SECOND SECTION
EXECUTIVE BRANCH
MINISTRY OF HEALTH

Mexican Official Standard NOM-241-SSA1-2012, Good manufacturing practices for establishments engaged in the manufacture of medical devices

On the margin a seal with the National Crest, that reads: United States of Mexico. - Ministry of Health.

MIKEL ANDONI ARRIOLA PEÑALOSA, Federal Commissioner for the Protection against Sanitary Risks and Chairman of the National Advisory Committee for Standardization of Health Regulation and Promotion, based on the provisions under articles 39 of the Organic Law of the Federal Public Administration; 4 of the Administrative Procedure Federal Law; 3 sections XXIII and XIV, 17 Bis sections I, II, III, VI and VII, 194 section II, 194 Bis, 195, 197, 201, 210, 213 and 214, of the General Health Law; section II, 40 sections I, V and XI, 41, 44, 46 and 47 section IV of the Federal Law on Metrology and Standardization; 28 of the Regulation of the Federal Law on Metrology and Standardization; 9, 11, 15, 100, 102 and 111 of the Regulation on Health Supplies; 2 literal C section X, and 36 of the Internal Regulation of the Ministry of Health; and 3 sections I literal b and II and 10 sections IV and VII of the Regulation of the Federal Commission for the Protection against Sanitary Risks, and

CONSIDERING

That in compliance with the provisions in article 46 section I of the Federal Law on Metrology and Standardization, the Subcommittee for Health Supplies submitted the preliminary draft of this Mexican Official Standard on April 27th 2011 to the National Advisory Committee for Standardization of Health Regulation and Promotion.

That as of November 15th 2011, in compliance with the agreement of the Committee and the provisions in article 47 section I of the Federal Law on Metrology and Standardization, the final draft of the present Standard was published in the Official Journal of the Federation, to the effect that within the next sixty calendar days after such publication, those interested will submit their commentaries to the National Advisory Committee for Standardization of Health Regulation and Promotion.

That on a previous date, the responses to the comments received by the aforementioned Committee were published on the Official Journal of the Federation, under the terms of article 47 section III of the Federal Law on Metrology and Standardization.

That in view of the previous considerations, with the approval of the National Advisory Committee for Standardization of Health Regulation and Promotion, I hereby issue and ordain the publishing of the Mexican Official Standard NOM-241-SSA1-2012, Good manufacturing practices for establishments engaged in the manufacture of medical devices on the Official Journal of the Federation.

PREFACE

The following Dependencies, Institutions and Organizations participated in the preparation of this Standard:

MINISTRY OF HEALTH.
Federal Commission for the Protection Against Sanitary Risks..
National Center of Excellence in Health Technology.
GENERAL HEALTH COUNCIL.
Interinstitutional Commission for the Essential Medicines List and Catalogue of Supplies for the Health Sector.
MEXICAN INSTITUTE OF SOCIAL SECURITY
INSTITUTE FOR SECURITY AND SOCIAL SERVICES FOR STATE EMPLOYEES.
UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO.
Faculty of Chemistry.
Applied Sciences and Technology Development Center.
University Program for Health Research.
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0. Introduction

Health is a factor of the utmost importance for the wellbeing and social development of the community, reason why it is the duty of the Federal Executive, through the Ministry of Health, to establish the requirements that must be complied with during the manufacturing process of medical devices that ensure their quality and functionality.

The implementation of Good Manufacturing Practices (GMP) is a fundamental part of a quality management system which is a strategic decision of the Organization; the design and implementation thereof is influenced by the manufactured product, the followed process, size and structure of the Organization.

The Ministry of Health will enforce the sanitary control in the establishments engaging in manufacturing, conditioning warehouses and distribution of medical devices following the established criteria in this Mexican Official Standard.

1. Objective and Scope

1.1. Objective

This standard specifies the requirements that processes must comply with, from the design of facilities, development, acquisition, preparation, mixing, production, assembly, handling, packaging, conditioning, stability, analysis, control, storage and distribution of the medical devices marketed in the country, related to the nature of the product; and is intended to ensure that devices consistently meet quality and performance requirements to be used by the end-user or patient.

1.2. Scope

This Standard is mandatory in the national territory, for all establishments related to the process of medical devices marketed in the country.

2. References

For the correct application of this Standard, review of the following current Mexican Official Standards or those that supersede them, is suggested:


2.5. Mexican Official Standard NOM-005-STPS-1998, Concerning health and safety conditions in the workplace for handling, transportation and storage of hazardous chemical substances.


2.10. Mexican Official Standard NOM-003-NUCL-1994, Classification of facilities or laboratories using open sources.
2.11. Mexican Official Standard NOM-007-NUCL-1994, Radiological safety requirements that must be observed in permanent implants of radioactive material with therapeutic purposes for human beings.


3. Definitions

For the purposes of this Standard the following are defined as:

3.1. Sanitary surface finish, the finish given to the internal surfaces of areas with the purpose of avoiding accumulation of viable and non-viable particles and to facilitate cleaning.

3.2. Corrective action, action taken to eliminate the cause of a detected non-conformity or another undesirable situation with the purpose of preventing its recurrence.

3.3. Preventive action, action taken to eliminate the cause of a potential non-conformity or another potential undesirable situation to prevent its occurrence.

3.4. Conditioning, the necessary operations a bulk product must go through to achieve its presentation as a finished product.

3.5. Waste water, discharged water resulting from activities related to the manufacturing, in the terms set forth in the Mexican Official Standard referred to in item 2.6, section 2, references.

3.6. Storage, Preservation of supplies, bulk, semi-processed and finished product of the medical device kept in areas under the established conditions according to their nature.

3.7. Risk analysis, method to assess in advance the factors that may affect the functionality of: systems, equipment, processes or the quality of supplies and products.

3.8. Area, room or group of rooms and spaces designed and built according to defined specifications.

3.9. Aseptic area, area designed, built and maintained with the purpose of keeping within previously established limits the number of viable and non-viable particles on surfaces and in the environment.

3.10. Clean area, area where the number of viable and non-viable particles must be controlled through humidity, pressure and temperature conditions established for a particular situation.

3.11. Audit, the systematic, independent and documented process to obtain evidence and objectively assess it in order to determine the level to which the established criteria are met.

3.12. Bioterium, area specialized in the maintenance, control and/or reproduction of different animal species destined the conduction of laboratory tests.

3.13. Good manufacturing practices, series of guidelines and related activities, destined for ensuring that the manufactured medical devices have and maintain the quality, safety, efficacy, effectiveness and functionality requirements for their use.

3.14. Calibration, series of operations that determine, under specified conditions, the relation between the values shown by an instrument or a measuring system, or the values represented by the material measurement and the known values corresponding to a reference standard.

3.15. Quality, compliance with established specifications to ensure adequateness for use.

3.16. Performance Qualification, documented evidence showing that the facilities, systems and equipment perform in compliance with previously established acceptance criteria.

3.17. Installation Qualification, documented evidence showing that the facilities, systems and equipment have been installed according to previously established design specifications.

3.18. Design qualification, documented evidence showing that the proposed design of the facilities, systems and equipment is appropriate for the intended purpose.

3.19. Operational qualification, documented evidence showing that the equipment, facilities and systems operate consistently, according to the established design specifications.

3.20. Training, activities intended to provide knowledge to the personnel or to reinforce it.
3.21. **Certificate of analysis**, document endorsing the product has been tested before its release from the site to ensure its safety, efficacy, quality and functionality once it has shown compliance with the established acceptance parameters based on the type of product and its risk level. It must include the batch or serial number, specifications and results of the finished product issued by the manufacturer, or copy of a certificate of analysis issued by an authorized laboratory and signed by the Quality Assurance Responsible or by the Sanitary Responsible (corporate compliance officer) of the establishment applying for the Sanitary Registration in Mexico.

3.22. **Component**, any material or ingredient used in the manufacturing of a medical device, present in the final product.

3.23. **Storage conditions**, those conditions required to preserve or conserve the quality characteristics of the supplies, bulk, semi-processed and finished product.

3.24. **Dynamic conditions**, those conditions under which the facilities work in the defined mode of operation and with the specified number of personnel.

3.25. **Static conditions**, those conditions under which the facilities operate with a complete production equipment but without the presence of personnel.

3.26. **Contamination**, presence of undesired physical, chemical or biological entities.

3.27. **Cross-Contamination**, presence of undesired physical, chemical or biological entities, originated from a different process or product.

3.28. **Control of Changes**, assessment and documentation of changes with an impact on the quality, performance and operation of the medical device.

3.29. **Acceptance criteria**, predefined conditions, specifications, standards or intervals that must be complied with.

3.30. **Deviation (non-conformance)**, non-compliance of a previously established requirement.

3.31. **Medical device**, substance, mixture of substances, material, apparatus or instrument (including the software necessary for its appropriate use or application), used alone or combined for the diagnosis, monitoring or prevention of human diseases or auxiliary in the treatment thereof and of disabilities, as well as those used in the replacement, correction, restoration or modification of the human anatomy or physiological processes. Medical devices include products in the following categories: medical equipment, prosthesis, orthoses, functional aids, diagnostic agents, dental supplies, surgical and wound dressing/healing material and hygiene products.

3.32. **Primary Container or Packaging**, elements of the container system in direct contact with the medical device.

3.33. **Secondary Packaging**, elements that are part of the package in which the medical device is marketed and that are not in direct contact with it.

3.34. **Specification**, quality parameters, their limits or acceptance criteria, and reference to the methods to be used for their determination.

3.35. **Stability**, the capacity of a medical device to stay within the established quality specifications, inside the primary or secondary container when this is an essential condition for its shelf life.

3.36. **Sterility**, absence of viable microorganisms.

3.37. **Stability studies**, tests conducted on a medical device to establish its expiry period or shelf life and the storage conditions under the influence of different factors.

3.38. **Accelerated stability studies**, those that take into account extreme storage conditions, in order to increase the speed of chemical or biological degradation or physical changes a medical device may suffer during the established exposure time in the corresponding study and in order to establish a tentative expiration date or shelf life, as well as the storage conditions.

3.39. **Long-term stability studies**, studies designed under the established storage conditions during the expiration period, assessing the operational, physical, chemical, biological or microbiological characteristics of the medical device to show it complies with the quality specifications.

3.40. **Label**, any label, heading, inscription, mark or graphic image written, printed, stenciled, marked, embossed or bas-relieved, adhered or sealed on any material susceptible to contain the medical device including the container itself.
3.41. **Batch file,** series of documents that prove a batch of the medical device was manufactured and controlled according to the Master File.

3.42. **Legal File,** series of documents that prove a medical device complies with the current regulations set forth by the Ministry of Health.

3.43. **Master File,** authorized document containing the information to carry out and control the process operations and activities related to the manufacturing of a product.

3.44. **Manufacturing,** operations involved in the production and conditioning of a medical device from the reception of materials until its release as a finished product.

3.45. **Expiration date,** date that indicates the end of the shelf life period of a medical device and is calculated from its manufacturing, sterilization or calibration date.

3.46. **Inspection,** Assessment of conformity through measurements, assays/tests or comparisons to patterns accompanied by a report.

3.47. **Supplies,** all raw materials, assembly components, primary container material, conditioning material and products received in an establishment.

3.48. **Cleaning,** process for reducing the number of non-viable particles to established levels.

3.49. **Batch,** specific quantity of any raw material or (health) supply, manufactured during a production cycle, under equivalent operating conditions during a specified period of time.

3.50. **Pilot scale batch,** quantity of a medical device manufactured in a representative procedure simulating the production procedure.


3.52. **Contract manufacturing,** process or stage of a process involved in the manufacturing of a medical device, carried out by an establishment other than the titleholder of the sanitary registration or manufacturer; it may be national, international, temporary or permanent.

3.53. **Raw material,** substance, material or component of any origin used to manufacture a medical device.

3.54. **Sample,** part or portion extracted from a group by methods that allow it to be considered as representative of thereof.

3.55. **Retention sample,** sufficient quantity of raw material or product to carry out two complete analyses, exception for the sterility test.

3.56. **Batch or serial number,** numeric or alphanumeric combination that specifically identifies a batch.

3.57. **Production Order (manufacturing record),** copy of the production order or master formula to which a batch number is assigned, it is used as a guideline and record of the operations carried out during the production of a batch of a medical device.

3.58. **Conditioning order,** copy of the conditioning formula or master list to which a batch number is assigned (it may be the same as the production order) and is used as a guideline and record of the operations carried out in the conditioning of a batch of a medical device.

3.59. **Viable particles,** any particle that may reproduce under appropriate environmental conditions.

3.60. **Worst-case scenario,** condition or group of conditions that take into account upper and lower limits and circumstances of a process, that have the best chance of causing a failure in the medical device or in its process when compared to the established conditions.

3.61. **Validation Master Plan,** document that outlines the activities to be conducted for qualifying the elements of the process and subsequently validate the processes.

3.62. **Standard Operating Procedure (SOP),** document that contains the instructions necessary to carry out an operation in a reproducible manner.

3.63. **Conditioning Procedure,** document containing the detailed instructions to transform a bulk product into a finished product.

3.64. **Production Procedure,** document containing the detailed instructions to transform raw materials, materials or components into bulk medical devices prior to their conditioning in the packaging intended for their marketing.
3.65. **Production**, operations involved in the processing of raw materials, materials or components to transform them into a bulk medical device for its conditioning in the package intended for its marketing.

3.66. **Bulk product**, product placed in a container of any nature and whose content may be variable, which may be subjected to different stages prior to becoming a finished product.

3.67. **Environmental monitoring program**, plan according to which the surveillance of viable and non-viable particles level is conducted.

3.68. **Stability study protocol**, document that sets forth the study design regarding tests and acceptance criteria, batch characteristics, sample handling, study conditions (analysis frequency, temperature, humidity, or light), analytical methods and container materials.

3.69. **Complaint**, any remarks of non-satisfaction from an internal or external client, related to the quality and functionality of the product.

3.70. **Traceability**, capacity to reconstruct the history, placement of an element, component or activity, using records as evidence.

3.71. **Reconditioning**, change of the packaging of any medical device, provided its quality is guaranteed.

3.72. **Cross reference**, quote of other documents that serve as reference, support or complement to another.

3.73. **Record**, document showing the results obtained or providing evidence of the activities conducted.

3.74. **Final yield**, quantity of the finished medical device obtained at the end of the manufacturing process.

3.75. **Theoretical yield**, quantity of the medical device that will be obtained through a process.

3.76. **Temporary hold (Quarantine)**, action by which products, raw materials or primary container or conditioning materials are temporarily held, in order to verify if they comply with the established quality specifications and the corresponding regulations.

3.77. **Reprocessing**, action by which a complete or partial batch is subjected to a repetition of a previous step of the validated manufacturing process due to deviations from the established specifications.

3.78. **Rework**, action by which a complete or partial batch is subjected to an additional step of the manufacturing process due to deviations from the established specifications.

3.79. **Revalidation**, repetition of the validation process to provide assurance that the changes in the process/equipment introduced according to the change control procedures do not affect adversely the process characteristics and product quality.

3.80. **Sanitation**, process of reducing the number of viable particles by means of special germicidal agents after the cleaning activity in workspaces.

3.81. **Critical systems**, those systems in direct contact with the processes and that affect the quality of the medical devices.

3.82. **Supply**, delivery of raw materials, components, bulk product and materials used in the manufacturing of the medical device according to the requirements of the formula or its master list.

3.83. **Validation**, documented evidence that proves the obtention through a specific process of a medical device that consistently and reproducibly complies with the specifications and quality attributes.

3.84. **Process validation**, documented evidence that the process, operated within the defined parameters, can perform effectively and reproducibly to produce a medical device that satisfies its established specifications and quality attributes.

3.85. **Shelf life**, period of time during which a medical device maintains its quality and functional properties.

4. **Symbols and abbreviations**

4.1. °C  Celsius degrees

4.2. GMP  Good Manufacturing Practices

4.3. DQ  Design Qualification

4.4. FQ  Facility Qualification
5. **Classification of medical devices**

5.1. Based on the risk involved in their use, medical devices are classified as follows:

5.1.1. **Class I**: defines those medical devices known in medical practice whose safety and efficacy are proven and that are not generally introduced into the organism.

5.1.2. **Class II**: defines those medical devices known in medical practice which may have variations in the materials of which they are made of or in their concentrations, and are generally introduced into the organism for a period of less than thirty days.

5.1.3. **Class III**: defines those medical devices which are new or recently accepted in medical practice or that when introduced into the organism remain there for more than thirty days.

5.2. Medical devices considered by the General Health Law are:

5.2.1. **Medical equipment**: apparatus, accessories and instruments for a specific use, intended for medical care, surgical or exploratory procedures, patient diagnostic, treatment and rehabilitation, as well as those to carry out biomedical research activities.

5.2.2. **Prosthesis, orthoses and functional aids**: those devices intended to substitute or complement a function, an organ or a tissue of the human body.

5.2.3. **Diagnostic reagents**: all supplies including antigens, antibodies, calibrators, verifiers, reagents, reagent sets, culture and contrast media and any other similar that may be used as an auxiliary of other clinical or paraclinical procedures.

5.2.4. **Dental supplies**: all substances or materials used for dental health care.

5.2.5. **Surgical and wound dressing/healing material**: devices or materials that are used alone or in combination with antiseptics or germicides in the surgical practice or in the treatment of solutions of continuity and lesions of the skin or its appendages.

5.2.6. **Hygiene products**: materials and substances applied on the skin surface or body cavities that have a pharmacological or preventive action.

6. **Organization of a Facility**

6.1. The establishment must implement, document and maintain the Quality Management System established in a quality manual, as well as maintain its effectiveness according to the requirements of this Standard.

6.2. The establishment must identify the processes’ needs for the GMP system and their implementation throughout the organization.

6.3. The establishment must have an internal organization according to the company size and the risk class of the medical device, determining the sequence and interaction of the processes; likewise, necessary criteria and methods must be determined to ensure that both the operation and control of those processes are effective.
6.4. The establishment must ensure the availability of the necessary resources and information to support, monitor, measure and analyze the installed processes.

6.5. There must be an updated organizational chart showing that the Manufacturing Responsible and the Quality Area Responsible do not depend on each other.

6.6. The Sanitary Responsible must have the highest hierarchy level of the quality area of the establishment and must report directly to the highest position.

6.7. The Sanitary Responsible will appoint in writing the person(s) that will attend any eventuality whenever he/she is absent and who must comply with the requirements set forth by the General Health Law and the Regulations for Health Supplies for the Sanitary Responsible. In case of foreigners, they must have the equivalent documents.

6.8. There must be an adequate number of area supervisors to cover and supervise operative functions during the established working hours.

6.9. The persons responsible for the manufacturing and quality areas of the highest hierarchy level, must have at least a degree in pharmacy, chemistry, biology, medicine, biomedicine, biochemistry or akin to the process, and, in the case of foreigners, a degree and professional license or equivalent document.

6.10. The Manufacturing Responsible of the highest hierarchy level will be in charge of ensuring that the manufacturing and conditioning of the medical device comply with the established specifications and requirements set forth by this Standard, without prejudice to the obligations and responsibilities that correspond to the Sanitary Responsible, according to the applicable legislation.

6.11. The Quality Area Responsible of the highest hierarchy level will have all responsibility and authority to ensure the establishment complies with the specifications and requirements set forth by this Standard. The following are some of its most important tasks:

6.11.1. To establish and supervise the implementation of procedures that allow the approval or rejection of supplies; bulk, semi-processed and finished product, including those that are contract manufactured (see section 10.7)

6.11.2. To supervise that all tests are carried out in accordance with the description in the FEUM, Supplement for medical devices, the corresponding Mexican Official Standards, pharmacopeias or internationally known references, or, in their absence, using a manufacturer's validated method (see section 15.7).

6.11.3. To supervise compliance with all quality related SOP’s, as well as the approval of all technical documentation of the establishment that has an impact on the quality of the processes or medical devices.

6.11.4. To authorize in writing the Validation Master Plan, protocols and reports and the Standard Operating Procedures.

6.11.5. To supervise allocation of dates for retest of raw materials and expiration dates for medical devices.

6.11.6. To supervise that the file, product test records and distribution records of every batch are kept for a year after the expiration date of the product.

6.11.7. To supervise that the corresponding investigation is carried out for every complaint received, to ensure that the necessary corrective and preventive actions are implemented, and that a system is set in place to measure the effectiveness of the actions used (see section 13).

6.11.8. To supervise that there is a supplier approval system according to the provisions of the Quality Management System.

6.11.9. To supervise that there is an audit system (see section 19).

6.11.10. To assist in the compliance with current applicable regulations, giving immediate notice to the Ministry of any sanitary irregularity detected.

6.11.11. To supervise that any deviation to the established procedures is investigated, reviewed and reported (see section 18) and to authorize the final destination of the batch.

7. Personnel

7.1. The personnel must be reflected in the establishment's organizational chart. Also, the obligations, responsibilities and authority level must be documented.
7.2. Personnel responsible of manufacturing and control of medical devices, including temporary staff, must be qualified, based on their experience, education or training, for the function performed. The qualification must be documented in their personnel file.

7.3. There must be an ongoing and documented personnel training and coaching program according to the functions assigned. This program should be carried out according to the competence needs of the personnel in the execution of the work that affects product quality.

7.3.1. This program must include at least the following areas: induction to the position, GMP, knowledge of SOP’s applied in the assigned work area, equipment operation, special garments and use of safety equipment.

7.3.2. Training on GMP must be performed at least once a year and every time changes in the Regulations or applicable SOP’s occur, this training must be documented.

7.3.3. This training program must include at least: subjects related to the activity assigned, job descriptions, frequency and evaluation system and must be authorized by the person assigned by the company’s management or the highest rank in the establishment. There must be evidence of its completion.

7.4. Personnel must wear clean and comfortable work clothes and safety equipment, designed to avoid contamination of products and manufacturing areas, as well as occupational health risks.

7.4.1. The clothing requirements for each manufacturing area will depend on the area classification based on the risk level of the medical device and must be defined in writing, including the disposal of disposable garments.

7.5. New personnel must undergo a medical examination in order to verify that the person’s health condition does not compromise the product’s quality.

7.6. Periodically, all personnel in the manufacturing and quality areas must undergo a medical examination, as well as those who directly intervene in the dispensing of supplies. All personnel absences caused by communicable diseases must be documented, as well as health check-ups at the time the subject resumes his/her activities, and if applicable, necessary actions in case the diagnosis is positive.

7.7. Any member of the personnel who shows signs of a potential disease or an open lesion, according to a medical examination or physical check, and that may adversely affect the quality of the medical devices, must be excluded from direct contact with the components and supplies used in their manufacturing and from the in-process materials of the finished product until their condition is determined by the qualified medical staff. All personnel must be instructed to report to the supervisor any signs of disease that may cause adverse effects on the manufacturing processes of the medical devices.

7.8. If the personnel of the manufacturing areas where the medical device or the supplies are exposed, they must have to leave the areas and change the work clothes, as applicable.

7.9. Personnel must comply with the corresponding SOP’s of every area.

7.10. Personnel must not wear jewelry nor cosmetics in the manufacturing areas, including the conditioning area where the medical device or its materials are exposed.

7.11. External staff offering technical assistance or consulting, as well as contractors, for any of the sections included in this Standard, must have adequate education, training and experience needed to make recommendations for the services required, as well as to perform their tasks without jeopardizing the quality of the manufactured medical devices.

7.11.1. Records including the name, experience and type of service provided by the external staff or consultant must be kept.

7.11.2. Temporary personnel or consultants shall not issue final official decisions regarding the medical device.

7.12. Personnel must not eat or store food or drinks of any kind in the manufacturing or laboratory areas, nor smoke in any area of the company except for those designated to do so.

7.13. Temporary operative personnel must comply with the same requirements as the employed personnel, prior an induction course for the activity to be performed.

7.14. New personnel, both temporary and employed personnel, must work under supervision of qualified personnel until they show to be qualified to perform their function.

8. Documentation

8.1. Overview
8.1.1. A label must be placed on a visible place, indicating the establishment's name, activity and, if applicable, Sanitary License Number. It must also include the information of the Sanitary Responsible such as: name, professional license number, working hours and name of the institution which issued the degree.

8.1.2. All documents regarding manufacturing, conditioning, storage, tests and control of medical devices, as well as of the facilities, must be written in Spanish and issued by any means that ensure its readability and traceability, using simple vocabulary, stating the type, nature, purpose or use of the document. The organization of its content must be such that it allows its easy comprehension. Original documents must not be altered.

8.1.3. Documents where data are registered must comply at least with the following requirements:

8.1.3.1. Data must be registered by the person performing the activity and at the time it was performed. Preferably, no acronyms shall be used and when used, as well as signatures, a catalogue must exist.

8.1.3.2. Data should be legible and indelible.

8.1.3.3. Data required in the corresponding form must be registered in the spaces provided and, when non applicable, spaces must be canceled.

8.1.3.4. Any correction must allow seeing the original data and must be signed and dated by the person who made the correction.

8.1.4. Documents must be reproduced through a system that ensures a document is a true copy of the original.

8.1.5. Documentation must be archived in such a way that it is easy and quick to access, and ensuring its conservation and integrity.

8.1.6. There must be a control system that allows the review, distribution and modification or cancellation of documents. This system must include detailed instructions, personnel involved and definition of responsibilities to ensure the distribution of updated documents and withdrawal of the obsolete.

8.1.7. All original master and operative documents regarding the manufacturing and storage of the medical device must be authorized by the Sanitary Responsible, as well as any modification of the aforementioned documents.

8.1.8. Records of the changes made to documents and at least the immediately previous version of the modified document must be kept.

8.1.9. The establishment must have at least the following updated documents:

8.1.9.1. Quality Manual. As well as containing the description of the implemented Quality Management System, this document must refer to those sections of the present Standard that do not apply based on the specific characteristics of the medical device or the processes performed in the establishment, including the corresponding justification.

8.1.9.2. SOPs list.

8.1.9.3. Establishment's organization chart stating the job positions and the people who fill them.

8.1.9.4. Current version of the FEUM (as applicable), the corresponding supplement and the Mexican Official Standards applicable to the manufactured or marketed medical devices.

8.1.9.5. List of the medical devices marketed, stating their Sanitary Registration.

8.1.9.6. List of the medical devices that have a Sanitary Registration.

8.1.9.7. Blue prints, lay outs or diagrams showing the flow of materials, personnel and products, and diagrams of critical systems.

8.1.9.8. List of the manufacturing equipment including their characteristics and location.

8.1.9.9. List of the test equipment and instruments including their characteristics and location.

8.2. Legal documentation

8.2.1. The establishment must have at least the following legal documents, which may be distributed among its different facilities, according to the processes performed:

8.2.2. Operating Notice or Sanitary License issued by de Ministry of Health.
8.2.3. Sanitary Responsible Notice.

8.2.4. Legal file of every medical device, which must consist of at least the following documents:

8.2.4.1. Original of the Sanitary Registration, original extension or last modification to the Registration’s conditions and the modifications of the Registration’s conditions, issued by the Ministry of Health.

8.2.4.2. Project of Label fulfilling the requirements set forth by the current corresponding Standard and the authorized conditions; including instructions and manuals given the case.

8.2.5. Information submitted to obtain the Sanitary Registration and its modifications, in the terms of the applicable legal provisions.

8.3. Master document

8.3.1. Based on the authorized activity and the type of product, the establishment must have a master document for each product, including the originals of at least the following documents:

8.3.1.1. Master Production Order, which must include: name of the medical device, batch size, master production list or formula, including the quantity of supplies required for its production, and, when applicable, the authorized use and expiration period.

8.3.1.1.1. In case of diagnostic agents with radioactive isotopes and contrast media, in addition to the provisions of section 8.3.2, it must include the quantity of each component per dosage unit.

8.3.1.2. Manufacturing procedure including the following detailed instructions: equipment, critical parameters, in-process controls and safety measures. The maximum and minimum theoretical yield of each intermediate stage as well as at the end of the process must be indicated in this document. This document includes spaces for the registration of critical operations.

8.3.1.3. Conditioning Master Order for every presentation, which must include: name and presentation (how supplied) of the medical device, complete list of the materials stating their ID, and when applicable, the authorized expiration period.

8.3.1.4. Conditioning procedure including complete instructions for the product’s conditioning, specifying equipment, critical parameters, in-process controls and safety measures. This document must include a section to list all used components including labels and stating the maximum and minimum theoretical yield of the finished product. This document includes spaces for the registration of critical operations.

8.3.1.5. Specifications of the medical device in-process and as a finished product.

8.3.1.6. Analytical methods for the analysis of the in-process product (when applicable) and as a finished product.

8.3.1.7. Specifications and analytical methods of all supplies.

8.3.1.8. Specifications of the primary and secondary packaging materials.

8.3.1.9. Specifications of printed materials.

8.4. Operative documentation.

8.4.1. The establishment must have at least the following SOPs:

8.4.1.1. SOP to draft SOPs.

8.4.1.2. SOP for the operation of equipment used in the manufacturing and conditioning of such medical devices.

8.4.1.3. SOP for the cleaning or sanitation of equipment, product manufacturing and conditioning areas.

8.4.1.4. SOP for the operations related to the establishment’s critical systems.

8.4.1.5. SOP for the calibration of measuring instruments, including the corresponding program.

8.4.1.6. SOP and program for preventive and corrective maintenance of equipment, measuring instruments, critical systems and facilities.

8.4.1.7. SOP for the cleaning and sanitation of the microbiology and/or vivarium area, when applicable.

8.4.1.8. SOP for deviation or non-conformity management.

8.4.1.9. SOP for change control.
8.4.1.10. SOP for complaint management.

8.4.1.11. SOP for the management of product returns from the customer.

8.4.1.12. SOP or technical specifications for supply purchasing.

8.4.1.13. SOP for medical device recalls.

8.4.1.14. SOP describing the safety measures and personnel and material controlled access to the storage, manufacturing, conditioning and analytical laboratory areas.

8.4.1.15. SOP for pest control and/or harmful fauna.

8.4.1.16. SOP for supplier assessment.

8.5. Records and reports.

8.5.1. Depending on the type of product, the establishment must have the file for every manufactured batch; including at least the following:

8.5.1.1. Records that prove the medical device was manufactured, conditioned and controlled according to the current master documents.

8.5.1.2. Batch number, serial number or internal identification control of the supplies that allow their traceability in the manufacturing batch or serial number.

8.5.1.3. Records that allow identification of the areas and equipment used for manufacturing and conditioning.

8.5.1.4. Samples of the coded labels used, when due to the nature of the label it is impossible to include it; evidence of the placed label may be attached.

8.5.1.5. Records or cross reference of the environmental monitoring results, when applicable.

8.5.1.6. Records of the investigation of the deviations that occur during the process including corrective and preventive actions taken, responsible people and formal evidence of the effectiveness of such actions.

8.5.1.7. Record endorsing that the batch file was reviewed and ruled by the Quality Department.

8.5.1.8. Certificate of analysis (or equivalent) of the finished product stating the final documented decision according to the type of product.

8.5.2. Depending on the type of product, the establishment must have the following records and analytical reports:

8.5.2.1. Analytical reports of the supplies used in the manufacturing batch.

8.5.2.2. Records of the analysis conducted on: supplies, in-process product and finished product.

8.5.2.3. Investigation reports of the results for medical devices out of specification in which the corrective and preventive actions taken are determined, the people responsible and formal evidence of the effectiveness of such actions.

8.5.3. The establishment must have the medical device’s distribution or outgoing records containing, at least, the following information for every batch of distributed or delivered product:

8.5.3.1. Name of the medical device.

8.5.3.2. Presentation or ID.

8.5.3.3. Client or recipient ID.

8.5.3.4. Quantity and batch number or serial number to the client or recipient.

8.5.3.5. Shipping and delivery date.

8.5.3.6. Document proving its reception.

8.5.4. The reports and records of the analysis of raw materials, in-process and finished product of every batch must be kept for five years or until one year after the product’s shelf life.

8.5.5. Complaint records must include complete information related to the following:
8.5.5.1. Name of the medical device, presentation or ID and batch or serial number, including the date of receipt.

8.5.5.2. Quantity of the product involved in the complaint.

8.5.5.3. Reason for the complaint.

8.5.5.4. Name and address of the person making the complaint.

8.5.5.5. Result of the complaint's investigation.

8.5.5.6. Actions taken related to the complaint.

8.5.6. Return records must have the following information:

8.5.6.1. Name of the medical device, presentation or ID and batch or serial number, including the date of receipt.

8.5.6.2. Quantity returned.

8.5.6.3. Reason for the return.

8.5.6.4. Name and address of the person making the return.

8.5.6.5. Final decision and final destination of the medical device, endorsed by the quality department.

8.5.7. There must be an SOP that allows the conduction of a product risk analysis and evidence of its implementation for its correct management, which must include at least the following information:

8.5.7.1. Risk analysis method used.

8.5.7.2. Determination of critical control points.

8.5.7.3. Parameters and critical limits.

8.5.7.4. Monitoring of critical control points.

8.5.7.5. Corrective actions to take when a critical control point is out of control.

8.5.7.6. Assessment plan to ensure that the risk analysis and critical control points are working effectively.

9. Design and Construction of an Establishment Engaged in the Manufacturing, Conditioning, Storage and Distribution of Medical Devices

9.1. Design

9.1.1. The establishment must be designed, built and maintained according to operations performed based on the risk level of the medical device. Its design and build must allow its cleanliness, order, maintenance and prevent contamination, as well as the unidirectional flow of personnel and materials.

9.1.2. There must be a plan to define the requirements of the medical device based on its risk classification, including the processes used, the critical systems and the scope of the facility.

9.1.3. There must be a list for every area including the process requirements, critical systems, general services and products.

9.1.4. The design must consider the construction, environmental, safety and good manufacturing practices requirements.

9.2. Construction

9.2.1. Construction of facilities must take into account the risk level of the medical device.

9.2.2. Any change required during the construction must be reviewed, approved and documented prior its implementation.

9.2.3. In case of construction or redesign works the establishment must implement measures to avoid contamination of the areas and/or products.

9.2.4. Cleaning of air systems must take place before the beginning of operations for the first time or after repair and maintenance of such system, environment monitoring of the areas according to their classification must be performed afterwards.
9.2.5. The must be designated areas for: reception, inspection and/or sampling, supply weighing and/or dispensing; supply, bulk product and finished product warehouse; as well as a shipping area,

9.2.6. Facilities and building maintenance activities must me scheduled, documented and performed in such a way that they avoid contamination risks to both the production areas as well as to the medical device.

9.2.7. In case the use of water is needed for the manufacturing of the medical device, the establishment must have waste water discharge systems. The waste water discharge system must be independent to the storm drainage system.

9.2.8. The size of the different areas must be according to the manufacturing capacity of the different medical devices, the safety level and the type of operations performed designated to each one.

9.2.9. According to the process and product nature, risk analysis and contamination control; the production areas must be classified considering the following (see Appendix A):

9.2.9.1. The area where the aseptic fillings and/or sterility tests are performed must be classified as ISO-Class 5.

9.2.9.2. Areas adjacent to areas where the aseptic filling and/or sterility tests are performed must comply at least with ISO-Class 7.

9.2.9.3. Areas mentioned in sections 9.2.9.1 and 9.2.9.2 must:

9.2.9.3.1. Have air injection and extraction that allows an appropriate balance of differential pressure to avoid contamination of the medical device.

9.2.9.3.2. Have differential pressure indicators.

9.2.9.4. Production, assembly and/or packing processes of the medical devices in which the environmental conditions may have an adverse effect on product quality must comply at least with ISO-Class 9.

9.2.10. According to the manufacturing area and product risk level classification; the ventilation duct system, power lines and other services inherent to the production areas must be hidden or installed outside. Their location and design must be such, that they allow their maintenance and, where volatile liquids are used in the production areas, an anti-blast system and extraction hoods must be installed.

9.2.11. Areas must be adequately illuminated and ventilated and must be submitted to environmental monitoring (when applicable)

9.2.12. Manufacturing areas must be defined and fully identified; when the possibility of contamination exists, they must be apart.

9.2.13. Storage areas must have the capacity and conditions necessary to preserve and/or conserve the supply, bulk product or finished product.

9.2.14. Work conditions (temperature, vibration, humidity, noise, dust, use of solvents, etc), must not directly or indirectly affect the medical device or the operator.

9.2.14.1. Classified areas must meet the comfort conditions for the operator of relative humidity of no more than 65% and temperature between 18-25°C.

9.2.15. Medical devices production areas where the process generates dusts must have dust collection systems.

9.2.16. The design of the air extraction systems must be such that it avoids possible contamination.

9.2.17. Fixed pipes must be identified, based on the color code in the terms set forth by the Mexican Official Standard referred to in section 2.3 sub-section 2, References. In addition, the outlet of the applicable critical systems must be identified.

9.2.18. Drinking water must be supplied by continuous positive pressure in pipes free of any defects that may contribute to contamination of the medical device.

9.2.19. If drainpipes are directly connected to a strainer or a gutter, they must have a trap or device to prevent contamination.

9.2.20. There must be specific and identified areas to perform the conditioning operations, facilitating personnel, supply and product flow.
9.2.21. In case the laboratory has facilities intended for handling laboratory animals, they must be isolated from the manufacturing areas and meet the technical specifications in the terms set forth by the Mexican Official Standard referred to in section 2.7 sub-section 2, References.

9.2.22. The analytical control laboratory must be physically apart from the production and storage areas, and in case of having facilities for in-process analysis inside the production areas, these must be properly identified.

9.2.22.1. If the manufacturer has areas intended for biological, microbiological and instrument testing, they must be physically apart.

9.2.22.2. In the case of in-process analysis, the establishment must ensure that the analytical equipment is not affected by the process and vice versa.

9.2.23. The establishment must have specific areas with adequate storage conditions for retention samples of raw materials and/or finished medical devices, when applicable, according to the product characteristics and corresponding risk analysis.

9.2.24. The establishment must have a specific area with safety and storage conditions for the records and reports generated during the manufacturing and marketing of medical devices.

9.2.25. Areas destined to changing and storing work clothes, must be in accessible locations and in accordance to the number of workers. According to the manufacturing area classification and the product’s risk level, the areas destine for changing to work clothes must precede the manufacturing areas where the materials and products are exposed.

9.2.26. Sanitation services must not be in direct communication or be placed in passage ways to the manufacturing areas and must be provided with:


9.2.26.2. Cold and/or hot water.


9.2.26.4. Urinals and toilets.

9.2.27. In case of having a canteen, it must be separate from the manufacturing areas.

9.2.28. If there is a maintenance shop, it must be physically separate from the manufacturing areas.

9.2.28.1. In case of having maintenance areas within the manufacturing areas, they must comply with the same conditions applicable to the area classification and risk level of the medical device.

9.2.29. In case of having an area destined for medical services, it must be physically separate from the manufacturing areas.

9.3. Any facilities used in the manufacturing, conditioning, storage or retention of medical devices must be in good conditions.

9.4. The establishment must have indicators and alarms to opportune detect failures in the critical systems to take the necessary measures according to the corresponding SOP.

9.5. The building design must consider harmful fauna prevention.

9.6. The establishment must have a program to prevent, control and eradicate harmful fauna.

10. Manufacturing control

10.1. Overview

10.1.1. Supply and product handling must be performed according to the established SOPs.

10.1.2. Components for the manufacturing of medical devices, semi-assembled and bulk medical devices procured as such, including imports, must be handled according to section 10.2.

10.1.3. At the beginning of and during the manufacturing process, supplies, packages with bulk medical devices, equipment and areas used, must be identified indicating their name, code, or both; medical device being manufactured, batch or serial number, and when applicable, production stage. The identification system must be clear and in compliance with an SOP.
10.1.4. Manufacturing areas must be maintained with the degree of cleanliness and sanitation corresponding to the classification and risk level of the medical device.

10.1.4.1. There must be an SOP describing the following:
   10.1.4.1.1. The manner and/or frequency of cleaning and sanitation of the areas.
   10.1.4.1.2. Preparation of cleaning and sanitation agents.
   10.1.4.1.3. Rotation of sanitation agents used. Only sanitation agents whose efficacy has been shown and approved by the Quality Department may be used.

10.1.5. Access to manufacturing areas is restricted to authorized personnel.

10.1.6. SOPs must be accessible to the personnel involved.

10.1.7. Sampling for the control of the in-process medical device must be performed based on an SOP.

10.1.8. The finished medical device inside its final package is considered in quarantine or temporary retention until all analyses are performed and until its release by the Quality Department for its distribution.

10.1.9. If there are defined requirements of environmental conditions for the storage of supplies, bulk product and finished product, the establishment must have records that prove such conditions are met.

10.1.10. In case maintenance is required during manufacturing there must be an SOP describing the measures to prevent impact on the quality characteristics of the supplies of the in-process medical device and the conditions of the areas.

10.1.11. In case of the performance of simultaneous operations within the same manufacturing area, absence of cross contamination of supplies or products must be ensured.

10.1.12. The records and verifications must be performed only by authorized personnel, documented in a reliable manner, immediately after the performance of every operation and before proceeding to the execution of the following step described in the process.

10.1.13. The flow of supplies must me defined in an SOP to prevent them from mixing.

10.2. Control of procurement and reception of supplies, bulk, semi-processed and finished product.

10.2.1. Procurement

10.2.1.1. There must be a system that ensures that all suppliers are evaluated before being approved.*

10.2.1.2. Supplies, bulk, semi-processed or finished product, must be procured from approved suppliers, according to the quality system implemented by the establishment. Procurement must be carried out according to current specifications.

10.2.2. Reception.

10.2.2.1. At the moment of receiving supplies, bulk, semi-processed or finished products, the establishment must verify that the containers are duly identified, closed, without deterioration or damage of any kind that may affect the quality characteristics of the material they contain and that they meet the corresponding specifications. For every batch or consignment, there must be a supplier’s Certificate of Analysis or Conformity, as applicable.

10.2.2.2. The containers, lids and other parts of the packaging materials that are in direct contact with supplies, bulk, semi-processed or finished products shall not interact with the material they contain, nor alter their quality.

10.2.2.3. Upon receiving every batch of supplies, and medical devices (bulk, semi-processed and finished) a control number must be assigned according to the internal system.

10.2.2.4. Containers must be placed on pallets or shelves to facilitate cleaning, inspection and handling.

10.3. Storage control of supplies, bulk, semi-processed or finished product.

10.3.1. Storage control must be carried out based on the corresponding SOP, considering clear identification and separation by physical media or control systems (quarantine, approval or rejection).

10.3.2. Movement of supplies, bulk, semi-processed or finished product, must be carried out considering the first in-first out or first expired-first out systems.
10.3.3. Supplies, bulk, semi-processed or finished product must be placed in such a way that they are not in contact with the floor.

10.3.4. Supplies, bulk, semi-processed or finished product, must be sampled, analyzed and ruled prior their use according to the corresponding SOP.

10.3.5. When applicable, supplies, bulk, semi-processed or finished product, whose expiration date on the identification label has been reached must be placed on temporary retention for their reanalysis or final disposal.

10.3.6. Rejected supplies or medical devices must be identified as such and must be transferred to a specific area to avoid their use in any productive process. They must be confined, destroyed, returned, reprocessed or recovered, according to the corresponding SOP.

10.3.7. Inventory records must be kept in such a way that they allow reconciliation and traceability by batch or serial number of the quantities received against the quantities dispensed.

10.3.8. Reconciliations of raw materials and conditioning materials must be carried out periodically. In case of discrepancies outside the established limits, an investigation must be carried out and a report issued.

10.4. Dispensing of supplies, components, primary package materials, conditioning materials and bulk, semi-processed and finished product.

10.4.1. For the dispensing of supplies and medical devices (bulk, semi-processed and finished), there must be the SOPs considering at least the following:

10.4.1.1. Only approved supplies, bulk, semi-processed and finished product are dispensed.

10.4.1.2. They are only handled by authorized personnel.

10.4.1.3. Ensuring they are measured, weighed or counted according to the Production Order, which must be registered in the same document. These operations must be verified by the person who receives them.

10.4.1.4. Measures to prevent mixture or cross contamination.

10.4.1.5. The system under which the supplies of a dispensed order will be identified in order to ensure their traceability.

10.4.1.6. Final disposal and handling of empty containers that held the dispensed material.

10.5. Production control

10.5.1. Overview.

10.5.1.1. Every batch of the medical device must be controlled from the beginning of the process by means of a Production Order.

10.5.1.2. When quantity of the medical device to be produced or supplies to be dispensed need to be adjusted, they must be dispensed and verified by authorized personnel and be documented in the Production Order.

10.5.1.3. The corresponding Production Order must be available at sight to the personnel who carry out the process before and during the production of the medical device.

10.5.1.4. The area or process line must be free of product, material, documents and identifications of different previously processed batches or foreign to the batch to be processed.

10.5.1.5. Prior to the start of production, the use of the area must be authorized by previous verification and documentation that the area and the equipment are clean and identified (line clearance), according to the corresponding SOP.

10.5.1.6. The responsible of the process must verify that the personnel participating in the production is wearing the necessary clothing and safety equipment, according to the manufacturing procedure or the corresponding SOP.

10.5.1.7. Operations must be carried out according to the manufacturing procedure and be registered at the same moment.

10.5.1.8. Verify that the equipment, auxiliary components and critical systems are suitable to process every batch of the medical devices.

10.5.1.9. The manufacturing procedure must indicate the critical operations that must be supervised.
10.5.1.10. The manufacturing procedure must set forth the process parameters and control activities required to ensure the medical device stays within the previously established specification.

10.5.1.11. The execution of the control activities of the in-process product within the production areas must not affect the process or the quality of the medical device.

10.5.1.12. The results of tests or analysis performed during the process must be registered or attached to the Production Order.

10.5.1.13. Personnel in charge of production and quality areas, must review, document and assess any deviation in the manufacturing process according to the established procedure and must define the actions to be taken according to each case.

10.5.1.14. When applicable, the final and intermediate yields must be registered in the Production Order and compared against their limits. In case of a deviation, it must be documented and the corresponding investigation carried out.

10.5.1.15. There must be an SOP ensuring the correct separation and identification of the medical devices during each stage of the process.

10.5.1.16. When applicable, there must be defined times for every critical stage of the manufacturing process and when the medical device is not packaged immediately, its storage conditions and maximum storage time must be defined. All this must be supported by stability and validation studies.

10.5.1.17. The tools, equipment components and accessories must be stored in a designated area, and their handling and control must be carried out according to the corresponding SOP.

10.5.1.18. The areas must be classified according to the Regulatory Appendix A.

10.5.1.19. Only the minimum necessary personnel should be inside the aseptic areas and they must follow the applicable aseptic techniques, according to the corresponding SOP. In the extent possible, manufacturing activities must be inspected and controlled from the outside.

10.5.1.20. The Production Responsible must ensure that the preventive maintenance program is followed according to the corresponding SOP.

10.5.1.21. The Responsible of the Quality Department must ensure that the environmental monitoring program is followed according to the corresponding SOP.

10.5.1.22. The medical devices must be inspected according to the established sampling plan and the product’s risk level.

10.5.1.23. The tests set forth by the specification or monograph of every product must be performed.

10.6. Conditioning control.

10.6.1. Overview.

10.6.1.1. All conditioning operations must be performed with the materials specified in the corresponding Conditioning Order and the instructions set forth by the specific Conditioning Procedure must be followed. These documents must be available at sight to the personnel who carry out the process before and during the conditioning.

10.6.1.2. Only one batch or consignment and presentation of a medical device must be conditioned at a time on each line. Prior to the conditioning of a specific batch, the personnel must verify that the equipment and areas are clean and free of components, conditioning materials, documents, identifications and materials foreign to the batch or consignment to be conditioned. The line must be authorized by previous supervision, leaving written evidence thereof.

10.6.1.3. The process yield must be calculated at the end of the conditioning operations; the balance of the conditioning materials used must also be performed. The final yield and balance of the conditioning materials must be recorded and compared against their limits and, in case of a deviation from these limits, and investigation must be carried out and the result must be attached to the file of every conditioned batch.

10.6.1.4. During the conditioning process, the materials used must be identified with the necessary conditions to avoid mixing, confusion and errors.

10.6.1.5. In case the conditioning operation is not finished, there must be an SOP describing the actions to prevent material or component mixing or loss of identification of the batch at issue, as well as the conditions in which they must be conserved.
10.6.2. Batching/codification control.

10.6.2.1. There must be an SOP ensuring the safety during the handling of materials to be batched/codified and the printed materials.

10.6.2.2. There must be specific areas for conditioning material batching/codification, that allow avoiding confusions, errors and mixing.

10.6.2.3. The batched/codified material must be stored in controlled areas with restricted access and must be incorporated in the batch they will be used.

10.6.2.4. When individual printed materials are used, when printing is performed outside the conditioning line or when manual conditioning operations are carried out, the necessary and sufficient control activities must be implemented to avoid confusions, mixing and errors.

10.6.2.5. Batching/codification of materials must be inspected by Quality Department personnel.

10.6.2.6. In case the batching/codification operation is not finished, there must be an SOP describing the actions to prevent mixing or loss of identification of the materials and products.

10.6.3. Returned batched/codified conditioning materials must be conciliated and destroyed.

10.6.3.1. In case the return of leftover material is justified, as long as it is not batched/codified, it must be performed under controlled conditions, documented and approved by the Quality Department.

10.6.3.2. Leftover material that is batched/codified must be separate from any other material and destroyed according to an SOP. Such destruction must be documented and be part of the file of every conditioned batch.

10.6.4. Personnel in charge of the Conditioning and Quality areas, must review, document and assess any deviation in the conditioning process and define the actions to be taken according to each case.


10.7.1. The contractor is obliged to meet the applicable requirements set forth by this Standard.

10.7.2. There must be an SOP describing the activities and responsibilities of both establishments involved in the contract manufacturing.

10.7.3. The responsibilities of the contractor and the title holder must be clearly established in a document which must contain the required technical stages such as: manufacturing, conditioning and analysis, properly described, agreed by both parties and controlled in such a manner that it prevents omissions, confusions and deviations that may affect the quality of the medical device.

10.7.4. To ensure the technology transfer the title holder must be present at the start of the contract manufacturing, which must be documented.

10.7.5. The contract manufacturing stages must be validated at the contractor’s facilities according to this Standard (see section 15).

10.7.6. The title holder will be responsible for the quality of the medical device and the contractor must follow the specific procedure provided by the title holder.

10.7.7. The title holder or manufacturer must supervise the manufacturing stage(s) of the product and audit the contractor’s operations.

10.7.8. The contractor must deliver the ruled manufactured medical device according to the specifications provided by the registry holder, together with the original documentation signed by the contractor’s Quality Department Responsible. The contractor must keep a copy of the records of the manufacturing process for the time set forth by this Standard.

10.7.9. The title holder or manufacturer is responsible to ensure that the necessary analyses are carried out on the products manufactured by the contractor that allow making a final decision of the medical device. These analyses must be performed directly by the contractor (provided he has the infrastructure), by the title holder or by an authorized third party.

10.8. Analytical laboratory control.

10.8.1. The establishment must have validated analytical methods (when applicable) and tests, current and written specifications for supply, bulk, semi-processed and finished product analysis.

10.8.2. When applicable, representative retention samples of every batch of the finished medical device must be kept. These samples must be stored under the conditions described on the label of the finished
medical device; in case of not requiring specific conditions for its conservation they will be stored at room temperature. The retention times must be five years or one year after the shelf life of the product.

10.8.3. The conservation of retention samples per batch should be performed as per an SOP that considers the quantity to carry out two complete analysis with the exception of sterility tests.

10.8.4. There must be an SOP for cleaning, maintenance and operation of every instrument and equipment used in the analytical laboratory and for their calibration, contrast and qualification when applicable.

10.8.5. There must be an SOP to ensure the proper handling, identification, preparation, assay and reassay (when applicable), storage and final disposition of reference substances or materials, reagents, solutions, strains and culture medium used in the laboratory.

10.8.6. The reagents used in the analytical laboratory must be prepared according to the FEUM and current supplements. In case it does not include this information, internationally recognized pharmacopeias, information of national reference centers, international agencies whose analytical procedures are performed according to the specifications of specialized agencies or another internationally recognized scientific bibliography may be used. In case this information is not found in any of the aforementioned, it must be used according to the manufacturer’s validated method.


10.9.1. The Quality Department must make the official decision to release the finished product according to an SOP describing the complete review process for that manufacturing batch/serial number file.

10.9.2. To release the finished product, the following must be considered in addition to the batch file:

10.9.2.1. If there is a change that impacts the manufacturing batch or serial number, it must be closed before the release of the batch or serial number of the medical device in question.

10.9.2.2. The results of the environmental monitoring program to verify they do not have an impact on the batch or serial number of the medical device to be released, when applicable.

10.9.2.3. That the corresponding retention samples have been taken (see sections 10.8.3 and 10.8.4).

10.9.2.4. Any other document or notification related to the quality of the product, including deviation reports (see section 18).

10.9.2.5. That all documents comply with the provisions of section 8.1.3.

10.9.3. The Production and Conditioning Order, as well as the records, analytical results, labels and other documentation involved in the conditioning of every batch and presentation must be reviewed in order to verify that the established conditions, controls, instructions and process specifications have been met.

10.9.3.1. All documentation involved with the conditioning operations must be transferred to the corresponding area to complement the batch file and be kept during the previously established periods.

10.10. Distribution control.

10.10.1. An SOP to control the distribution of the medical devices describing the following, must be established:

10.10.1.1. Transportation form and conditions.

10.10.1.2. Storage instructions throughout the distribution chain.

10.10.1.3. That the products must be handled in the necessary conditions to preserve and/or conserve the medical device according to what is set forth on the label.

10.10.2. The medical device distribution system must be established according to the first in, first out or first expired first out policy.

10.10.3. Identification and integrity of the products must be ensured.

10.10.4. A distribution record of every product batch or serial number must be kept in order to facilitate its recall if necessary, according to what is set forth in section 8.5.3.

11. Manufacturing equipment

11.1. Overview
11.1.1. All equipment with the purpose of being used for the manufacturing, packaging, conditioning and storage of a medical device must be designed and comply with the necessary quality characteristics and be located in such a way that it allows its installation, operation, cleaning, maintenance and qualification.

11.1.1.1. At the moment of designing and installing equipment the handling, operation and cleaning aspects must be considered. The control systems must be those required for the proper operation, be located in accessible places and according to the area classification and the risk level of the medical device in which it will be operated.

11.1.1.2. When evaluating different alternatives for equipment, the required acceptance criteria for the process, the availability of process controls and the availability of spare parts and service must be considered.

11.2. Equipment design.

11.2.1. Materials considered for the design and construction of the equipment and its accessories in direct contact with solvents, formula components, in-process or finished medical device must not be reactive, additive, absorbent or adsorbent so that the quality of the product is not at risk.

11.2.2. Tanks and hoppers must be provided with covers to ensure their safety.

11.2.3. Equipment or containers subject to pressure must comply with the applicable regulations.

11.2.4. The required substances for the equipment operation, such as lubricants, coolants or others, should not be in direct contact with the formula components, primary packaging materials of the medical device or the product. These substances must be procured by a specification and their handling must be determined.

11.2.4.1. In case of substances that are in direct contact with the product, they must be at least food grade substances.

11.2.5. The gears and mobile parts must be protected to avoid contamination of the in-process medical device and the safety of the operator.

11.3. Equipment cleaning and maintenance.

11.3.1. The equipment and tools must be cleaned and maintained according to an SOP and an established program, that must consider at least the following:

11.3.1.1. Name of the responsible operator.

11.3.1.2. Description of the cleaning methods, equipment and materials used.

11.3.1.3. Equipment disassembly and assembly methods.

11.3.1.4. Verification list of the critical points.

11.3.1.5. There must be an SOP for the maintenance and operation of all equipment used.

11.4. All equipment used in the manufacturing, packaging or handling of medical devices must be located and installed in such a way that it:

11.4.1. Does not obstruct personnel movements and facilitates the flow of materials.

11.4.2. Ensures order during the processes and controls the risk of confusion or omission of any stage of the process.

11.4.3. Allows their cleaning and that of the area where they are located, and does not interfere with other operations of the process.

11.4.4. Is delimited, and when necessary, isolated from any other equipment to avoid congestion of production areas, as well as the possibility of the mixture of components.

11.5. Automatic equipment, mechanical and electrical.

11.5.1. The equipment or instruments used for monitoring or controlling the critical parameters of the process must be calibrated and inspected, according to a written program designed to ensure their performance. The calibration and inspection operations must be documented according to the following:

11.5.1.1. There must be evidence of the calibration frequency, calibration method, approved limits for accuracy and precision as well as the identification of the equipment or instrument.

11.5.1.2. Control of calibration labels must be set forth in an SOP and they must be placed on the calibrated equipment; their control will be carried out according to the calibration program.
11.5.1.3. The calibration records must be safekept and controlled.

11.5.2. The software installed in the computerized equipment used to control the manufacturing process must be validated, when applicable.

11.5.3. With the purpose of ensuring the accuracy of the data handled by the computerized equipment used to control the manufacturing process, a protection system must be implemented to avoid modification to the formulas or the records by unauthorized personnel.

11.5.4. An updated backup of all information filed in computers or related systems must be kept to ensure the information issued by these systems is accurate, complete and that there are no unnoticed modifications.


12.1. Every product that does not meet the established specifications or that are manufactured outside the established procedures must be identified and controlled until their final disposal, to prevent their non-intentional use.

12.2. There must be an SOP describing the actions to take for the treatment of non-compliant products and their final decision.

12.3. A deviation report must be issued to define if it may be reconditioned, reworked, reprocessed, rejected or approved by concession, this final decision must be issued by the Quality Department.

12.4. All reworked or reprocessed batches must undergo a quality analysis or assessment (as applicable) and the documentation must show that the quality of the batch is equivalent to that obtained in the original process.

12.5. When non-compliance of the product is recurrent, the corresponding investigations must be carried out and changes made must be validated, if applicable.

12.6. All rejected products must be identified and segregated until their destruction or final disposal, which must be performed according to an SOP and the applicable legal provisions.

12.7. A specific rework or reprocess order must be completed for the non-compliant product including the instructions that must be followed to carry out any of these activities. For product reworking or reprocessing where the sterility or the primary package integrity is lost, a batch number, different to the original and traceable, must be assigned, as well as proof that the sterilization rework does not affect the quality of the medical device through cross reference; in any case it should be authorized by the Sanitary Responsible.

12.8. Release of a reworked or reprocessed batch must follow the steps described in section 10.9 and must be authorized by the Sanitary Responsible.

13. Returns and complaints.

13.1. There must be an SOP to control the returned products taking into consideration at least the following:

13.1.1. They must be kept in temporary retention and evaluated by the Quality Department in order to determine if they should be reworked, reprocessed, destroyed, approved by concession or their final disposal.

13.1.2. Records of reception, evaluation and destination. The report must include the elements described in section 8.5.6.

13.2. There must be an SOP to manage complaints indicating the following:

13.2.1. Obligation to handle attend all received complaints.

13.2.2. The need to identify the cause for the complaint.

13.2.3. Define the corrective and preventive actions to take regarding the issue.

13.2.4. The cases that require notifying the Health Authority and the way to do so, according to the current regulations.

13.2.5. The way and time to answer the customer, when applicable.

13.2.6. Records of the obtained results and decisions taken regarding the complaints must include the elements stated in section 8.5.5.

14.1. There must be a system to effectively and timely recall products from the market in case of sanitary alerts and for products to be known or suspected to be out of specification.

14.2. There must be an SOP describing the following:

14.2.1. The person responsible for the recall coordination and its execution is the Sanitary Responsible.

14.2.2. The product recall activities that allow them to be started quickly and at all levels.

14.2.3. Storage instructions for recalled products.

14.2.4. Notification to the Health Authority according to the product distribution and the current regulations.

14.2.5. Review of the records of product distribution for sale or clinical trials that allow an effective product recall.

14.2.6. On-going verification of the recall process.

14.2.7. The final report including the conciliation between the distributed quantity and the recovered quantity, the actions to be taken to avoid the recurrence and final destination of the product.

15. Validation.

15.1. Policy.

It is a requirement of this Standard that the manufacturers of medical devices determine which validation activities are necessary to show the control of critical aspects of the particular operations.

An approach of risk analysis of the medical device must be used to assess the scope and degree of validation.

All facilities, equipment, critical systems that have impact on the quality of the medical device, must be qualified and the manufacturing processes, cleaning and analytical methods must be validated.

15.2. Validation planning.

15.2.1. The validation activities must be described in a Validation Master Plan (VMP) or equivalent which must be a brief and clear document including at least the following:

15.2.1.1. Manufacturing processes (including assemblies and their verification)

15.2.1.2. Primary package processes.

15.2.1.3. Cleaning processes or methods.

15.2.1.4. Manufacturing and conditioning equipment.

15.2.1.5. Analytical methods.

15.2.1.6. Software or computer applications that have impact on the quality of the product.

15.2.1.7. Critical systems.

15.2.2. The VMP must contain the following information:

15.2.2.1. Validation policy.

15.2.2.2. Organizational structure for the validation activities, including the person responsible of the project.

15.2.2.3. Summary of the facilities, systems, equipment and processes to validate.

15.2.2.4. Form to be used for protocols and reports.

15.2.2.5. Planning and scheduling.

15.2.2.6. Change control.

15.2.2.7. Reference to existing documents.

15.2.3. The VMP must indicate:

15.2.3.1. Validity
15.2.3.2. Scope

15.2.3.3. Purpose

15.2.3.4. Maintenance of the validated status (revalidation)

15.2.4. In the case of big projects, the creation of different Validation Master Plans may be needed.

15.3. Documentation.

15.3.1. A written protocol that specifies how the validation will be performed must be established. The protocol must specify the critical steps, its schedule, the person responsible for the critical processes and the acceptance criteria. Prior its execution, the protocol must be reviewed by the person responsible for the process or system and finally approved by the Quality Department Responsible.

15.3.2. A report that makes reference to the validation protocol must be prepared, it should compile the obtained results, making remarks on any observed deviation and stating the conclusions, including the changes needed to correct the deficiencies. The Validation Reports must be approved at least by the person responsible of the process or system and by the Quality Department Responsible.

15.3.3. Any change to the defined plan in the protocol must be documented with the appropriate justification. The changes must be reviewed by the person responsible of the process or system and approved by the Quality Department Responsible.

15.4. Qualification

15.4.1. The first stage of the validation process of facilities, critical systems, equipment, new or that are incorporated in the process, that have impact on the quality of the medical device is the design qualification (DQ).

15.4.2. Compliance of the design with the provisions of this Standard must be proved and documented.

15.4.3. The Facilities Qualification (FQ) must be carried out in facilities, critical systems and new or modified equipment that have an impact on the quality of the medical device.

15.4.4. The FQ includes, but it is not restricted to the following:

15.4.4.1. Areas construction or modification;

15.4.4.2. Equipment, pipe, services and instruments installation reviewed against blueprints and current engineering specifications;

15.4.4.3. Compilation and review of the operating instructions, work and the supplier's maintenance requirements.

15.4.4.4. Calibration requirements;

15.4.4.5. Verification of building materials;

15.4.4.6. Compliance of the facilities with the provisions of this Standard must be proved and documented.

15.4.5. The operational qualification (OQ) must follow a satisfactory Facilities Qualification.

15.4.6. The OQ includes, but it is not restricted to the following:

15.4.6.1. Proof obtained from the knowledge of the system and equipment to show that the equipment complies with the design specifications.

15.4.6.2. Proof including a condition or group of conditions that meet the upper and lower operational limits or the “worst case scenario” conditions.

15.4.7. The completion of a satisfactory operational qualification must allow ratification or modification of the calibration, operation and cleaning procedures, the training of the operator and the requirements of preventive maintenance.

15.4.8. Compliance of the operation with the provisions of this Standard must be proved and documented.

15.4.9. The execution or Performance Qualification (PQ) must follow a satisfactory Facilities Qualification and Operational Qualification. When justified, it may be performed together with the OQ.

15.4.10. The PQ must include proof developed to show that the equipment performs according to the specified process and product parameters and specifications.
15.4.11. The PQ must include, but it is not limited to the following:

15.4.11.1. Proof and materials used in the manufacturing, qualified substitutes or simulated products, that have been developed from the process knowledge and the facilities, systems or equipment;

15.4.11.2. Proof including a condition or group of conditions that meet the upper and lower operational limits or the “worst case scenario” conditions.

15.4.11.3. Compliance of the execution or performance with the provisions of this Standard must be proved and documented.

15.4.12. For the qualification of the facilities, equipment and services in use there must be available evidence that supports and verifies the operational parameters and limits of the critical variables of the operative equipment. In addition, the calibration, cleaning, preventive maintenance and operation procedures must be documented, as well as the personnel training procedures and records and supplier assessment.

15.5. Process validation.

15.5.1. The process validation must be completed before distribution and commercialization of the product.

15.5.2. The process validation may be concluded in a retrospective manner taking into account a sufficient number of runs or batches based on the risk analysis of the medical device, with satisfactory results, as long as there are no changes in the process and all elements involved and that have impact on the manufacturing processes have been previously qualified and/or validated. Each application of this type of validation must be justified and documented.

15.5.2.1. The retrospective validation is not applicable to systems or critical processes.

15.5.3. In exceptional circumstances, a process validation during routine manufacturing (concurrent validation) may be needed. The rationale for the concurrent approach must be documented and all elements involved and that have impact on the manufacturing processes must have been previously qualified and/or validated. The manufactured batches under this approach may be released individually if they meet their specifications.

15.5.4. The number of process runs needed for the validation will depend on the complexity of the process or the magnitude of the change. A minimum of 3 runs or consecutive batches with satisfactory results are needed to consider a process validated.

15.5.5. The critical parameters must be controlled and monitored during the validation studies.

15.5.6. The facilities, systems and equipment to be used must be qualified and the analytical methods must be validated.

15.5.7. Personnel who participate in the validation activities must be appropriately trained and qualified.

15.6. Cleaning validation.

15.6.1. The cleaning validation must be performed in order to confirm the effectiveness of a cleaning procedure or method of the production areas and surfaces that are in direct contact with the product.

15.6.2. The validation must reflect the current use patterns of the equipment. If different products are processed in the same, and it is cleaned using the same process, a representative product may be used for the validation or the “worst case scenario” criteria. The established limits or acceptance criteria must be attainable and verifiable.

15.6.3. Validated analytical methods whose detection and quantification limit is sensible enough to detect and quantify the established acceptable level of the residue or pollutant must be used.

15.6.4. Three consecutive runs of the cleaning procedure with satisfactory results and according to the criteria set forth by the protocol must be performed, to demonstrate that the method is validated.

15.7. Analytical methods.

15.7.1. The analytical methods used for the following, must be validated prior their application:

15.7.1.1. Raw material evaluation.

15.7.1.2. Bulk, in-process and finished product evaluation.

15.7.1.3. Process evaluation,

15.7.1.4. Stability trials.
15.7.2. The suitability of the method must be proved in the case of pharmacopoecic methods, internationally recognized or internally validated by a central office or a corporation, used for the evaluation of conformity of raw materials, processed products or finished products.

15.7.3. Any change on the validated analytical method must be subject to the change control process.

15.8. Computer systems.

15.8.1. Computer systems and applications that have impact on the quality of the product related to the following must be validated:

15.8.1.1. Material and product transfers.


15.8.1.3. Control of processes and analytical instruments.

15.8.1.4. Control of critical systems.

15.8.1.5. When a computer system or application generates electronic records and/or uses electronic signatures, sections 15.8.2 and 15.8.3 must be considered.

15.8.1.6. This does not apply to records on paper that are or have been transmitted through electronic media, as long as they do not serve or are used to make decisions or used to carry out regulated activities based on these documents.

15.8.2. The following are considered electronic records:

15.8.2.1. Documents and records required by this or other applicable Standards which are created, modified, maintained, filed, recovered and/or transmitted through electronic systems.

15.8.2.2. Procedures and controls designed to ensure the authenticity, integrity and when applicable, the confidentiality of the electronic records, and to ensure that the electronic signatures cannot be declared not genuine must be established when electronic systems are used to create, modify, maintain, file, recover and/or transmit electronic records. The procedures and controls must include the following:

15.8.2.2.1. System validation to ensure the accuracy, reliability, functionality, consistency and capacity to distinguish between invalid or altered records.

15.8.2.2.2. Capacity of the computer systems or applications to generate copies of the exact and complete records, legible in both their manual as well as their electronic version that allows their inspection, review and copy.

15.8.2.2.3. Record protection, that allows their recovery in a quick and exact manner during their conservation period.

15.8.2.2.4. Allowing access to the system only to authorized personnel.

15.8.2.2.5. Use of computer generated safe tracking audit processes to independently record employee system access, as well as the actions that create, modify or erase electronic records.

15.8.2.2.6. Operational comparison of the system to oblige that the steps and events occur in the established sequence.

15.8.2.2.7. Comparisons to ensure that only authorized personnel can access the system, electronically sign a record, access the operation of the input and output device of the computer system, modify a record or perform a manual operation.

15.8.2.2.8. Determination that the persons who develop, maintain or use the electronic signature/record systems have the capacity, training and experience to perform the assigned tasks.

15.8.3. For the case of electronic signatures:

15.8.3.1. They must include information associated with the signature that clearly indicates the printed name of the signatory, date and time of the signature and the purpose associated with it.

15.8.3.2. They must be unique for each person and in the case of changes, they must not be repeated or reassigned to a different person.

15.8.3.3. When the use of electronic signatures is adopted, the date from which the electronic signatures are valid and equivalent to autograph signatures must be established, for which a record signed by two witnesses is necessary.
15.8.3.4. Electronic signatures that are not based on biometrics must:

15.8.3.4.1. Use at least two different elements such as an identification code and a password.

15.8.3.4.2. The entry of a person to a controlled access system must be carried out using all the elements of the electronic signature described in the previous section, the subsequent accesses during the same session may be performed using only one of the elements.

15.8.3.5. People who use electronic signatures based on the use of identification codes in combination with passwords, will use controls to ensure their safety and integrity and they must include:

15.8.3.5.1. Maintenance of every combination of identification code and password in such a manner that no other person has the same combination.

15.8.3.5.2. Assurance that the issue of identification codes and passwords is periodically renewed or reviewed.

15.8.3.5.3. To have approved procedures in case of contingencies such as loss, theft or disappearance of tokens, cards or other devices that carry or generate information of identification codes or passwords to issue temporary or permanent replacements using proper and strict controls.

15.8.3.5.4. Protection mechanisms of the transactions to avoid unauthorized use of passwords and/or identification codes, to immediately and urgently detect and inform the Security System Unit, and when appropriate, the establishment’s management of any attempt of unauthorized use.

15.8.3.5.5. Initial and periodical trials of the devices such as tokes or cards that carry or generate information of identification codes or passwords to ensure they function properly and that they have not been altered.

15.8.3.5.6. Electronic signatures and autograph signatures executed in electronic records, will be linked in such a manner that ensures they cannot be eliminated, copied or transferred in any other way to forge an electronic record by ordinary means.

15.9. Critical systems and processes.

15.9.1. At least the following critical systems and processes must be validated:

15.9.1.1. Purified water and for the manufacture of injection (drugs/devices).

15.9.1.2. Air (compressed and environmental).

15.9.1.3. Clean vapor.

15.9.1.4. Sterilization (by physical or chemical means).

15.9.1.4.1. Simulated filling, among others.

15.10. Suppliers of services or supplies that have direct impact on the quality of the product.

15.10.1. They are considered qualified as long as:

15.10.1.1. They have been approved according to what is described in section 10.2 of this standard.

15.10.1.2. There is documented evidence of the historical performance regarding the quality of every supply provided.

15.10.1.3. An audit has been performed, either documental or through a physical visit to their facilities, according to section 19 of this Standard, proving they have an established Quality System.

15.10.1.4. A statistical study is performed between the results provided by the supplier in their Certificate of Analysis and the results obtained in the assessment according to the corresponding specification to prove their equivalence, when applicable.

15.10.2. The Ministry of Health may authorize the implementation of a reduction in the number of analysis or analytical tests as long as the suppliers of these supplies are qualified.

15.11. Maintenance of the validated status.

15.11.1. The maintenance of the validated status must be ensured through the verification of the compliance of the following systems and support programs:

15.11.1.1. Change control system.
15.11.1.2. Calibration system.
15.11.1.3. Preventive maintenance program.
15.11.1.4. Personnel qualification system.
15.11.1.5. Technical audit program.
15.11.1.6. Preventive and corrective action system.

15.11.2. When significant changes are made to the aforementioned programs and systems a requalification or revalidation must be carried out.

15.11.3. The validity of the qualifications and validations must be defined in the corresponding protocols.

15.11.4. If after five years, no significant changes are made to the validated system, a verification must be performed in order to ensure the maintenance of the validated status.


16.1. If required for the medical device to prove that the functionality and the quality characteristics of the medical device are maintained during its shelf life, the following must be performed:

16.1.1. Accelerated Stability Studies. When applicable, they must be carried out on pilot or production batches with the formulation and packaging material proposed to commercialize the finished product. The number of batches will be defined by the manufacturer based on the function or characteristics of the product.

16.1.2. Long term Stability Studies. When applicable, they must be carried out on pilot or production batches in particular conditions, for at least a period equal to the proposed shelf life, to confirm that. The number of batches will be defined by the manufacturer based on the function or characteristics of the product.

16.2. Study Protocol. It must contain the following information, as appropriate:

16.2.1. Name of the medical device, as well as its presentation and concentration, if applicable.
16.2.2. Number of batches and their size (when applicable).
16.2.3. Description, size and container’s or primary packing composition (when applicable).
16.2.4. Study conditions.
16.2.5. Sample and analysis times.
16.2.6. Test parameters.
16.2.7. Acceptance criteria (or stability specifications).
16.2.8. Reference of the analytical or test methods per parameter and their validation, where applicable.
16.2.9. Reduced analysis design, when justified.

16.3. Study Report. It must contain the following information:

16.3.1. Name of the medical device, as well as its presentation and concentration, if applicable.
16.3.2. Batch number, manufacturing date and when applicable, batch size.
16.3.3. Analytical results per storage condition and date of analysis.
16.3.4. When applicable, individual data, average, standard deviation and coefficient of variation.
16.3.5. Data analysis; including graphics, when applicable.
16.3.6. Statistical methods and formulas used, when applicable.
16.3.7. Statistical analysis results and conclusion.
16.3.8. Expiration period proposal.

16.4. General considerations.

16.4.1. The studies must be carried out in the primary package proposed for its storage and distribution.
16.4.2. All analysis performed during the stability studies, must be performed in duplicate and reported.
16.4.3. When applicable, the long term stability studies of the batches submitted in the registry file must continue until the completion of the shelf life period granted in the product’s registry.

16.4.4. A stability program must be implemented to ensure the expiration period of the medical device, which must be endorsed or authorized by the Sanitary Responsible.

16.4.5. An extension of the expiration period may be requested to the sanitary authorities submitting documented evidence of the long term stability studies.

16.4.6. The manufactured batches for the performance of the stability studies must be subject to manufacturing standard procedures.

16.4.7. When the analytical or test method is changed during the stability study, it must be proved that both methods are equivalent.

16.4.8. All analysis performed during the stability study, as well as the sample size, must be included in the protocol and be reported.

16.4.9. The stability of the product in the medical device must be confirmed with regard to the original, when the following occurs:

16.4.9.1. A change in the formulation not involving the active ingredient, for formulated products.

16.4.9.2. Or a change in the primary package, according to the product’s characteristics and risk.

16.4.10. The stability studies may be extended to those products that belong to the same family, as long as the composition, formulation or characteristics are the same in all cases.

16.4.11. The manufacturer must consider all test parameters corresponding to the type of product, that allow ensuring the medical device is stable during its shelf life.

17. Change control.

17.1. There must be a change control system to evaluate and document the changes that impact the product’s manufacturing and quality. Unplanned changes must be considered as deviations.

17.2. A Technical Committee composed by representatives of the areas involved must be created for every change to evaluate and make a final decision on the proposed change.

17.3. There must be an SOP including the identification, documentation, review and approval of the changes in: supplies, change of manufacturer, specifications, procedures, analytical methods, manufacturing processes, facilities, equipment, critical systems and computer systems.

17.4. All changes must be documented and approved by the Quality Department.

18. Deviations.

18.1. There must be a system that ensures all deviations from specifications, procedures and analytical methods are investigated, assessed and documented.

18.2. A Technical Committee composed by representatives of the areas involved in the deviations must be created to evaluate and make a final decision on the deviation.

18.3. There must be an SOP indicating the process to follow in the investigation, assessment, documentation and final decision for all deviations.

18.4. There must be a documented follow up plan for all actions resulting of a deviation or a potential deviation and evaluate the effectiveness of such actions.

18.4.1. Corrective actions.

The organization must take actions to eliminate the cause of the non-conformities with the purpose of preventing from occurring again. The corrective actions must be appropriate to the effects of the non-conformities found.

18.4.1.1. A documented process must be established to define the requirements for:

18.4.1.1.1. Review of non-conformities (including customer complaints).

18.4.1.1.2. To determine the causes of the non-conformities.

18.4.1.1.3. To assess the need of taking actions to ensure the non-conformities do not occur again.
18.4.1.4. To determine and implement the necessary actions, including, the documentation update, when applicable.

18.4.1.5. To record the results of any investigation and the actions taken, and

18.4.1.6. To review the implemented corrective action and its efficacy.

18.4.2. Preventive actions.

The organization must take actions to eliminate the causes of potential non-conformities with the purpose of preventing from occurring. The preventive actions must be appropriate to the effects of the potential issues.

18.4.2.1. A documented process must be established to define the requirements for:

18.4.2.1.1. To determine the potential non-conformities and their causes.

18.4.2.1.2. To assess the need to take action to prevent the occurrence of non-conformities.

18.4.2.1.3. To determine and implement the necessary actions.

18.4.2.1.4. To record the results of any investigation and the actions taken, and

18.4.2.1.5. To review the implemented preventive action and its efficacy.

18.5. The investigation must be extended to other batches of the same product and to other products if they are associated in the deviation. A written report of the investigation, including the conclusion and the follow-up, must be issued.

18.6. All deviation reports must be approved by the Manufacturing area and Quality Department Responsible before deciding the final destination of the product involved.


19.1. Technical audits include internal and external audits.

19.1.1. Internal audits must cover all points included in the Standard, based on an audit program.

19.1.2. External audits performed by the organization include suppliers, service providers and contract manufacturers that have impact on the manufacturing process and the quality of the product, according to the applicable by this standard.

19.2. There must be an SOP describing the audit system, including at least the following:

19.2.1. A scheduled program.

19.2.2. Auditor selection, training and qualification.

19.2.3. Documented evidence of the audits and their follow up.

19.2.4. Effectiveness of the preventive and corrective actions taken.

20. Destruction and final Destination of Pollutant and/or Hazardous Residues

20.1. There must be a documented system in an SOP ensuring compliance with the current legal regulations in terms of ecology and sanitary areas for the final destination of pollutants and/or hazardous residues, notifying the corresponding authorities when applicable.


This Standard partially agrees with the following Standards:


22. Bibliography

22.1. General Health Law

22.2. General Law of Ecological Balance and Environmental Protection.

22.3. Federal Law on Metrology and Standardization.

22.4. Regulation for Health Supplies.

22.5. Regulation of the Federal Law on Metrology and Standardization.


23. **Compliance with this Standard.**

Surveillance of the compliance with this Standard is the responsibility of the Ministry of Health and the governments of the Federal Entities, in the scope of their corresponding competencies, whose personnel will carry out the necessary verification and vigilance.

24. **Compliance Assessment.**

Assessment of the compliance may be requested by the Sanitary Responsible, the Legal Representative or the person with the required faculties, before the competent authority or the accredited or authorized persons for such effects.

25. **Validity**

This Standard will be effective after 180 calendar days of its publication in the Federal Official Journal.

Effective Suffrage, No Re-election.

Mexico, D.F., June 20, 2012.- Federal Commissioner for the Protection against Sanitary Risks and Chairman of the National Advisory Committee for Standardization of Health Regulation and Promotion, **Mikel Andoni Arriola Peñalosa.**- Rubric.
## STANDARD APPENDIX A

<table>
<thead>
<tr>
<th>Classification</th>
<th>Non-viable particles/m³, size equals to or large than:</th>
<th>Viable particles</th>
<th>Air speed and change</th>
<th>Particle retention &gt; 0.5 µm</th>
<th>Differential pressure, air flow</th>
<th>Dress code</th>
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</thead>
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<tr>
<td></td>
<td>Static/dynamic Conditions</td>
<td>Monitoring Frequency</td>
<td>(CFU)</td>
<td>Monitoring Frequency</td>
<td>Vertical laminar flow</td>
<td>Terminal filters</td>
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<td>5 µm</td>
<td></td>
<td></td>
<td>0.3 m/s*</td>
<td>99.9995% efficiency</td>
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<tr>
<td>ISO-Class 4</td>
<td>352</td>
<td>0</td>
<td>Per manufacturing shift</td>
<td>≤ 1/m³ and ≤ 1/plate and ≤ 1/print</td>
<td>Daily/ manufacturing shift</td>
<td>Vertical laminar flow</td>
</tr>
<tr>
<td></td>
<td>3 520</td>
<td>29</td>
<td>Per manufacturing shift</td>
<td>≤ 1/m³ and ≤ 1/plate and ≤ 1/print</td>
<td>Daily/ manufacturing shift</td>
<td>Vertical laminar flow</td>
</tr>
<tr>
<td>ISO-Class 6</td>
<td>35 200</td>
<td>293</td>
<td>Every 6 months</td>
<td>≤ 10/m³ and ≤ 5/plate and ≤ 5/print</td>
<td>Daily/ manufacturing shift</td>
<td>Terminal filters</td>
</tr>
<tr>
<td>ISO-Class 7</td>
<td>352 000</td>
<td>2 930</td>
<td>Every 6 months</td>
<td>≤ 100/m³ and ≤ 50/plate</td>
<td>Weekly</td>
<td>n.a. / ≥ 20 h</td>
</tr>
<tr>
<td>ISO-Class 8</td>
<td>3 520 000</td>
<td>29 300</td>
<td>Every 6 months</td>
<td>≤ 200/m³ and ≤ 100/plate</td>
<td>Monthly</td>
<td>n.a. / ≥ 10 h</td>
</tr>
<tr>
<td>ISO-Class 9</td>
<td>35 200 000</td>
<td>293 000</td>
<td>Must be defined by each establishment*</td>
<td>≤ 200/m³ and ≤ 100/plate</td>
<td>Monthly</td>
<td>n.a. / ≥ 10 h</td>
</tr>
<tr>
<td>Grey area (Free of classification)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>See section 9.2.11</td>
</tr>
</tbody>
</table>

### NOTES:

* The monitoring frequency must be established based on policies and the qualification results.
# Sedimentation plate, with exposure for no less than 30 minutes per plate the time the operation lasts.
### 5 finger print on the contact plate.
#### The manufacturing shift refers to the time the manufacturing of a batch lasts.
n.a. Not applicable.