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REPUBLIC OF COLOMBIA

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MINISTRY OF HEALTH AND SOCIAL PROTECTION · ~ L -, + - ____

ACT numer ~U'- **S 21 2017**

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16 AY 2017

By which establishes the emergency technical regulation for the obtaining of the registry And adopting the Good Manufacturing Practices Guide for manufacturing

THE PRESIDENT **OF THE REPUBLIC OF COLOMBIA**

In exercise of its constitutional and legal powers, in particular, give the cOi1fer ~ Numeral 11 of article 189 of the Political Constitution, and in development of articles 245 Law 100 of 1993 and 2.2.1.7.5.12 of Decree 1074 of 2015, as amended by Decree 1595 of the same year and,

CONSIDERING

That Law 170 of 1994 Colombia approved the *"Agreement of the World Trade Organization Trade "and* its Annexes Multilateral agreements, among which is the *"Agreement on Technical Barriers to Trade (TBT)"* enshrining the development, Adoption and implementation of technical regulations, based on scientific and technical information available. Related processing technology or the end-uses to which the Products, which have as objectives, among others, the protection of health and safety Human.

That the Andean Community - CAN is a subregional integration mechanism created Through the Cartagena Agreement of May 26, 1969, with the purpose of improving the And balanced development of the inhabitants of the member countries through the Integration and economic and social cooperation, of which Colombia is a member.

That the CAN in Decision 562 of 2003 establishes the guidelines for the elaboration, adoption And application of technical regulations in the member countries of the Andean community and at Community, providing the wording of Article 4 that the emergency technical regulation is a *"document adopted to address problems* or *issues threats could affect the safety, health, environmental protection* or *national security "*

That the second paragraph of Article 245 of Law 100 of 1993 determined that it corresponds to the National Government regulate, among others, the health records system of the Products of the National Institute for Drug Surveillance and Food - INVIMA, including medications are as antivenoms Highly effective in the accidents that occur in the country, caused by animals Poisonous

That Article 2.2.1.7.2.1 of Decree 1074 of 2015 that compiles the rules of character Regulations governing the Trade, Industry and Tourism sector, as amended by Decree 1595 of the same year, has in the section of definitions, that without prejudice of the established In Andean decisions and laws, for the purposes of Chapter VII of the Subsystem Of Quality, will be used those provided there among which is the one of technical regulation of emergency or urgency and *"technical regulation adopted in events that arise* or *threaten* to *arise urgent security issues, health, environmental protection* or *national security* to *a country. "*

Article 2 .2.1.7.5.12. *ibidem* technical regulations concerning emergency or That, exceptionally, the regulatory body may issue That for this the requirements of the list of problems must be fulfilled, impact analysis Normative, public consultation, international notification and prior concept of the Regulation of the Ministry of Commerce, Industry and Tourism, before its issuance.

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Then the decree *Whereby the emergency technical regulations for obtaining set antivenom* and *veterinary manual Good Manufacturing Practices adopted "*

That according to the Public Health Surveillance Protocol of the INS Environmental and geographical conditions, and because of these characteristics, accidents Public health surveillance, which has highlighted the difficulties National production of antivenoms against the needs of the country, motivating the Ministry of Health and Social Protection declare in recent years the health emergency Due to a shortage of some of these medicines, to guarantee the proper Protection of the health of the inhabitants of the national territory.

That ophidiotoxicosis is an intoxication produced by the inoculation of venom due to the Bite of a snake (ophidian), that triggers physiological alterations in the victim, With undesirable outcomes in morbi-mortality, therefore, the ophidian accident is of Compulsory notification in the Public Health Surveillance System -SIVIGILA, and mortality Caused by snakebite poisoning is recorded as a cause The frequency and severity of such an event makes it Interest in public health.

That the World Health Organization - WHO recognizes that it is necessary to support the Measures aimed at the design of agents used as antivenom for various areas The protection of human health and safety, and to prevent Possible damages to it.

That the recommendations contained in Report 32 of the World Health Organization WHO and the *"WHO guidelines for the production monitoring and regulation of Snake Antivenom Immunoglobulin "by* the WHO Expert Committee on Biological Satandarization (WHO, 2010)" Requirements and criteria that serve as a guide to ensure Manufacture in the manufacture of antivenoms.

That for reasons of public health, and given the threat of public health by the Persistence in increasing notifications of accidents caused by animals

Poisonous, it is necessary to determine a specific health regulation of
Emergency, aimed at establishing the requirements of local manufacture and import of
Antivenoms used in the pars, through an emergency technical regulation that
Health requirements without prejudice to their quality, safety and efficacy.

That, likewise, the Benefit Plan Administrator Entities - EAPB must
Ensure that the providers of health services that make up their network, maintain the
Availability and allow the timely provision of antivenoms for the care of Jos
Accidents throughout the national territory, and in the case
Covered by the Health Benefits Plan charged to the
Capitation -UPC, the Territorial Health Entities must, in turn, ensure their
Availability, provision and distribution.

In light of the foregoing,

DECREES

TITLE I
ANIMAL HEALTH RECORD

Chapter I
GENERAL DISPOSITION

Article 1: ***Purpose.*** The purpose of this decree is to establish the technical regulation of
~ mergencla, to which .través health requirements for the listed
Interesad.os Import ~ ro manufactured within the national territory antivenom to be used in
The occurrence of accidents caused by venomous animals, in the registration process
san / jar before INVIMA and adopt the *"Gula of Good Manufacturing Practices*
for the manufacture, .de Antivenoms "containing the requirements and criteria for the
Interested parties are certified in Good Manufacturing Practices (BPM) before the IMI.

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Sanitary registry of antivenoms and adopts the manual of Good Manufacturing Practices "

Article 2. *Scope.* The provisions set out here apply to persons
Natural and legal entities that develop activities of production, storage, distribution,
Import, marketing and use of antivenoms used in the country for the treatment
Of accidents caused by venomous animals and to the respective health authorities
Which exercise inspection, monitoring and control functions for production activities,
Storage, distribution, importation, marketing and use of anti-venoms.

Article 3. *Definitions.* For the application of this decree,
In addition to the definitions established in Decree 677 of 1995 or the rule that
Modify or replace. the following:

3.1 Antiveneno. Purified fractions of immunoglobulins or fragments of
Immunoglobulins from the plasma of animals that have been immunized with a
. Poison or a mixture of poisons.

3.2. Immunoglobulin. An antibody molecule obtained by immunizing an animal
(Usually a equine) against the venom or mixture of poisons of an animal
Poisonous Immunoglobulin G (IgG) is the most abundant type of antibody.

3.3. Toxin. Toxic substance, which can be a protein, which is produced by cells
Or organisms and is capable of causing disease when it comes into contact with
Some tissues of the body. It is also often capable of inducing antibodies or
Neutralizing antitoxins.

3.4. Poison. Toxic secretion of a specialized gland, which upon inoculation provokes
Toxic effects. Poisons generally comprise many components,
They have proteins and peptides of varying structure and toxicity.

CHAPTER 11
PROCEDURE FOR THE APPLICATION OF HEALTH RECORDS OF
ANTIVENNES

Article 4. *Procedure for requesting sanitary registration of new antivenom.*
Requests for new antivenom health records will be evaluated before INVIMA
Complying with the requirements indicated in the present technical regulation and following the
Procedure established in article 128 of Decree-Law 019 of 2012 or the rule that the
Modify or replace. And in the provisions of the Code of Administrative Procedure and
Administrative Litigation -CPACA.

Article 5. *Procedure for requesting sanitary registration of antivenoms*
included in *pharmacological standards.* Requests for health records of antivenoms
Pharmacological standards will be evaluated before INVIMA in compliance with the
requirements identified in this technical regulation and following the procedure
Established in article 127 of Decree - Law 019 of 2012 or the standard that modifies it or
and replace the Code of Administrative Procedure and the
Administrative Litigation -CPACA.

Article 6. *Validity of medical records.* The health records that are issued
In accordance with this technical regulation. Shall have a validity of eighteen (18) months, counted
Based on the finality of the administrative act granting it.

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CHAPTER 111

PHARMACOOLOGICAL EVALUATION FOR THE OBTAINING OF THE HEALTH REGISTER OF ANTIVENNES

Article 7. *Pharmacological evaluation.* It is the procedure by which ellNVIMA, Forms a judgment on the efficacy and safety of an antivenom. Pharmacological Evaluation The Specialized Chamber for Medicinal Products and Biological Products of the Commission Revisora of that entity, (hereinafter the Specialized Chamber) taking into account the following Product features:

7.1. Effectiveness

7.1.1. Indications, contraindications, interactions, precautions and warnings
7. 12. Studies supporting product efficacy against venoms greater Importance of the country.
7.1.3. Studies of physicochemical characterization that include the content of protein and the Degree of purity of the product.
7.1.4 Dosage.
7.1.5. Specific trials (pre-clinical studies) that Technically the neutralizing capacity against the poison involved.

7.2. Security

7.2.1. Adverse effects.
7.2.2. Nonspecific toxicity (safety).
7.2.3. Storage conditions.
7.2.4. Special Restrictions.
7.2.5. Quality summary.

Paragraph. EIINVIMA prior scientific technical justification may request, once only, Additional information that supports the effectiveness of the antivenom for the specific product.

CHAPTER IV
PHARMACEUTICAL ANALYSIS EVALUATION FOR THE OBTAINMENT OF THE ANIMAL HEALTH RECORD

Article 8. *Pharmaceutical Evaluation.* It is the study carried out by INVIMA, which allows Conception of the technical capacity of the manufacturer, the manufacturing process' and the Quality of an antivenom. For this purpose, the applicant must provide the following information:

8.1. Pharmaceutical form and commercial presentation.

8.2. The composition or qualitative-quantitative formula of the product, identifying the name of the Antivenom, per unit.

8.3. Standardized batch manufacturing formula.

8.4. Specifications and results of reference material used as a standard for The quality control (in-house standard) of the active principle (s).

8.5. Detailed description and definition of parameters for the selection of animals, Obtaining of poisons, plasma, serum, active pharmaceutical ingredient (Immunoglobulins or their fractions); And validation of the manufacturing process, (Including the purification, precipitation, filtration, formulation, filling, Packaging and closure), or, failing this, compliance protocols and schedules to be Verified in the renewal of the certification.

8.6. Quality specifications and results of quality controls on Raw materials (poisons, plasma, serum and immunoglobulins or their fractions and Formulation aids) and to the packaging / closure system, providing the certificates Analytics issued by manufacturers and suppliers.

8.7. Quality specifications, description of controls performed on the product During the manufacturing process (in all stages from obtaining the poison To the finished product) and the results of such controls.

8.8. Methodology of finished product analysis. The manufacturer must provide a A detailed description of the methodologies used and their validation (or Failing that, protocols and compliance schedules to be verified in the Renewal of certification) or the current official pharmacopoeia used.

8.9. Studies of natural stability to determine the useful life of the Finished product and when applying the reconstituted product.

8.10. Draft scale of the project of labels and projects of the packaging and packaging, Which includes: name of the product, name of the manufacturer, lot number, shape Drug, labeled volume, specificity (neutralized venom including Common name of the animals against which the product is effective), potency Neutralizing, storage conditions, including those of the product Reconstituted when applicable, description of the reconstitution process, route of Administration, recommended dosage, contraindications, warnings and date of expiration.

CHAPTER V
LEGAL EVALUATION FOR THE OBTAINING OF THE HEALTH REGISTER OF ANTIVENNES

Article 9. *Legal Evaluation.* Comprises the legal study carried out by ellNVIMA to the following Information and documentation to be submitted by the interested party to obtain a health record Of an antivenom:

9.1. For the antivenoms that occur in the country:

9.1.1. Name of the product for which registration is requested and modality of the same.

9.1.2. Name or business name of the natural or legal person on whose behalf the registry.

9.1.3. Name of the pharmaceutical laboratory or manufacturing industry, or copy (s) Contract (s) when the product is manufactured by third parties. In said The contract must indicate the products to be manufactured, the manufacturing stages And if it will be in charge of the quality controls. The manufacturer must The Certificate of Good Manufacturing Practices (BPP). What this act is about administrative.

9.1.4. Proof of the constitution, existence and legal representation of the petitioner.

9.1.5. Special power to a lawyer to handle the procedure, if you are going to advance the procedure By delegation.

9.1.6. Certificate issued by the Superintendency of Industry and Commerce, which contains That the mark is registered in the name of the person concerned or that the mark has Registration, which is in process. When the owner of the mark is a third party The authorization for the use of it must be attached.

9.2. For the antivenoms that are imported to the country, the previous ones must be fulfilled Requirements and also provide the following documents:

9.2.1. Certificate of Free Sale (CVl) or Certificate of Pharmaceutical Product (CPP) Issued by the competent authority of the country of origin.

9.2.2. Certificate of analysis issued by the manufacturer or by whom has been contracted for Such an end. .

9.2.3. Summary of the manufacturing protocol signed by the laboratory manager maker.

Paragraph. Documents issued abroad must be duly provided Apostilled or consularized and legalized with the respective official translation, according to the provisions of Resolution 3269 of 2016 or the standard amend or replace it .

CHAPTER VI
RENEWAL OF HEALTH RECORDS

Article 10. *Renewal of medical records automatically.* the requests of Of renewal of the antivenom health registries used in the treatment Accidents caused by poisonous animals, they will be supplied automatically, provided that When the following conditions are met:

10.1. Keep the information and characteristics that were approved during the Validity of the health registry.

10.2. It complies with the provisions of Articles 129 and 130 of Decree - Law 019 of 2012.

10.3. Have the Certificate of Good Manufacturing Practices (BPP).

10.4. Present the results of natural stability studies that have been carried out From the time the health registry was granted. These correspond to the Stability studies, in which a lot will be year.

Paragraph 1. For imported antivenoms, the Certificate of Sale must also be attached Free -CVL or Certificate of Pharmaceutical Product -CPP in force, issued by the authority Competent authority of the country of origin.

Paragraph 2. Requests for renewals of the health records of antivenoms Used in the treatment of accidents caused by poisonous animals involving Changes or have. Significant changes in the information at the discretion of the INVIMA, will be processed through the procedure established in article 17 of Decree 677 of 1995 or standard that modifies or replaces.

Article 11. *Validity of the renewal of health records.* EIINVIMA shall issue the Corresponding renewal to the sanitary registry, for a term of eighteen (18) months, Counted from the firmness of the administrative act granting it.

Paragraph. If the health record has expired without the request for Renewal, the application is abandoned, the application is withdrawn or the application has not Provided that the relevant product can not be imported into the country or manufactured, the case.

Article 12. *Subsequent revision of requirements.* EIINVIMA once grants renewal to the Sanitary registry, shall carry out the verification of compliance with the requirements established in This technical regulation and may request information from the interested party who will have A period of one (1) month to supply it.

If, as a consequence of the subsequent review, it is verified that the owner of the renewal Of the health registry does not meet the requirements or does not respond to the Information, by means of an administrative act duly motivated and based on the Risk, it will proceed to cancel the sanitary registration, following the administrative procedure Which for the purpose establishes iIINVIMA.

CHAPTER VII
MODIFICATIONS TO THE HEALTH REGISTER

Article 13. *Amendments to* the *sanitary registration of antivenom used in the Treatment of accidents caused by poisonous animals.* Modifications to the Health records of antivenoms used in the treatment of accidents caused by Animals, will be supplied automatically, and with subsequent revision of the Documentation that supports the fulfillment of the exigible requirements, following for the Effect the procedure for the subsequent revision of requirements referred to in the previous article, and In the following cases:

13.1. Changes in the name or business name or address, or address of headlines and Importers.

13.2. Changes in name or reason Manufacturers, packers, packers or Conditioners.

13.3. Changes of nomenclature in the direction of the manufacturer or: of the packer, Packer, conditioner, holder, importer; Providing the respective support.

13.4. Assignments, additions or exclusions of holders, packers, conditioners and Importers.

13.5. Change in commercial presentation, as long as the composition is maintained And volume per unit.

13.6. Changes in labels that do not modify the texts previously approved by The INVIMA, and that relate to the modifications dealt with in the present Article.

13.7. Changes in indications, contraindications, precautions and warnings for the Same active principle, pharmaceutical form and concentration when they have Of the Specialized Chamber for Medicinal Products and Biological Products IINVIMA Review Committee.

13.8. Elimination of inserts containing pharmacological aspects, when these are On the label, label or packaging.

13.9. Brand of products.

13.10. Reduction of useful life, as long as the conditions are preserved initially Evaluated and approved by the I NVIMA.

Paragraph. Modifications to the health registry in cases different from those previously Shall be provided in accordance with the procedure established in article 18 of Decree 677 of 1995 or the standard that modifies or replaces it.

CHAPTER VIII
EXHAUSTION OF PRODUCT AND PACKAGING STOCKS IN THE MARKET

Article 14. *Exhaustion of stocks of product and packaging* in *the market.* The Antivenoms that have been granted the health registry may exhaust the Of the medicine with the number of the health registry initially assigned, up to the useful life Of the product approved by elNNVIMA

In the case of having packaging material with the health registry number initially Assigned, this situation must be informed to INVIMA, in order to allow the Exhaustion, in accordance with the procedure that that entity indicates for that purpose.

Paragraph. If the health record expired, stocks remain in the market, elNVIMA will allow interested dispose of them within the approved shelf life Corresponding sanitary registration.

TITLE 11
CERTIFICATE OF GOOD MANUFACTURING AND RELEASE PRACTICES LOTS OF ANTIVENNES

Chapter I
CERTIFICATE OF GOOD MANUFACTURING PRACTICES

Article 15 *Guide to good manufacturing practices for manufacturing Antivenoms.* Adopt the *"Guide to Good Manufacturing Practices for manufacturing antivenom "contained* in the Technical Annex which is an integral part of this act administrative.

Article 16. *Certificate of Good Manufacturing Practices -BPM.* Manufacturers of Antivenoms located in the national territory must be certified in Good Practices of Manufacturing -BPM before eIINVIMA, fulfilling for the purpose the requirements of this act Administrative procedure and the Guide referred to in Article 15, in accordance with the procedure Define for the effect the INVIMA

For the importation of antivenoms, INVIMA will accept the Certificate of Good Practices Of Manufacturing - BPM granted by the competent health authority of the country of origin or its defect must obtain it before the INVIMA, of. Accordance with the provisions of this chapter.

Article 17. *Validity of the Certificate of Good Manufacturing Practices.* The certificates Of Good Manufacturing Practices issued by the National Institute of Medicines and Food -INVIMA, will have a validity of eighteen (18) months.

CHAPTER 11
RELEASE OF LOTS OF ANTIVENESS

Article 18. *Release of lots.* Manufacturers and importers of antivenoms used in The treatment of accidents caused by domestic animals used in the country, Must present the samples and / or the supporting documentation of each batch for the respective Release by INVIMA, prior to its commercialization, in accordance with the Guidelines that define that entity.

Part 111
HEALTHCARE, INSPECTION, MONITORING AND CONTROL AND PROVISION OF PREVENTIVE

Article 19. *Pharmacovigilance.* The head of veterinary antivenom used in the Treatment of accidents caused by poisonous animals, will report to INVIMA, in the Periodicity it defines, the adverse events presented with the product and the reports Of monitoring its use, incorporating information from different sources of notification, As established in · the current regulations. The holder of the health Active follow-up of any adverse reactions Of the antivenoms and notify the I NVIMA.

Health registry holders should emphasize their post-surveillance activities Marketing, because of its importance in the evaluation of the effectiveness and safety of The antivenoms.

Paragraph. For applications for new and new Been placed on the market in other countries, the Security newspapers.

Article 20. *Inspection, monitoring and control.* It is incumbent upon INVIMA to exercise the functions Inspection, monitoring and control, in coordination with territorial health entities, and In development of the Model of Inspection, Surveillance and Sanitary Control, defined by the Ministry Health and Social Protection through Resolution 1229 of 2013 or the norm that the Modify or replace.

Article 21. *Sanitary and sanctioning procedure.* Health authorities Security measures and impose the corresponding sanctions, in accordance with In accordance with the provisions of Law 9 of 1979, Following the procedure contemplated In the Code of Administrative Procedure and Administrative Litigation -CPACA or The standard that modifies or replaces it.

Article 22. *Provision* of *antivenom.* The Management Entities of Benefits - EAPB must ensure that the Health Service Providers that make up Maintain availability and allow the timely provision of The attention of ophidian accidents throughout the national territory, and in the event that said Medicines are not covered by the Health Benefits Plan charged to the Health Unit. Payment by Capitation -UPC, the Territorial Health Entities must, in turn, ensure their Availability, provision and distribution.

Likewise, Health Service Providers, with the purpose of facilitating activities Pharmacovigilance, must record in the patient's medical history the name of the Laboratory manufacturer, the identification and batch number of the antivenom used.

Paragraph. In case of breach of the provisions herein, the National Superintendency of Health and other competent entities, shall take appropriate measures and initiate The sanctioning processes that may occur.

Title IV
FINAL PROVISIONS

Article 23. *Health records expired* or *canceled.* Manufacturing laboratories That are certified in Good Manufacturing Practices in accordance with the requirements Indicated in this regulation that have had sanitary registration in the modality And for the kind of antivenom approved there that is expired or canceled, may request A new health registry complying with the provisions of Article 5 of this Act administrative.

Article 24. *National* and *international donations of antivenom.* people Natural or legal, of national or international character, may donate antivenoms for the Accidents caused by poisonous animals, in which case the Sanitary registration, without prejudice to complying with the requirements established in the Article 3 of Decree 919 of 2004 or the norm that amended or replaced, and others provisions on donation.

Article 25. *normative integration.* Where not provided in this order and as Law 019 - it does not oppose herein shall, Articles 129 and 130 of the Decree shall apply 2012 and Decree 677 of 1995 and 843 of 2016 in Chapter 111 or rules that modify or replace.

Article 26. *Notification.* This technical regulation will be notified through the point Contact SPS / TBT Ministry of Commerce, Industry and Tourism, countries members of the World Trade Organization-WTO, within twenty-four (24) hours after shipment, as provided in Article 16 of Decision 562 2003.

Article 27. *Validity.* The technical regulation established through this decree governs from the date of its publication, is valid for twelve (12) months.

PUBLISH, notifiquese and ENFORCED,

16MAY2017

Given in Bogotá, DC,

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ORDER NUMBER \) U '- 821. DE 2017 SHEET No. 11 25

Then the decree · *For which* is *the emergency technical regulations for obtaining sets*
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TECHNICAL APPENDIX
"Guide to Good Manufacturing Practices - GMP · for manufacturing ANTIVENENOS"

Introduction.

For drug regulation, the Ministry has adopted different technical guidelines issued by the World Health Organization / Pan American Health Organization, in order to seek a harmonization regulations in the context of the member countries of the organization, which is part of Colombia.

Whereas antivenoms require special surveillance deIINVIMA part, through this technical regulation, establishing the *"Guia Good Prgctice* Manufacturing *for* / a *Production gf antivenom"* document containing the requirements and criteria for stakeholders to become certified in Good Manufacturing Practices, -BPM-ante eIINVIMA, taking as international benchmarks, the recommendations contained in: · *WHO guidelines for the production monitoring and regulat; on ..Snake Antivenom Immunoglobulin "* by the WHO Expert Committee on Biological Satandarization (WHO, 2010)
And the WHO report 32.

DEFINITIONS. In addition to the definitions contained in the present technical regulation, the following will be considered:

Apheresis: A procedure in which blood drawn from the donor is separated by physical means into components and one or more of those components returned to the donor.

Antivenoms combined: antivenoms against different poisons prepared by mixing different plasma prior to fractionation process monospecific or monospecific antivenom purified fractions prior to the process aseptic filling.

Manufacturing Special Area: One that required in the manufacturing process of drugs, be separated or segregated from other products manufactured in the respective property, meaning that, physical facilities independent of other production areas, including equipment, management systems and independent air locks. access independent personnel and materials handling clothing and proper training that includes policies, procedures and Precautions for personnel entering in these areas, in order to avoid risks of contamination and from these areas.

Independent area: That which must be separated or segregated from other products and / or processes to prevent the risk of confusion or contamination, for the manufacture of drugs.

Clean Area: An area that has a defined environmental control over particulate contamination or Microbiological, with facilities constructed and used so that the introduction, generation and retention is reduced contaminants within the area.

Good Manufacturing Practices: Part of Quality Assurance which ensures that products are consistently produced and controlled according to appropriate standards for use caudad and which is required for marketing authorization or specifications. This is concluded by both production and quality control.

Pollution: Introduction of unwanted impurities by microbiological or chemical, or foreign material outside, in or on a premium or packaging material or intermediate material during production, sampling, packaging or repacking. storage or transport.

cross contamination: Contamination of raw material, intermediate or finished product with another material starting or during production.

Process Controls: Inspections during production to monitor, if necessary, to adjust the process to ensure that the antivenom is in accordance with specifications. Control of the environment or equipment may also because of the control process.

Venom Poisoning: The process by which the poison is injected to a human by a bite of a venomous snake, leading it to pathological manifestations.

Fractionation: large scale process by which plasma is separated animal to isolate the fraction of inmunoglobuUna which is extensively processed for therapeutic use or can be digested with pepsin or papain to generate immunoglobulin fragments. The term fractionation is generally used to describe a sequence of process steps, which generally includes the precipitation of plasma proteins and / or chromatography, ultrafiltration and filtration steps.

Batch or Lot: A defined amount of raw material. packaging material, or processed product in one process or in a series of processes, so that can be expected to be homogeneous.

Neutralization Cross: Ability to an antivenom raised against a poison or a group of poisons. to react and neutralize the toxic effect of a poison related species not included in the immunization mixture.

Command: The process of collecting venom from live snakes.

Technical or package Batch Records All documents related to the manufacture of a batch of bulk or finished product. These documents contain a history of each batch of product and circumstances relevant to the final product quality.

Plasma portion of the remaining liquid after separation of the cellular elements of the blood collected in container containing anticoagulant; or separated by continuous filtration or centrifugation of anticoagulated blood in a apheresis procedure.

Bulk product: Any product that has completed all processing stages, but not including aseptic packaging and final packaging.

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Immunization process: A process by which an animal is injected with poison to produce a long lasting and high antibody titer response against lethal or harmful component.

TECHNICAL REQUIREMENTS FOR GMP certification.

Qualification Criteria (CC)

C: Critical	Failure to comply with this clause has high impact on safety v efficacy of the product quality.
M: Mayor:	Failure to comply with this paragraph has medium impact on product quality.
1: Informational:	Liene no impact on product quality, however it is important to contextualize audit process.

The items inspected each section are presented in list form · of referring questions to the item corresponding the Good Manufacturing Practices (GMP) as cofIlJrobación or check list. the questions refer to the various aspects of cUfIlJlimento GMP for producing antivenom.

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1.	ACITAC Y ADIN RIAL	
11.1	Is there an organizational chart with clearly defined lines of authority? Reviewed already tried?	M
1.2	Do you know the staff the organization with clearly defined lines of authority?	M
1.3	Are there written procedures describing the roles and responsibilities of company staff?	M
1.4	Does the staff know their responsibilities?	M
1.5	What is the Quality Control staff, Production and Technical Department has appointed his deputy in writing? What is the best professional staff have in Pharmaceutical Chemistry	M

his deputy in writing? What is the best professional staff have in Pharmaceutical Chemistry Colombia?

1.6	.It has Hiaiene Personal Standards?	C	
1.7	Are there Programs Occupational Health and Industrial Selluridad?	M	
1.8	Are there training v V control equipment fire prevention?	M	
1.9	Does the company staff receives ongoing training on Good Practices Manufacturing in the manufacture of antivenom and basic principles Assurance Quality and hygiene? Do you have training programs and records and their evaluation?	M	
1 10	"It trains personnel in the specific tasks of their work and the desempei \ or those areas that require special precautions? Are you registered?	M	I
1.11	Will the new staff receive induction training in their job before start your work? Is reaistros leave?	C	
1.12	Do you have programs ongoing training and qualification of personnel working in the aseptic area. including basic knowledge of hygiene and microbiology? HE ca records:! acitación 1. evaluation?	C	
1.13	Are there protocols and reports qualification of personnel performing the optical Review finished product?	M	
1.14	A seQuimiento is performed at training events?	M	
1.15	Do staff optical product review is finished during rest periods review of a batch of product?	M	
1.16	Does your revision of review activities ... Is it documented?	C	
1.17	Are there written for personnel entry procedures: production. visitor and I maintain different areas of the plant?	C	
1.18	Are there written instructions for entry and exit clean area of personnel, equipment, Materials? Do you meet?	C	
1.19	Does the staff who have been involved in the processing of animal tissue materials or cultures of microorganisms different from those used in the present process manufacturing does not enter areas preparation of sterile products, unless have implemented procedures ... v clearly defined decontamination?	and	
1.20	Are there procedures in hygiene and cleanliness are taken according to the classification of areas, and employees involved in the manufacture of sterile preparations are instructions required to report any situation that may cause detachment of an abnormal number of pollutants? ¿Medical examinations are conducted newspapers to determine whether those conditions?	C	1
1.21	A competent person designated especially responsible for deciding on the measures to be taken in respect of the staff could be causing abnormal situations microbiological hazard?	C	
1.22	To clean areas do not enter people wearing street clothes, and personnel entering production to areas with specific allocation entering the area? With respect to change of clothes V to grooming. siouen written procedures?	M	
1.23	Do people entering clean areas do not wear wristwatch or jewelry, nor cosmetics which ... des (! renderse partlculas?	C	
1.24	Do accesses to extinauidores are free and delimited? Are viaentes?	M	I
1.25	It is frequently check the correct operation of Extinguishers, Hydrants ¿? .Manaueras? Any other equipment for fire control?	I	
1.26	Are there plans and evacuation signs? Are mock evacuation performed? With what frequency?	M	
2.	I OCCUPATIONAL HEALTH AND HYGIENE		
2.1	optical and / or laboratory tests to joining the company and newspapers frequently defined? Which? Is it documented?	M	II

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2.2	surfaces staff, including gloved hands: a microbiological monitoring is performed and environments in different areas of production? Do I have set frequency, specifications v reaistros?	M
2.3	<.- There are restrictions on entry of plant personnel, such as: do not eat or smoke within the plant do not enter open wounds or infectious diseases, among others?	and
2.4	Are there procedures to establish those responsible, metodologla, often times Contact sanitizers for cleaning and sanitization of the different areas production and storage? Are there procedures preparation Sanitizing solutions and detergents? Are records are carried the preparation and filtration sterilant solutions of sanitizers used in aseptic areas?	M
2.5	Is there validation of the efficiency and effectiveness of sanitizers used in areas Aseptic? Or there are protocols validation and compliance schedules to be verified in the recertification?	M
2.6	Are Cleaning implements required are supplied? Duly found stored and identified for each area of use?	M
2.7	Does the State periodically finds ... used in the different production areas?	M
2.8	Are there special devices (floor mats, disinfectant solutions, adhesives, air showers, others) to reduce pollutants?	I
2.9	¿Staff (temporary and permanent) of the Dress properly for each area is provided? Is the dress of people in the workplace is according to the degree of air area respective to prevent product contamination? So: What is the degree D: hat, tapaboca Used and covers beard; as well as protective clothing and footwear or overshoes own area? What is the degree C: Hair and, where appropriate, the beard is covered. suits one or two are used parts, closed at the wrists and with high neck, and footwear or shoe covers appropriate. What is the degree A and B: A head cover or diving completely covers the hair and when appropriate beard; the lower edges of said cover or diving remain inside the neck of the suit; glasses, sterilized rubber gloves or plastic material are used powder-free, sterilized as footwear; armholes of pants are kept within the shoe and the ends of the sleeves of the clothes They remain inside the gloves. Clothing retains all particle discards of the human body?	M
2.10	To each employee in the area of Grade A and B is supplied with clean protective clothing and sterilized for each work session, or at least once a day if monitoring results warrant? Are the gloves are disinfected regularly during work operations, and masks and gloves are changed for each work session, as mlnimo? Does the staff working in aseptic areas has training records in sterile posture uniform?	C I I'
2.11	¿Disposable clothes used? If no, what it is supported and the maximum number is controlled sterilization cycles?	and
2.12	¿The personnel required personal protective equipment is provided according to work area?	M
2.13	Are there written procedures on handling the provision of work-: jopa-ra-e: -ip-e-rs-one ""; I-1 -: cM in each of the areas?	
2.14	Are there written procedures and documented records on washing and sterilization uniform, each of the areas? Does the fold of sterile uniforms is performed in a classified area in order to prevent contamination of these particles?	M
2.15	Just the mrnimo required number of personnel present in clean areas? Especially during aseptic processes?	and
2,16	Do they have contracts or documents that support the service wash uniform (if applicable) and your audit reports?	M
I 3.	FACILITIES AND MAINTENANCE	
3.1	Do you have architectural drawings, flow of personnel and materials, systems critical support and evacuation routes? Are they properly coded and approved?	M
32	Are there programs and procedures for preventive and corrective maintenance plant facilities' antivenom reduction? Are registered?	M
3.3	Are there procedures for collecting, handling, sorting and disposal waste generated by the company?	M
3.4	Are they clean, free of pests and sources of contamination to adjacent areas plant?	M
3.5	¿Contaminaciónpor prevention systems neighboring industries are taken?	I
3.6	Are areas of production, storage and quality control laboratories are found in good repair?	M
3.7	¿Written procedures and records sanitation and pest control have?	M
3.8	... n-located separately convenient and sanitary and locks of income for personal? Are they sufficient according to the number of people and have air supply filtered out?	M
3.9	Are the locker rooms and floor entrance locks are equipped with dryer (air or towels Disposable) and soap dispensers and sanilizantes? Are there procedures and posters alluding to hand washing clothes v placement?	M
3.10	Are toilet area separated ... raw aterias and materials and have no direct contact?	
3.11	Are there locker rooms and showers for female and male staff?	I

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3.12	Are there individual sites to store personal items? Are they clean. ordered and well ventilated?	M	
3.13	Is there an independent site production areas aimed at workshops maintenance and metrology? Do you find this site limeio and organized?	I	
3.14	Are properly stored tools and parts used in the maintenance eroducción teams?	M	I
3.15	They are social areas (cafeteria. Casino and rest) separate areas production and storage of materials? You are entering these areas with clothing different from production areas?	M	I
3.16	Production takes place in segregated in order to avoid cross-contamination areas?	C	
	SUPPORT SYSTEMS CRITICO	C	
4.1.1	raw materials, manufacturing. erimario and creasing package? Packing?	I	
4.1.2	¿Bodegas?	I	
4.1.3	¿Laboratory Quality Control fisicoguimícos Microbiological?	I	
4.2	Are there specifications pressure differentials between production areas and the air handling units? Are they recorded during the eroceso?	M	
4.3	Are records temperature and humidity are maintained in production areas and warehouses They require them?	M	
4.4	Are the instruments for measuring differential pressure, temperature and relative humidity They have the respective calibration certificates in force and cover the ranges of work?	M	
4.5	¿Written procedures for preventive and corrective maintenance of ES have different support systems critical {ventilation systems, compressed air. water level pharmaceutical, clean steam; as well as the teams' production? Are records kept?	M	
4.6	Are there written procedures for handling outside systems specifications air? Which?	M	
4.7	Is measured recorded daily efficiency of ventilation systems?	M	
4.6	What are the levels of filtering the handling units attending areas clean?	I	
4.9	What kind of water supply available to the company: Aqueduct? How well? Others?		
4.10	Does storage tanks of drinking water? They are sanitized regularly? HE They keep records	M	
4.11	What water purification processes used: Deionized? ¿Distilled? ¿Bidistilled? By Inverse osmosis? Other?	I	
4.12	Are there documented procedures for cleaning and sanitizing tanks pharmaceutical grade water storage?	C	
4.13	Are there specifications for each type of quality of water used (Potable, Purified and WFI); ace! such as physical and chemical analysis, microbiological, endotoxins. Y the rest. according to the provisions in force in Colombia official pharmacopoeia? HE has monitoring records of the above analysis and if resullado outside Specifications corrective measures are taken?	C	
4.14	Are they properly identified are suitable sampling points?	M	
4.15	Is there a plan pharmaceutical grade water sampling specifying when and how take samples?	C	
4.16	¿Endotoxin test water used by each product manufacturing is made sterile? Is it documented?	C	
4.17	Are there written procedures for cleaning and disinfection collection system pharmaceutical grade water and the water leading pipe used in the manufacture? How often is it done? "It is documented properly?	M	
4.18	Does the ductwork system obtaining ... pharmaceutical grade is medical supplies?	C	
4.19	Does desagoes systems suitable siphons, sufficiently protected?	M	I
4.20	Do you have uneven floors suitable to the siphon or drain channel?	M	I
4 twenty-one	Does the system diseflo obtaining water for injection, in its final process is the distillation or other process or above having an effective capacity for reduce bacterial endotoxins?	C	
4.22	Are they clean steam supply?	I	
4.22.1	What type of boiler used?	I	
4.23	¿Controls are performed gue water boiler feed?	M	
4.24	In gué clean steam is used?	I	
4.25	¿Condensate quality analysis is performed as an endotoxin test monthly frequency?	and	
4.26	Does the system compressed air supply is exempt 'oil and controls humidity?	C	
4.27	Is the air is filtered comerimido nitrogen through a sterilizing filter before use?	C	
4.26	Are there protocols and qualification reports: installation, operation and obtaining system performance compressed air and nitrogen? They are made these gases microbiological and physicochemical periodic monitoring, and checks its sterility, when it comes into direct contact with the sterile product?	M	
5.	STORAGE AREA OF RAW MATERIALS, MATERIALS FOR PACKING AND PACKAGING AND FINISHED PRODUCT		
5.1	It has enough space and are properly separated and sefializados: Reception? Quarantine area? Storage area? ¿Area returns? Area of rejections? Areas of retention samples?	M	
5.2	Are you restricted the entry of foreign personnel to the stores?	M	

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5.3	Are raw materials sensitive to temperature and humidity. light and oxygen are stored correctly? Are storage conditions recorded?	C	I
5.4	Do you have an adequate protective system for handling flammable materials? Are they properly identified materials and flammable solvents?	M	
5.5	Are areas are clean. tidy and in good repair? ¿Shelves. Walls, Floors, Estibas, ceilings, windows, doors?	M	
5.6	Are there adequate ventilation and lighting?	M	
5.7	Is the protected area of the external environment?	M	
5.8	Are raw materials, packaging materials and packaging and finished products are stored on separate shelves from the walls with enough space for review and toilet? Do they use pallets? Is the protected area of the external environment? ¿Systems are used refrigerated if required?	M	
5.9	Are raw materials, packaging materials are found and packaging and finished products identified by: Name? Code? Number Of entrance to the store? Number of analysis? Date of analysis? Lot Number? Provider? Date to reanalysis? ¿Amount approved? Due date? Number Of containers? As appropriate.	M	
5.10	What system used for handling raw materials rotation FIFO or FEFO? He it is documented? Are the finished products are released for agreement order of entry (the first coming in the first Salel.?	M	
5.11	They are raw materials. packaging materials and packaging and finished product located and identified according to quality status (approved. returns. Quarantine, Declined, etc)?	C	
5.12	Do you have procedures, registration and reception control, sampling, storage, production or warehouse delivery approval and release of raw materials. materials container 'f, empaque 'f, finished product?	M	
5.13	Do you have a registration system and inventory control for handling products Finished?	M	
5.14	Does each of the areas with procedures, control and temperature records and humidity according to raw materials and finished product stored? And recorded?	C	
5.15	Do you use a system of labeling in accordance with national standards for handling hazardous substances?	C	
5.16	The blood or plasma is received in sealed containers, previously cleaned and Sterilized? Are identificados'f. properly stored?	C	
5.17	Do you have written procedures indicating how to act in case of poisoning?	C	
5.18	Are there security measures to dispose Commodity labels. materials packaging and packing and finished product?	C	
5.19	Are there refrigerators and / or cold rooms for storage of products require cold chain? Are they properly qualified and / or recorder temperature?	C	
5.20	Is there validation cold chain storage and transportation for products that require it?	C	
6.	AREA DISPENSACIÓN D WEIGHING AND SAMPLING AREA		
6.1	Is there an area of weighing and sampling properly identified according to their status cleaning use separated physically?	C	
6.2	Are you properly lighted a supply system and. air extraction qualified?	M	
6.3	Are there written procedures for handling, cleaning and storage of utensils used in weighing or fractionation of raw materials show ()?	C	
6.4	Do you find the area equipped with the necessary balances and current calibration?	C	
6.5	Records of calibration verification of the balances are carried before his use? And it has calibration schedules?	C	
6.6	Are you accredited calibrations are performed by outside companies, at least once I alailo?	C	
6.7	Is it dispenses with Production Order and in accordance with the guidelines established in	C	

the dispensing procedure of raw materials? And weighing verified by the head and / or area supervisor?
6.8 They are weighed and arranged separately each of the different production orders lots? C
6.9 They are transported and delivered properly dispensed raw materials to area production? In containers clean, dry, sealed and marked in such a way that avoid contamination and confusion? M
6.10 Do you use the staff uniforms and elements suitable protection for weighing or Sampling of raw materials and packaging material? M
6.11 Do you have a special place to properly store heavy materials? You are described precautions for dispensing or sampling of raw materials require cold chain? M
6.12 the quantities are defined according to sample analysis to be performed? M
7. AREAS OF PRODUCTION
7.1 Are they defined and identified areas for each manufacturing operation? M
7.2 Are they clean. You sanitized and orderly? M
7.3 Do you have areas designated for: Storage in process? ¿Laundering tools and production equipment? ¿Wash purification and primary containers preparation? Container? ¿Clean or sterile storage containers? ¿Sterilizing primary packaging and production materials? ¿Review and optical control? Quarantine? ¿Storage Material cleaning implements? M
7.4 Are all facilities are designed in such a way as to avoid unnecessary entry supervisory or control? Where possible, the design of the areas grade A 'LB C

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allows all operations can be observed from the outside or through *the* Cameras?
7.5 Do all clean areas, all exposed surfaces should be smooth, waterproof, without cracking, to reduce the mlnimo detachment or accumulation or partlculas microorganisms and allow consistent application of cleaning substances and disinfectants, where appropriate? M
7.6 To reduce dust accumulation and facilitate cleaning, facilities do they have with a minimum number of shelves, racks, shelves and equipment that are easy to clean? Are doors are constructed in such a way that their surfaces are easy to clean? NOTE: There should be no sliding doors in grade A, B, C or wood materials areas in areas classified M
7.7 If any false ceilings, are they are sealed to prevent pollution from space? M
7.8 Will installing sinks and drains, or is avoided, are excluded from areas where Aseptic Operations performed? Where there is need to install, they are designed, located and maintained such as to reduce to mlnimo the risk of microbial contamination; They have airlocks traps that are efficient and easy to clean, in order to prevent overflow? Everything channel located on the floor is open type and easy to clean, and it is connected with drains that are outside the area to prevent the entry of microbial contaminants? M
7.9 the locker rooms for the change of clothes are they designed as airlocks, to separate the different stages of the change, in order to minimize possible contamination of protective clothing with microbes and particles? Do these locks are Cleans efficiently with filtered air downloads? Are the facilities for washing hands are located only in rooms change of clothes, never in the places where work is done? M
7.10 the locks do not open simultaneously. Is there a system of interlocking closure a¡¡ertura to prevent more than one door at a time in critical areas? C
7.11 A positive air pressure is maintained relative to surrounding areas in all operating conditions, by providing sufficient air filter and effective cleaning with volleys of it? Note: It is possible that the recommendations concerning air supply and pressure differences have to be modified, if necessary to contain materials such as pathogenic, highly toxic or live microbial material. C
7,12 Is shows that the airflow patterns present no risk of contamination? Is special care is taken to ensure that air flows do not distribute partlculas from people, machines or operations that generate particles, into an area of I increased risk for! roducts? C
7,13 Between the two areas where the air pressure difference is important (for example, manufacturing and filling), have pressure indicator instrument and spreads pressure are recorded regularly? C
7.14 If you have a conveyor belt, does it not allowed to pass through a partition positioned between a grade B area and an area processing degree of sorting 6 it is subjected to continuous sterilization? M
7,15 Do you have uniform sterilization equipment and materials production ensure efficient sterilization either by steam, dry heat or other methods? They are validated sterilization methods for each of the loads Used? C
7.16 Do all items that come into direct contact with the product and that can be a source pollution are sterilized prior to use? C
7.17 Are callerías, lumlnicos fixtures, ventilation points and other services are disellados .} 'gue located so they do not cause difficulties in? C
7.18 Whenever possible, is the assembly of equipment and maintenance thereof is such that maintenance and repairs can be carried out outside the area Aseptic? If the teams need to be dismantled for maintenance Sterilize desi again! ues of the assembly, if this is viable? I
7.19 When equipment maintenance is performed within an aseptic area Is used instruments and tools disinfected *YLO* sterilized, and the area is sanitized again? M
7.20 Are critical production equipment (ovens, depyrogenation tunnels, sterilizers, autoclave, packaging and lyophilizer) have installation qualification, operation, performance? others have production equipment installation qualification and Vprotocolos operation and schedules for qualifying performance? C
7.21 Does (s) planla (s) water treatment (n) is (are) designed (s) built (s) and maintained (s) so that ensure reliable production and of appropriate quality? M !
7.22 Can processes each time a production order for a product? C
7.23 Before starting a unitary manufacturing process, it is checked whether the equipment and place work are free of products, documents or materials corresponding to the process above that are no longer required for the process is about to start, and that teams are clean and sterilized, as required and ready for use? Does such verification *YLO* Line clearance is recorded? M
7.24 During the process and the time when each action carried out, recorded the data listed below ?: M
a) The product name.
b) The number of the batch being manufactured.
c) dates and start times of the important intermediate steps, and completion of the production. ...

d) The name of the person responsible for each production stage.
e) Initials (the) operator (s) of the various main stages of production and, where appropriate, the (s) person (s) who verified (verified) each of these operations (control weight for example).
f) The batch number *and / or* number of control analysis, and the amounts of each of the raw materials have been weighed (including the batch number and the amount of any recovered or reprocessed material that has been added).
g) Any operation or indeed related to the processing and equipment used.
h) controls during processing and initials (s) of person (s) that you have made. as the results obtained.
i) The amount of product obtained in the various relevant stages of manufacture (performance). together with comments or explanations for deviations expected performance significant.
j) detailed notes about special problems. including a signed authorization concerning any deviation from the master formula.
k) Adjustment amounts to fractionate according to the power.
A once completed processing. that record is signed and dated by the person responsible for processing operations?
7.25 Is the production of antivenoms is carried out in clean areas? Is the income to which closures effected through hermetic air, both for personnel and for C

closures effected through hermetic air, both for personnel and for materials?

7.26 Do the various operations of preparation of components (such as containers and closures). preparation product. Filling and esterización. They are carried out in separate zones within the clean area? C

7.27 There are written instructions for washing, sterilization *and / or* depyrogenation materials entering the clean area: Uniforms? Primary packaging? Materials? ¿Filtration system components (casings and hoses) and others entering sterile product contact? Tools? Others? M

7.28 The materials discharged from the autoclaves or ovens are transported so that retain their quality until the area sterile grade? Like for example the use of triple wrapping materials sterilized by autoclave? C

7.29 Are the areas clean for the manufacture of sterile preparations are classified according the characteristics required air. in grades A, B, C and O? C

7.30 Does the qualification of clean areas meet the following specifications count nonviable particles and viable ?: C

Grade	Maximum No. PARTICLE allowed per m 3 0.5-5 um	> 5um	Air ~ reo of Mues (CFU / m3)	Plates sedimentation 90 mm diameter (CFU / 4hl
A (station work current laminar air)	3,520	twenty	<1	<1
B	3520	29	10	5
OR	352,000 3,520,000	2,900 29,000	200	100 fifty

1 degree	Contact plates (diameter 55 mm) (CFU / plate)	Gloves (5 fingers) (CFU / 9uanten (B)
TO	< 1	< 1
B	5	5
C	25	I
or	fifty	

a) The state "at rest" is the condition where the installation is complete with equipment installed and operated according to the conditions established by the laboratory and the supplier, but no staff present.
b) The state "in operation" is the condition wherein the system operates in operating mode defined with the specified number of personnel present. Areas and systems environmental control must be associated disetiados to achieve both the conditions "in rest "as" operational. "
c) Settling plates must be exposed at least 4 hours and must cover the entire aseptic process.
d) The methodology given for obtaining maximum allowed partlculas must performed in accordance with the ISO 14644 standard.

7.31 Do airflow systems provide a laminar air velocity homogeneous about 0.30 mls for vertical current and approximately 0.45 for mls horizontal current. but the accuracy of air velocity depends on the type of equipment employee? C

7.32 To achieve air grades B and C does the number of air changes is generally more higher than 20 hours in an area with a good pattern of air flow and air filters particulate high efficiency (HEPA)? Does the pressure differential between productive areas critical greater 5 Pascals? C

7.33 count: In the rating of the ventilation system the following tests are performed nonviable particles at rest, air changes per hour. recovery times and HEPA filter integrity? C

7.34 What type of sterilization used for primary packaging? dry heat, moist heat, oxide ethylene, another radiation which? and

7.35 Does each of the sterilization processes validated? I

7.36 They are sufficiently lighted areas. with pressure, temperature and relative humidity adequate? and

7.37 What are the Risks of cross contamination are identified? Are measures are taken to prevent it? and

7.38 Are aseptic conditions are guaranteed during the production process when the product It is exposed? and

8. Fractionation and purification

8.1 Are there areas, equipment and protocols for plasma separation? The ~ ermiten records traceability in the Batch Record ~ roduct0? M

8.2 ¿Plasma analysis are performed: before bleeding and plasma pool ?, Included tests as concentration prote / nas, bioburden test. power neutralizing protein, profiles run in SDS-PAGE or profiles cromatográficos size or molecular exclusion? ¿Specifications are taken? HE recorded these analyzes? and

8.3 Do you have standardized plasma purification procedures for obtaining Immunoglobulin? and

8.4 Are records in the Batch Record are taken? and

8.5 Does the purification process is standardized? C

8.6 ¿Process controls performed? Is it documented? C

9. FORMULATION PROCESS

9.1 Does the formulation corresponds to the master formula approved? C

9.2 How necessary power adjustment is performed during elproceso'y formulation? and

9.3 Do all solutions used in formulation pass through a filter that retains microorganisms? C

9.4 Are areas according to the process is properly identified. lot. Product name etc? M

9.5 Are sterile materials are identified to differentiate them from non sterile? and

9.6 Orders from Production and manufacturing instructions for each batch are taken product? and

9.7 Are there procedures in antivenom for manufacturing are taken from plasmas polyvalent or monovalent? and

9.8 During all stages of the process precautions are taken to minimize the pollution, even during the stages before sterilization? and

9.9 Are areas of all production processes are separated or antivenom Segregated from other products manufactured in the company. understood as, flsicas independent facilities other production areas. including equipment, management systems and independent air locks, personnel access and material independent handling of clothing and proper training including standards, procedures and precautions to take for personnel entering in these areas. with the avoid risks of contamination to and from these areas? C

9.10 Are there protocols and reports performing aseptic process simulation (Filling of sterile media)? It is performed as mlnimo evaluation annually and always You need to be made as a check result of significant changes in the production process, facilities, equipment etc.? and

9.11 Do the actual operations are simulated as closely as possible, taking into account factors such as complexity of operations. the number of employees who are working, duration among others (for processes such as lyophilization, aseptic additions and other, You are simulated so that the properties of the nutrient medium are not affected)? and

9.12 Is it possible that in (the) average (s) selected (s) can grow a wide range of microorganisms, including those that would be expected in an environment where performs filling? and

9.13 A sufficient number of production units is included to a high degree it has security that exist, could be even detected low levels of contamination? Is all contamination is investigated? Note: A recommended mlnimo of 3,000 units or the actual size of the production batch in each filling culture medium. It seeks to reach zero growth level, unacceptable considering any figure greater than 0.1% of contaminated units and

9.14 It is verified that the simulation filled with media does not negatively affect the process? and

9.15 Do the activities carried out in sterile areas are reduced to mlnimo. especially when They are being made aseptic operations and turnover is methodical controlled, in order to avoid excessive shedding of particles and organisms effect of too vigorous activity? C

9.16 Are water treatment equipment and treated water is checked regularly. for check for chemical, biological contamination, and contamination with endotoxins, in order to ensure before use, the water meets specifications for the use you want to give? Do you keep records results and measures adopted? and

9.17 Are precautions taken to reduce microbial contamination to mlnimo "charge biological "the bulk and verified before sterile filtration? Note: The manufacturer must ensure the sterility of the finished product. I

9.18 Does the interval between washing, drying and sterilization of the components, containers, and other equipment, as well as the interval between sterilization and use, are as short possible, and subjected to a time limit in accordance with the storage conditions proven? and

9.19 Everything gas used to purge or coating a product is passed through a filter sterilizer? and is com? stolen such sterilization? and

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I . 9 twenty Are all components, bulk product containers and any other item that is needed in aseptic sterile areas where work is done, and being sterilized may be introduced to these areas through sterilizers double door Imbedded on the wall or use the triple wrapped for example? C I ! I

9.21 Always possible, any deviation from the instructions is avoided or procedures? When any deviation has to be made, it is approved in writing by the person designated, involving the quality control department. when appropriate? C I

9.22 What operations are not carried out with different products simultaneously or consecutively in the same area unless there is no risk of confusion or cross-contamination? C

9.23 Does the labeling is done as soon as possible after packaging operations and closing? If labeling is delayed, appropriate measures are taken to ensure that no there is confusion or error in labeling? M

9.24 Are verified if correct printing (codes and expiration dates. For example) whether it is effected independently or as part of the packaging process, and that check register? If printing is done manually, it is checked at intervals regular? C I

9.25 If during conciliation any significant or unusual discrepancy observed between the quantity of bulk product and printed packaging materials and the number of units produced, the fact is investigated until a satisfactory explanation before to authorize the dispatch of the products? C

9.26 Are the production and control records are examined, and if a lot does not meet the established specifications, a full investigation is submitted? Is this research if necessary, it is extended to other batches of the same product and other products They may have had some connection with the effect or inconsistency? The investigation it made is recorded p - written. including Conc: lusiones of it and its follow - up? C

10. Process Controls

10.1 Are there written procedures for process controls for each stage manufacturing (Weighing, production, packaging, filtration, sterilization, depyrogenation, lyophilization, and secondary packaging) which stated: responsible, often amounts to sampling, specifications etc.? Are registered? C

10.2 Are equipment and / or instruments used in process controls have certificates I yio calibrated current rating? Does it have calibration schedule? C

10.3 Are quality attributes are checked during the encoding process? Are there records Batch Record? C

10.4 ¿Performance monitoring and reconciliation of the amounts is done to ensure that there are no discrepancies that exceed acceptable limits? M

eleven. ESTERILIZACION

11.1 What kind of sterilization is performed to the product? sterilizing filtration and subsequent filling aseptic? Another what? I

11.2 Are all sterilization methods are validated? The sterilization method is pursuant to effect permitted!) - in manufacturing and marketing? C

11.3 Before approving a sterilization method. It is shown that is suitable for materials in question and which is effective to achieve desired levels of sterilization in all parts of each type of load to be processed? Does this verification work repeated at preset intervals, or yearly as mlnimo. also when you have introduced significant changes in equipment or load. Likewise. remain i records the results? and

11.4 Are biological indicators are considered only as additional factors for Control of sterilization? In case they are used, strict precautions are taken to avoid being due to microbial contamination? They are stored and used accordance with the manufacturer's instructions, and performance is verified by Positive controls? C

11.5 Do you have an unequivocal means of distinguishing the products and materials that have been Sterilized those who have not been? Does each basket, tray. or other conveyor clearly labeled with the material name, batch number and an indication of whether It has been sterilized or not? They are used indicators such as autoclave tape. when appropriate. to indicate whether a batch (or sublot) or material has been subjected or not to a process sterilization? C

12. THERMAL STERILIZATION

12.1 Does each heat sterilization cycle is recorded by appropriate equipment, and the due accuracy. for example in a table with a scale tiempoltemperatura printed right size of the instrument? Is inclul '.. in within the batch record? and

12.2 Is the temperature is recorded by a probe placed at the coldest point of the load or chamber loaded, this point has been determined during the validation? I preferably does temperature is verified, compared with other temperature taken by another independent probe placed in the same position? C

12.3 Does the above time table! printed temperature measuring instrument, or a photocopy of it, is part of the batch record? Are employees also indicators chemical or biological, Qero they do not replace checks by fisicos media? C

12.4 Do you allow sufficient time for the entire load reaches the required temperature before you start measuring the sterilization time? For each type of cargo determine this time? C

12.5 Was then the high temperature phase of a heat sterilization cycle. they take precautions to prevent a sterilized load during cooling contamination? Everything cooling liquid or gas that comes into contact with the product is sterilized, unless it can be demonstrated that the use of a leaky container not authorize? and

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13. Moist heat sterilization

13.1 Does moist heat sterilization is used only for materials that can wet and aqueous solutions? To control this process takes into account both the temperature and pressure? Does reading is regularly compared to the recorder the table during the sterilization? If it is sterilizers have a bottom drain chamber, is verified to be necessary to record also temperature at this position, throughout the sterilization period? When part cycle phase vacuum, regular checks are made to see if the camera loses pressure (leak test)? C I I

13.2 Are the products to be sterilized, provided that no case of hermetically closed, wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilization? Are all parts I load are in contact with water or saturated steam at the required temperature and the time required? C I

14. ESTERILIZACION IN DRY HEAT

14.1 When the sterilization process is used in dry heat, the air circulates within the Camera and maintains a positive pressure to prevent the entry of non-sterile air? The air supplied is passed through a filter that retains microorganisms under all qualified yes Air parameters grade 8? Do you qualify regularly (at least annually)? C

14.2 If the process of dry heat sterilization is also intended to eliminate pyrogenic, how part of the verification tests are performed using challenge endotoxins? C

fifteen. ESTERIIIZACION RADIATION

15.1 Do they use radiation sterilization "? This is primarily used for the sterilization of materials and heat sensitive products only? Are you allowed to use this method when the absence of deleterious effects on the product has been confirmed experimentally? C

15.2 If radiation sterilization is entrusted to an independent contractor, the manufacturer is responsible for ensuring that the rules of the section are met, and that the process Sterilization is validated? Are the responsibilities of the operator of the plant are specified radiation (to use the correct dose, for example)? C

15.3 Does the radiation dose is measured radiation during the procedure? They are used dosimeters that are independent of the rate of radiation. indicating a measure quantitative dose received by the product itself? C

15.4 Are the dosimeters are inserted in the load in sufficient number and close enough each other to ensure that a dosimeter in the chamber at all times? When It is plastic dosimeters. They are used within the time limit after calibration? C I I

15.5 Are dosimeter absorbances are checked shortly after exposure to radiation? C

~ 5.6 Are biological indicators are used only as an additional control? Are discs radiation sensitive colors are used to distinguish between packages that I C They have been subjected to radiation and those who do not? Do these disks are not taken as final decision indicators adequate sterilization? I

15.7 Is the information obtained form - in of the batch record? C

I 15.8 In the validation procedures ensure they take due account of the effects of variations in the density of packaging? C

15.9 Are materials handled in such a way as to avoid confusion between the materials They have been irradiated and non? ¿Cad¡il container has a radiation sensor C

indigue which it has been subjected to radiation treatment?
15.10 Is the total dose of radiation is given within a preset period? C
16. ETHYLENE OXIDE ESTERILIZACION
16.1 I ¿El6xido ethylene is used only when no other method is feasible? During the C . I
validation procedure shows that the gas does not take any harmful effect to the Equipment and / or product and that the conditions and time are assigned to the degassing sufficient to reduce the residual gas and reaction products to acceptable limits defined for the type of product or material? Do these limits are incorporated into the Specifications?
16.2 contact between the gas and the surfaces to be sterilized is essential; Are precautions loman to avoid the presence of organisms which can be wrapped in materials such as crystals or dried protein. Is it verifies that the nature and quantity of materials packaging do not significantly influence the process? C I
16.3 Before exposure to the gas. material balance is established. moisture and temperature required by the process? Is the time spent on this operation is considered in relation to the need to reduce to a minimum the time elapsed before the sterilization? C
16.4 Does each sterilization cycle is controlled by biological indicators, using a appropriate number of test pieces across the load? Is the information obtained by this earte medium is a member of the dellole record? C
16,5 Are biological indicators are stored and used in accordance with instructions manufacturer, 'L performance is checked by positive controls? C
16.6 For each sterilization cycle records are maintained time spent to complete cycle, pressure, temperature. and humidity within the chamber during process. as well as the concentration of gas? Does the pressure and the temperature is recorded in a table throughout the cycle? Do these data are part of the batch record? C
16.7 After sterilization. the charge is stored in a controlled and proper ventilation. to allow residual gas and reaction products to reduce defined level? Does this process is checked? C I

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17.1 It is verified that products can be sterilized in the final container, preferably by heat sterilization? When such a case is not possible, can the solutions are filtered through a sterile filter with pore size 0.22 micron nominal (or less), or one CHARACTERISTICS Sources have equivalent retention of microorganisms, and charged into You previously sterilized containers? C I I
17.2 Due to the potential additional risks that could mean the use of the method filtration, unlike other methods sterilized, employs a double filter layer filtration or carries out a second filtration with another retaining filter microorganisms, immediately before filling? I I
17.3 Do not release fibers filters are used? Does the use of filters containing asbestos discarded altogether? C
17.4 Is the integrity of the filter using an appropriate method is controlled as test bubble point after each use? and
17.5 ¿ Sterilizing filters are used - discarded later? C
i 18. ESrERILES FINISHING PRODUCTS
18.1 Are containers are closed to ensure tightness? Is the integrity is verified some samples using appropriate procedures? and
! 18.2 Do vacuum sealed containers are verified by monitoring samples thereof, to determine if the vacuum has remained after elapsed a predetermined time? C
18.3 Do the girls antivenom containers are inspected individually? If the inspection is visual, is it done under controlled conditions and adequate lighting? The Inspectors undergo regular controls vision, with glasses on if they use normally during inspections and have frequent breaks? If others are used inspection methods. Are these devices are checked and controlled employees regular intervals? C
19. EQUIPMENT
19.1 Is the installation of the equipment is such that the risk of error and contamination mlnimo be? C
I 19.2 Are production equipment no risk for products? Do the parts of the production equipment coming into contact with the product are nonreactive additives. neither absorbents, to such an extent that may influence product quality? C
r 19.3 Always possible. defective equipment are removed from areas production and quality control, or at least clearly identified as such? M
19.4 Are there written procedures regarding changes, cleaning and maintenance of: Filters ventilation system filters and filter equipment used in production? Are registered? C
19.5 Do teams are suitable materials and parts in contact with product They can be disassembled and thoroughly cleaned? They can be sterilized? .. I M
196 Are the equipment properly identified according to the state of cleanliness in which They find? M
19.7 Are equipment and materials are exclusivo.f use! Ara area? C
I 19.6 Are the equipment properly identified with the name of the product being developing? M
I 19.9 Are microbiological controls are made periodically to the surface of the equipment? HE record the results? ESl'ecificaciones will have defined and the sampling points? C
19.10 Are there reports of installation qualification, operation and discharge of the laminar flow systems? Does it include: filter integrity. counting viable particles and not viable. laminarity airflow and calibration of instruments? On an annual basis as minimum? C !
19.11 Is there respective procedures, management. cleaning, sterilization and maintaining each of the teams? M~ ..
19.12 Are you all validated cleaning process vial bottles? M
twenty. DOCUMENTATION
20.1 Is there a best practice process documentation and records? M
20.2 Is there a process for the preparation, review and periodic updating orocedimientos writings? C
20.3 .Retiran no written procedures in place? M !
20.4 Does each written procedure is properly coded, bears the date of issue and validity, name, signature and title of the (s) person (s) responsible (s) and authorized (s) for elaboration. V review approval? C
I 20.5 Are written procedures properly located available to staff who required? C
20.6 l.EI ~ ersonal knows the ~ ROCEDURES writings of your competition? C
20.7 Are these procedures written in a clear and concrete language for easy understanding? M
20.6 Does the company verifies that the relevant people know and understand the procedures written? .The Deian records? C I
20.9 They are clear and legible original and. co ~ ias? C
20.10 Do I have a master list of Standard Operating Procedures indicating the V effective date of issue? M
20.11 Perform control document distribution for ensuring that no consultation obsolete documents? M
20.12 Extemal documents that are involved in maintenance. validations. scores calibrations and analysis by third parties or other technical considered feature verification and approval of technical personnel involved? M I

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twenty-one Labels and packaging
21.1 Are there written for sampling defined criteria and classification of defects in labels and packaging? M
21.2 Are there written specifications and tolerances for acceptance or rejection of the labels and packaging? C
21.3 Are the results of the checks carried out to labels are documented and ern [lliques? M
21.4 Are the entries packaging and labels are recorded, noting the origin of the amount received and the date of receipt? M
21.5 They are closed, sealed and properly identify the components that have been sampled? M
22. RAW MATERIALS AND PACKAGING MATERIAL PRIMARY
22.1 Are there written procedures for classifying defects packaging material and primary packaging? C

22.2	Is there a register of suppliers of raw materials and properly classified Qualified?	M	
22.3	Do they have written or official specifications and procedures for procurement own and analysis of raw materials?	M	
22.4	They are closed, sealed and properly identify the components that have been sampled?	C	
22.5	They are properly documented and filed the results of the tests?	M	
22.6	Is there an updated inventory and full of all raw materials and materials?	M	
2. 3.	QA		
23.1	Does the laboratory quality control is independent in its flsicas facilities, the other areas of the plant?	I	
23.2	Is there in this area equipment and safety equipment needed? Fire extinguishers, Cam !! ells extraction, eye showers, safety goggles, safety masks?	M	
23.3	Does Quality Control staff always used these implements security?	C	
23.4	Are safety conditions at work are acceptable?	C	
23.5	The laboratory. Quality Control is under the responsibility of a chemical Pharmacist?	C	
23.6	Did the Chief Quality Control has autonomy in their decisions?	C	
23.7	Does the person! QC receives regular training? Is it documented?	C	
23.8	Do you have facilities and qualified to perform physical and chemical analysis equipment, microbiologist, molecular biology, sterility and endotoxin of raw materials, and finished product? Or it has staff reports installation and operation, and protocol compliance schedule for qualifying performance to recertification?	C	
~ 3.9	Do you have areas for storage of retention samples of raw materials, reference standards, reagents, strains, culture media? New users of are carried environmental conditions?	C	
2310	Are retention samples of materials are sufficient to allow at least two analyzes Complete? Retention samples of finished product are sufficient to enable the compl least one new analysis "to and other analysis !! ermitagarantizar quality?	M	
23.11	Are there specifications and procedures for the analysis of raw materials, Packaging and Packaging material, work in progress (when required), Bulk Products and finished products? Do these specifications are taken into account? It liene into account You established for sterile products according to pharmacopoeia officially accepted Colombia?	C	
23.12	Do they use primary or secondary standards?	C	
23.13	Do you have procedures for: sampling of raw materials, Packaging Material and packing bulk material Finished, Water, Air, sterility, endotoxins etc. Do these procedures apply? Are registered?	C	I
23.14	Do you have a procedure for handling equipment and program analysis calibration? Are these procedures recorded?	C	
23.15	Is has established specifications neutralization titre plasma as raw material to form the starting material?	M	
23.16	Do they have quality certificates of poisons used for immunization animals, either as material for evaluation or development of preparations reference?	M	
23.17	Do you have quality control records for poisons and extracted sera animals?	M	
23.18	Are quality controls the bulk product and finished products as are realized: neutralization (EDSO), protein concentration, purity, determination of contaminants, pyrogen test, sterility test, concentration of excipients, osmolarity, pH, trace determinations used in manufacturing agents. safety, subvisible particles and visible profiles run in SDS-PAGE or chromatographic profiles of size or molecular exclusion, moisture content (when applicable) and reconstitution time (Where applicable}?	C	I
23.19	In the sterility test product not only include representative samples of all the lot, but samples taken from parts of the batch considered more at risk of contamination, such as: a) In the case of products which have It has been aseptically filled between the samples from containers include filled at the beginning, middle and end of the batch and after some intemu ~ ion imeortante work?	M	
23.20	Does the sterility test which subjected the product is considered only as fa last a series of control measures by which sterility is assured? And only interpreted as part of a set that includes records of environmental conditions yel !! I rocesado of lots?	C	
23.21	Are there procedures and record specific quality controls to lots of poison such as protein concentration, assessment of biochemical activity. activity	C	I

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I	biological profiles run on SDS PAGE or chromatographic profiles · size exclusion or molecular, among others?		
, 23.22	¿Tltulos analysis of neutralizing antivenom is done? They are made to plasma?		
23.23	Do you have procedures for handling analysis equipment and its program calibration?	C	
23.24	Do you have procedures for handling reagents, reference standards and retention samples?	C	
2325	¿TrazabUidad It takes all data *r* results of analytical tests carried out ?	C	
23.26	¿Firman all results persons responsible (who did them, who the revised and who approved?)?	M	I '
23.27	Are containers of reagents solutions are found and properly labeled benchmarks?	C	I I
I-- 23.28	Do you collect and review documents the history of the lot by the person authorized?	C	
23.29	Does each batch is released only by the authorized person?	C	
23.30	Are there written procedures indicating the measures that are applied when there results out of specification and research?	C	
23.31	Are there procedures written: s :: ::: q u :::: e: ..: ::: e.I.g as · ::: .. :: u '- "' rec ....: n: ..: q: ..: u :::: e ~ ::: I s ".. 710 ~ t: e;" S7H-a = -n = -s: -: Ido " oap-ro-; b: -a -d; -: osp-: or - quality?		
24.	VALIDATIONS		
24.1	Is there validations master plan which includes objectives. responsible, lipos validations performed (prospective or concurrent) and overtakes processes validation cleaning, analytical techniques, manufacturing processes antivenom systems critical support etc .; ace! It establishes controls changes to be made and the evaluation validated state?	C	
24.2	Is there validations systems ~ ion?	C	
24.3	Validations have processes and analytical methodologies? Or failing that, protocols and timetables for compliance to be verified in the renewal of the certification?		
24.4	I. Highlights critically important processes are validated: ProsQectiva and / or concurrently?	I	
24.5	Is it recorded a substantial change in the manufacturing process is validated, including equipment or materials that may affect product quality *YLO* reproducibility process?	M	
24.6	Do you have registered, evaluated and filed the results of the validations performed?	C	

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I 24.1	Written procedures and validation records when the following are used processes:		
'24 .1.1	¿Dry heat sterilization?	C	I
24.1.2	¿Steam sterilization?	C	I
r 24.1.3	¿Ethylene oxide sterilization?	C	
I 24.1.4	¿EsterilizaciónJl..or radiation?	C	
24.2	Is there written procedures and validation records aSeQtico filling processes?		
26.	STABILITY		
26.1	Are there written procedures for defining the characteristics of stability antivenom?	C	
...... ,, 2	appropriate these conditions ... - l (,, ·?.		
26.3	An appropriate record of the conditions of relative humidity and temperature of this is carried storage area?		
26.4	Are there protocols and registration for the development of stability testing of each product?	C	
26.5	Is there a written procedure to set the date of expiry of the antivenom?	C	
26.6	Does the area, equipment, procedures and reagents suitable for development Stability studies?	C	
26.7	.There is an appropriate contract for the development of these studies? (If applicable)	C	
26.8	If a significant modification of the manufacturing process, the equipment and manufacturing conditions of the area, reprocessing, a change of supplier of raw materials and packaging material. etc. • Are new studies are conducted stability?	C	
I 26.9	.The estabitidad studies conducted *on-go.JrlJt?*	C	
26.10	Will these new studies are properly documented?	C	
! 26.11	¿Assessments and conclusions of each of the stability studies are conducted finished product? And intermediate product, when required?	C	
27,	vivarium		
27.1	*I.* It has areas separated ~ z .. .. ::: ex :: e ::: ::: s ::: lu iv ~ a :::: s ~ -:? -	C	
27.2	Is there a written procedure to establish the origin and supplier animals test? You Are Documented?	C	
27.3	Are there written procedures for cleaning. disinfecting and general maintenance the Bloterio?	C	
27.4	¿Adequate ventilation and temperature are taken? Are the conditions are recorded Environmental?	C	
27.5	Does the relative humidity, temperature and noise level properly documented Bioterio? Do you have defined your specifications?	C	
27.6	Are there written procedures for inspection of animals in health, weight. feed and rest period? Does this activity documented?	C	
28.	QUALITY GUARANTEE		
28.1	Is there in the company - " An '::' 'of. OG-'ra-ma-d7 "e: G" Arantia Quality?	I C II	I
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28.2 Is there a person responsible for it? and
28.3 How clearly defined and written roles and responsibilities Guarantee Quality? C I
28.4 ¿YEN: orta directly to the management of the EMJ: RESA? C
28.5 Are all levels of the company is reported? Does your understanding is evaluated by all those involved? C !
28.6 ¿Auto inspections are undertaken periodically? How often? C
28.7 Are there written procedures for the development of auto inspections where it is defined. Scope responsible, metodologla, classification of findings, follow up corrective and preventive actions resulting from the findings, implementation time and their frequency? Are registered? C
28.8 Does updating or changing manufacturing processes and is implemented operating procedures after a com~leta evaluation and approval? C
29. COMPLAINTS AND CLAIMS
29.1 Is there a written procedure that reflects the policy and procedures for handling complaints and complaints about potentially defective products? Do you have defined responsible for meeting them, investigate the cause and decide what measures should be drink? And if the case is considered the withdrawal from the market? Are registered? M
29.2 ¿Details are recorded and fully all decisions and measures taken as a result a complaint? archived? M
29.3 The Quality Control Department and production make J: Art res20nsables your evaluation? M
29.4 If a defect is discovered in a lot or if you suspect that a defect exists, is taken into whether other lots also have to be controlled to define whether they have been affected by the defect? M
29.5 They are regularly reviewed in order to assess recurrences? They are reported to health authorities? M
30. WITHDRAWAL OF PRODUCTS MARKET
30.1 Is there a written procedure that reflects the policy and methodology of the company for the Ploductos withdrawal from the market? C
30.2 Is it revises and efficiency of the retirement system evaluated? M
30.3 Should the development of the withdrawal process is recorded and a report on it is drawn? M
30.4 Is there a record that includes the reconciliation of the quantities produced, distributed and Recalled? M
30.5 Is there a list (name, address, telephone number) of the competent authorities give notice of withdrawal from the market, and report the reason? and
30.6 Is there a written procedure ~an destruction of ~roducts removed? C
30.7 Is a record of destructions kept? M I
31. RETURNS I
31.1 Do you have a separate returns and / or claims properly identified area? Y with restricted access? M
31.2 Are they recorded and documented returns and their causes? M
31.3 Do you have policies and procedures excel ~ for handling d ~ revolutions? M
31.4 Do you have staff responsible for handling returns and measures to take? M
32. MANUFACTURE and ANALISIS CONTRACT
32.1 The contract manufacturing and quality analysis is correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a job or analysis unsatisfactory quality? M I
32.2 Everybody contract analysis including any proposed change in technical provisions or otherwise, are consistent with the authorization of marketing dell! roduct in question? M
32.3 The contract allows the contractor to audit the contractor's premises? It is available the registers? M I

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32.4 Does the contractor has evidence of assessment of competence of the contractor to carry out work or tests required for approval of contract activities, contract the contractor is required to apply the principles of quality control established by pharmacopoeia and such compliance is verified by the contractor? C
32.5 Is there evidence regarding the contractor provides the contractor all the information necessary to properly carry out the contracted operations and other legal requirement? Are there supports in that the contractor ensures that the contractor is aware of the problems associated with the product, work or tests that might pose a peliaro ~an facilities, equipment, personnel, other materials or other products? M

The contractor

32.6 During the evaluation of the contractor, the contractor obtains evidence that this has with adequate facilities. equipment, knowledge. experienced and competent staff to perform satisfactorily the work ordered? and
32.7 Does the contractor verifies that the contractor has the legal authorization to manufacture and perform quality analysis antivenoms? M
32.8 Does the contractor has evidence regarding verification that the work entrusted to Contracting are executed by him and not by other third parties in which case part of the evaluation and approval of the subcontractor and the contract includes this provision? M I
32.9 Are the agreements concluded between the contractor and subcontractors ensure that information manufacturing and analytical information are available in the same way that between the original contractor and contractor? M

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r - s2.11 : Is there a written contract between the contractor and the contractor where clearly state responsibilities of each party? C
32.12 The contract establishes the procedure for release of product for sale or issue of analysis certificate? The contract clearly states the way in which the person authorized to release each batch of product for sale or to issue the certificate of analysis. It exerts its full responsibility and ensures that each batch was manufactured and revised in compliance with the requirements for authorization release product to market or analyzed and issued the certificate of analysis according to the methodology of análisi: = s - " 'e .., s, = ta:; :: b:;: le: ::; C1 :::;..... · d: :: a: + -...? - ::: - + -_ + j -_-- C
32.13 Are the technical aspects of the contract are made by qualified personnel technology pharmaceutical, analysis and Good Manufacturing Practices? M
I- = 32 -.- - "The': s = m:' :: odalidades production and analysis are consistent with the authorization of marketing and agreement between both parties? M
32.15 The contract describes responsible for purchasing, analysis and release of materials and performing production control and quality, including controls for the process? M
32.16 Are they available to the contracting manufacturing records, analysis, distribution and reference samples? M

· CC: Qualification Criteria