of the pharmacologically active substances in foodstuff of animal origin, revokes the Regulation (CEE) No. 2377/90 of the Council and modifies the Directive 2001/82/CE of the European Parliament and the Council and the Regulation (CE) No. 726/2004 of the European Parliament and the Council.

São Paulo, August 18, 2016

ANNEX 1

Information to include in the Registration application

1. Product Information
    a. Product name
    b. Name of active ingredients
    c. Dosage Form
    d. Administration Route
    e. Product presentation
    f. Product expiry date
    g. Target species
    h. Information on precautions, contraindications and proposed waiting periods
2. information of the manufacturer and/or warehouse or storehouse
    a. Name and country of laboratory(s) that participate in the manufacture
    b. Address, telephone, fax and electronic mail
    c. License number and expiry date for national product
3. Product owner information
    a. Name
    b. Address, telephone, fax and electronic mail
    c. Country
4. Distributor Information:
    a. Name of Distributor(s)
    b. Address, telephone, fax and electronic mail
    c. License number and Expiry date
5. Legal Representative Information
    a. Name
    b. Identification Document Number
    c. Address, telephone, fax and electronic mail
6. Information of the Professional Responsible
    a. Name
    b. Professional Identification Number
    c. Address, telephone, fax and electronic mail

Annex IV:

May 3rd 2017

Guide for conducting bioequivalence studies for veterinary medicines

Contents

Contents

CONDUCTING BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINES

1. INTRODUCTION

In order to deliver an optimal therapeutic action, an active ingredient must be released at the site of action at an effective concentration during the intended period of time. To reliably predict the therapeutic effect of a drug, the performance of the dosing form containing the active ingredient must be suitably characterised.

Several therapeutic failures observed in the past associated with differences in bioavailability indicate the need to evaluate the performance of dosing forms in transporting the active ingredient to the systemic circulation, and from there to the site of action. Hence, the bioavailability of the active ingredient of a pharmaceutical product must be known and reproducible. If it is assumed that, in a given subject, a specific plasma concentration profile relative to time will result in essentially similar concentrations at the site of action as another drug and, therefore, will have an essentially similar effect, pharmacokinetic information can be used instead of therapeutic results to establish equivalence: bioequivalence.

In practice, evidence of bioequivalence generally constitutes the most suitable proof to support therapeutic equivalence between medicinal products. Therefore, reasonable evidence must be furnished in order to establish that the product studied is equivalent in therapeutic terms to the reference product.

It should be noted that current background information concludes that bioequivalence studies are generally not suitable to support a restriction period for use prior to slaughter, milking, or collection of eggs or honey. Residue depletion studies are very rarely covered adequately by a bioequivalence study, as is the case with the limit of quantification of the method, study duration, and statistical analysis of results. When these conditions are not met, studies will be required in addition to bioequivalence studies to confirm residue depletion in pharmacological medicines destined for food producing species.

The objective of this technical guide is to establish requirements for the design, execution and evaluation of bioequivalence studies. Addendum I envisages the possibility of using supplementary *in vitro* studies to demonstrate therapeutic equivalence.

This guideline, as every guideline, is not intended for establishing a mandatory or specific regulatory requirement. It is a tool created to allow, under the decision of the register owner and in consensus with the regulatory authorities, the use of this kind of tests to assure therapeutic equivalence, avoiding the unnecessary animal sacrifices.

2. DEFINITIONS

2.1 Pharmaceutical equivalent:

Two medicinal products are pharmaceutical equivalents when they contain the same quantity of the same active ingredient with the same salt or ester in the same pharmaceutical form, are destined for administration by the same route, and meet identical or comparable quality standards. However, pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in excipients and/or in the

manufacturing process may generate faster or slower dissolution or absorption, which may lead to differences in product behaviour (WHO).

2.2 Pharmaceutical alternative:

Two products are pharmaceutical alternatives when they contain the same molar quantity of the same active principle, but differ in terms of their pharmaceutical form (eg: capsule vs. pill) and/or chemical form (eg: different salts or esters). Pharmaceutical alternatives deliver the same active principle through the same route of administration, but are not pharmaceutical equivalents. They may, or may not, be bioequivalent to, or therapeutic equivalents of, the reference product.

2.3 Bioavailability:

Bioavailability refers to the rate and degree at which an active substance or its active ingredient is released from a pharmaceutical form and becomes available to the general circulation to exert an effect.

The bioavailability of a veterinary medicine is defined by the speed and magnitude at which the active substance reaches the systemic circulation and becomes available at the site or sites of action. The speed of absorption is measured in terms of the maximum plasma concentration obtained (Cmax), the time to reach maximum concentration (Tmax) and the area under the curve (AUC).

In most cases, substances have been developed to exhibit a systemic therapeutic effect. Therefore, a more practical definition can be provided to reflect that the substance in the general circulation is undergoing a dynamic exchange with the substance at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosing form – as compared with the 100% bioavailability obtainable from the administration of an IV solution of the same drug (ex: oral versus IV solution), and the "relative bioavailability" – as compared with another form administrated via an extravascular route (ex: pills versus oral solution).

2.4 Bioequivalence:

Two medicinal products are bioequivalent when they are pharmaceutical equivalents or pharmaceutical alternatives to one another, and when their bioavailability (amount of active principle absorbed and speed of absorption) following administration at the same molar dose is similar to the extent that their effects in terms of efficacy and safety in the target species are essentially the same (and not necessarily similar in terms of safety in humans or for the environment). These products should be suitably labelled and manufactured in compliance with the prevailing Good Manufacturing Practices (CAMEVET GMP or WHO GMP).

Bioequivalence is said to exist between veterinary medicines when: following administration of the same molar dose using the same route of administration, under standardised experimental conditions, the speed of absorption and quantity of active substance absorbed differ only within pre-established limits.

The active substances to be compared must have similar physical and chemical properties, i.e. dissolution profile, crystalline form and particle size. In the case of active principles presented in a racemic mixture, these must display the same proportion of isomers.

2.5 Therapeutic equivalence:

A medicinal product is only considered a therapeutic equivalent of another medicinal product when they are **pharmaceutical equivalents or alternatives,** and it has the same quality and displays the same efficacy

and safety - through *in vivo* or *in vitro* studies – as the reference product, whose efficacy and safety have already been established.

2.6 Reference product

A reference product is one whose quality, efficacy and safety have been established, assessed and approved by the competent health authority of the country where bioequivalence test is submitted to endorse a new register, a new administration way or a formulation change.

3. SCOPE AND OBJECTIVES OF BIOEQUIVALENCE STUDIES

Bioequivalence studies are valid scientific methods used to compare:

3.1 A significant change in formulation that may affect the bioavailability of the active principle. *When a change is made to the composition of a pharmaceutical form, these studies may be used to show that the new product is bioequivalent to the product used to carry out the clinical trials.*

3.2 Different routes of administration for the same product. *A product with a sole qualitative and quantitative formula may be applied using different routes of administration. Two routes of administration are bioequivalent when their plasma concentration profiles are similar within pre-established limits.*

3.3 Different veterinary medicinal products that are pharmaceutical equivalents. To avoid cruel and unnecessary safety and/or efficacy studies when bioequivalence can be demonstrated with another approved product for which these studies have already been carried out. *Ex: new product vs. reference product. When comparative reference is made to an approved product in terms of efficacy and/or safety, bioequivalence with that product must be demonstrated (where the regulatory authority accepts bioequivalence as a tool for product registration).*

Although certain *in vitro* equivalence studies exist which are sufficient in some cases to fulfil this objective, these studies most often apply to solid pharmaceutical forms (ex: pills). These studies are presented in Addendum I.

4. CASES THAT DO NOT REQUIRE *IN VIVO* BIOEQUIVALENCE STUDIES

Generally, *in vivo* bioequivalence studies are not required when a product meets one or more of the following conditions:

a) The product is manufactured as a solution for administration only via the **intravenous** route and contains the same active substance as a previously approved product for use via the same route in the same target species that is the subject matter of the new application.

b) The product is an oral dosage form designed not to be absorbed (ex: antacid, radiopaque medium).

c) The product meets all of the following conditions:

- It is an **oral solution**, syrup or other similar rapid-release and high-absorption solubilised form, or a solid pharmaceutical form whose rapid dissolution has been demonstrated previously, and which contains one or more highly soluble and high-absorption active principles (BCS - Biopharmaceutics Classification System).
- Contains an active substance in the same molar dose as the reference product.

- Has been shown not to contain inactive substances that could significantly affect the absorption of the active substance.

d) The product has been reformulated by the original manufacturer and is identical to the reference product except for colouring, flavouring and/or conserving agents, which have been shown not to have an effect on bioavailability.

e) Inhalation volatile anaesthetic solutions that contain the same active principle at the same dose.

f) Topical solutions indicated for obtaining local therapeutic effects. Other topical pharmaceutical forms for local use only in animals not destined for human consumption.

The fact that *in vivo* bioequivalence trials are not carried out does not imply that *in vitro* trials are not conducted.

5. SAFETY CONSIDERATIONS RELATING TO FOOD FOR HUMAN CONSUMPTION

In general, the fact that two formulations have been shown to be bioequivalent does not guarantee that they both need the same withdrawal period. Small variations in absorption at very low concentrations could produce significant differences in the elimination slope, which is used to determine the withdrawal period.

Consequently, a product may only be exempted from the requirement to submit a withdrawal period determination study when:

a. The method used to quantify the active ingredient in plasma has a quantification limit equivalent to or below half the MRL,

b. At least two determinations have been carried out at time points subsequent to the restriction period (withdrawal period) of the original product.

c. It is shown that there are no significant differences between the results obtained for the two products in these determinations.

In any other case, the submission of a bioequivalence study will not constitute an exemption from the requirement to conduct a withdrawal period determination study.

6. CRITERIA FOR EVALUATING BIOEQUIVALENCE STUDIES FOR PRODUCTS THAT CONTAIN HIGH VARIABILITY OR NARROW THERAPEUTIC INTERVAL PHARMACEUTICALS

In specific cases where the active principle of the product analysed offers a narrow therapeutic interval (NTI), in other words, where small variations in plasma levels can cause serious therapeutic failures (sub-therapeutic concentrations) or serious adverse reactions (supra-therapeutic concentrations), it is necessary to assess the need to narrow the bioequivalence acceptance intervals, for example: establishing a smaller AUC acceptance interval, generally of 90-110%. This would require clinical justification, because the dose-response curve displays a sharp slope, indicating that small changes in plasma concentrations generate significant variations in clinical results (ex: cyclosporine). This requires narrower acceptance limits in order to guarantee safety in the use of these drugs.

In the case of drugs with high intra-individual variability, i.e. with significant/major variability (CV ≥ 30%) in terms of the quantity and/or speed of absorption in a given individual, a broader interval could be accepted, but would require scientific justification based on safety and efficacy considerations. It should be noted that, for drugs with high variability in the Cmax parameter, it is recommended to plan a larger sampling quantity close to Tmax, in order to suitably characterize both the speed and quantity of absorption.

In both cases, therapeutic equivalence must be demonstrated through comparative *in vivo* studies.

7. DESIGN OF SINGLE DOSE BIOEQUIVALENCE STUDIES

Whenever possible, the products or routes of administration to be evaluated in the target animal species must be compared with a single dose *in vivo* bioequivalence study. Section 7 provides examples of situations where a multiple dose *in vivo* bioequivalence study may be necessary.

7.1 Reference product

Whenever bioquivalence tests are used to endorse the register of a new product, proposed as therapeutic equivalent of other one, the most suitable reference product is the first authorised product with a complete dossier. When there are several approved products with different labels, applications or target species, a bioequivalence study must be carried out with the reference product that has obtained approval for the same indications as those of the problem (or test) product.

The reference product must be taken from a valid batch of a product that has been approved in the country where registration of the drug is sought, which contains the same active substance as the new formulation, new dosing form or salt. For example, different esters of the same therapeutic entity are considered different products.

For a given product, a formulation can serve as a reference to show its bioequivalence with other formulations that formed part of the development process.

Reference Products or Comparators will be proposed by the study sponsor upon approval of the protocol, and defined by the health authority of the corresponding country.

7.2 Reference route of administration

The reference route of administration is the one used during clinical or toxicological trials, and the one used as a reference in terms of efficacy and safety.

7.3 Standards for test and reference pharmacological products

Both the test product and the reference product must be shown to meet all the standards included in compendia or other applicable standards relating to identity, concentration, quality and purity, and must comply with all the requirements of the Good Manufacturing Practices (CAMEVET GMP or WHO GMP).

7.4 Animals

Animals used in bioequivalence studies must be clinically healthy and form a homogeneous group (in terms of age, breed, weight, hormonal and nutritional status, production level, etc.). Wherever possible, it is recommended to restrict studies to the same sex when there is no evidence of interaction between sex and products. When it is difficult to maintain the homogeneity of all the animals included in a study (ex: horses), it will be acceptable to use non-homogenous cattle provided that the animals in each treatment group have been matched by age, weight, sex (where relevant), etc. This must be done using restricted randomization based on the relevant blocking factor(s).

The animals selected must belong to the target population for which the product is intended.

Group size: the appropriate number of animals must be estimated carefully and will depend on several factors, including variation in response, differences in the two formulations and level of rejection of the hypothesis. The cross-over study design offers advantages in terms of potency and number of animals required. It is recommended to use a minimum of 6 animals per group for cross-over study design, and 12 animals per group for the parallel group trial design.

7.5 Conditions of the trial

Bioequivalence must be carried out in compliance with the requirements of Good Clinical Practices (GCP) and Good Laboratory Practices (GLP).

For products administrated via the oral route, special attention must be paid to the different factors known to affect the arrangement of the active substance. The administration of food can improve or interfere with the absorption of the drug, depending on the characteristics of the drug and the formulation. Feed intake can also increase inter- or intra-subject drug absorption speed and magnitude variability. The protocol must include justification for conducting a bioequivalence study with unfed or fed subjects. The protocol must describe the diet and eating schedule to be followed during the study. For all species, the prandial state and exact time of feeding must be in line with animal welfare considerations (for example, ruminants must not be subjected to fasting), and with the pharmacokinetics of the active principle. Studies concerning drugs for canines and felines for oral administration must be carried out using unfed animals, unless the reference product label indicates that the product must be administrated only after being fed. Animals must have remain unfed for 8 hours before being dosed and 4 hours after the administration of the drug. For prolonged release oral medication indicated for non-ruminants, bioequivalence studies must be carried out in fed and unfed state, unless another condition is duly justified. The protocol must contain the rationale for carrying out the bioequivalence study in unfed or fed animals, and must describe the diet and feeding schedule.

If the reference product label indicates that the product must be administrated only to unfed animals or fed animals, the bioequivalence study must be carried out following the same indications relating to feed.

7.6 Dose to be tested

The approved dose must be used, and must be effective.

When several doses have been approved for the reference product, the bioequivalence test must be carried out using the highest dose.

7.7 Sampling

The concentrations of active principle and/or its active metabolites can be determined in biological samples such as blood, serum, plasma and other biological fluids (ex: milk, urine).

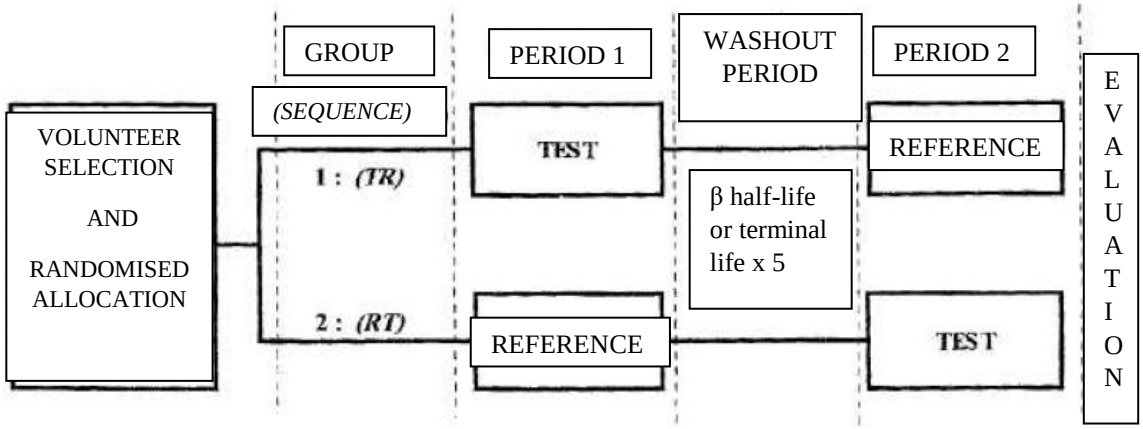
Sampling must be carried out so as to suitably measure Cmax and AUC. Measurements must include at least 2 points before Cmax, 2 to 3 points around Cmax, and 3 to 4 points during the active principle elimination phase.

7.8 Experimental design

The design of bioequivalence studies must seek to reduce to the greatest extent possible any variability not associated with the formulations studied - test (T) and reference (R). Generally, a two-sequence (TR/RT), two-period (Period 1/Period 2), two treatment, balanced, non-replicated, randomised cross-over design is

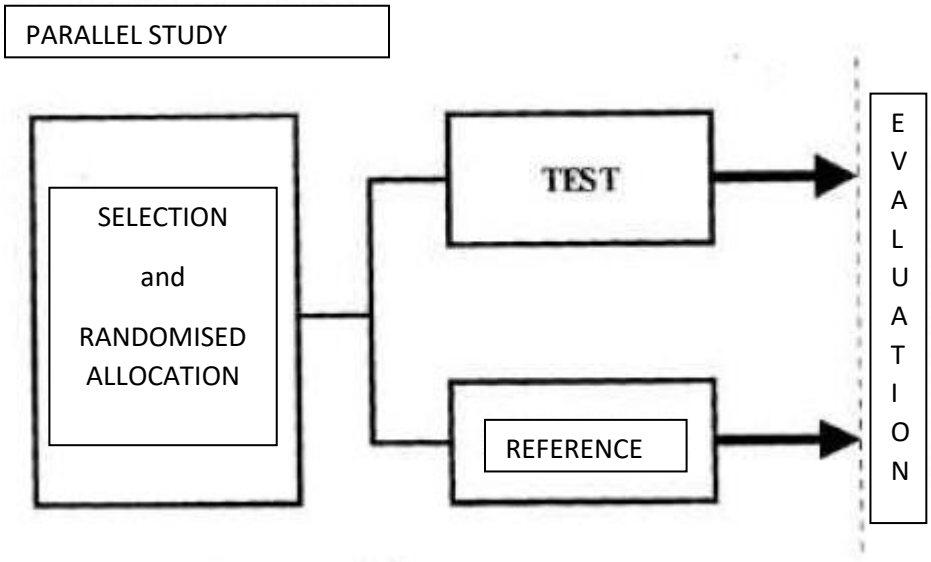
used for bioequivalence studies, with a single dose in each period. All animals included in the study (equal number in each sequence) must receive the two treatments - T and R. This design avoids possible confusion between treatment effects and period.

The time elapsed between the administration of each dose of T or R formulation is called the washout period, and must be sufficiently long to ensure that no concentration of the active principle administered in the first period is detected at the time of the second administration, or that any concentration detected is sufficiently low to have no pharmacokinetic impact on the new administration. The classical cross-over design is illustrated in the figure below.

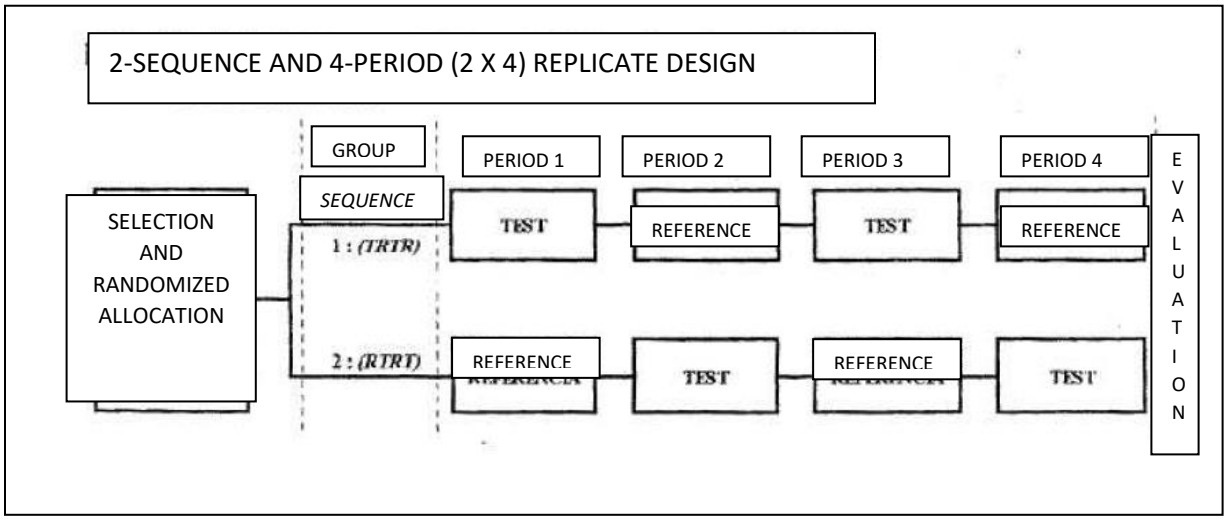


The washout period must be similar in all the animals, and its duration must be at least ten times the elimination half-life of the active substance or its metabolites. An additional period of time may be required to ensure the disappearance of any pharmacological effect, such as the induction of microsomal enzymes.

If the washout period is not compatible with a classical cross-over design, as is the case with drugs with an extended half-life, or when studies must be carried out in growing animals, a parallel design may be used comprising two groups with an identical number of animals (group 1 and group 2), where one group receives only one dose of a different product from the one assigned to the other group. The parallel design is illustrated in the figure below.



When formulations contain an active principle with high pharmacokinetic variability (CV ≥ 30%), and a short elimination half-life, a possible model is a two-sequence, four-period replicate study design, where: Sequence 1: TRRT, and Sequence 2: TRRT. Figure 4 of the annex illustrates the two-sequence, four-period replicate design.



7.9 Sample size

The number of animals needed to carry out a bioequivalence study is determined according to the level of significance established, the difference expected to be detected, the expected potency of the trial, and the variation error associated with the primary characteristic to be studied expressed as intra-individual CV. The value of the intra-individual CV can be obtained from the results of a pilot study, the results of studies carried out previously, or from data contained in publications.

The number of animals must be calculated using appropriate methods and must not be less than 6 animals per group for a cross-over study design and no less than 12 animals per group for a parallel study design.

The method for calculating the number of animals for a multiplicative model (natural log-transformed data) is presented in equation 1 of the annex. This method of calculation allows the estimation of the number of individuals for a classical cross-over design based on several CV values, values for the ratio of the geometric means (μ_T/μ_R) of the pharmacokinetic parameters used, and of the potency expected from the statistical method (1-β). For a parallel design, this value must be multiplied by 2.

The statistical test for showing bioequivalence must display a potency of no less than 80%, with a risk to the consumer of 5% (α risk; 0.05) and a risk for the pharmaceutical industry of 20% (β risk; 0.20). Since potency is estimated as 1-β, the risk for the pharmaceutical industry can be reduced by increasing the potency of the statistical test. This is achieved by increasing the number of animals included in the study. Table 1 of the annex presents the number of individuals needed to carry out a bioequivalence study for various potency values of the statistical test, different CV values, and different ratios of the geometrical means of the fundamental pharmacokinetic parameters.

Study sponsors must select a suitable number of subjects taking into account possible losses or withdrawals from the study. Since the replacement of animals during the study can hinder the model and the statistical analysis, it is generally recommended not to replace losses. Therefore, it is recommendable to recruit a greater number of animals than required for the study based on the sample size calculation.

7.10 Considerations relating to sampling time

Sampling times must be selected in order to describe, to the extent possible, the active principle plasma concentration profile and allow an accurate determination of Tmax and Cmax.

To maximize sampling time efficiency, a pilot study may be necessary to help identify the shape of the concentration/time curve and the probable variability in concentration values.

7.11 Analysis

The analytical methods used in bioequivalence studies must be fully validated in order to meet the standard validation criteria set forth in the Guidance for Industry, Bioanalytical Method Validation, FDA, Guidance for bioanalytical method of validation, EMEA, or the CAMEVET Guide for validation of residue studies.

8. DESIGN OF MULTIPLE DOSE BIOEQUIVALENCE STUDIES

8.1 Basic Principles

In some cases, it is necessary to compare the Test product with the Reference product after repeated administration in order to determine plasma concentrations during the stationary equilibrium state. This may be the case with very potent active principles that cause pharmaceutical effects at very low plasma concentrations that are below the resolution of the analytical technique. This occurs very occasionally thanks to new developments in analytical techniques.

A multiple dose study is required in the following cases:

a) When the product´s action depends on the active ingredient plasma concentrations in the stationary state.

b) When the active principle displays non-linear and/or time-dependent kinetics.

c) When the concentration of the active substance following a single dose is too low to be determined accurately using the analytical method.

d) For prolonged-release pharmaceutical forms with a tendency to accumulation.

8.2 Reference product and experimental conditions

As stipulated previously.

8.3 Dose

Dose selection for Test and Reference products will be defined as set forth in point 5.6.

8.4 Frequency of administration

The frequency of administration that results in the highest concentrations of the drug in stationary state (Css) must be selected. This can be determined through a pilot study.

8.5 Sampling

Samples must be taken to establish that stationary equilibrium conditions have been achieved (ex: by measuring two or more maximum (Cmax) or minimum (Cmin) blood, plasma or serum concentrations, or by collecting approximately 10 blood samples (including immediately prior to administration of the following dose) during the dosing interval.

Blood samples must be taken with sufficient frequency to suitably assess Cmax, AUC, Cmin and other parameters. Experimental sampling points must include a pre-dosing sample, at least 1 or 2 time points before Cmax, 2 sampling points close to Cmax, and 3 to 4 sampling points during the elimination phase.

8.6 Experimental design

Bioavailability can be determined in a state of stationary equilibrium without requiring a washout period between the administration of the Test and Reference formulations.

This type of trial comprises a single group of animals, and the two formulations - Test and Reference – are administrated to each animal using a pre-established interval between doses, until the stationary equilibrium state is reached (E_{ss}).

The number of doses required to reach E_{ss} is given by the time established as the interval between doses (τ) and the elimination half-life of the formulation. It is accepted that E_{ss} is reached when the pre-established doses have been administrated during a period of time equivalent to 4-5 times the value of the formulation´s elimination half-life. Under these conditions, the AUC estimated based on administration carried out after reaching E_{ss} ($AUC_{R,SS\ 0\text{-}\tau}$) is equal to the one that would be estimated following administration of a single dose of the formulation ($AUC_{R\ 0\text{-}\infty}$). Following the administration of the last dose of Reference formulation, the Test formulation begins to be dosed at the pre-established intervals during the time required to reach a new E_{ss}. Once this condition is reached, the AUC obtained following the administration of the last dose of Test formulation ($AUC_{T,SS\ 0\text{-}\tau}$) is estimated. An illustration of the experimental design for demonstrating bioequivalence through the administration of multiple doses is provided in Figure 5 of the annex.

9. STATISTICAL ANALYSIS OF BIOEQUIVALENCE TRIALS

9.1 Pharmacokinetic parameters to be analysed

The pharmacokinetic parameters derived from the concentration curves of the active principle in the biological matrix used for making the determination must be analysed. To avoid any possible bias, the calculation of the fundamental parameters must be based on the experimental data observed, avoiding the use of data estimated using any mathematical procedure. Exceptionally, the use of data estimated through pharmacokinetic modelling, interpolation or other procedures must be suitably justified for their inclusion in the bioequivalence study, and calculation methods must be defined previously in the study protocol.

There are numerous situations in which the data obtained for a given animal during a drug bioequivalence study may be eliminated in full or in part. Technical justification must be provided in the study for this type of elimination.

The repetition of certain circumstances may require these to be stipulated in the study protocol. For example: loss of dose administered due to regurgitation by the animal. In these cases, criteria for data elimination must be specified previously in the study protocol. Additionally, data elimination must be evaluated in these cases, taking into account factors such as:

- Acceptable time elapsed between drug administration and regurgitation event.
- The amount of material lost (food with drug) is considered relevant to the study.

Additionally, if an animal is re-dosed following a loss event, criteria for re-dosing must be clearly established in the study protocol.

Lastly, it is important to include all available data in the statistical analysis.

9.2 Single dose studies

In single dose studies, the essential parameters for demonstrating bioequivalence are: area under the plasma drug concentration-time curve (AUC) and maximum plasma concentration observed (C_{max}).

The AUC value must be calculated using plasma concentration data observed using the linear trapezoidal method.

The AUC value may only be used in the study if the estimated AUC from zero time to the time of the last plasma concentration measurement was observed (AUC_{0-tz}) is equal to or greater than 80% of the AUC extrapolated to infinity ($AUC_{0-\infty}$).

The values for C_{max} observed will only be useful for estimating bioequivalence if they are clearly defined and have been determined with relative accuracy. This is achieved through appropriate sampling times in the region of maximum probability of appearance of the peak plasma concentration, determined based on a pilot study or from data available in literature.

Other complementary parameters can be calculated and included in the study to provide additional information on the pharmacokinetic behaviour of the products to be tested, such as time at which the maximum plasma concentration is observed (T_{max}), area under the first moment curve (AUMC), mean residence time (MRT), and apparent elimination half-life ($t_{1/2el}$).

T_{max} is derived from the speed of absorption and elimination constants. This value is useful when the same considerations are applied for C_{max}. However, T_{max} is less robust than C_{max} because it quantifies a discrete variable (sampling times) whose values were pre-established in the experimental design. Consequently, it is included in the group of complementary parameters.

The AUMC is a pharmacokinetic parameter with no direct interpretation, however its calculation is mandatory in order to estimate the MRT, and therefore, its values may be included in the study.

MRT may be used as a complementary variable when it reflects mean absorption time (MAT). MRT can only be used when it has been determined following IV administration in the same animals.

If the design requires biological matrices other than plasma, justification must be provided for the parameters selected.

9.3 Multiple dose studies

The essential pharmacokinetic parameter for the determination of bioequivalence in multiple dose studies is the area under the curve in a state of equilibrium between administrations ($AUC_{0-\tau}$).

Average concentration in stable state (estimated as $AUC_{0-\tau}$ relative to the interval between administrations (τ) ($AUC_{0-\tau}/\tau$)), and the fluctuation range between maximum concentration and minimum concentration observed once a state of stationary equilibrium has been reached (C_{max} - C_{min}), may be considered as supplementary parameters.

9.4 Criteria for determining bioequivalence (bioequivalence interval)

Criteria must be selected prior to the commencement of the experiment and described in the protocol. The bioequivalence interval must be justified in relation to the expected clinical or pharmacological effects.

To establish that two formulations are bioequivalent, the 90% confidence interval must be established (IC90%) as a ratio of the geometric means (μ_T/μ_R) for AUC and Cmax, and must be shown to fall within an interval whose lower and upper limits are 0.80 and 1.25.

In specific cases where the active principle of the test product has a narrow therapeutic interval, as is the case with compounds with sharp dose-response curves (with large variations in small time intervals), the limits should be narrower.

To demonstrate bioequivalence between products under research whose active principles have a broad therapeutic interval, limits may be extended to 0.7 -1.43. This is very frequent in the case of C_{max}. The use of these extended limits must be based on clinical evidence and specified in the protocol.

9.5 Data analysis

Detailed data analysis must be furnished. A variance analysis must be carried out (including formulation, period, sequence, sequentially nested animals, and, where applicable, effect of sex per formulation) to estimate the variation risk, which will be used subsequently to calculate the confidence interval. For AUC and C_{max}, before conducting a variance analysis, log transformation of data is recommended. Transformation does not apply to time-dependent parameters observed; in this case, a non-parametric approach may be better. To conclude the bioequivalence analysis, the upper and lower limits of the confidence interval -calculated with the estimated variance error- must be compared. These are contained in the Analysis of Variance tables (ANOVA), with the predetermined limits, i.e. 0.8 to 1.25 or 0.7 to 1.43 for log-transformed data, or 0.8 to 1.2 or 0.7 to 1.3 for untransformed data.

If an effect is detected in the sequence, the first period of the cross-over design must be analysed as a parallel design.

When several criteria are used to demonstrate bioequivalence (which is generally the case), the final conclusion in favour of bioequivalence is only reached if the null hypothesis of non-equivalence is rejected for all the relevant parameters.

Other validated and duly justified statistical analysis techniques may also be used.

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Guide for conducting bioequivalence studies for veterinary medicines

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CONDUCTING BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINES

1. INTRODUCTION

In order to deliver an optimal therapeutic action, an active ingredient must be released at the site of action at an effective concentration during the intended period of time. To reliably predict the therapeutic effect of a drug, the performance of the dosing form containing the active ingredient must be suitably characterised.

Several therapeutic failures observed in the past associated with differences in bioavailability indicate the need to evaluate the performance of dosing forms in transporting the active ingredient to the systemic circulation, and from there to the site of action. Hence, the bioavailability of the active ingredient of a pharmaceutical product must be known and reproducible. If it is assumed that, in a given subject, a specific plasma concentration profile relative to time will result in essentially similar concentrations at the site of action as another drug and, therefore, will have an essentially similar effect, pharmacokinetic information can be used instead of therapeutic results to establish equivalence: bioequivalence.

In practice, evidence of bioequivalence generally constitutes the most suitable proof to support therapeutic equivalence between medicinal products. Therefore, reasonable evidence must be furnished in order to establish that the product studied is equivalent in therapeutic terms to the reference product.

It should be noted that current background information concludes that bioequivalence studies are generally not suitable to support a restriction period for use prior to slaughter, milking, or collection of eggs or honey. Residue depletion studies are very rarely covered adequately by a bioequivalence study, as is the case with the limit of quantification of the method, study duration, and statistical analysis of results. When these conditions are not met, studies will be required in addition to bioequivalence studies to confirm residue depletion in pharmacological medicines destined for food producing species.

The objective of this technical guide is to establish requirements for the design, execution and evaluation of bioequivalence studies. Addendum I envisages the possibility of using supplementary *in vitro* studies to demonstrate therapeutic equivalence.

This guideline, as every guideline, is not intended for establishing a mandatory or specific regulatory requirement. It is a tool created to allow, under the decision of the register owner and in consensus with the regulatory authorities, the use of this kind of tests to assure therapeutic equivalence, avoiding the unnecessary animal sacrifices.

2. DEFINITIONS

2.1 Pharmaceutical equivalent:

Two medicinal products are pharmaceutical equivalents when they contain the same quantity of the same active ingredient with the same salt or ester in the same pharmaceutical form, are destined for administration by the same route, and meet identical or comparable quality standards. However, pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in excipients and/or in the

manufacturing process may generate faster or slower dissolution or absorption, which may lead to differences in product behaviour (WHO).

2.2 Pharmaceutical alternative:

Two products are pharmaceutical alternatives when they contain the same molar quantity of the same active principle, but differ in terms of their pharmaceutical form (eg: capsule vs. pill) and/or chemical form (eg: different salts or esters). Pharmaceutical alternatives deliver the same active principle through the same route of administration, but are not pharmaceutical equivalents. They may, or may not, be bioequivalent to, or therapeutic equivalents of, the reference product.

2.3 Bioavailability:

Bioavailability refers to the rate and degree at which an active substance or its active ingredient is released from a pharmaceutical form and becomes available to the general circulation to exert an effect.

The bioavailability of a veterinary medicine is defined by the speed and magnitude at which the active substance reaches the systemic circulation and becomes available at the site or sites of action. The speed of absorption is measured in terms of the maximum plasma concentration obtained (Cmax), the time to reach maximum concentration (Tmax) and the area under the curve (AUC).

In most cases, substances have been developed to exhibit a systemic therapeutic effect. Therefore, a more practical definition can be provided to reflect that the substance in the general circulation is undergoing a dynamic exchange with the substance at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosing form – as compared with the 100% bioavailability obtainable from the administration of an IV solution of the same drug (ex: oral versus IV solution), and the "relative bioavailability" – as compared with another form administrated via an extravascular route (ex: pills versus oral solution).

2.4 Bioequivalence:

Two medicinal products are bioequivalent when they are pharmaceutical equivalents or pharmaceutical alternatives to one another, and when their bioavailability (amount of active principle absorbed and speed of absorption) following administration at the same molar dose is similar to the extent that their effects in terms of efficacy and safety in the target species are essentially the same (and not necessarily similar in terms of safety in humans or for the environment). These products should be suitably labelled and manufactured in compliance with the prevailing Good Manufacturing Practices (CAMEVET GMP or WHO GMP).

Bioequivalence is said to exist between veterinary medicines when: following administration of the same molar dose using the same route of administration, under standardised experimental conditions, the speed of absorption and quantity of active substance absorbed differ only within pre-established limits.

The active substances to be compared must have similar physical and chemical properties, i.e. dissolution profile, crystalline form and particle size. In the case of active principles presented in a racemic mixture, these must display the same proportion of isomers.

2.5 Therapeutic equivalence:

A medicinal product is only considered a therapeutic equivalent of another medicinal product when they are **pharmaceutical equivalents or alternatives,** and it has the same quality and displays the same efficacy and safety - through *in vivo* or *in vitro* studies – as the reference product, whose efficacy and safety have already been established.

2.6 Reference product

A reference product is one whose quality, efficacy and safety have been established, assessed and approved by the competent health authority of the country where bioequivalence test is submitted to endorse a new register, a new administration way or a formulation change.

3. SCOPE AND OBJECTIVES OF BIOEQUIVALENCE STUDIES

Bioequivalence studies are valid scientific methods used to compare:

3.1 A significant change in formulation that may affect the bioavailability of the active principle. *When a change is made to the composition of a pharmaceutical form, these studies may be used to show that the new product is bioequivalent to the product used to carry out the clinical trials.*

3.2 Different routes of administration for the same product. *A product with a sole qualitative and quantitative formula may be applied using different routes of administration. Two routes of administration are bioequivalent when their plasma concentration profiles are similar within pre-established limits.*

3.3 Different veterinary medicinal products that are pharmaceutical equivalents. To avoid cruel and unnecessary safety and/or efficacy studies when bioequivalence can be demonstrated with another approved product for which these studies have already been carried out. *Ex: new product vs. reference product. When comparative reference is made to an approved product in terms of efficacy and/or safety, bioequivalence with that product must be demonstrated (where the regulatory authority accepts bioequivalence as a tool for product registration).*

Although certain *in vitro* equivalence studies exist which are sufficient in some cases to fulfil this objective, these studies most often apply to solid pharmaceutical forms (ex: pills). These studies are presented in Addendum I.

4. CASES THAT DO NOT REQUIRE *IN VIVO* BIOEQUIVALENCE STUDIES

Generally, *in vivo* bioequivalence studies are not required when a product meets one or more of the following conditions:

a) The product is manufactured as a solution for administration only via the **intravenous** route and contains the same active substance as a previously approved product for use via the same route in the same target species that is the subject matter of the new application.

b) The product is an oral dosage form designed not to be absorbed (ex: antacid, radiopaque medium).

c) The product meets all of the following conditions:

- It is an **oral solution**, syrup or other similar rapid-release and high-absorption solubilised form, or a solid pharmaceutical form whose rapid dissolution has been demonstrated previously, and which

contains one or more highly soluble and high-absorption active principles (BCS - Biopharmaceutics Classification System).
- Contains an active substance in the same molar dose as the reference product.
- Has been shown not to contain inactive substances that could significantly affect the absorption of the active substance.

d) The product has been reformulated by the original manufacturer and is identical to the reference product except for colouring, flavouring and/or conserving agents, which have been shown not to have an effect on bioavailability.

e) Inhalation volatile anaesthetic solutions that contain the same active principle at the same dose.

f) Topical solutions indicated for obtaining local therapeutic effects. Other topical pharmaceutical forms for local use only in animals not destined for human consumption.

The fact that *in vivo* bioequivalence trials are not carried out does not imply that *in vitro* trials are not conducted.

5. SAFETY CONSIDERATIONS RELATING TO FOOD FOR HUMAN CONSUMPTION

In general, the fact that two formulations have been shown to be bioequivalent does not guarantee that they both need the same withdrawal period. Small variations in absorption at very low concentrations could produce significant differences in the elimination slope, which is used to determine the withdrawal period.

Consequently, a product may only be exempted from the requirement to submit a withdrawal period determination study when:

d. The method used to quantify the active ingredient in plasma has a quantification limit equivalent to or below half the MRL,

e. At least two determinations have been carried out at time points subsequent to the restriction period (withdrawal period) of the original product.

f. It is shown that there are no significant differences between the results obtained for the two products in these determinations.

In any other case, the submission of a bioequivalence study will not constitute an exemption from the requirement to conduct a withdrawal period determination study.

6. CRITERIA FOR EVALUATING BIOEQUIVALENCE STUDIES FOR PRODUCTS THAT CONTAIN HIGH VARIABILITY OR NARROW THERAPEUTIC INTERVAL PHARMACEUTICALS

In specific cases where the active principle of the product analysed offers a narrow therapeutic interval (NTI), in other words, where small variations in plasma levels can cause serious therapeutic failures (sub-therapeutic concentrations) or serious adverse reactions (supra-therapeutic concentrations), it is necessary to assess the need to narrow the bioequivalence acceptance intervals, for example: establishing a smaller AUC acceptance interval, generally of 90-110%. This would require clinical justification, because the dose-response curve displays a sharp slope, indicating that small changes in plasma concentrations generate

significant variations in clinical results (ex: cyclosporine). This requires narrower acceptance limits in order to guarantee safety in the use of these drugs.

In the case of drugs with high intra-individual variability, i.e. with significant/major variability (CV ≥ 30%) in terms of the quantity and/or speed of absorption in a given individual, a broader interval could be accepted, but would require scientific justification based on safety and efficacy considerations. It should be noted that, for drugs with high variability in the Cmax parameter, it is recommended to plan a larger sampling quantity close to Tmax, in order to suitably characterize both the speed and quantity of absorption.

In both cases, therapeutic equivalence must be demonstrated through comparative *in vivo* studies.

7. DESIGN OF SINGLE DOSE BIOEQUIVALENCE STUDIES

Whenever possible, the products or routes of administration to be evaluated in the target animal species must be compared with a single dose *in vivo* bioequivalence study. Section 7 provides examples of situations where a multiple dose *in vivo* bioequivalence study may be necessary.

7.1 Reference product

Whenever bioquivalence tests are used to endorse the register of a new product, proposed as therapeutic equivalent of other one, the most suitable reference product is the first authorised product with a complete dossier. When there are several approved products with different labels, applications or target species, a bioequivalence study must be carried out with the reference product that has obtained approval for the same indications as those of the problem (or test) product.

The reference product must be taken from a valid batch of a product that has been approved in the country where registration of the drug is sought, which contains the same active substance as the new formulation, new dosing form or salt. For example, different esters of the same therapeutic entity are considered different products.

For a given product, a formulation can serve as a reference to show its bioequivalence with other formulations that formed part of the development process.

Reference Products or Comparators will be proposed by the study sponsor upon approval of the protocol, and defined by the health authority of the corresponding country.

7.2 Reference route of administration

The reference route of administration is the one used during clinical or toxicological trials, and the one used as a reference in terms of efficacy and safety.

7.3 Standards for test and reference pharmacological products

Both the test product and the reference product must be shown to meet all the standards included in compendia or other applicable standards relating to identity, concentration, quality and purity, and must comply with all the requirements of the Good Manufacturing Practices (CAMEVET GMP or WHO GMP).

7.4 Animals

Animals used in bioequivalence studies must be clinically healthy and form a homogeneous group (in terms of age, breed, weight, hormonal and nutritional status, production level, etc.). Wherever possible, it is recommended to restrict studies to the same sex when there is no evidence of interaction between sex and products. When it is difficult to maintain the homogeneity of all the animals included in a study (ex: horses),

it will be acceptable to use non-homogenous cattle provided that the animals in each treatment group have been matched by age, weight, sex (where relevant), etc. This must be done using restricted randomization based on the relevant blocking factor(s).

The animals selected must belong to the target population for which the product is intended.

Group size: the appropriate number of animals must be estimated carefully and will depend on several factors, including variation in response, differences in the two formulations and level of rejection of the hypothesis. The cross-over study design offers advantages in terms of potency and number of animals required. It is recommended to use a minimum of 6 animals per group for cross-over study design, and 12 animals per group for the parallel group trial design.

7.5 Conditions of the trial

Bioequivalence must be carried out in compliance with the requirements of Good Clinical Practices (GCP) and Good Laboratory Practices (GLP).

For products administrated via the oral route, special attention must be paid to the different factors known to affect the arrangement of the active substance. The administration of food can improve or interfere with the absorption of the drug, depending on the characteristics of the drug and the formulation. Feed intake can also increase inter- or intra-subject drug absorption speed and magnitude variability. The protocol must include justification for conducting a bioequivalence study with unfed or fed subjects. The protocol must describe the diet and eating schedule to be followed during the study. For all species, the prandial state and exact time of feeding must be in line with animal welfare considerations (for example, ruminants must not be subjected to fasting), and with the pharmacokinetics of the active principle. Studies concerning drugs for canines and felines for oral administration must be carried out using unfed animals, unless the reference product label indicates that the product must be administrated only after being fed. Animals must have remain unfed for 8 hours before being dosed and 4 hours after the administration of the drug. For prolonged release oral medication indicated for non-ruminants, bioequivalence studies must be carried out in fed and unfed state, unless another condition is duly justified. The protocol must contain the rationale for carrying out the bioequivalence study in unfed or fed animals, and must describe the diet and feeding schedule.

If the reference product label indicates that the product must be administrated only to unfed animals or fed animals, the bioequivalence study must be carried out following the same indications relating to feed.

7.6 Dose to be tested

The approved dose must be used, and must be effective.

When several doses have been approved for the reference product, the bioequivalence test must be carried out using the highest dose.

7.7 Sampling

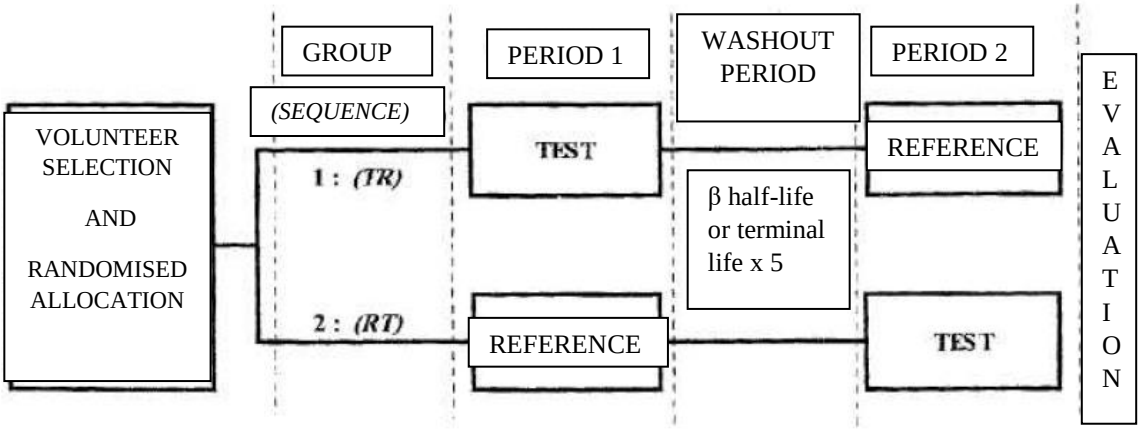
The concentrations of active principle and/or its active metabolites can be determined in biological samples such as blood, serum, plasma and other biological fluids (ex: milk, urine).

Sampling must be carried out so as to suitably measure Cmax and AUC. Measurements must include at least 2 points before Cmax, 2 to 3 points around Cmax, and 3 to 4 points during the active principle elimination phase.

7.8 Experimental design

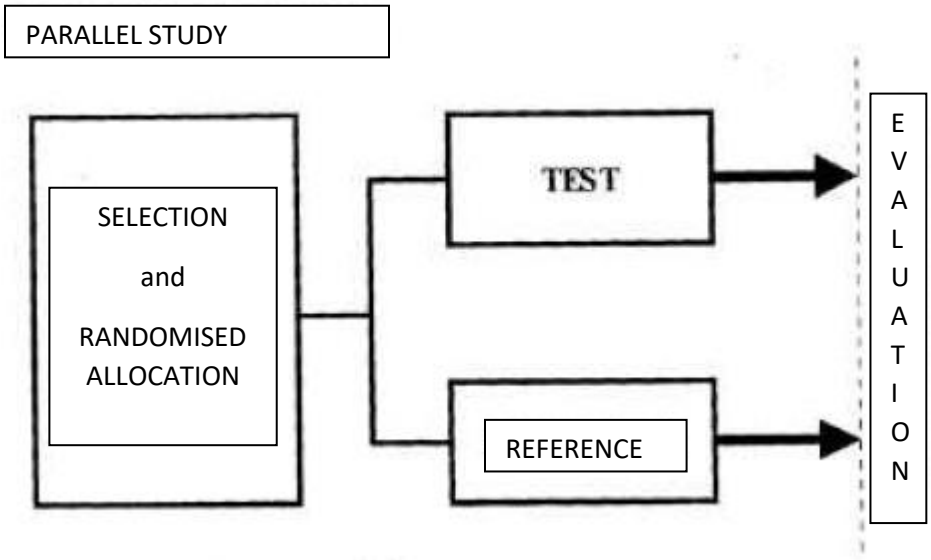
The design of bioequivalence studies must seek to reduce to the greatest extent possible any variability not associated with the formulations studied - test (T) and reference (R). Generally, a two-sequence (TR/RT), two-period (Period 1/Period 2), two treatment, balanced, non-replicated, randomised cross-over design is used for bioequivalence studies, with a single dose in each period. All animals included in the study (equal number in each sequence) must receive the two treatments - T and R. This design avoids possible confusion between treatment effects and period.

The time elapsed between the administration of each dose of T or R formulation is called the washout period, and must be sufficiently long to ensure that no concentration of the active principle administered in the first period is detected at the time of the second administration, or that any concentration detected is sufficiently low to have no pharmacokinetic impact on the new administration. The classical cross-over design is illustrated in the figure below.

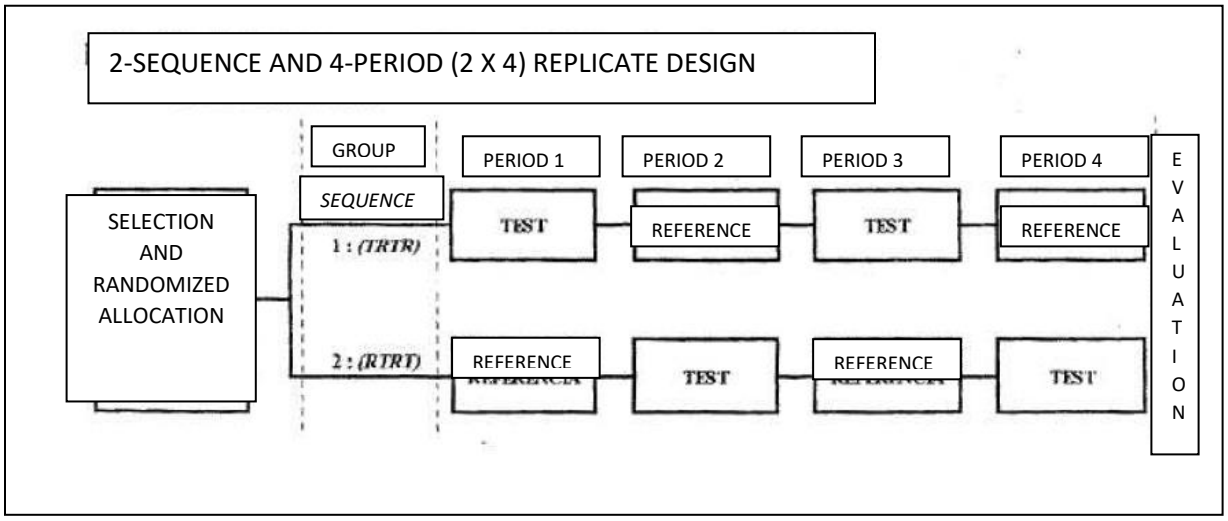


The washout period must be similar in all the animals, and its duration must be at least ten times the elimination half-life of the active substance or its metabolites. An additional period of time may be required to ensure the disappearance of any pharmacological effect, such as the induction of microsomal enzymes.

If the washout period is not compatible with a classical cross-over design, as is the case with drugs with an extended half-life, or when studies must be carried out in growing animals, a parallel design may be used comprising two groups with an identical number of animals (group 1 and group 2), where one group receives only one dose of a different product from the one assigned to the other group. The parallel design is illustrated in the figure below.



When formulations contain an active principle with high pharmacokinetic variability (CV ≥ 30%), and a short elimination half-life, a possible model is a two-sequence, four-period replicate study design, where: Sequence 1: TRRT, and Sequence 2: TRRT. Figure 4 of the annex illustrates the two-sequence, four-period replicate design.



7.9 Sample size

The number of animals needed to carry out a bioequivalence study is determined according to the level of significance established, the difference expected to be detected, the expected potency of the trial, and the variation error associated with the primary characteristic to be studied expressed as intra-individual CV. The value of the intra-individual CV can be obtained from the results of a pilot study, the results of studies carried out previously, or from data contained in publications.

The number of animals must be calculated using appropriate methods and must not be less than 6 animals per group for a cross-over study design and no less than 12 animals per group for a parallel study design.

The method for calculating the number of animals for a multiplicative model (natural log-transformed data) is presented in equation 1 of the annex. This method of calculation allows the estimation of the number of individuals for a classical cross-over design based on several CV values, values for the ratio of the geometric means (μ_T/μ_R) of the pharmacokinetic parameters used, and of the potency expected from the statistical method (1-β). For a parallel design, this value must be multiplied by 2.

The statistical test for showing bioequivalence must display a potency of no less than 80%, with a risk to the consumer of 5% (α risk; 0.05) and a risk for the pharmaceutical industry of 20% (β risk; 0.20). Since potency is estimated as 1-β, the risk for the pharmaceutical industry can be reduced by increasing the potency of the statistical test. This is achieved by increasing the number of animals included in the study. Table 1 of the annex presents the number of individuals needed to carry out a bioequivalence study for various potency values of the statistical test, different CV values, and different ratios of the geometrical means of the fundamental pharmacokinetic parameters.

Study sponsors must select a suitable number of subjects taking into account possible losses or withdrawals from the study. Since the replacement of animals during the study can hinder the model and the statistical analysis, it is generally recommended not to replace losses. Therefore, it is recommendable to recruit a greater number of animals than required for the study based on the sample size calculation.

7.10 Considerations relating to sampling time

Sampling times must be selected in order to describe, to the extent possible, the active principle plasma concentration profile and allow an accurate determination of Tmax and Cmax.

To maximize sampling time efficiency, a pilot study may be necessary to help identify the shape of the concentration/time curve and the probable variability in concentration values.

7.11 Analysis

The analytical methods used in bioequivalence studies must be fully validated in order to meet the standard validation criteria set forth in the Guidance for Industry, Bioanalytical Method Validation, FDA, Guidance for bioanalytical method of validation, EMEA, or the CAMEVET Guide for validation of residue studies.

8. DESIGN OF MULTIPLE DOSE BIOEQUIVALENCE STUDIES

8.1 Basic Principles

In some cases, it is necessary to compare the Test product with the Reference product after repeated administration in order to determine plasma concentrations during the stationary equilibrium state. This may be the case with very potent active principles that cause pharmaceutical effects at very low plasma concentrations that are below the resolution of the analytical technique. This occurs very occasionally thanks to new developments in analytical techniques.

A multiple dose study is required in the following cases:

a) When the product´s action depends on the active ingredient plasma concentrations in the stationary state.

b) When the active principle displays non-linear and/or time-dependent kinetics.

c) When the concentration of the active substance following a single dose is too low to be determined accurately using the analytical method.

d) For prolonged-release pharmaceutical forms with a tendency to accumulation.

8.2 Reference product and experimental conditions

As stipulated previously.

8.3 Dose

Dose selection for Test and Reference products will be defined as set forth in point 5.6.

8.4 Frequency of administration

The frequency of administration that results in the highest concentrations of the drug in stationary state (Css) must be selected. This can be determined through a pilot study.

8.5 Sampling

Samples must be taken to establish that stationary equilibrium conditions have been achieved (ex: by measuring two or more maximum (Cmax) or minimum (Cmin) blood, plasma or serum concentrations, or by collecting approximately 10 blood samples (including immediately prior to administration of the following dose) during the dosing interval.

Blood samples must be taken with sufficient frequency to suitably assess Cmax, AUC, Cmin and other parameters. Experimental sampling points must include a pre-dosing sample, at least 1 or 2 time points before Cmax, 2 sampling points close to Cmax, and 3 to 4 sampling points during the elimination phase.

8.6 Experimental design

Bioavailability can be determined in a state of stationary equilibrium without requiring a washout period between the administration of the Test and Reference formulations.

This type of trial comprises a single group of animals, and the two formulations - Test and Reference – are administrated to each animal using a pre-established interval between doses, until the stationary equilibrium state is reached (E_{ss}).

The number of doses required to reach E_{ss} is given by the time established as the interval between doses (τ) and the elimination half-life of the formulation. It is accepted that E_{ss} is reached when the pre-established doses have been administrated during a period of time equivalent to 4-5 times the value of the formulation´s elimination half-life. Under these conditions, the AUC estimated based on administration carried out after reaching E_{ss} ($AUC_{R,SS\ 0\text{-}\tau}$) is equal to the one that would be estimated following administration of a single dose of the formulation ($AUC_{R\ 0\text{-}\infty}$). Following the administration of the last dose of Reference formulation, the Test formulation begins to be dosed at the pre-established intervals during the time required to reach a new E_{ss}. Once this condition is reached, the AUC obtained following the administration of the last dose of Test formulation ($AUC_{T,SS\ 0\text{-}\tau}$) is estimated. An illustration of the experimental design for demonstrating bioequivalence through the administration of multiple doses is provided in Figure 5 of the annex.

9. STATISTICAL ANALYSIS OF BIOEQUIVALENCE TRIALS

9.1 Pharmacokinetic parameters to be analysed

The pharmacokinetic parameters derived from the concentration curves of the active principle in the biological matrix used for making the determination must be analysed. To avoid any possible bias, the calculation of the fundamental parameters must be based on the experimental data observed, avoiding the use of data estimated using any mathematical procedure. Exceptionally, the use of data estimated through pharmacokinetic modelling, interpolation or other procedures must be suitably justified for their inclusion in the bioequivalence study, and calculation methods must be defined previously in the study protocol.

There are numerous situations in which the data obtained for a given animal during a drug bioequivalence study may be eliminated in full or in part. Technical justification must be provided in the study for this type of elimination.

The repetition of certain circumstances may require these to be stipulated in the study protocol. For example: loss of dose administered due to regurgitation by the animal. In these cases, criteria for data elimination must be specified previously in the study protocol. Additionally, data elimination must be evaluated in these cases, taking into account factors such as:

- Acceptable time elapsed between drug administration and regurgitation event.
- The amount of material lost (food with drug) is considered relevant to the study.

Additionally, if an animal is re-dosed following a loss event, criteria for re-dosing must be clearly established in the study protocol.

Lastly, it is important to include all available data in the statistical analysis.

9.2 Single dose studies

In single dose studies, the essential parameters for demonstrating bioequivalence are: area under the plasma drug concentration-time curve (AUC) and maximum plasma concentration observed (C_{max}).

The AUC value must be calculated using plasma concentration data observed using the linear trapezoidal method.

The AUC value may only be used in the study if the estimated AUC from zero time to the time of the last plasma concentration measurement was observed (AUC_{0-tz}) is equal to or greater than 80% of the AUC extrapolated to infinity ($AUC_{0-\infty}$).

The values for C_{max} observed will only be useful for estimating bioequivalence if they are clearly defined and have been determined with relative accuracy. This is achieved through appropriate sampling times in the region of maximum probability of appearance of the peak plasma concentration, determined based on a pilot study or from data available in literature.

Other complementary parameters can be calculated and included in the study to provide additional information on the pharmacokinetic behaviour of the products to be tested, such as time at which the maximum plasma concentration is observed (T_{max}), area under the first moment curve (AUMC), mean residence time (MRT), and apparent elimination half-life ($t_{1/2el}$).

T_{max} is derived from the speed of absorption and elimination constants. This value is useful when the same considerations are applied for C_{max}. However, T_{max} is less robust than C_{max} because it quantifies a discrete variable (sampling times) whose values were pre-established in the experimental design. Consequently, it is included in the group of complementary parameters.

The AUMC is a pharmacokinetic parameter with no direct interpretation, however its calculation is mandatory in order to estimate the MRT, and therefore, its values may be included in the study.

MRT may be used as a complementary variable when it reflects mean absorption time (MAT). MRT can only be used when it has been determined following IV administration in the same animals.

If the design requires biological matrices other than plasma, justification must be provided for the parameters selected.

9.3 Multiple dose studies

The essential pharmacokinetic parameter for the determination of bioequivalence in multiple dose studies is the area under the curve in a state of equilibrium between administrations ($AUC_{0-\tau}$).

Average concentration in stable state (estimated as $AUC_{0-\tau}$ relative to the interval between administrations (τ) ($AUC_{0-\tau}/\tau$)), and the fluctuation range between maximum concentration and minimum concentration observed once a state of stationary equilibrium has been reached (C_{max} - C_{min}), may be considered as supplementary parameters.

9.4 Criteria for determining bioequivalence (bioequivalence interval)

Criteria must be selected prior to the commencement of the experiment and described in the protocol. The bioequivalence interval must be justified in relation to the expected clinical or pharmacological effects.

To establish that two formulations are bioequivalent, the 90% confidence interval must be established (IC90%) as a ratio of the geometric means (μ_T/μ_R) for AUC and Cmax, and must be shown to fall within an interval whose lower and upper limits are 0.80 and 1.25.

In specific cases where the active principle of the test product has a narrow therapeutic interval, as is the case with compounds with sharp dose-response curves (with large variations in small time intervals), the limits should be narrower.

To demonstrate bioequivalence between products under research whose active principles have a broad therapeutic interval, limits may be extended to 0.7 -1.43. This is very frequent in the case of C_{max}. The use of these extended limits must be based on clinical evidence and specified in the protocol.

9.5 Data analysis

Detailed data analysis must be furnished. A variance analysis must be carried out (including formulation, period, sequence, sequentially nested animals, and, where applicable, effect of sex per formulation) to estimate the variation risk, which will be used subsequently to calculate the confidence interval. For AUC and C_{max}, before conducting a variance analysis, log transformation of data is recommended. Transformation does not apply to time-dependent parameters observed; in this case, a non-parametric approach may be better. To conclude the bioequivalence analysis, the upper and lower limits of the confidence interval -calculated with the estimated variance error- must be compared. These are contained in the Analysis of Variance tables (ANOVA), with the predetermined limits, i.e. 0.8 to 1.25 or 0.7 to 1.43 for log-transformed data, or 0.8 to 1.2 or 0.7 to 1.3 for untransformed data.

If an effect is detected in the sequence, the first period of the cross-over design must be analysed as a parallel design.

When several criteria are used to demonstrate bioequivalence (which is generally the case), the final conclusion in favour of bioequivalence is only reached if the null hypothesis of non-equivalence is rejected for all the relevant parameters.

Other validated and duly justified statistical analysis techniques may also be used.

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Annex V

CAMEVET

Code:
Procedure:
Effective date:

GUIDE OF GOOD PRACTICES OF WAREHOUSING, TRANSPORT AND DISTRIBUTION OF PRODUCTS FOR VETERINARY USE

Guide of Good Practices of Warehousing, Transport and Distribution of Products for Veterinary Use.

1. INTRODUCTION

1.1 The products for veterinary use will be stored, transported and distributed according the established in this guide and in the pertinent legislation. Places that sell or warehouse must have authorization from the official office, *according to the legislation of each country*

1.2 For application purposes of this Guide the terminology will follow the glossary according to the Attachment I.

2. OBJECTIVE AND SCOPE

2.1 The objective is to establish the requirements of warehousing, transport and distribution of products of veterinary use.

2.2 This document applies to all employees involved in the warehousing, transport and distribution of products of veterinary use.

2.3 All the places that warehouse products of veterinary use must be registred by the official agencies according the legislation of each country.

2.4 Each kind of product that will be warehoused must be clearly definite according to the legislation of each country.

3. PROCEDURE

3.1 ORGANIZATION AND HUMAN RESOURCES

3.1.1 In each warehouse will be available an updated document indicating clearly the working positions, attributions and respective descriptions.

3.1.2 *Places that sell and t*he warehouses must have only one technician responsible for the quality of the stored products, *as well an annual program of internal audits (autoinspections)*

3.1.3 The employees involved in the products carrying~~, including drivers~~, must be trained and capacitated according to his activity, which will be updated at least once a year. *The training plan will be included in the necessary documentation*

3.1.4 The employees that carry the products in the warehouse must have access to a security guide to orientate for the prevention of physic, chemical and biological risks in case of accident.

3.2 DOCUMENTS

3.2.1 All the procedures must be objectively, clearly and precisely written, without~~,~~ *subjectivities*, in an understandable way for the person that will execute the activity.

3.2.2 It must be assured that all the procedures will be *known*, understood and applied for all the people involved. Whenever a changing is necessary, the procedures will be rewritten and identified as the last version of the document.

3.2.3 All the warehouses must contain the following procedures as the respective reports of execution of the following actions:

- *Organization chart*
- *training*
- cleaning, disinfection and *pest control*
- humidity and temperature control;
- criteria for reception, warehousing, translate, shipment and/or veterinary products sales;
- *batches release in case of importers*
- products devolutions;
- complaining and/or system fails;
- maintenance of installations and equipment;
- internal transport *(forklifts, clarks, etc)*
- *usage in case of leaks*
- *Product destruction*

3.2.4 All the warehouses must have available the following information:

- inventory of the veterinary products available for sales;
- inventory of the returned products *and final destination*
- reports of *the refrigerator temperature (data logger)and, if necessary, in the products carrying.*

3.2.5 Wholesalers and warehouses must have files with information of each batch product to facilitate, if necessary, the removal of this product of the market. Such files must contain, at least, the name of the product, the batch number, the expiration date, the quantity, date of admission and expedition in the stock, name and address of the client, including, in case of product with special control, the data required in the specific legislation *of each country.*

All information must be available in the database for *no more than 1(one)* year after the *expiration* date.

3.3 WAREHOUSING FACILITIES

3.3.1 The WAREHOUSING sites must follow the conditions:

- *the warehousing facilities must have the health authorizations issued under the laws of each state.*
- ventilation, lighting, humidity and temperature according to the *conservation* requirements for each product category; *it is suggested to carry on a study of environmental conditions (mapping) in the different seasons, which aims to locate critical points of fluctuation of temperature and relative humidity (highest and lowest) within the storage area*
- *protection of flammable or dangerous products*
- *area for quarantine well identified*
- *refrigeration and/or freezing equipment with enough capacity and temperature and relative humidity registration*
- protection against dust, rain, insects and sunlight;
- access signs to corridors if needed, including security signs *and evacuation routes if necessary*
- walls, shelves, roofs and floors *must be smooth*, which can be maintained clean, *in good conditions of use and it must be ensured the correct handling of spills.*
- *rest areas, food and cleaning areas, locker rooms, lavatories and sanitary services should be enough for the number of users. These areas must be with no direct communication with storage areas*
- *warehousing sites must comply with the provisions herein and the rules of each Member State*

3.3.2 The warehouses must have:

- restriction signs, such as: do not smoke, do not eat, wear personal protective equipment;
- first aid kits;
- refrigeration or controlled temperature if it is a product requirement;

- garbage *and spills* collection sites, *following regulations of each country*
- area for returned products, *quarantine, rejected, expired, returned, destined to destruction*
- *area of special controlled products (psychotropic) which should be stored in restricted areas and locked safe*

3.3.3 The separation and dispatch site of veterinarian products must be designed with facilities, space and lighting which allow working with efficiency and safety.

3.3.4 The construction and localization of shelves must have:

- tracking system of each product;
- appropriate distance from the floor and walls which allows cleaning, insects control and products handling *and adequate air circulation*
- *maximum storage height in order to avoid excessive temperature, specially in summer and when the ceilings are not well insulated*

3.3.5 The veterinary products must not be stored in the floor, but on pallets or similar structures in order to allow an easy cleanliness

3.4 RECEIPT, STORAGE AND DISTRIBUTION

Wholesale distributors should have procedures to ensure that products come from legally established suppliers and are shipped to authorized retail outlets (veterinary pharmacies)

3.4.*1 Only finished and registered veterinary products within the period of validity and veterinary products without registration required, can be received and stored;*

3.4.2 Expired, returned and collected products must be warehoused in separated and identified areas *(quarantine areas*) until appropriated destination, in order to avoid their dispatch.

3.4.3 Products with special control, must be kept in a restricted area, in order to fulfill the specific legislation *of each country*

3.4.4 Products can be put in the storage site only after inspection and verification of their purchase order and fiscal document.

It is not allowed to keep in the warehouse (storage) products with different purpose from the establishment. Unauthorized products, products without registration in the official office or exempt of registration cannot be kept in the warehouse.

3.4.5 The product disposition in the storage must allow the correct turnover according to the expiration date and avoid mixing products with different expiration dates; the first product to *expire* is always the first to leave the storage.(FEFO)

3.4.6 During all period in the warehouse the products must be kept in their original package and

preserved in proper temperature, humidity and lighting. These conditions must be controlled and recorded *The conditions of storage must be documented ensuring the integrity of the stored product as required in the labeling, according to the climate area where it is marketed.*

3.4.7 The biological products or those which require controlled temperature will have their conservation, transport and delivery conditions specified.

3.4.8 The separation and dispatch must be done by qualified and trained employees in order to avoid shipment mistakes, product devolution and mishandling, which can damage the product quality.

3.4.9 The product package must ensure protection when the product is handled and transported.

3.5 TRANSPORT

Wholesale distributors must demonstrate that the transport used ensures the required storage conditions

3.5.1 The means of transport must keep the integrity and quality of the product until the final destination *according to the temperature and humidity conditions of storage, indicated in the labeling, to the final destination and it must comply with local or international legislation for veterinary products*

3.5.2 Besides the driver and loader names, also date and place of delivery must be included in the cargo manifest. Emergency form *(MSDS)* is compulsory for dangerous products *according to local legislation*

3.5.3 Products which require controlled *temperature* must be transported in refrigerated transport means or in isothermal boxes which guarantee proper temperature. *The transport pathway must be validated* or temperature must be controlled and recorded.

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Workgroup
Current Coordinator: Dr. Carlos A. Rufrano (CLAMEVET - Argentina)
Initial Coordinator: Dr. Milson da Silva Pereira (Sindan Brazil)

Members:
Dr. Nestor Guerrero Lozano (Colombia Oficial)
Dr. Emigdio Lemes Anaya (Cuba Oficial)
Dra. Berta Chelle Chetrit (Uruguay Oficial)
Dr. Henrique Uchio Tada (Alanac Brasil)
Dr. Carlos Francia (Caprove Argentina)
Dra. Mercedes Etcheverry CEV Uruguay)
Dra. Milena Martín Zárate (Fenalco Colombia)
Lic. Rocío Alexandra Luna Orta (Infarvet México)
Dra. Claudia Re Huerzo (ASIFAN Costa Rica)
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ATTACHMENT I – GLOSSARY

Cargo Manifest – Document which summarizes all fiscal documents related to the transported products.

–*Marketing*: All kinds of introduction of products for veterinary use in the market. Sale.

Distributor – Company which distributes the products for veterinary use and supplies the wholesalers, retailers and consumers.

Final product – Product which–*has passed* through all production steps, including labeling and

packaging.

GPWTD – Good Practices of Warehousing, Transport and Distribution. It consists on activities planned and regulated with written documents which guarantee the quality of products for veterinary use while their warehouse and transport.

Psychotropic Product – *final* product that contains substances which can cause chemical and/or psychic addiction and therefore must be warehoused and transported according to the regulation.

Quarantine: The status of veterinary products isolated physically or by other effective means whilst awaiting a decision on their release or rejection

Recall: voluntary, or required by the Competent Authority, procedure by which a batch of product is retired of the market.

Retailer Company – Company which sells the product for veterinary use to the final consumer (user). Retail distribution channels: the retailer represents the end of the distribution chain because they serve directly the consumer. Examples: resellers, pet shops, drugstores, *pharmacies*, clinics and veterinary hospitals.

Returned product – Final Product which is returned to the manufacturer.

Storage conditions:they are those recommended by the manufacturer and declared on the labeling, based on stability studies, ensuring the maintenance of quality, safety and efficacy, through the entire product shelf life

Traceability: the ability to reproduce the history of movements and locations of a batch of product

through a documentary tracking system

Transport – Consists on choosing the mean of transport to deliver the product for veterinary use to the wholesaler, retailer or final consumer, and also to keep the products biological and physical-chemical characteristics are preserved them until they reach the final destination.

Transport of products with controlled temperature – Products for veterinary use which must be kept in appropriate temperature *(cold chain). They* require specific instructions of warehouse and transport, which must be included in the protocols. The temperature register and tracking must be checked and signed. The temperature deviations must be investigated and evaluated.

Warehouse – Site where the final products for veterinary use are stored in appropriated and regulated conditions, until they are distributed and commercialized. Besides big and small warehouses, industries, logistic operators, distributors, wholesalers and retailers can also be considered as warehouse.

Warehousing – Safety storage, movement and conservation of final products for veterinary use.

Wholesaler – Company which sells to a retailer company or *directly* to the consumer. The sale in small quantities attends to the retailers' financial conditions and storage room. *It also enables the retailer to shop for different products from a single source.*