ALEJANDRO ERNESTO SVARCH PÉREZ, Federal Commissioner for Protection against Sanitary Risks and President of the National Consultative Committee for Standardization of Regulation and Sanitary Promotion, based on Articles 39 of the Organic Law of the Federal Public Administration; 4 of the Federal Law of Administrative Procedure; 3, sections XXIII and XXIV, 13, paragraph A, section I, 17 Bis, sections I, II, III, VI and VII, 194, section II, 194 Bis, 195, 197, 201, 210, 212, 213, 214, 263 and 264 of the General Health Law; 38, section II, 40, sections I, V, XI and XII, 43, and 47, section IV of the Federal Law on Metrology and Standardization; 28 and 33 of the Regulations of the Federal Law on Metrology and Standardization; 9o., 11, 15, 100, 102 and 111 of the Regulation of Health Supplies; 3, sections I, paragraph b) and I) and II, as well as 10, sections IV and VIII of the Regulation of the Federal Commission for the Protection against Sanitary Risks; and

WHEREAS

That on June 14, 2019, in compliance with the agreement of the National Consultative Committee for Standardization of Regulation and Sanitary Promotion and the provisions of Article 47, Section I, of the Federal Law on Metrology and Standardization, the Draft of this Standard was published in the Official Gazette of the Federation, so that within 60 calendar days following such publication, interested parties could submit their comments to said Committee;

That on a previous date, the response to the comments received by the aforementioned Committee was published in the Official Gazette of the Federation, pursuant to Article 47, Section III of the Federal Law on Metrology and Standardization, and

In view of the foregoing considerations, and with the approval of the National Consultative Committee for the Standardization of Regulation and Health Promotion, I have had the good will to issue and order the publication in the Official Gazette of the Federation of the

MEXICAN OFFICIAL STANDARD PROY-NOM-241-SSA1-2021, GOOD MANUFACTURING PRACTICES FOR MEDICAL DEVICES

PREFACE

The following participated in the development of this Standard:

HEALTH SECRETARIAT.
Federal Commission for the Protection against Sanitary Risks.
Permanent Commission of the Pharmacopoeia of the United Mexican States.
National Center of Technological Excellence in Health.

GENERAL HEALTH COUNCIL.
Interinstitutional Commission of the Basic List and Catalog of Health Sector Supplies.

MEXICAN INSTITUTE OF SOCIAL SECURITY.

Coordination of Technical Control of Inputs.

INSTITUTE OF SAFETY AND SOCIAL SERVICES OF THE WORKERS OF THE STATE.
Infrastructure Sub directorate.

NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO.
Faculty of Chemistry.

NATIONAL POLYTECHNIC INSTITUTE.
National School of Biological Sciences.

NATIONAL CHAMBER OF THE TRANSFORMATION INDUSTRY.
Medical Industry Sector.

NATIONAL CHAMBER OF THE PHARMACEUTICAL INDUSTRY.
Health Auxiliary Products Section.
Reagents and Diagnostic Systems Section.

NATIONAL CHAMBER OF THE COSMETIC PRODUCTS INDUSTRY.

NATIONAL ACADEMY OF PHARMACEUTICAL SCIENCES, A.C.

MEXICAN PHARMACEUTICAL ASSOCIATION, A.C.

MEXICAN PHARMACEUTICAL ASSOCIATION OF THE WEST, A.C.

NATIONAL COLLEGE OF PHARMACEUTICAL CHEMISTS AND BIOLOGISTS MEXICO, A.C.

CHEMICAL PHARMACEUTICAL PRODUCTION, A.C.

MEXICAN ASSOCIATION OF PHARMACEUTICAL LABORATORIES, A.C.

MEXICAN ASSOCIATION OF INNOVATIVE MEDICAL DEVICE INDUSTRIES, A.C.

COLLEGE OF BIOMEDICAL ENGINEERS OF MEXICO, A.C.

INDEX

0 Introduction

Health is a factor of utmost importance for the welfare and social development of the community, so it is up to the Federal Executive through the Ministry of Health, to establish the requirements that must be met during the manufacturing process of medical devices to ensure the quality and functionality of the same.

The implementation of Good Manufacturing Practices is a fundamental part of a quality management system which is a strategic decision of the organization; its design and implementation is influenced by the product manufactured, process used, size and structure of the organization.

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

1 Objective and scope of application

1.1 Objective

The purpose of this Standard is to establish the minimum requirements for the processes of design, development, manufacture, storage, and distribution of medical devices, based on their level of risk, in order to ensure that they consistently meet the requirements of quality, safety and functionality for use by the final consumer or patient.

1.2 Scope of application

This Standard is mandatory in the national territory, for all establishments dedicated to the manufacture of medical

devices, warehouses for conditioning, storage, and distribution of medical devices.

2 Normative references

For the correct application of this Standard, it is necessary to consult the following Mexican Official Standards in force or those that may replace them:

2.1 Official Mexican Standard NOM-002-SEMARNAT-1996, which establishes the maximum permissible limits of contaminants in wastewater discharges to urban or municipal sewage systems.

2.2 Official Mexican Standard NOM-003-NUCL-1994, Classification of facilities or laboratories that use open sources.

2.3 Official Mexican Standard NOM-005-STPS-1998, Safety and Hygiene Conditions in Workplaces for the Handling, Transport and Storage of Hazardous Chemical Substances.

2.4 Official Mexican Standard NOM-007-NUCL-2014, Radiation safety requirements to be observed in permanent implants of radioactive material for therapeutic purposes to humans.

2.5 Official Mexican Standard NOM-011-STPS-2001, Safety and hygiene conditions in workplaces where noise is generated.

2.6 Official Mexican Standard NOM-017-STPS-2008, Personal protective equipment-Selection, use and handling in the workplace.

2.7 Official Mexican Standard NOM-020-STPS-2011, Pressure vessels, cryogenic vessels and steam generators or boilers - Operation - Safety conditions.

2.8 Official Mexican Standard NOM-026-STPS-2008, Safety and hygiene colors and signs, and identification of risks due to fluids conducted in pipelines.

2.9 Official Mexican Standard NOM-028-NUCL-2009, Radioactive waste management in radioactive facilities that use open sources.

2.10 Official Mexican Standard NOM-030-STPS-2009, related to Preventive Occupational Safety and Health Services - Functions and Activities.

2.11 Official Mexican Standard NOM-036-1-STPS-2018, Ergonomic risk factors at work-Identification, analysis, prevention, and control.

2.12 Official Mexican Standard NOM-052-SEMARNAT-2005, which establishes the characteristics, identification procedure, classification and lists of hazardous wastes.

2.13 Official Mexican Standard NOM-059-SSA1-2015, Good Manufacturing Practices for Medicines.

2.14 Official Mexican Standard NOM-062-ZOO-1999, Technical specifications for the production, care and use of laboratory animals.

2.15 Official Mexican Standard NOM-073-SSA1-2015, Stability of drugs and medicines, as well as herbal remedies.

2.16 Official Mexican Standard NOM-087-SEMARNAT-SSA1-2002, Environmental Protection-Environmental Health-Biological and infectious hazardous waste-Classification and handling specifications

2.17 Official Mexican Standard NOM-137-SSA1-2008, Labeling of medical devices.

2.18 Official Mexican Standard NOM-164-SSA1-2015 Good Manufacturing Practices for Medicines.

2.19 Official Mexican Standard NOM-240-SSA1-2012, Installation and operation of techno vigilance.

3 Terms and definitions

For the purposes of this Standard, the following is understood as:

3.1 Sanitary finish, the finish given to the interior surfaces of the areas in order to prevent the accumulation of viable and non-viable particles and to facilitate cleaning.

3.2 Corrective action is the activity that is planned and executed to eliminate the cause of a deviation or nonconformity in order to prevent its recurrence.

3.3 Preventive action is the activity that is planned and executed to eliminate the cause of a deviation or nonconformity or other potentially undesirable situation and prevent its occurrence.

3.4 Conditioning, all the operations to which a bulk product has to undergo until it is presented as a finished product. Primary packaging is considered to be the elements that are in direct contact with the medical device and secondary packaging is that which includes the medical device in its primary packaging.

3.5 Technical Agreement, the document formalizing and detailing the conditions under which activities or services will be carried out between the parties and clearly describing the obligations and responsibilities of each party, especially with regard to quality aspects and GMP and GAP.

3.6 Wastewaters, to those discharged as a result of activities related to manufacturing, in the terms indicated in the

Official Mexican Standard mentioned in section 2.1 of this Standard.

3.7 Storage, to the conservation of supplies, bulk, semi-finished and finished product of the medical device that are kept in an area with established conditions according to their risk level.

3.8 Risk analysis, the method to evaluate in advance the factors that may affect the functionality of systems, equipment, processes or quality of inputs and outputs.

3.9 Area, to the room or set of rooms and spaces designed and constructed under defined specifications.

3.10 Aseptic Area, the area built and maintained under specific conditions of temperature and relative humidity percentage, in order to have within pre-established limits the number of viable and non-viable particles on surfaces and ambient air.

3.11 Clean area, the place in which the number of viable and non-viable particles must be controlled under conditions of humidity, pressure and temperature established for a particular situation.

3.12 Quality assurance, the set of planned and systematic activities carried out by an organization to provide confidence that a product or service meets specified quality requirements.

3.13 Audit, the systematic, independent, and documented process of obtaining evidence and evaluating it objectivelyto determine the level of compliance with established criteria.

3.14 Bioburden, the level, and type of microorganisms that may be present in any of the manufacturing elements (inputs, facilities, personnel, among others).

3.15 Biotheriums, the set of facilities, furniture and real estate used for the housing and maintenance of laboratory animals during one or more of the phases of their life cycle, i.e., birth, development, reproduction, and death.

3.16 Good storage and distribution practices (GDSP), the part of quality assurance, which ensures that the quality of medical devices is maintained throughout all stages of the supply chain from the manufacturing site to the site of supply to the public.

3.17 Good manufacturing practices (GMP), the set of interrelated guidelines and activities aimed at ensuring that the medical devices manufactured have and maintain the requirements of identity and purity (when applicable), quality, safety, efficacy, effectiveness, and functionality for their use.

3.18 Good Laboratory Practice (GLP), the set of rules, operational procedures and practices established to ensure the quality and integrity of the activities performed in the laboratory and of the analytical data obtained from tests or trials.

3.19 Calibration, the demonstration that a particular instrument or device produces results within specified limits as compared to those produced by a traceable reference or standard over an established range of measurements.

3.20 Quality, to the fulfillment of specifications established to guarantee the suitability for use.

3.21 Qualification, the performance of specific tests based on scientific knowledge, to demonstrate that the equipment, critical systems, facilities, personnel, and suppliers comply with the previously established requirements, which must be concluded before validating the processes.

3.22 Execution or performance qualification (CE), documented evidence that the facilities, systems, and equipment perform in compliance with previously established acceptance criteria.

3.23 Design qualification (CD), documented evidence demonstrating that the proposed design of facilities, systems and equipment is suitable for the intended purpose.

3.24 Installation qualification (IC), documented evidence that facilities, systems, and equipment have been installed in accordance with previously established design specifications.

3.25 Operational qualification (OC), documented evidence that equipment, facilities, and systems operate consistentlyin accordance with established design specifications.

3.26 Training refers to activities aimed at generating or reinforcing knowledge among personnel.

3.27 Certificate of analysis, the document that indicates the tests, specifications and results obtained in the evaluation of the medical device, according to the type of product and its risk level. It should include the name, description of the product, lot or serial number, date of manufacture and/or expiration date.

3.28 Certificate of conformity, the document issued by the manufacturer stating that compliance with the requirements, national or international technical standards and/or applicable specifications based on the type and level of risk of the medical device has been demonstrated.

3.29 Life cycle, all stages of the life of a medical device from initial conception to discontinuation.

3.30 Storage conditions are those required to preserve or conserve the quality characteristics of inputs, bulk, semi-finished and finished products.

3.31 Dynamic conditions are those in which the facility is operating in the defined operating mode and with the specified number of personnel.

3.32 Static conditions are those in which the Facility is operating with the production equipment complete and installed, with no personnel present.

3.33 Contamination, the presence of undesirable physical, chemical, or biological entities.

3.34 Cross-contamination means the presence of undesirable physical, chemical, or biological entities from a differentprocess or product.

3.35 Contaminant means undesirable impurities of a chemical or microbiological nature, or foreign matter, present in an input, intermediate and/or finished product.

3.36 Change control, the evaluation and documentation of changes that impact the quality, performance, or operationof the medical device.

3.37 In-process control, the checks carried out during manufacture to monitor and, if necessary, adjust the process.

3.38 Acceptance criteria, to predefined conditions, specifications, standards, or intervals to be met under pre-established test conditions.

3.39 Quarantine, the state of inputs and outputs that prevents their disposition for further processing and/or release, and which may be evidenced by physical separation or other means.

3.40 Deviation or nonconformity, failure to comply with a previously established requirement.

3.41 Medical device means an instrument, apparatus, appliance, utensil, machine, *software*, implantable product or material, diagnostic agent, material, substance, or similar product, to be employed, alone or in combination, directly or indirectly, in human beings; for any of the following purposes of use:

- Diagnosis, prevention, surveillance, or monitoring, and/or aid in the treatment of diseases;
- Diagnosis, surveillance or monitoring, treatment, protection, absorption, drainage, or aid in the healing of an injury;
- Substitution, modification, or support of the anatomy or of a physiological process;
- Life support;
- Conception control;
- Disinfection of medical devices;
- Disinfectant substances;
- Provision of information by *in vitro* examination of samples taken from the human body for diagnostic purposes;
- Devices incorporating tissues of animal and/or human origin, and/or
- Devices used in *in vitro* fertilization and assisted reproductive technologies;

And whose primary purpose of use is not through pharmacological, immunological, or metabolic mechanisms, however, they may be assisted by these means to achieve their function. Medical devices include health supplies of the following categories: medical equipment, prostheses, orthoses, functional aids, diagnostic agents, dental supplies, surgical and healing materials, and hygienic products.

3.42 Master document, the authorized document that contains the information to carry out and control the operations of the processes and activities related to the manufacture of a product.

3.43 Primary packaging means the elements of the packaging system that are in direct contact with the medical device.

3.44 Secondary packaging means the elements that are part of the packaging in which the medical device is marketed and that are not in direct contact with the medical device.

3.45 Specification, the description of a material, substance, or product, including the quality parameters, theiracceptance limits, and the reference of the methods to be used for their determination.

3.46 Stability, the ability of a medical device to remain within the established quality specifications, in the primary vessel containing it or secondary container when this is an essential condition for its shelf life.

3.47 Sterility, to the absence of viable microorganisms.

3.48 Stability studies are tests carried out on a medical device for a certain period of time, under the influence of temperature, humidity or light in the vessel that contains it, to demonstrate its shelf life and determine its expiration date.

3.49 Accelerated stability studies are those designed under extreme storage conditions to increase the rate of chemical, biological degradation or physical changes of a medical device.

3.50 Accelerated aging studies are those designed under extreme storage conditions to increase the rate of physical changes that a medical device may undergo during the exposure time established in the corresponding study and to

establish a tentative expiration date or shelf life, as well as the storage conditions.

3.51 Real-time (long-term) stability studies, those designed under storage conditions of temperature and humidity and/or those defined by the manufacturer through the application of risk management, which allow testing the storage conditions and expiration date of a medical device, through a program of sampling times and evaluation of the physical, chemical, and biological requirements, which check the preservation of its properties during its expiration period.

3.52 Real time (long term) aging studies, those designed under temperature and humidity storage conditions and/or those defined by the manufacturer through the application of risk management, which allow to check the storage and shelf-life conditions of a medical device, through a program of sampling times and evaluation of the physical requirements, which check the preservation of its properties during its shelf life.

3.53 Label shall mean any tag, label, inscription, mark, or graphic image that has been written, printed, stenciled, marked, embossed or intaglio engraved, affixed, or sealed on any material capable of containing the medical device including the container itself.

3.54 Batch manufacturing record, the set of documents that demonstrate that a batch of medical device was manufactured and controlled in accordance with the master document.

3.55 Legal file, the set of documents that demonstrate that the medical device complies with the regulations issued by the Ministry of Health.

3.56 Manufacturing, the operations involved in the production and packaging of a medical device from receipt of inputs, release, storage, and distribution as a finished product.

3.57 Expiration date, which indicates the end of the shelf life of the medical device and is based on stability studies.

3.58 Electronic signature, the compilation of computer data or any symbol or series of symbols, executed, adopted, or authorized by an individual to be legally attached and equivalent to the individual's autograph signature.

3.59 Quality risk management, the systematic process for the assessment, control, communication, and review of risksto the quality of medical devices throughout their life cycle.

3.60 Inspection means the assessment of conformity by measurement, test or comparison with standards accompanied by an opinion.

3.61 Facility, the set of areas, equipment and services intended to carry out a specific operation or process.

3.62 Work instructions, a detailed, sequential, and specific description of a task.

3.63 Inputs are those raw materials, components for assembly, primary packaging material, packaging material and product that are received at an establishment.

3.64 Concurrent release means the release for distribution of a batch of the manufactured device following a process qualification protocol that meets the release criteria established before the protocol is completed.

3.65 Lot release, the opinion that indicates the disposition of the product from a systematic review to ensure quality from all aspects, particularly those of GMP.

3.66 Cleanliness, to the process for the reduction of non-viable particles to established levels.

3.67 Batch means the specific quantity of any raw material or (health) input that has been produced in a production cycle, under equivalent operating conditions and during a specified period.

3.68 Quality manual, the document that describes the quality management system of an establishment, in accordance with the quality policy and objectives established in the manual.

3.69 Maquila, the process or stage of a process involved in the manufacture of a medical device, carried out by an establishment other than the holder of the sanitary registration or manufacturer; it may be national or international; temporary or permanent.

3.70 Raw material means a substance, material or component of any origin that is used for the manufacture of a medical device.

3.71 Printed material means any label, instruction, or packaging material present on the final product.

3.72 Sample means the quantity of material whose composition is representative of the lot to be examined.

3.73 Retention sample, to a sufficient quantity of raw materials or product to carry out two complete analyses, except sterility test.

3.74 Lot or serial number means the numeric or alphanumeric combination that specifically identifies a lot.

3.75 Packaging order, a copy of the master packaging order which is assigned a lot number and used for the assortment and recording of materials for the packaging of a batch of medical device.

3.76 Production order, a copy of the master production order or formula to which a batch number is assigned, is used for the assortment, and recording of supplies for the production of a batch of medical device.

3.77 Viable particles mean any particle that under appropriate environmental conditions can reproduce.

3.78 Worst case, a condition or set of conditions encompassing upper and/or lower limits and circumstances of a process, within standard operating procedures, that have the greatest opportunity for process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

3.79 Validation Master Plan (VMP), the document that specifies the information regarding the validation activities to be carried out by the facility, where details and time scales are defined for each validation work to be performed. The responsibilities related to this plan should be established.

3.80 Packaging procedure means a document containing detailed instructions for transforming a bulk product into a finished product.

3.81 Production procedure, the document that contains the detailed instructions to transform raw materials, materials, or components into bulk medical devices prior to their conditioning in the packaging intended for their commercialization.

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

3.83 Production, the operations involved in the processing of inputs into a bulk product.

3.84 Semi-finished product is the product in its primary packaging that will undergo subsequent stages to become a finished product.

3.85 Bulk product means product at any stage of the production process prior to primary packaging.

3.86 Environmental monitoring program, the establishment of a chronological sequence of activities to evaluate compliance with established parameters of viable and non-viable particles in a controlled environment.

3.87 Protocol, the written work plan that establishes the objectives, procedures, methods, and acceptance criteria forconducting a study.

3.88 Stability study protocol, study design related to testing and acceptance criteria, batch characteristics, sample handling, study conditions, analytical methods, and primary and secondary packaging materials.

3.89 Complaint, any observation of dissatisfaction from an internal or external customer, related to the quality, safety,and functionality of the product.

3.90 Traceability or traceability, the ability to reconstruct the history, location of an element, component, or activity,using records as evidence.

3.91 Reconditioned, to the change of packaging of any medical device, provided that the quality of the same is guaranteed.

3.92 Cross-reference, to the citation of other documents that serve as reference, support, or complement to another.

3.93 Record, the document that presents evidence of actions taken to demonstrate compliance with activities or instructions.

3.94 Electronic record, the set of information that includes electronic data (text, numerical, graphic) that is created, modified, maintained, archived, restored, or transmitted through a computerized system.

3.95 Remanufacturing means processing, reconditioning, refurbishing, repackaging, refurbishing or any other activity performed on a new or used finished medical device that significantly changes the performance of the device, the safety specifications, or the intended use of the device.

3.96 Final Yield, the amount of finished medical device obtained at the end of the manufacturing process.

3.97 Theoretical yield, the amount of medical device that will be obtained through a process.

3.98 *Refurbished*, the restoration of the medical device to a condition of safety and effectiveness that is comparable to when new. This includes refurbishment, repair, installation of certain software/hardware upgrades and/or replacement of worn parts that do not change the intended use of the original medical device.

3.99 Repair, to the re-establishment of the medical device or component to original specifications, including the replacement of non-functioning components or parts outside of routine or periodic maintenance for the current owner of such device.

3.100 Reprocessing, the subjection of a total or partial lot to one or more defined stages of the validated manufacturing process due to non-compliance with specifications.

3.101 Rework, the subjection of a total or partial lot to one or more undefined stages of the validated manufacturing process due to non-compliance with specifications.

3.102 Annual product review (APR) or annual product quality review (APQR) is the historical analysis of the quality of a product, which takes as a reference all current regulatory documents applicable to medical devices, generally recognized international criteria, as well as the internal guidelines of each company.

3.103 Robustness, the capacity of a process to be insensitive, to some known extent, to factors that could affect it under the established conditions.

3.104 Sanitization, the action of eliminating or reducing the levels of viable particles by means of physical or chemical agents, subsequent to the cleaning activity.

3.105 Safety, the assessment of the benefit of a medical device versus its potential risks at a given time.

3.106 Computerized/computerized system means any equipment, process or operation that has one or more computers and associated software, or a group of hardware components designed and assembled to perform a specific set of functions.

3.107 Quality Management System (QMS), the way in which the organization directs and controls the activities associated with quality.

3.108 Critical systems, those that have a direct impact on processes and products.

3.109 Software as a medical device, when used for one or more medical purposes, whose main characteristic is that it does not need to be part of the hardware of the medical device to fulfill the intended medical purpose; it is capable of running on general computing platforms and can be used alone and/or in combination with other products (e.g., as a module, other medical devices, etc.). Mobile applications that meet this definition are considered software as a medical device. Software that runs the physical medical device is excluded from this definition.

3.110 Assortment, the delivery of raw materials, components, bulk product, and materials used in the manufacture ofthe medical device as required by the medical device master formula or master list.

3.111 Holder of the sanitary registry, the individual or legal entity that holds the authorization granted by the Ministry of Health for the manufacture, distribution and/or commercialization of a medical device.

3.112 Technology transfer, the systematic process that is followed to pass knowledge and experience during development and/or commercialization to another responsible and authorized unit. This process includes the transfer of documentation and the demonstrated capability of the receiving unit to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and compliance with applicable regulations.

3.113 Validation, the documentary evidence generated through the scientific collection and evaluation of data obtained in the process qualification and specific tests, throughout the life cycle of a product, whose purpose is to demonstrate the functionality, consistency, and robustness of the process, in terms of its ability to deliver a quality product.

3.114 Cleaning validation, documented evidence that a cleaning procedure for areas and equipment used in the manufacture of medical devices reduces residues of the cleaning agent and processed product to a pre-established level.

3.115 Software validation as a medical device, the documentary evidence generated through the collection and evaluation of a software's ability to generate the intended functions accurately, completely, and precisely from the input data.

3.116 Prospective validation, which is concluded prior to the commercialization of the medical device.

3.117 Shelf life, the time within which a medical device retains its quality properties.

4. Symbols and abbreviated terms

When reference is made in this Standard to the following symbols or abbreviations, it shall mean:

4.1 Symbols.

4.1.1	ºC	Celsius degree .
4.1.2	%	Percentage.
4.1.3	±	More less.
4.1.4	>	Greater than.
4.1.5	≤	Less than or equal to.
4.1.6	≥	Greater than or equal to.

4.2 Abbreviated terms

4.2.1	GDP	Good Documentation Practices.
4.2.2	BSE	Bovine Spongiform Encephalopathies.
4.2.3	CAPAA	Corrective Action and Preventive Action.
4.2.4	COFEPRIS	Federal Commission for Protection against Health Risks.
4.2.5	PUMS	Pharmacopoeia of the United Mexican States.
4.2.6	HEPA	High Efficiency Particulate Air Filter
4.2.7	RH	Relative humidity.
4.2.8	HVAC	Heating, Ventilation and Air Conditioning system.

4.2.9	n.a.	Not applicable.
4.2.10	NAT	Nucleic Acid Test
4.2.11	m/s	Meter over second.
4.2.12	m^3	Cubic meter.
4.2.13	µm	Micrometer.
4.2.14	Pa	Pascals.
4.2.15	TSE	Transmissible Spongiform Encephalopathies
4.2.16	UDI	Unique Device Identifier.
4.2.17	CFU	Colony Forming Units.
4.2.18	HIV	Human Immunodeficiency Virus.
4.2.19	HAV	Hepatitis A virus.
4.2.20	HBV	Hepatitis B virus.
4.2.21	HCV	Hepatitis C virus.

5. Classification of medical devices

5.1 Medical devices are classified, according to the risk posed by their use, as follows:

5.1.1 Class I: medical devices known in medical practice for which safety and efficacy are proven and which are generally not introduced into the body.

5.1.2 Class II: medical devices known in medical practice, and which may have variations in the material with whichthey are manufactured or in their concentration and, generally, are introduced into the organism for less than thirty days.

5.1.3 Class III: medical devices that are new or recently accepted in medical practice, or that are introduced into the body and remain in it for more than thirty days.

5.2 The medical devices considered in the General Health Law are:

5.2.1 Medical equipment: apparatus, accessories, and instruments for specific use, intended for medical or surgical care or procedures for the examination, diagnosis, treatment, and rehabilitation of patients, as well as those for biomedicalresearch activities.

5.2.2 Prostheses, 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 agents: all supplies including antigens, antibodies, calibrators, verifiers, reagents, reagent kits, culture, and contrast media and any other similar that may be used as ancillary to other clinical or paraclinical procedures.

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

5.2.5 Surgical and healing materials: devices or materials that, with or without antiseptics or germicides, are used in the surgical practice or in the treatment of continuity solutions, skin lesions or their annexes.

5.2.6 Hygienic products: materials and substances that are applied to the surface of the skin or body cavities and have pharmacological or preventive action.

6. Quality Management System

6.1 General

6.1.1 The Quality Management System represents the set of measures adopted in a planned and systematized manner to ensure that medical devices are of the required quality for their intended use. Quality management therefore incorporates GMP, GLP, GLAD, and risk management principles. Including the use of appropriate tools.

6.1.2 The facility shall design, implement, document, and maintain the Quality Management System and maintain its effectiveness in accordance with the requirements of this Standard by establishing a quality manual.

6.1.3 It is the responsibility of the General Management or top management to implement and maintain the Quality Management System, determining and providing appropriate resources (human, financial, facilities and equipment) to continuously improve its effectiveness.

6.1.3.1 The management of the facility shall have a formal process for reviewing the Quality Management System at least annually.

6.1.4 The manufacture of medical devices shall be carried out following a Quality Management System supported by:

6.1.4.1 A quality policy and documentation system that is designed, planned, implemented, maintained and subject to continuous improvement, which allows products to be marketed or supplied only after they have been released by the

quality unit in compliance with the quality attributes authorized in the sanitary registration.

6.1.4.2 Knowledge of the product, the purpose of use and the process, managed throughout the product life cycle.

6.1.4.3 The design, development and/or technology transfer of medical devices taking into account the requirements of GMP.

6.1.4.4 Production and quality control operations, which are clearly described and adopt GMP and GLP.

6.1.4.5 Personnel responsibilities in the Quality Management System, which should be referenced in the quality manual.

6.1.4.6 Taking timely measures to ensure that the manufacture, supply, use of raw materials, packaging materials, and the selection and follow-up of suppliers are correct, and that each delivery is verified as coming from the supply chain approved by the Quality Assurance area.

6.1.4.7 Procedures and/or technical quality agreements to ensure the management of subcontracted activities, in accordance with their level of risk.

6.1.4.8 The establishment and maintenance of a state of control of process performance and product quality through monitoring measures and the results of such measures, which are taken into account for batch release, investigation of deviations and for corrective actions to prevent recurrence.

6.1.4.9 Carry out all necessary controls on intermediate products, as well as in-process controls and validations.

6.1.4.10 Continuous improvement.

6.1.4.11 Measures implemented for prospective evaluation of planned changes.

6.1.4.12 Conduct an evaluation to confirm that quality objectives have been achieved following implementation of any planned changes.

6.1.4.13 Root cause analysis applied during investigation of deviations or nonconformances, complaints, nonconforming product, audit findings, returns, recalls, adverse event reports, suspected product defects or other types of problems. This analysis can be determined based on risk management principles. In cases where the root cause(s) cannot be determined, the most probable cause(s) should be considered and addressed. Appropriate corrective actions should be identified and taken in response to the investigations conducted. The effectiveness of these actions should be monitored and evaluated in line with Quality Risk Management principles.

6.1.4.14 The release of the product by the health officer and/or in accordance with subsection 9.1.3, prior to the sale or supply of each manufacturing batch or unit, to ensure that the medical device has been produced and controlled according to the requirements set forth in the marketing authorization and any other regulations relating to the production, control, and release of devices.

6.1.4.15 Adoption of measures to ensure that medical devices are stored and distributed in such a way that quality is maintained throughout the shelf life, useful life and/or expiration date.

6.1.4.16 Procedure for self-inspections and/or quality audits evaluating the effectiveness and implementation of the Quality Management System.

6.1.5 The minimum elements to be contained in the Quality Management System are:

6.1.5.1 Quality Manual.

6.1.5.2 Audit System.

6.1.5.3 Complaint handling.

6.1.5.4 Handling of out-of-specification or nonconforming product.

6.1.5.5 Deviation management and CAPA system.

6.1.5.6 Product withdrawal.

6.1.5.7 Change Control.

6.1.5.8 PMV.

6.1.5.9 Product monitoring and measurement.

6.1.5.10 Technology Transfer.

6.1.5.11 Risk Management.

6.1.5.12 Document Control.

6.1.5.13 Returns.

6.2 Documentation.

6.2.1 Generation of documentation.

6.2.1.1 Documents shall be defined and adhered to in your Quality Management System. The requirements apply equally to all forms of documentation media. Electronic document generation systems that impact product quality need to be understood, well documented, available, and validated.

6.2.1.2 Quality control system documents shall be written in Spanish. When documents are in two or more languages, the Spanish version should be included. Some documents may exist in hybrid form, for example, one part in electronic format and another in paper.

6.2.1.3 Documents containing instructions should be written in an orderly manner and be easy to understand. The style and language of documents should be consistent with their intended use.

6.2.2 Documentation control.

6.2.2.1 Relationships and control measures for master documents, official copies, data, and records management shallbe established in the document control system for both hybrid and homogeneous systems.

6.2.2.2 Controls shall be implemented for electronic documents such as templates, forms, and master documents. Controls should be in place to ensure the integrity of records throughout the retention or retention period.

6.2.2.3 Documents shall be designed, prepared, reviewed, authorized, modified, distributed and/or cancelled in accordance with the Quality Management System.

6.2.2.4 Documents shall comply with the applicable parts of the product specifications, manufacturing, and marketing authorization dossiers. Reproduction of working papers from original documents shall not allow for the introduction of any errors in the reproduction process.

6.2.3 Document safeguard.

6.2.3.1 The storage location of all documents related to the manufacture of medical devices should be defined in the documentation system. Control measures should be implemented to ensure the integrity of the documents during the entire storage period and these measures should be evaluated.

6.2.3.2 The manufacturing file of each batch or unit manufactured must be kept for at least one year after its expiration date or shelf life or five years after the batch or unit was released by the sanitary officer or foreign equivalent. In this case it should be retained for whichever period is longer.

6.2.3.2.1 For medical devices that do not have an expiration date or shelf life, the average lifetime that will remain in use should be considered; the period of time determined should be justified.

6.2.3.3 For other types of documents, the retention period will depend on the activity that the documentation supports. Critical documentation, including primary data (e.g., validation or stability data), that supports the information in the sanitary registration or marketing authorization should be retained as long as the authorization remains in force. It may be considered acceptable to remove certain documentation (e.g., primary data to support a validation or stability report) when the data have been replaced by a completely new data package.

6.2.3.3.1 A justification for this should be documented and the retention requirements for batch or unit documentation should be taken into account; for example, in the case of validation process data, the accompanying primary data should be retained for a period at least as long as the records of all batches whose release is supported by that validation exercise.

6.2.3.4 Any type of safeguarding other than the aforementioned time must be based on the applicable provisions.

6.2.4 BPD.

6.2.4.1 Documents containing instructions shall be approved, signed, and dated. All types of documents shall be defined and shall be in accordance with the quality manual. The requirements apply equally to all forms of documentation media applicable to the Quality Management System.

6.2.4.2 Quality Management System documents shall be reviewed for currency and kept up to date.

6.2.4.3 Quality Management System documents shall not be handwritten; however, where documents require data entry, space shall be left to allow for such entries to be made.

6.2.4.3.1 Handwritten records on documents shall be made clearly, legibly, and indelibly.

6.2.4.3.2 The recording of activities shall be made at the time of the activity in chronological order.

6.2.4.4 Any correction to an activity record or document shall be signed, dated, and allow the original information to be read.

6.2.4.5 When an explanation of the reason for the correction is required, it should be documented; records should contain the date and identify who performed the activity.

6.2.4.6 There must be a mechanism to identify the signatures of the personnel executing the operation.

6.2.5 Types of documents.

This Standard addresses different types of documents, however, the manufacturer should design its documentation according to its products and processes, particularly those that do not use the batch concept.

The documents that make up the documentation system include, but are not limited to:

6.2.5.1 Quality Manual.

There should be a quality manual or document containing the description of the Quality Management System, including management responsibilities. The manual should determine and ensure the periodic review of the Quality Management System.

6.2.5.2 Specifications and certificates of analysis and/or certificate of conformity.

6.2.5.2.1 There must be specifications for inputs, bulk product and finished product, the certificate of analysis and/or certificate of conformity must comply with the characteristics indicated in clause 3.26 or 3.27 of this Standard, as applicable.

6.2.5.2.2 Specifications for raw materials, packaging and packing materials shall include or refer to at least:

6.2.5.2.2.1 Description of materials: name, internal code, reference (FEUM, if applicable).

6.2.5.2.2.2 Approved input supplier.

6.2.5.2.2.3 A sample and/or a true electronic copy of the printed materials.

6.2.5.2.2.4 Instructions for sampling and testing to be performed.

6.2.5.2.2.5 Acceptance limits for qualitative and quantitative determinations.

6.2.5.2.2.6 Storage conditions according to the level of risk or stability of the material or product.

6.2.5.2.2.7 Period of retesting and number of retests, if applicable.

6.2.5.2.2.8 Precautions for material handling.

6.2.5.2.3 There should be specifications for intermediate and bulk product, including maximum time and storage conditions.

6.2.5.2.4 Finished product specifications shall include or refer to at least the following:

6.2.5.2.4.1 Product name and internal code assigned.

6.2.5.2.4.2 Instructions for sampling.

6.2.5.2.4.3 Method of analysis.

6.2.5.2.4.4 Acceptance limits for qualitative and quantitative determinations.

6.2.5.2.4.5 Storage conditions.

6.2.5.2.4.6 Shelf life, expiration date or useful life of the product.

6.2.5.2.4.7 Precautions for product handling.

6.2.5.3 Master production order.

6.2.5.3.1 There shall be a written order and master production instructions for each product, these master documents shall be used to generate the working papers.

6.2.5.3.2 The production order must include at least:

6.2.5.3.2.1 Product designation and an assigned internal code.

6.2.5.3.2.2 Lot size and/or serial number.

6.2.5.3.2.3 The list of raw materials, materials, code, and quantities, including those that do not appear in the finished product.

6.2.5.3.2.4 Theoretical performance with acceptance limits for each process step.

6.2.5.3.3 The production instructions shall include at least:

6.2.5.3.3.1 The area in which each stage of the process is carried out.

6.2.5.3.3.2 Equipment to be used.

6.2.5.3.3.3 Methods or cross-references for the preparation of critical equipment in the production process such as cleaning, assembly, calibration, sterilization.

6.2.5.3.3.4 Clearance of the manufacturing area or line, with proper segregation to ensure that it is free of previous products, equipment, and unneeded materials.

6.2.5.3.3.5 Verification that the area is in a clean condition to start product production.

6.2.5.3.3.6 Detailed instructions on how to perform each step of the process, including critical process parameters, such as times, temperatures, and speeds.

6.2.5.3.3.7 In-process controls to be performed, frequency and acceptance limits.

6.2.5.3.3.8 Specific conditions necessary for handling and storage, according to the nature of the product.

6.2.5.3.4 For medical device assembly processes, there shall be an instruction manual detailing how to carry out the process.

6.2.5.4 Master conditioning order.

6.2.5.4.1 There should be a master order and instructions for packaging for each product and for an estimated lot size, these master documents will be used to generate the working papers.

6.2.5.4.2 The master conditioning order shall include at least the following:

6.2.5.4.2.1 Generic name of the product and, if applicable, distinguishing name, internal code assigned.

6.2.5.4.2.2 Bulk product lot or serial number.

6.2.5.4.2.3 Final presentation.

6.2.5.4.2.4 Complete list of all materials required for product packaging and packing, including codes, quantities andif applicable cross reference to their specifications.

6.2.5.4.2.5 Theoretical performance with acceptance limits for each process step.

6.2.5.4.3 The conditioning order shall include at least the following:

6.2.5.4.3.1 Graphical representation of product packaging or cross reference for reference.

6.2.5.4.3.2 Clearance of the work area to ensure that it is free of previous products or unneeded materials.

6.2.5.4.3.3 Verification that the area is in a clean condition to start product conditioning.

6.2.5.4.3.4 Detailed instructions on how to perform each step of the process and the equipment to be used, including critical process parameters.

6.2.5.4.3.5 In-process controls to be performed, instructions for sampling, frequency and acceptance limits and cross references to procedures or other documents.

6.2.5.4.3.6 Instructions for reconciliation of printed materials.

6.2.5.4.3.7 Storage conditions for finished product.

6.2.5.4.3.8 Specific conditions necessary for handling and storage, according to the nature of the product.

6.2.5.4.4 For medical devices that only require packaging, there should be an instruction manual that clearly details how to carry out this process, the label should indicate at least the product in question, the sanitary registration, and precautions for handling.

6.2.5.5 Medical device file.

6.2.5.5.1 For each type of medical device or family of medical devices, the facility shall generate and maintain one or more dossiers either containing or referencing documents generated to demonstrate compliance with the requirements of this Standard.

6.2.5.5.2 The files shall include, but are not limited to:

6.2.5.5.2.1 General description of the medical device, intent or purpose of use, labeling, including instructions foruse.

6.2.5.5.2.2 Product Specifications.

6.2.5.5.2.3 Specifications or procedures for manufacturing, packaging, storage, handling, and distribution.

6.2.5.5.2.4 Measurement and monitoring procedures.

6.2.5.5.2.5 Installation requirements.

6.2.5.5.2.6 Maintenance procedures.

6.2.5.6 Product manufacturing record.

6.2.5.6.1 There must be a manufacturing file for each batch, series, or unit of product, according to the conditions authorized in the sanitary registration and contain the order and instructions for production and packaging with the record of the activities.

6.2.5.6.2 This file must contain the following:

6.2.5.6.2.1 Production order and instructions.

6.2.5.6.2.2 Product lot or serial number.

6.2.5.6.2.3 Lot numbers or item identifier and assorted quantities of all materials included in the manufacture.

6.2.5.6.2.4 Start and end dates and times of the most important stages of production.

6.2.5.6.2.5 Identification of who performed the operation with first initial and last name, this information must be traceable to a registry of operators and supervisors in the production areas.

6.2.5.6.2.6 Supervision records.

6.2.5.6.2.7 Record of in-process controls with the results obtained and the persons who performed them.

6.2.5.6.2.8 Final yield obtained during the different production stages.

6.2.5.6.2.9 Any deviation from the production instructions shall be recorded, investigated, and evaluated. The investigation must be concluded for batch release.

6.2.5.6.2.10 Each production file must be signed by the sanitary officer or qualified quality assurance person certifying that the product was produced in compliance with GMPs.

6.2.5.6.3 Conditioning file.

6.2.5.6.3.1 There must be a packaging file for each batch, series or unit of product and it must correspond to the conditions authorized in the sanitary registration, contain the instructions and the record of the activities carried out for packaging.

6.2.5.6.3.2 The packaging file shall be integrated with the product manufacturing file and shall contain at least the following:

6.2.5.6.3.2.1 Order and instructions or conditioning procedure.

6.2.5.6.3.2.2 Product lot or serial number.

6.2.5.6.3.2.3 Lot numbers or item identifier and quantities of bulk product, packaging and packing materials.

6.2.5.6.3.2.4 Reconciliation of packaging materials to determine the quantity used, the quantity sent for destruction and the materials returned.

6.2.5.6.3.2.5 Date and time of start and end of conditioning stages.

6.2.5.6.3.2.6 Identification of who performed the operation with first initial and last name, this information must be traceable to a registry of operators and supervisors of the conditioning areas.

6.2.5.6.3.2.7 Supervision records.

6.2.5.6.3.2.8 Record of in-process controls with the results obtained and the persons who performed them.

6.2.5.6.3.2.9 Final yield obtained during the different conditioning stages.

6.2.5.6.3.2.10 Any deviation from the packaging instructions or procedure must be recorded, investigated, and evaluated. The investigation must be completed for product release.

6.2.5.6.3.2.11 Each packaging file must be signed for compliance by the sanitary officer or qualified person in the quality assurance area to ensure that the release of the product complies with GMP.

6.2.5.7 Analytical and test methods.

6.2.5.7.1 There shall be written procedures describing the methods, equipment and instruments used for the analysis or evaluation of inputs and outputs at the different stages of manufacture.

6.2.5.7.2 Records of analyses and evaluations performed shall be kept.

6.2.5.8 Other documents related to GMP compliance.

6.2.5.8.1 Written documentation related to GMP compliance shall be available to personnel responsible for the activities described in such documentation, which shall correspond to the level assigned in the quality management system and may be in the form of policies, SOPs, protocols, work instructions, reports, agreements, among others.

6.2.5.8.2 There shall be documented evidence of the use of these documents, or the performance of the activities described therein.

6.2.5.8.3 There shall be written documentation for the following activities or processes, this list is not limitative and there may be more related documents:

6.2.5.8.3.1 Cleaning and/or sanitization of critical areas, equipment, and systems.

6.2.5.8.3.2 Operation and maintenance of equipment and instruments.

6.2.5.8.3.3 Equipment and systems qualification and process validation.

6.2.5.8.3.4 Training, qualification, and verification of the effectiveness of personnel training on GMP and technical issues related to their activity.

6.2.5.8.3.5 List of signatures of personnel involved in the manufacture of medical devices at all stages, in accordance with its quality management system.

6.2.5.8.3.6 Technology Transfer.

6.2.5.8.3.7 Environmental monitoring.

6.2.5.8.3.8 Pest control.

6.2.5.8.3.9 Investigation of deviations or nonconformities.

6.2.5.8.3.10 Reporting of complaints.

6.2.5.8.3.11 Change Control Report.

6.2.5.8.3.12 Product returns.

6.2.5.8.3.13 Product recall.

6.2.5.8.3.14 Self-inspection reports, supplier audits, regulatory audits, customer audits.

6.2.5.8.3.15 Purchase of inputs and purchase orders for imported products, invoices, import/export permits.

6.2.5.8.3.16 Receipt of Inputs.

6.2.5.8.3.17 Storage.

6.2.5.8.3.18 Distribution.

6.2.5.8.3.19 Annual product quality review report as indicated in 6.6.6.1 and 6.6.6.5.

6.2.5.8.3.20 Sampling records.

6.2.5.8.3.21 Technical manufacturing, distribution, and quality agreements.

6.2.5.8.3.22 Product release records.

6.2.5.8.3.23 Each facility in the country must have the following legal documents:

6.2.5.8.3.23.1 Notice of operation or original of sanitary license and notice of sanitary officer.

6.2.5.8.3.23.2 Current GMP certificate.

6.2.5.8.3.23.3 Current copy of the FEUM medical device supplement.

6.2.5.8.3.23.4 Original sanitary registration, certified copy or validated digital file.

6.2.5.8.3.23.5 Instructions or indications for use.

6.3 Change control.

6.3.1 There shall be a documented change control system that includes risk management for the evaluation and impact of the proposed change on processes, suppliers, critical systems, computer systems, areas, services, equipment, analytical methods, specifications, documentation, regulatory provisions, and product quality.

6.3.2 Unplanned changes shall be considered as deviations or nonconformities.

6.3.3 A committee or technical group shall be formed, made up of representatives of the areas involved and the head of the quality unit, who shall review, evaluate, and approve the proposed change.

6.3.4 The implementation of approved changes shall be followed up and closure shall be ensured as previously established.

6.4 Purchasing management.

6.4.1 There must be a procedure establishing the activities for the purchasing process to ensure that the purchased input conforms to the authorized specification.

6.4.2 Non-compliance with purchasing requirements should be addressed with the supplier according to the risk associated with the purchased input and compliance with authorized specifications.

6.4.3 Purchase Information.

6.4.3.1 The purchase information shall make reference to the purchased input which shall include:

6.4.3.1.1 Input specifications.

6.4.3.1.2 Requirements for acceptance of the input.

6.4.3.1.3 Supplier Qualification Requirements.

6.4.3.1.4 Quality Management System Requirements.

6.4.4 It shall be ensured that purchase requirements or specifications are in force prior to their communication to the supplier.

6.4.5 A technical agreement shall be in place, in which the supplier notifies the buyer prior to implementation of any changes that affect the characteristics of the purchased input to meet purchasing requirements.

6.4.6 Purchasing records and documents shall be maintained in accordance with paragraph 6.2 of this Standard.

6.4.7 Verification of purchased input.

6.4.7.1 Inspection or other activity necessary to ensure that the purchased input meets the purchasing requirements shall be established and implemented. The scope of verification activities shall be based on the results of the supplier's assessment, considering the associated risks.

6.4.7.2 When any changes in the purchased input are detected or reported, it should be determined whether these changes affect the manufacturing process of the product.

6.4.7.3 Where the facility intends to conduct the assessment at the supplier's premises, it shall indicate in the purchase agreement the planned verification activities and the method of product release.

6.4.7.4 Assessment records shall be maintained in accordance with subsection 6.2 of this Standard.

6.5 Returns.

6.5.1 There should be a procedure for the control of returned products, indicating:

6.5.1.1 To be quarantined and evaluated by the quality unit to determine whether they should be released or destroyed.

6.5.1.2 Records of receipt, identification, evaluation, and final disposal. The report shall contain at least the following:

6.5.1.2.1 Product name, presentation, lot/serial number and expiration date or shelf life.

6.5.1.2.2 Date of return, amount returned.

6.5.1.2.3 Reason for return.

6.5.1.2.4 Name and location of returner.

6.5.1.2.5 The evaluation to prove that the product complies with the specifications, integrity, safety, quality, identity,and purity standards, according to the type and characteristics of the type of medical device, shall include:

6.5.1.2.5.1 Recovery of returned product is not permitted if, during the evaluation, the condition of the container, cartons or boxes, or labeling text raises doubts as to the integrity, safety, identity, concentration, quality, or purity of the product.

6.6 Measurement, analysis, and improvement.

6.6.1 General.

The organization shall plan and implement monitoring, measurement, analysis, and improvement to demonstrate product conformity; ensure conformity; and maintain the effectiveness of the Quality Management System.

6.6.2 Monitoring and Measurement.

6.6.2.1 Feedback.

6.6.2.1.1 Information related to compliance with input, product and process specifications shall be collected and controlled. Methods for obtaining and using this information shall be documented.

6.6.2.1.2 Procedures for the feedback process shall be documented. This process should include provisions for collecting data from production, distribution and marketing related to product quality.

6.6.2.1.3 The information gathered in the feedback process will serve as potential input into risk management to control and maintain product specifications, as well as manufacturing or improvement processes.

6.6.3 Complaint handling.

6.6.3.1 There shall be a person responsible for handling complaints.

6.6.3.2 There shall be a procedure for handling complaints, which shall include:

6.6.3.2.1 Mandatory attention and documentation of all complaints.

6.6.3.2.2 The process of investigating and ruling on the type of complaint that includes impact to product quality, safety, and efficacy.

6.6.3.2.3 Definition of the CAPAs to be carried out regarding the problem.

6.6.3.2.4 The form and time of response to the client.

6.6.3.2.5 Indicate in which cases the product shall be withdrawn from the market and notify the Ministry of Health,

through COFEPRIS.

6.6.3.3 As part of the investigation of a complaint of a defective lot or unit of product, prospective and retrospective evaluation should be extended to other lots to determine if they are also affected.

6.6.3.4 Complaint records should at a minimum contain the following:

6.6.3.4.1 Product name, presentation, and lot/serial number.

6.6.3.4.2 Date of receipt of the complaint by the holder of the sanitary registration.

6.6.3.4.3 Quantity involved.

6.6.3.4.4 Reason.

6.6.3.4.5 Name and location of generator.

6.6.3.4.6 Date of complaint.

6.6.3.4.7 Result of the investigation.

6.6.3.4.8 Actions taken.

6.6.3.4.9 All complaints should be cross-referenced to the investigation reports generated and refer to the corresponding lot, serial number and/or presentation records involved.

6.6.3.5 A review of complaints should be conducted to identify trends in specific or recurring problems and take the necessary measures and if necessary, notify the Ministry of Health through COFEPRIS.

6.6.3.6 They must have a procedure for notifying COFEPRIS of adverse incidents related to a complaint in accordance with the Mexican Official Standard mentioned in paragraph 2.19 of this Standard.

6.6.4 Audits.

6.6.4.1 There should be procedures that establish the process for the execution of an audit that contains at least the following:

6.6.4.1.1 The scope of each type of audit.

6.6.4.1.2 Qualification of the audit group including:

6.6.4.1.2.1 Experience, training, skills, availability, and independence of the audited area.

6.6.4.1.2.2 Execution process: planning, responsibilities, requirements, records, reporting.

6.6.4.1.2.3 The frequency of audits and the establishment of a permanent audit program.

6.6.4.2 For the purposes of this Standard, audits are classified as: internal audits (self-inspections), supplier audits and external audits (regulatory bodies or authorized certifying units).

6.6.4.2.1 Internal audits (self-inspections):

There should be a self-inspection system for the evaluation of the Quality Management System and the level of GMP compliance.

6.6.4.2.1.1 Self-inspection audits shall be conducted by personnel independent of the audited area. They may also be conducted by external personnel.

6.6.4.2.1.2 The following aspects shall be evaluated following a pre-established program to verify their conformity with the principles of the Quality Management System:

6.6.4.2.1.2.1 All self-inspections shall be recorded. Reports shall include all observations made during inspections and, where appropriate, proposals for corrective actions shall be recorded in the facility's CAPA system.

6.6.4.2.1.2.2 The results of self-inspections shall be communicated to the personnel involved.

6.6.4.2.2 Supplier audits.

6.6.4.2.2.1 Establishments should determine based on a risk assessment those suppliers of inputs that have an impact on the quality, safety, and efficacy of medical devices.

6.6.4.2.2.2 Criteria should be established for the evaluation and selection of suppliers that include: **6.6.4.2.2.2.2.1** The supplier's ability to provide products that meet the organization's requirements.**6.6.4.2.2.2.2.2** Supplier performance.

6.6.4.2.2.2.1 The effect of the purchased product on the quality of the medical device.

6.6.4.2.2.2.2 Risk associated with the medical device.

6.6.4.2.2.2.3 There shall be a procedure for the execution of audits for suppliers of inputs, analytical service providers,critical systems and equipment service providers, and manufacturing process assemblers.

6.6.4.2.2.3 There shall be a periodic audit program, and documentary evidence shall be available to demonstrate compliance.

6.6.4.2.2.4 The periodicity of supplier audits shall be established based on the level of risk in the process, the impact and on previous qualification reports.

6.6.4.2.2.5 Supplier audit reports shall be part of the supplier qualification file.

6.6.5 Process monitoring and measurement.

6.6.5.1 The facility shall have a formal process to review at least annually the Quality Management System. The review shall include:

6.6.5.2 Measurement of compliance with the objectives of the Quality Management System.

6.6.5.3 The evaluation of performance indicators that can be used to monitor the effectiveness of processes within the Quality Management System includes at least:

6.6.5.3.1 Complaints, product recalls, returns, deviations, CAPA, process changes; feedback on contracted activities; audits and risk management.

6.6.5.4 Standards, guidelines, and quality issues that arise and may impact the Quality Management System.

6.6.5.5 Innovations that may improve the Quality Management System.

6.6.5.6 Changes in target and business environment.

6.6.6 Product Monitoring and Measurement.

6.6.6.1 There should be an annual systematic review of the quality of each product. The sanitary manager shall ensure the implementation of the monitoring and measurement system and designate the person responsible for its execution and dissemination.

6.6.6.2 The objectives of product monitoring and measurement are to verify product performance, manufacturing process consistency, identify improvements to the product and manufacturing process, and determine the need for requalification of manufacturing processes.

6.6.6.2.1 Based on product monitoring and measurement, trend analysis and risk assessment, the need for changes in the manufacturing process, process controls and specifications may be determined.

6.6.6.3 There shall be a procedure for conducting product monitoring and measurement that contains the objectives for determining and justifying the areas selected for review, as well as the possible extent of the review.

6.6.6.4 Product monitoring and measurement may be carried out by grouping product families, when justified.

6.6.6.5 There should be a record of the APR or RACP; according to the nature of the medical device and based on risk management:

6.6.6.5.1 Name, presentation, and expiration date.

6.6.6.5.2 Number of batches manufactured in the year, number of approved batches with deviations or nonconformities and number of rejected batches.

6.6.6.5.3 Review of starting materials.

6.6.6.5.4 Summary of critical operations, process controls and finished product data to allow trend analysis.

6.6.6.5.5 Record of deviations or nonconformities, out-of-specification results, change control, returns, complaints, recalls including the investigation report and conclusions of the actions taken.

6.6.6.6 The PAR must contain at least the following information:

6.6.6.6.1 Name, presentation, and expiration date;

6.6.6.6.2 Number of batches manufactured in the year, number of approved batches, number of approved batches with deviations or nonconformities and number of rejected batches;

6.6.6.6.3 Review of starting materials;

6.6.6.6.4 Summary of critical operations, process controls and finished product data to allow trend analysis, and

6.6.6.6.5 Recording of deviations or nonconformities, out-of-specification results, change control, returns, complaints, recalls including investigation report and conclusions of actions taken, summary of stabilities and maintenance of validated status.

6.6.6.7 The RACP must contain at least the following information:

6.6.6.7.1 Name, useful life;

6.6.6.7.2 Serial numbers/identification of products manufactured in the year, serial numbers of approved products, serial numbers of approved products with deviations or nonconformities and serial numbers of rejected products;

6.6.6.7.3 Review of starting materials;

6.6.6.7.4 Summary of critical operations, process controls and finished product data to allow trend analysis, and

6.6.6.7.5 Recording of deviations or nonconformities, out-of-specification results, change control, returns, complaints,

recalls including the investigation report and conclusions of actions taken.

6.6.7 Control of nonconforming product.

6.6.7.1 Deviations or nonconformities.

6.6.7.1.1 Products at any stage that do not meet the established specifications or that are manufactured outside the established procedures must be identified and placed in temporary holding or quarantine.

6.6.7.1.2 A deviation or nonconformance report shall be issued to define the level and extent of the nonconformance and establish corrective actions to determine if the product can be reconditioned, recalled, reworked, or rejected.

6.6.7.1.3 There shall be an investigation of deviations or nonconformities to determine the root cause analysis. This analysis can be determined based on risk management principles.

6.6.7.1.3.1 A methodology shall be established for the investigation of deviations, nonconformities or increasing trends that includes the use of technical and/or statistical tools to determine root cause(s), definition of responsible parties and commitment dates. In cases where the root cause(s) cannot be determined, the most probable cause(s) shouldbe considered and addressed. The depth of the investigation should be commensurate with the significance and associated risk.

6.6.7.2 Handling of nonconforming product.

6.6.7.2.1 There must be a procedure that describes:

6.6.7.2.1.1 Identification of nonconforming product.

6.6.7.2.1.2 Control of nonconforming product including segregation and prevention of inadvertent use of the product or the facility where it was processed.

6.6.7.2.1.3 Actions to be taken in cases of reconditioning, recovery, reprocessing or reworking of Batches.

6.6.7.3 Recovery, reprocessing or rework.

6.6.7.3.1 Recovery, reprocessing or reworking processes must be authorized by the sanitary officer or his/her designee.

6.6.7.3.2 The sanitary officer or authorized person must establish the final disposition of the product.

6.6.7.3.3 Rework or reprocessing is not permitted on sterile medical devices dosed in the primary container.

6.6.7.3.4 Recovered lots shall be subjected to quality analysis and documentation shall demonstrate that the quality of the recovered lot is equivalent to that of the original process.

6.6.7.3.5 Rejected products should be identified and segregated until disposal or final destination.

6.6.7.3.6 A specific rework, reclamation or reprocessing order and instructions should be issued for each lot or batch.

6.6.7.3.7 In the case of reprocessing, rework and/or reconditioning, a lot/serial number different from the original must be assigned, which must be authorized by the sanitary officer.

6.6.7.3.8 Release of a reworked, reclaimed, or reprocessed lot must follow the steps described in Chapter 14 of thisStandard and be authorized by the sanitary officer or his/her designee.

6.6.8 Data analysis.

6.6.8.1 Procedures shall be in place to determine, collect and analyze data to demonstrate the suitability, adequacy,and effectiveness of the Quality Management System.

6.6.8.2 Procedures should include the determination of appropriate methods, including statistical techniques and the extent of their use.

6.6.8.3 Data analysis should include information generated as a result of monitoring and measurement and from other relevant sources and include, at a minimum, the following:

6.6.8.3.1 Feedback; complaints, product recalls, returns, deviations, CAPA, process changes; process and product trends, feedback on contracted activities; audits and risk management.

6.6.8.4 If the data analysis shows that the Quality Management System is not adequate or effective, the facility shall use this analysis as input for improvement as outlined in 6.6.9 of this Standard.

6.6.9 Improvement.

6.6.9.1 The Quality Management System Manager shall identify and implement any changes necessary to ensure and maintain the continued suitability and effectiveness of the Quality Management System, as well as the safety and performance of the medical device, through the use of quality policy, quality objectives, audit results, techno vigilance, data analysis, CAPA, and management review.

6.6.10 LAYER.

6.6.10.1 A system shall be in place for the implementation of CAPAs resulting from nonconformities, complaints, returns, out-of-specification, audits, trends, and those defined by the system itself.

6.6.10.2 A methodology shall be established for the investigation of deviations, nonconformities or increasing trends

that includes the use of technical and/or statistical tools to determine root cause, definition of responsible parties and commitment dates.

6.6.10.3 The CAPAs implemented should be followed up to verify their effectiveness.

6.6.10.4 When a CAPA results in a design change or changes to the manufacturing process, it shall be verified that any new risks are assessed in accordance with risk management principles.

6.6.10.5 Corrective Action.

6.6.10.5.1 The person responsible for the process in which the nonconformity or deviation is detected shall take action to eliminate the cause of the nonconformity or deviation in order to prevent recurrence. All necessary corrective actions shall be taken immediately or justify delay. The type of corrective actions should be proportional to the effects of the nonconformities found.

6.6.10.5.2 Verify that the corrective action does not adversely affect the ability to meet authorized specifications or conditions of registration, the safety and performance of the Medical Device.

6.6.10.6 Preventive action.

6.6.10.6.1 The person responsible for the process in which the nonconformity or deviation is detected shall determine the action to eliminate the causes of the nonconformity or deviation in order to prevent its recurrence. Preventive actions shall be proportional to the potential effects associated with the risk.

6.6.10.6.2 Verify that the action does not adversely affect the ability to meet the requirements or the safety and performance of the medical device.

6.7 Establishments that have certification under the current ISO13485 standard issued by bodies authorized by national or internationally recognized accreditation bodies shall be recognized in the conformity assessment as equivalent to the requirements established in Chapter 6 of this Standard.

6.7.1 During the conformity assessment of this Standard, the inspection shall be carried out under a reduced approach except for Chapter 6 and its subsections.

7 Quality Risk Management

7.1 The facility shall have a Quality Risk Management System that scientifically and systematically ensures actions to identify, mitigate and control potential failures in systems, operations and processes that affect product quality.

7.2 The methodology for Risk Management in systems, operations and processes shall be based on proven analysis tools and in accordance with their risk level, in order to ensure the effective and logical management of priorities and strategies for Quality Risk Management.

7.3 There shall be a set of procedures that evidences the implementation, training, and qualification of the personnelin charge of the Quality Risk Management System and its application.

7.4 The risk assessments performed shall be documented in such a way that they form the basis for the preparation of the LMP and serve as support and technical evidence for deviations and critical changes to systems, operations and processes and support CAPA's evaluation.

7.5 There shall be an efficient method of communication to ensure that the analysis and actions documented in the risk methodology are known to the organization as part of the Quality Management System.

7.6 Continuous verification of the results of the Quality Risk Management process must be established to ensure its validity and the robustness of the Quality Management System.

7.7 For the implementation of Quality Risk Management, the Appendix "Application of Risk Management to Medical Devices" of the FEUM Medical Device Supplement may be consulted.

8 Design and development

8.1 General.

8.1.1 The person in charge of the development area shall document the design and development procedures.

8.2 Design and development planning.

8.2.1 The development manager shall plan and control product design and development. As appropriate, design and development planning documents shall be maintained and updated as design and development progresses.

8.2.2 During design and development planning, document:

8.2.2.1 The design and development stages.

8.2.2.2 The review(s) required at each stage of design and development.

8.2.2.3 The design verification, validation and transfer activities that are appropriate at each stage of design anddevelopment.

8.2.2.4 Responsibilities and authorizations for design and development.

8.2.2.5 Methods to ensure traceability of design and development inputs and outputs.

8.2.2.6 The necessary resources, including the necessary competence of personnel.

8.3 Design and development inputs.

8.3.1 Records of inputs related to product requirements shall be determined and retained.

8.3.2 These entries should include:

8.3.2.1 Performance, functionality, and safety requirements, according to the purpose of use.

8.3.2.2 Applicable requirements and provisions.

8.3.2.3 Applicable Risk Management Result(s).

8.3.2.4 Information derived from previous similar designs.

8.3.2.5 Other essential requirements for product and process design and development.

8.3.3 Records of design and development inputs shall be reviewed by the development area manager for appropriateuse and approval.

8.3.4 Requirements shall be complete, unambiguous, available for verification or validation, and not contradictory.

8.4 Design and development products.

8.4.1 Design and development products shall:

8.4.1.1 Meet the input requirements for design and development.

8.4.1.2 Provide adequate information for purchasing production and service provision.

8.4.1.3 Contain or refer to product acceptance criteria.

8.4.1.4 Specify the characteristics of the product that are essential for its safe and proper use.

8.4.2 Design and development results shall be in a form suitable for verification against design and developmentinputs. They should be approved by the development manager and the health manager prior to implementation.

8.4.3 Records of design and development products shall be retained.

8.5 Design and development review.

8.5.1 Systematic design and development reviews shall be conducted in accordance with pre-established and documented plans for:

8.5.1.1 Evaluate the ability of the design and development results to meet requirements.

8.5.1.2 Identify and propose actions necessary for the medical device to meet the approved design intent for use.

8.5.2 Participants in such reviews shall include representatives of functions related to the design and stage ofdevelopment being reviewed.

8.5.3 Records shall be kept of the results of reviews and any necessary action and shall include identification of thedesign under review, the participants involved and the date of the review.

8.6 Design and development verification.

8.6.1 Design and development verification shall be performed as planned and documented to ensure that the designand development products have met the input requirements.

8.6.2 The development manager shall document verification plans that include methods, acceptance criteria such asstatistical techniques with a justification for sample size.

8.6.3 If the intended use requires the Medical Device to be connected to or interface with other medical device(s), verification shall include confirmation that the products comply with the design inputs when connected or interfaced.

8.6.4 Records of the results and conclusions of the verification and necessary actions shall be kept.

8.7 Design and development validation.

8.7.1 Design and development validation shall be performed as planned and documented to ensure that the resultingproduct is capable of meeting the requirements for the specified application or intended use.

8.7.2 The facility shall document validation plans that include methods, acceptance criteria such as statistical techniques with a justification for sample size.

8.7.3 Design validation shall be carried out on a representative product. Representative product includes initial production units, batches, or their equivalents. The rationale for the choice of product used for validation shall be recorded.

8.7.4 As part of the design and development validation, the development manager should conduct clinical evaluationsor performance evaluations.

8.7.5 A medical device used for clinical evaluation or performance evaluation is not considered released for

customeruse.

8.7.6 If the intended use requires the Medical Device to be connected to or interface with other Medical Device(s), validation shall include confirmation that the requirements for the application or intended use have been met when connected or interfaced.

8.7.7 Validation should be completed prior to release or implementation of the product for commercialization.

8.7.8 Records of the results, and the conclusion of the validation, and the necessary actions shall be kept.

8.8 Transfer of design and development.

8.8.1 The development manager shall document procedures for the transfer of products from design and development to manufacturing. These procedures shall ensure that design and development products are verified as suitable for manufacturing before becoming final production specifications and that production capability can meet product requirements.

8.8.2 The results and conclusions of the transfer should be recorded.

8.9 Control of design and development changes.

8.9.1 The person responsible for the development area shall document procedures for controlling design and development changes.

8.9.2 The person responsible for the development area shall determine the significance of the change in terms of performance, functionality, safety, and regulatory requirements for obtaining the medical device's sanitary registration and its intended use.

8.9.3 Design and development changes should be identified prior to implementation. Changes should be:

8.9.3.1 Revised.

8.9.3.2 Verified.

8.9.3.3 Validated.

8.9.3.4 Approved.

8.9.4 Review of design and development changes shall include evaluation of the effect of changes on components, in- process or delivered products, risk management inputs or outputs, and manufacturing processes.

8.9.5 Records of changes, their revision and any necessary action shall be kept.

8.10 Design and development file.

8.10.1 The facility shall maintain a design and development dossier for each type of medical device or family of devices. This file shall include, or cross-reference records generated to demonstrate compliance with the requirements for design and development and changes made.

9 Staff

9.1 There shall be an authorized and updated organization chart, clearly establishing the levels of authority and interrelationships of the different departments or areas. Responsibilities should be clearly indicated in the job description.

9.1.1 The manufacturing unit and the quality unit shall be completely independent within the organizational structure,not depending on or reporting to each other.

9.1.2 The sanitary manager should be the highest level in the quality area of the facility and report directly to the highest position in the facility.

9.1.2.1 The person responsible for sanitation should have at least a degree in the pharmaceutical, chemical, biological, medical, biomedical, biochemical or other profession, as long as it is related to the process; a degree and professional license issued and registered by the competent educational authorities or equivalent document in the case of foreigners, recognized by the competent educational authorities; as well as knowledge and experience demonstrable through the curriculum vitae, according to the process, that allows decision making in GMP or GHP aspects.

9.1.2.2 The sanitary manager is responsible for product quality, in conjunction with the highest authority of the organization, and is responsible for ensuring that a Quality Management System is in place.

9.1.2.3 The person in charge of health shall designate in writing his/her assistant, who shall be the person who shall attend to any eventuality when he is absent and shall comply with the requirements established by the General Health Law, theHealth Supplies Regulation, and other applicable provisions for those in charge of health.

9.1.3 Delegation of functions.

9.1.3.1 The sanitary officer may designate in writing the person(s) who will attend to various tasks, including the signing of operational documents, when absent or under special circumstances, e.g., concurrent projects and workload.

9.1.3.2 The designated person(s) shall comply with the requirements established in the applicable provisions for sanitary officers.

9.1.4 The person in charge of health shall authorize the master documents that guarantee compliance with GMP and the basic documents of the Quality Management System; the documents generated from these documents may be signedin accordance with what is stated in its documentation system.

9.1.5 For manufacturing plants established in Mexico, the owner of the establishment shall be jointly responsible withthe sanitary officer for compliance with this Standard and other applicable provisions.

9.1.5.1 For manufacturing plants established abroad, the holder of the sanitary registration and/or its legal representative in Mexico, together with the sanitary responsible (responsible for the quality unit), shall be responsible forcompliance with this Standard.

9.2 A selection, training, evaluation, and qualification system must be in place to ensure that personnel have the necessary academic background, knowledge, and experience to perform their duties and responsibilities in accordance with the profile.

9.3 There should be an annual training program that includes GMP or GHPs, job-specific operations, hygiene and safety, and evidence of its implementation should be kept. Training should include specific topics for personnel working in areas where there are risks of contamination or handling of highly active, toxic, or sensitive materials or products.

9.3.1 The effectiveness of training shall be evaluated at least once a year, through competency tests that demonstrate the ability or expertise of personnel in their assigned tasks.

9.4 Personnel shall wear clean and comfortable work clothes and protective equipment designed to avoid contamination of products and manufacturing areas, as well as occupational health hazards.

9.4.1 The clothing requirements for each manufacturing area shall depend on the classification of the area based on the risk level of the medical device and shall be defined in writing in the standard operating procedures, including the disposable clothing provision.

9.5 New personnel must undergo a medical examination to verify that their state of health does not compromise the quality of the products.

9.6 The periodic medical evaluation requirements for manufacturing and quality personnel will depend on the type of product and manufacturing process they perform.

9.6.1 The causes of absence due to communicable diseases of personnel must be documented and their state of health must be verified at the time of their return to work, and the necessary actions must be taken if the diagnosis is positive.

9.7 Any personnel showing a possible overt illness or injury, as determined by medical examination or physical supervision, which may adversely affect the quality of medical devices, shall be excluded from direct contact with the components and supplies used in the manufacture of medical devices, in-process materials and finished product until their condition is determined by competent medical personnel. All personnel shall be instructed to report to supervisory personnel any disease condition that may have adverse effects on medical device manufacturing processes.

9.8 If the personnel in the manufacturing areas where the medical device or supplies are exposed have to leave the area, they should change their work clothes, in accordance with the provisions of subsection 12.3.

9.9 Personnel must comply with the SOPs corresponding to each area.

9.10 Personnel shall not wear jewelry or cosmetics in manufacturing areas including packaging where the medical device or its materials are exposed.

9.11 External personnel that provide technical advice, consultancy, as well as contractors, for any of the items included in this Standard, must have the academic background, training, and experience demonstrable through curriculum vitae, to make recommendations on the services for which they are required, as well as to perform their functions without jeopardizing the quality of the manufactured medical devices.

9.11.1 Records shall be maintained indicating the name, experience and type of service provided by the external personnel or consultant.

9.11.2 Temporary personnel or consultants shall not carry out the final judgment of the Medical Device.

9.12 Personnel shall not ingest or store food or beverages of any kind in the manufacturing, laboratory, and storage areas, nor shall they smoke in any of the areas of the facility except those designated for this purpose.

9.13 Temporary operative personnel shall be subject to the same requirements as base personnel, after an induction course on the activity to be performed.

9.14 Newly hired personnel, both temporary and permanent, shall work under the supervision of qualified personnel until they demonstrate that they are qualified to perform their duties.

10. Facilities and equipment

10.1 General.

10.1.1 The facility shall be designed, constructed, and maintained in accordance with the operations carried out therein, based on the risk level of the medical device. Its design and construction should allow for cleanliness, order,

maintenance and prevention of contamination, and the flow of personnel and materials should follow a logical sequence.

10.1.2 There shall be a risk assessment to define the requirements of the Medical Device based on its risk classification, including the processes employed, critical systems and the scope of the Facility.

10.1.3 The size of the facility and the number of areas should be commensurate with the manufacturing capacity, equipment, diversity of medical devices and type of activities performed in each area.

10.1.4 Areas and equipment shall be located, designed, constructed, installed, and maintained in conditions that allowtheir correct operation.

10.1.5 Critical areas, manufacturing equipment and systems that directly impact product quality shall be qualified andvalidated.

10.1.6 Alternate power supply systems shall be available to maintain the condition of critical systems involved in the manufacture of sterile medical devices manufactured by aseptic processing.

10.1.6.1 Indicators and alarms must be in place to detect failures in critical systems in a timely manner, in order to take the necessary measures in accordance with the corresponding SOP.

10.2 Facilities.

10.2.1 Considerations.

10.2.1.1 There shall be manufacturing areas, laboratory and other rooms involved in manufacturing, which shall be made of materials that allow them to be cleaned, kept free of dust, insects, pests and facilitate their maintenance, in orderto minimize the risk of contamination.

10.2.1.2 Activities for the prevention, control and eradication of noxious fauna shall be carried out according to an established program.

10.2.1.3 Maintenance activities should be carried out on facilities and buildings under a program to ensure that repairand maintenance operations do not pose a risk to product quality.

10.2.1.4 In the case of construction or remodeling work, the required measures based on risk management should beapplied to avoid contamination of areas and/or products.

10.2.1.5 Facilities and buildings shall be subject to written instructions for cleaning and sanitizing, according to the classification of the areas.

10.2.1.6 Lighting, temperature, humidity, and ventilation should be adequate for the activities carried out in each areaand should not directly or indirectly affect the product, equipment, and personnel.

10.2.1.7 Entry of personnel into facilities or areas should be controlled according to the activities carried out there. Production and conditioning areas should not be used as passageways for personnel and supplies.

10.2.1.8 Manufacturing areas shall be identified and separated for each of the manufacturing processes; in the case of processes in which more than one operation is carried out continuously, risk management shall be carried out and thedesign of the areas shall be justified.

10.2.2 Production areas.

10.2.2.1 They must have specific areas for: reception, inspection and/or sampling, weighing and/or assortment of inputs; production, bulk product storage and conditioning.

10.2.2.2 The design and location of the areas shall be such that the flow of personnel, inputs, product in process, finished product and waste is carried out in a logical and sequential order according to the manufacturing process; avoiding cross flows, minimizing the risk of contamination to the product, and considering the levels of cleanliness according to the classification indicated in Appendix A of this Standard.

10.2.2.3 Production areas shall be classified in accordance with Appendix A of this Standard.

10.2.2.3.1 Environmental monitoring of classified areas must be in place.

10.2.2.4 The design of production areas shall include rooms for personnel access and change of clothing in accordancewith the classification in Appendix A of this Standard.

10.2.2.4.1 Access to production areas shall be restricted and controlled.

10.2.2.5 According to the classification of the manufacturing area and risk level of the product, ventilation duct installations, electrical power lines and other services inherent to the production areas shall be hidden or outside of them.Their location and design must be such that they can be maintained, and in cases where volatile liquids are used in the production areas, there must be anti-explosion installations and systems that maintain the concentrations allowed in theapplicable standards.

10.2.2.6 Fixed piping shall be identified according to the code of the Mexican Official Standard mentioned in paragraph 2.6 of this Standard, and in those cases where the direction of flow applies.

10.2.2.7 Pipelines through which raw materials, intermediate or bulk products are transferred should be made of inert, non-contaminating material and should be identified.

10.2.2.8 If the manufacture of medical devices requires the use of water, risk management should be carried out to determine the type of water required for the product and process being performed, as well as the type of generation and distribution system or generation equipment.

10.2.2.8.1 When the type of water is pharmaceutical grade, the generation and distribution system shall be designed,installed, qualified, and monitored in accordance with the FEUM.

10.2.2.9 Wastewater discharge systems must be in place. The sewage discharge system must be independent of the storm drainage system.

10.2.2.10 Drains shall have traps or some device to prevent backflow or contamination. In Class A/B areas (see Appendix A of this Standard) used for aseptic production, drains are prohibited.

10.2.2.11 They shall have areas for storage of manufacturing equipment accessories.

10.2.2.12 They shall have specific areas or cabinets, duly identified to store tools, substances or materials required forthe maintenance of manufacturing equipment, which shall comply with the same sanitary conditions as the area in which they are located.

10.2.2.13 Manufacturing areas, equipment and processes must have the required critical systems such as: HVAC, compressed air, pharmaceutical water, and pure steam.

10.2.2.14 Installation and maintenance access to HVAC, water and support systems shall be prevented from being a source of contamination to the product.

10.2.2.15 Production areas shall have identified intakes and/or piping for critical systems and services used.

10.2.2.16 The HVAC system shall be designed and configured in accordance with the minimum considerations set forth in the FEUM in a manner that allows it to meet the required area classification in accordance with Normative Appendix Aof this Standard.

10.2.2.17 They must have a monitoring system for critical variables according to the FEUM in order to comply with the classification in Appendix A of this Standard.

10.2.2.18 Formulated product areas where dusts are generated shall have dust extraction and collection systems designed to avoid cross-contamination and environmental contamination.

10.2.2.19 For aseptic processes, Facilities shall also consider the following:

10.2.2.19.1 In aseptic areas, false ceilings should be sealed to prevent contamination from the space above them.

10.2.2.19.2 Systems shall be in place to prevent two consecutive doors from being opened simultaneously and shall have an interlock system and a visual and/or audible alarm system.

10.2.2.19.3 It must be demonstrated that the air flow pattern does not represent a contamination risk.

10.2.2.19.4 An alarm system should be provided to indicate any failure in the air system. Differential pressure gaugesmust be calibrated, and differential pressures must be recorded.

10.2.2.19.5 Dressing rooms for entry to aseptic processing areas should be designed as air locks and provide physicalseparation of the different stages of changeover. The final stage of the changing rooms, under static conditions, should meet the same classification as the area to which it leads. Separate dressing rooms should be provided for personnel entryand exit.

10.2.2.20 It must be ensured that the equipment and instruments, as well as the sampling methods used to perform in-process controls are not directly or indirectly affected by the process and vice versa.

10.2.3 Storage areas.

10.2.3.1 Storage areas must be designed and constructed to ensure GAP, must comply with cleanliness, temperatureand RH conditions required by the type of inputs and/or products, and must be monitored and verified.

10.2.3.2 Storage areas shall have the capacity and conditions necessary to preserve and/or conserve the input, bulkproduct or finished product.

10.2.3.3 The reception area for inputs and products shall be designed and constructed in such a way as to protectthem from the outside environment, allowing inspection and cleaning.

10.2.3.4 They must have a shipping area that ensures the preservation of the properties of the medical devices.

10.2.3.5 They shall have delimited areas for the storage of inputs and recovered or returned products. Rejectedproducts shall be in segregated and identified areas.

10.2.3.6 Printed materials for conditioning shall be stored in an area with controlled and restricted access.

10.2.3.7 There shall be specific areas with storage conditions for holding samples of raw materials and/or finished medical devices, according to the characteristics of the product and the corresponding risk analysis.

10.2.4 Quality control areas.

10.2.4.1 The quality control laboratory should be physically separated from the production and storage areas and

havesufficient facilities and space for the tests and analyses carried out there.

10.2.4.1.1 If the laboratory is intended for microbiological analysis, it should have an air injection system, the characteristics of which should be determined according to the tests to be performed.

10.2.4.1.2 The laboratory for physicochemical analysis must have an air injection system, when applicable due to thenature of the tests.

10.2.4.2 Instruments sensitive to vibration, electrical interference, humidity or requiring special conditions, should beinstalled in separate rooms, or ensuring the conditions recommended by the manufacturer for their protection.

10.2.4.3 There shall be a specific area for receiving samples of inputs and products for analysis.

10.2.4.4 If the laboratory has facilities for handling laboratory animals, they must be isolated from the manufacturing areas and comply with the technical specifications, in terms of the Mexican Official Standard mentioned in Section 2.10 of this Standard.

10.2.4.5 Areas for biological, microbiological, and instrumental testing should be physically separated from each other.

10.2.5 Auxiliary areas.

10.2.5.1 Medical and dining areas shall be separate from manufacturing areas.

10.2.5.2 Areas for changing rooms, locker rooms, laundry and restrooms shall be in easily accessible places and theirsize shall correspond to the number of workers.

10.2.5.3 Sanitary facilities shall not communicate directly or be located in passageways with manufacturing areas.

10.2.5.4 Maintenance areas shall be separate and outside manufacturing areas. If a maintenance area is requiredwithin production areas, it shall comply with the sanitary conditions of the area where it is located.

10.2.5.5 They shall have a specific area, separate from the manufacturing areas, to store waste generated during themanufacture and/or analysis of the products.

10.3 Equipment.

10.3.1 General.

10.3.1.1 Manufacturing equipment shall be designed and located to meet the proposed use and avoid risk of contamination, and shall allow for disassembly/assembly, cleaning, and maintenance.

10.3.1.2 The location of manufacturing equipment should not obstruct personnel movements, nor the ventilation system louvers, they should facilitate the flow of materials, ensure the order of the processes to control the risk of confusion or mixing of any stage of the process.

10.3.1.3 Equipment control systems shall be accessible and in accordance with the type of area in which it will be operated.

10.3.1.4 According to the product and process to be carried out, the materials of the manufacturing equipment and accessories that are in direct contact with the product should be inert and not absorbent or adsorbent.

10.3.1.4.1 Lubricants, coolants, or other substances required for the operation of manufacturing equipment should not be in direct contact with the product or primary containers.

10.3.1.4.2 In case of lubricants or other substances required for the operation of manufacturing equipment that could be in contact with the product, they should be at least food grade, be purchased under a specification and establish theirhandling.

10.3.1.5 Gears and moving parts shall be guarded to prevent contamination of the Medical Device in process and foroperator safety.

10.3.1.6 Out-of-use manufacturing equipment shall be removed from production areas.

10.3.1.7 Damaged equipment awaiting maintenance shall be identified and shall not pose a risk to personnel andoperation.

10.3.1.8 Manufacturing equipment, its accessories, utensils, and all piping shall be cleaned and maintained in accordance with written procedures detailing the activities to be performed.

10.3.1.9 To maintain traceability and functionality there should be a record of the use and inspection of the conditionof the accessories.

10.3.1.10 Filters used in the production or primary packaging of products should be made of materials that do notrelease fibers or other foreign bodies.

10.3.1.11 Instruments used in the monitoring and control of critical process parameters should be calibrated andinspected according to a written program designed to ensure their performance.

10.4 Critical systems.

10.4.1 When water is used as an input in the manufacture of the medical device and the medical device is in direct contact with the patient, the water generation and distribution system or, if applicable, the water generation equipment, shall be treated as a critical system and its design, construction, qualification, and monitoring shall be in accordance with the FEUM.

10.4.2 The HVAC system shall be designed, constructed, and maintained in accordance with the FEUM to ensure the rating required in Normative Appendix A of this Standard.

10.4.2.1 Those corresponding to Class A (ISO-Class 5), B and C (ISO-Class 7) must have at least 99.97 % HEPA terminalfilters of 0.3 µm. In the case of Class D, they must have at least 95% efficiency filters (ISO-Class 8) and for ISO-Class 9 theymust have at least 85% efficiency filters, in accordance with the provisions of Appendix A of this Standard.

10.4.3 The compressed air generation and distribution system shall be designed, constructed, and maintained in accordance with the FEUM.

11. Qualification and validation

11.1 General.

11.1.1 An essential element of GMP compliance is qualification and validation to demonstrate that the manufacture of medical devices meets the fundamental characteristics of functionality, consistency, and robustness to ensure device quality.

11.1.2 Process validation is not a punctual event in time but involves the execution of activities for the maintenance of the validated state, which should consider that variability is an intrinsic characteristic of the manufacturing processes;knowing this variability, controlling it, and analyzing the impact on the quality, safety and functionality of the medical devices should lead to continuous improvement processes.

11.2 Scope of validation.

11.2.1 The scope of validation should be established using risk management, according to the medical device, the processes involved and the control of the critical aspects to be demonstrated.

11.3 An essential requirement for validation is the qualification of all elements involved in the process, system, or method to be validated.

11.4 PMV.

11.4.1 There shall be a written PMV for the development of qualification and validation activities, which shall be authorized by the highest hierarchical level of the organization and by the sanitary manager, in which the scope, responsibilities and priorities for qualification and validation shall be established.

11.4.2 The PMV must contain:

11.4.2.1 Validation Policy.

11.4.2.2 Organizational structure for validation activities.

11.4.2.3 Responsibilities.

11.4.2.4 Validation Committee or equivalent.

11.4.2.5 List of facilities, equipment, systems, methods, and processes to be qualified and/or validated.

11.4.2.6 Formats to be used for protocols and reports.

11.4.2.7 Personnel training and qualification matrix.

11.4.2.8 Change Control.

11.4.2.9 Reference to applicable documents.

11.4.2.10 Analytical methods.

11.4.2.11 Computer systems that impact product quality.

11.4.2.12 Critical systems.

11.4.2.13 Production and conditioning equipment.

11.4.2.14 Cleaning and/or sanitizing procedure or methods.

11.4.2.15 Production and conditioning processes.

11.4.2.16 Maintenance of validated status.

11.4.2.17 A program of activities, which shall be updated whenever there are changes in the processes or systems included in it.

11.5 Technology transfer shall have a planned and documented approach using risk management, which considers trained personnel, qualification and validation requirements, manufacturing systems and quality control, and shall be formalized through a protocol and its corresponding report.

11.6 Qualification and validation protocols.

There must be written protocols specifying how the qualification and validation will be carried out, specifying the critical stages, and including the acceptance criteria.

11.6.1 Qualification and validation reports.

There should be written qualification and validation reports that demonstrate traceability to the corresponding protocol, including results obtained, deviations observed and conclusions. Any changes to the protocol during execution should be documented and justified.

11.7 Qualification.

The qualification must be carried out through the following four consecutive stages:

11.7.1 They shall have CD based on user requirements, including functional and regulatory requirements.

11.7.2 They must have IC according to CD and manufacturer's requirements.

11.7.3 They must have CO based on the operating conditions and intervals established by the manufacturer and user.

11.7.4 They shall have a CE that demonstrates that the equipment and system comply with the previously establishedrequirements under routine use conditions and within the permitted working intervals for each product.

11.7.5 To proceed to the next stage of qualification they must satisfactorily complete the previous stage. They may start the next stage only when they demonstrate that there are no open major nonconformities and there is a documentedassessment that there is no significant impact on the next stage.

11.7.5.1 The measuring instruments involved in the qualification shall be calibrated with traceability to national and/orinternational standards.

11.7.6 When the manufacture of medical devices involves manual processes, controls shall be established to ensure the consistency of the process, considering the scope of qualification and/or calibration to elements such as personnel, equipment, or instruments.

11.8 HVAC System Rating.

11.8.1 The HVAC system shall be qualified in accordance with FEUM, taking into consideration at least the following parameters: temperature and % RH of the Areas it feeds, air injection volume, pressure differentials between areas, number of air changes, particle counts, air flows, cleanliness levels, flow velocity and HEPA filter integrity testing.

11.9 Qualification of water systems.

11.9.1 Qualification of pharmaceutical water generation and distribution systems or water generation equipment usedin the manufacture of medical devices shall be in accordance with the FEUM.

11.10 Qualification of the compressed air system.

11.10.1 Qualification of the compressed air generation and distribution system shall be in accordance with FEUM.

11.11 Process validation.

11.11.1 For the purposes of this Standard, process validation shall be understood as the process qualification stage.

11.11.2 Process Validation shall be completed prior to distribution and sale of the product.

11.11.3 Process validation shall be performed using a Quality Risk Management approach.

11.11.3.1 A documentary system shall be established to support the knowledge and continuous improvement of theprocess throughout the product life cycle, from its development to its discontinuation in the market.

11.11.3.2 The approach taken should be based on scientific knowledge, level of understanding and demonstrablecontrol on the part of the manufacturer.

11.11.4 Process qualification. This step can be carried out with a prospective or concurrent release approach:

11.11.4.1 Facilities, equipment, critical systems, and services shall be qualified.

11.11.4.1.1 Each of these elements may be rated with individual plans or all together with an overall plan.

11.11.4.2 Process EC.

11.11.4.2.1 Process qualification shall be performed with commercial size batches, using at least three consecutive batches over a defined period of time, which shall provide sufficient data to demonstrate that the process is capable, stable, and consistent.

11.11.4.2.2 At this stage the manufacturing conditions should be defined and confirmed. It is the combination, with the manufacturing process for the production of commercial batches, of all the previously qualified elements that comprise it, including qualified personnel, control procedures and inputs.

11.11.4.2.3 Objective measurement methods should be established using statistical tools.

11.11.4.2.4 Sampling, additional testing and greater scrutiny of process performance than would be typical in commercial production shall be conducted during this phase.

11.11.4.2.5 The level of monitoring and testing should ensure uniformity of product quality throughout the lot.

11.11.4.2.6 Batches produced for this purpose may be marketed if they comply with all GMP requirements, established acceptance criteria, satisfactory conclusions, and previously established release specifications.

11.11.5 Concurrent release of lots from the process qualification.

11.11.5.1 Concurrent release at the qualification stage of the process is only acceptable in cases such as: limited demand, short half-lives and for sanitary emergency, this decision must be previously justified and approved from the protocol by the sanitary responsible or authorized person. Documentation requirements should be the same as for prospective validation.

11.11.5.2 This allows that, even if the validation with the minimum number of lots necessary to complete it has not been concluded, the release of these lots can be made, if they comply with all their critical quality attributes.

11.11.5.3 Batches manufactured under this condition may be released and marketed if they comply with all GMP requirements, the acceptance criteria established in the validation protocol, the satisfactory conclusions of the validation report for each batch, and the release specifications authorized in the sanitary registration.

11.11.5.4 Any nonconformance report or event from customers shall be documented in the validation report for eachlot and investigated immediately to determine the root cause for correction.

11.11.5.5 Concurrently released Lots must be included in the stabilities program.

11.11.5.6 Concurrent release of process qualification batches should be an exceptional practice in process validation.

11.12 Validation of aseptic processes.

11.12.1 In products that are intended to be sterile and that are not subjected to terminal sterilization, each of the unitoperations involved should be validated independently and confirmed as a whole.

11.12.2 Aseptic process validation shall be performed in accordance with FEUM.

11.13 Cleaning validation.

11.13.1 Cleaning validation shall be performed for the purpose of demonstrating the effectiveness of cleaning procedures.

11.13.2 Cleaning procedures should be in accordance with the nature of the products.

11.13.2.1 They shall have a program for the use of sanitizers which shall include a sporicidal agent.

11.13.2.2 When the cleaning procedure includes sanitization, sterilization and/or decontamination processes, these shall be validated.

11.13.2.3 Interactions between the different sanitizing agents should be evaluated and included in the validation.

11.13.3 Validated analytical methods shall be used, considering the sampling technique, to detect traces of contaminants, detergents and/or sanitizers.

11.13.4 Cleaning procedures for surfaces in contact with the product should be validated.

11.13.5 If several products are processed in the same equipment, and the equipment uses the same cleaning procedure, a representative product may be used for validation or "worst case" criteria. This selection may be based on solubility and difficulty of cleaning and residual limit calculations based on a combination of concentration and toxicity.

11.13.6 Cleaning validation shall be performed on three consecutive applications of the cleaning procedure with satisfactory results.

11.13.7 The validity of the cleanliness of manufacturing equipment, accessories, utensils, and all piping shall be established based on the results of the validation.

11.13.8 A periodic program for trace determination of products included in the cleaning validation should be established. This periodicity should be established based on the risk assessment.

11.14 Validation of analytical methods.

11.14.1 Non-pharmacopeial analytical methods must be validated according to their protocols considering the FEUM.

11.14.2 When pharmacopeial methods are used, applicability to the product should be demonstrated under laboratory operating conditions and in accordance with the desired analytical method.

11.15 Validation of computer systems.

11.15.1 Computer systems that impact product quality and data integrity shall be validated.

11.15.2 They shall have an inventory of all computer systems.

11.15.3 Computer systems shall consider software components, instruments, equipment, and information technologyinfrastructure.

11.15.3.1 They shall have a system for protection, integrity, and backup of information, which shall be determined based on the risk assessment documentation of the computer system. Access and readability of data shall be ensured throughout the retention period.

11.15.3.2 Access to these shall be controlled.

11.15.3.2.1 Physical and/or logical controls shall be applied to restrict access to users with different levels of authorization. Security codes should be defined according to predetermined criteria and modified according to a risk assessment.

11.15.3.2.2 The System shall lock out a user after a defined number of unsuccessful login attempts.

11.15.3.3 When a computerized system generates electronic records and/or employs electronic signatures, these must be considered in the validation:

11.15.3.3.1 Documents and records that are created, modified, maintained, archived, retrieved and/or transmitted through electronic systems are considered electronic records.

11.15.3.3.2 If it is determined that a system generates and maintains regulated electronic data, there shall be documentary evidence to ensure traceability, easy access, and integrity of the data.

11.15.3.4 If critical data is captured manually, there must be an additional review of the accuracy of the data that maybe performed by a second person or through a validated electronic means.

11.15.3.5 Data shall be protected by tools such as backups performed at defined frequencies according to a procedure.

11.15.3.6 The ability to restore data, as well as the integrity and accuracy of data backup, shall be verified duringvalidation and monitored according to a risk assessment.

11.15.3.7 Based on a risk assessment determine the need for the system to include a data auditing system, programmed to independently record the date and time of user login, as well as the actions of creating, modifying, or deleting electronic records.

11.15.3.7.1 The *audit trail* shall prevent tampering and shall be available and convertible in an understandable form,during its retention period, to allow evidence in the chain of events.

11.15.4 The validation process shall encompass all relevant phases of the life cycle according to the category and architecture of the system, to ensure accuracy, completeness, and consistency in the expected performance of the computer systems.

11.15.4.1 Risk management shall be applied to the complete validation cycle, including the planning, specification, testing, system release, maintenance, and system retirement phases.

11.15.4.2 Components of the information technology infrastructure and any relevant tools or equipment shall be qualified.

11.15.4.3 For the validation process, the tests performed by the supplier can be used, however, the acceptance of the test records delivered by the supplier shall not substitute the validation tests performed at the facilities, equipment, and personnel, such as validation plan, user requirements, risk analysis, CE, and validation report.

11.15.4.4 If a centralized system is used at multiple sites, the validation process shall include verification of the processes executed through the system at each individual site.

11.15.5 They shall have a traceability matrix documenting the multiple stages of specification (including revisions) andtesting upon satisfactory completion.

11.15.5.1 All changes to a computer system shall be made in accordance with the change control system, including system configurations, shall be applied according to a predefined and controlled process comprising the definition of theimpact of the change and the resulting verification activities, including back testing.

11.15.5.2 Control procedures shall be implemented to ensure that data auditing is reviewed on a regular basis; the frequency and method shall be determined according to risk.

11.15.5.3 Systems with data auditing functionality shall output information that allows verification of whether any data has been altered since its original entry.

11.15.5.4 If data is transferred to another data format or system, validation shall include checking that the data is not altered in value and/or definition during the migration process.

11.15.6 For electronic signatures:

11.15.6.1 These must be unique to each person and non-transferable.

11.15.6.2 When the use of electronic signatures is adopted, the date from which electronic signatures are effective and equivalent to autographic signatures shall be established.

11.15.6.3 Electronic signatures must have at least two distinct elements such as an identification code and a password.

11.15.6.4 Electronic signatures shall be linked to their respective electronic records that ensure that the signatureshave not been altered, copied, or otherwise transferred to an electronic record for forgery by ordinary means.

11.15.6.5 In the event that the electronic signature is made by means of *tokens* or biometric devices, the system shallensure that it cannot be used by another person and that control measures have been implemented.

11.15.7 Warehouses that use *software* for inventory control shall have protocols for access controls and proceduresfor use that guarantee the integrity of the data.

11.16 Maintenance of validated status.

11.16.1 Maintenance of facilities, equipment and systems is another important aspect of ensuring that the process is kept under control. Once qualified/validated status has been achieved it should be maintained through routine monitoring, maintenance, procedures, and calibration programs.

11.16.2 A review, at a frequency determined by a risk assessment, of the facilities, systems and equipment should becarried out to determine if re-qualification is required. This should be documented as part of the maintenance of the validated condition.

11.16.2.1 If the facilities, systems, and equipment have not undergone significant changes, documentary evidence thatthey meet the predefined requirements is sufficient as evidence of their maintenance of validated status.

11.16.3 When a change affects the quality or characteristics of the product, or its components and/or process, a newqualification and/or validation shall be carried out.

11.17 Guidelines for qualification and validation.

11.17.1 The national and international guides described in the bibliography of this Standard may be used as support for qualification and validation.

12. Manufacturing Systems

12.1 Medical device manufacturing systems should follow written procedures to ensure compliance with GMP. The characteristics of each system will be conditioned by risk management, the nature of the processes and the quality specifications of each product.

12.2 Control of inputs.

12.2.1 General.

12.2.1.1 There shall be written procedures for the receipt, identification, sampling, storage, control, and handling of all Supplies used in the manufacture of Medical Devices.

12.2.1.2 It must be ensured that the certificates of analysis or conformity of the inputs are those issued by themanufacturer.

12.2.1.3 Supplier qualification and approval shall be performed prior to the purchase of any Input.

12.2.1.4 Inputs at any stage of manufacture shall be handled and stored in such a way as to prevent contaminationand alteration.

12.2.1.5 Inputs must be identified with a lot number to prove traceability.

12.2.1.5.1 When different lots are received in a shipment, each lot should be considered separately for sampling,analysis or evaluation and release.

12.2.1.5.2 Inputs shall be analyzed or evaluated by the quality unit of the medical device manufacturing site.

12.2.1.5.3 In the case of a consignment of a lot already received, the criteria for evaluating or analyzing the inputsshall be established.

12.2.1.6 The lot number shall be used to record the use of each input. Each lot should be identified with its status:quarantine, approved or rejected.

12.2.1.7 A system shall be in place to ensure that inputs are used on a First-In-First-Out or First-In-First-Out basis.

12.2.1.8 Inputs, bulk, semi-finished and finished products should be placed in such a way that they are not in directcontact with the floor.

12.2.1.8.1 When computerized systems are used in the control of inputs, they must be validated.

12.2.1.9 Inputs whose approval period has expired shall be placed in quarantine for re-analysis or final disposal.

12.2.1.10 Rejected inputs shall be identified and segregated to prevent their use in manufacturing.

12.2.2 Receipt.

12.2.2.1 Each container or group of containers must be checked for completeness, identified with at least name,quantity, and lot number.

12.2.2.2 Inputs should be identified for storage indicating at least the following information:

12.2.2.2.1 The name and international designation.

12.2.2.2.2 Lot/Serial Number.

12.2.2.2.3 Quantity and number of containers.

12.2.2.2.4 Status.

12.2.2.2.5 The expiration or re-analysis date.

12.2.2.2.6 When the nature of the inputs does not consider any of these general characteristics, it shall be justified based on risk management.

12.2.2.2.7 A certificate of analysis or certificate of compliance, as applicable, should be available from the supplier for each lot or batch received.

12.2.3 Sampling.

12.2.3.1 Inputs shall be stored in quarantine until they have been sampled, analyzed, or evaluated and released foruse by the quality unit.

12.2.3.2 Statistical criteria should be used to determine the number and position of samples to be taken, as well asconsidering the characteristics of the material to be sampled, according to the FEUM Medical Devices supplement.

12.2.3.3 Samples taken shall be identified.

12.2.3.4 The sampled containers must indicate it in their identification.

12.2.4 Assortment.

12.2.4.1 Traceability of inputs by lot, of quantities received versus quantities delivered, shall be ensured.

12.2.4.2 Inputs shall be weighed or measured according to written procedures and this activity shall be verified by asecond person.

12.2.4.2.1 When automated systems are used, they shall be validated.

12.2.4.2.2 It must be verified that the inputs supplied have been previously approved by the quality unit.

12.2.4.3 The quantities to be supplied shall correspond to the production or packaging order.

12.2.4.4 When adjustments to the quantity of the medical device and supplies to be manufactured are required, theymust be supplied and verified by authorized personnel and documented in the production order.

12.2.4.5 If an Input is removed from the original container to another, the new container must be identified in thesame way.

12.2.4.6 Printed materials should be stored and transported separately in closed containers to avoid mixing.

12.2.4.7 Assorted inputs for manufacturing shall be separated by product lot in which they will be used.

12.3 Control of manufacturing operations.

12.3.1 Manufacturing operations shall be performed by qualified personnel and supervised by personnel having theexperience, knowledge, and educational background appropriate to the activity they are supervising.

12.3.2 Access to manufacturing areas shall be restricted and controlled.

12.3.3 Controls should be in place to prevent cross-contamination. Based on risk management, the cleaning validationprotocol should be prepared.

12.3.4 Manufacturing areas shall be maintained to the degree of cleanliness and sanitation appropriate to the riskmanagement, nature of the processes and area classification indicated in Appendix A of this Standard.

12.3.4.1 There must be a SOP that describes:

12.3.4.1.1 The manner and/or frequency of cleaning and sanitizing areas.

12.3.4.1.2 Preparation of cleaning and sanitizing agents.

12.3.4.1.3 Rotation of the use of sanitizing agents. Only sanitizing agents whose efficacy has been validated by the quality area may be used.

12.3.5 Before starting manufacturing, the cleanliness of areas and equipment shall be verified and that there is no raw material, product, product residue or documents from the previous operation that are not required for the operation.

12.3.6 Medical device manufacturing areas shall maintain conditions appropriate to the risk management, nature ofthe processes and classification in accordance with Normative Appendix A of this Standard.

12.3.7 Operations of different products or batches should not be carried out simultaneously in the same room, exceptwhere there is no risk of cross-contamination.

12.3.8 The flow of inputs should be in a logical sequence so as to prevent the risk of cross-contamination.

12.3.9 Areas should be identified with the operations performed in them.

12.3.10 The production or assembly order shall remain in sight during the process.

12.3.11 The use of documents within production areas shall not represent a risk to product quality and personnel.

12.3.12 The addition and ordering of inputs during fabrication should be carried out and supervised according to thefabrication instructions. Recording of fabrication should be carried out at the time of fabrication.

12.3.12.1 The production procedure shall indicate the critical operations that require supervision.

12.3.13 The performance of in-process controls during production shall not affect the process or jeopardize productquality and personnel.

12.3.14 The results of tests and analyses carried out for process control shall be recorded or attached to the productionor packaging file.

12.3.15 Any deviation in the yields indicated in the production or packaging order must be investigated prior to batchrelease.

12.3.16 In the event that maintenance is required during manufacturing, procedures shall be established describingmeasures to prevent affecting the quality characteristics of inputs, products, and area conditions.

12.3.17 When the medical device is sterilized, the validation of the process shall be carried out in accordance with theFEUM.

12.3.17.1 In order to release a lot of sterile product, the results of the sterility test must be satisfactory.

12.3.17.2 For sterile medical devices, retention samples should be retained for at least one year after the expiration date indicated on the final packaging, stored under the conditions indicated on the label and in sufficient quantity for twocomplete analyses.

12.3.18 Finished product storage and distribution areas.

12.3.18.1 Finished product is considered quarantined until all analyses are performed, and it is released by the qualityunit.

12.3.18.2 All distribution activities shall be clearly defined in procedures and systematically reviewed.

12.3.18.3 When import and export activities are performed, they must be carried out in accordance with the applicable provisions.

12.3.18.4 Shall establish a system, either manual or computerized, that allows the correct distribution of medical devices.

12.3.18.5 An SOP should be established for the control of the distribution of Medical Devices, describing:

12.3.18.5.1 Data to be recorded for each shipment such as: Medical Device name, Batch/Serial Number, quantity, purchase order, release file number.

12.3.18.5.2 The form and conditions of transport.

12.3.18.6 They should have storage instructions throughout the distribution chain.

12.3.18.7 Medical Devices should be transported in containers that have no adverse effect on the quality of the products, and that provide adequate protection from external influences, including contamination.

12.3.18.8 The container and packaging should be selected according to the transportation requirements of the medical devices; the space needed for the quantity of medical devices, outside temperatures; the estimated maximum time for transport and the transit time through customs.

12.3.18.9 For products kept refrigerated, packaging qualification and cold chain validation should be performed.

12.3.18.10 A document (e.g., delivery note/packing list, invoice) must be attached to all shipments indicating the date;name of the Medical Device; the Batch/Serial Number; quantity; name and address of the supplier; the name and addressof delivery.

12.3.18.11 Product identification and integrity must be ensured.

12.3.18.12 A procedure shall be in place for the investigation and handling of deviations during transportation anddelivery of product, in accordance with Subsection 6.6.7.1.3.1.

12.3.18.13 Distribution records shall be kept for each product lot or serial number to facilitate recall, in accordancewith Chapter 16 of this Standard.

12.3.18.14 They must have transportation for distribution that guarantees the conditions of conservation, cleanliness,and hygiene of the medical devices.

12.3.18.15 There shall be written procedures for the operation, cleaning and maintenance of all conveyances andequipment used for the distribution process.

12.3.19 The following describes production lines that may be involved in the manufacture of a medical device.

12.3.19.1 When, due to the nature of the medical device, the production involves two or more lines, the compliancecorresponding to each of them shall be implemented.

12.4 Formulated.

12.4.1 Formulated products are those whose manufacture requires the incorporation of raw materials that need to be weighed and/or measured and that are presented as solutions, suspensions, tablets, capsules, creams, ointments, soaps, etc. This list is enunciative but not limitative.

12.4.2 Production and/or primary packaging processes shall comply at least with ISO Class 8, considering risk management, as established in subsection 10.1.2.

12.4.2.1 The HVAC system must be designed and integrated to meet the required area rating in accordance with Appendix A of the Standard and have at least 95% efficiency filters.

12.4.3 Feeding and dosing systems should be designed to minimize exposure of inputs to the environment.

12.4.4 Hoppers, tanks, or kettles must have lids, and when they require heating or cooling during the process, they must be jacketed and have agitation control systems.

12.4.5 The type of water used for final rinsing of product contact equipment, accessories and utensils should be determined based on risk management, product type and the intended use of the medical device.

12.4.6 The quality of water used in Production shall comply with the provisions of the FEUM.

12.4.7 For blends, homogeneity shall be maintained throughout the filling process, even after line stoppages.

12.4.8 Retention samples of raw materials and finished product shall be retained in accordance with paragraphs 13.11and 13.12 of this Standard.

12.4.8.1 Retention samples of primary packaging materials and those that contribute to product integrity should be retained for the same length of time as the shelf life of the last lot of product in which they were used.

12.5 Sterile formulations.

12.5.1 The production of sterile formulated medical devices must comply with the provisions of Section 10.4 and sub-sections of the Mexican Official Standard mentioned in Section 2.9 of this Standard and the report of product risk management results.

12.5.2 Retention samples of raw materials and finished product shall be retained in accordance with 13.11 and 13.12of this Standard.

12.5.2.1 Retention samples of primary packaging materials and those that contribute to product integrity should be retained for the same length of time as the shelf life of the last lot of product in which they were used.

12.6 Plastics, polymerics and elastomers.

12.6.1 The processes considered for this manufacturing line are, but are not limited to extrusion, injection, molding, dip forming, compression, braiding or twisting, vulcanizing, leaching, etc. Some of the medical devices considered for this manufacturing line are gloves, bags, probes, condoms, secretion suction bulb, connectors, syringes, endotracheal tubes,disposable vaginal mirrors, cannulation tubes, brushes, synthetic sutures, catheters, cannulas, masks, plastic rings for valves, plastic implants, contact lenses, etc.

12.6.2 For the approval of raw materials lot by lot, they may exempt the execution of tests such as systemic injection, intracutaneous reactivity, radiopacity and identification of the medical grade plastic, although these are referred to in the FEUM; as long as the type of plastic, polymer and/or elastomer has not changed with respect to the material authorized in the sanitary registration, the supplier is qualified and they have evidence of compliance with these tests in at least 3 lots of the raw material, as part of the qualification of the material.

12.6.3 In case the FEUM requires for the release of finished product batch by batch the systemic injection and intracutaneous reactivity tests, the execution of these tests may be exempted, however, the results of these tests shall be indicated in the certificate of analysis making reference to the original certificate of analysis and the date of execution ofthe tests, and not as tests carried out Batch by Batch of product.

12.6.4 When the medical device does not come into direct contact with the patient, manufacturing areas may be cleanareas free of classification in accordance with Normative Appendix A of this Standard.

12.6.5 When the medical device comes into direct contact with the patient, the Manufacturing Areas from the molding/forming process shall have at least ISO-Class 9 classification in accordance with Normative Appendix A of this Standard.

12.6.6 If the purpose of use of the Medical Device requires the sterility feature:

12.6.6.1 Manufacturing areas from the molding/forming/assembly process shall have at least Class D (ISO-Class 8) andshall establish specific procedures for bioburden control.

12.6.6.2 The water used for the final rinse of the equipment or as an input in the manufacture of the medical device must be purified water level 1 or demonstrate specific procedures for Bioburden control.

12.6.7 Retention samples of each Lot manufactured shall be retained for at least one year after the Expiration Date indicated on the final packaging, stored under the conditions indicated on the label and in sufficient quantity for two complete analyses except for the sterility test.

12.6.7.1 For medical devices that are custom manufactured, it shall not be necessary to retain Retention Samples of the finished product.

12.6.7.2 Manufacturing records should be retained for at least one year after the Expiry Date of the product.

12.6.7.2.1 For medical devices of this line, which do not have an expiration date, the manufacturing records shall be kept for at least the time of use recommended by the manufacturer.

12.6.8 An annual stability program should be implemented considering at least one Lotte per year of product manufactured for commercial purposes, in accordance with the FEUM.

12.7 Diagnostic agents (*in vivo* / *in vitro*).

12.7.1 They are all those diagnostic supplies that can be used alone or in combination as an auxiliary of other clinical or paraclinical procedures. Some of these include, but are not limited to agar plates and dehydrated culture media, anti-human globulin reagents, hemoclassifying reagents, antibacterial reagents, pregnancy tests, rapid HIV tests, liquid and lyophilized diagnostic agents, test strips, febrile antigens, buffer solutions, etc.

12.7.2 Personnel.

12.7.2.1 Operating personnel shall be under the supervision of a person who is qualified in techniques such as strain management, allergen collection, and who possesses specialized scientific knowledge in immunology, microbiology, virology, or other according to the type of product and processes they perform.

12.7.2.2 All personnel involved in the manufacture of these products shall receive specific training in strain handling,aseptic techniques and/or hygiene and microbiology or other areas of knowledge that are required according to the nature of the product and processes.

12.7.2.2.1 Equivalent measures for temporary employees shall be implemented.

12.7.2.3 There should be a personnel training program in biosafety and biological containment practices according tothe type of product and processes they carry out.

12.7.3 Facilities.

12.7.3.1 The manufacture of non-sterile *in vitro* diagnostic agents may be carried out in clean areas free of classification in accordance with Appendix A of this Standard.

12.7.3.2 The manufacture of *in vitro* diagnostic agents to be sterilized by a terminal method should be performed at least in Areas Class D (ISO-class 8).

12.7.3.3 For the manufacture of sterile *in vivo* diagnostic agents, they shall have:

12.7.3.3.1 With Class C Areas (ISO Class-7) for those that are sterilized by a terminal method.

12.7.3.3.2 With Areas classified as Class A (ISO Class-5) for those manufactured by aseptic processing. The environment for Areas classified as Class A (ISO Class-5) shall be at least Class C (ISO-7).

12.7.3.3.3 With water system for the manufacture of injectables in accordance with FEUM.

12.7.4 Production.

12.7.4.1 For aseptic production and filling of sterile *in vitro* diagnostic agents the data generated by Facility and processmonitoring should be recorded and evaluated as part of the product release.

12.7.4.2 Temperature records of freezers and/or refrigerators in which strains, serums and cultures are kept shall bemade.

12.7.4.3 Each lot of reagent should be tested by all methods recommended by the manufacturer on the labels and inthe instructions for use; for release.

12.7.4.4 Where the diagnostic agent requires a particular storage condition, controls shall be established to maintainthis condition and records shall be kept.

12.7.4.5 In the case of diagnostic agents containing antibodies, the expiration date of a lot shall be greater than one year and shall be established from the date of the last potency test.

12.7.4.6 Retention samples of each batch manufactured shall be retained for at least one year after the expiration date indicated on the final packaging, stored under the conditions indicated on the label and in sufficient quantity for two complete analyses, except for sterility testing. In case the retention time is less than this period, it should be justified based on risk management.

12.8 Metal-mechanical.

12.8.1 The processes considered for this manufacturing line include, but are not limited to casting, cutting,

stamping, hardening, turning, machining, sharpening, washing, lubricating, polishing, passivating, etc. Some of the Medical Devices considered for this manufacturing line, including but not limited to needles, screws, nuts, nails, external fixators, metallic staples, plates, connectors, wires, metallic implants, surgical and/or medical instruments, dental alloys, locking pins, reinsertion washers, saws, non-disposable vaginal mirrors, clinical thermometers, metallic rings for valves, intrauterine devices, etc.

12.8.2 For the approval of raw materials batch by batch, they may exempt the execution of tests such as composition in percent of the materials and corrosion resistance, even though these are referred to in the FEUM; provided that the type of metal has not changed with respect to the material authorized in the sanitary registration, the supplier is qualified and they have evidence of compliance with these tests in at least three batches of the raw material, as part of the qualification of the material.

12.8.2.1 Evidence of biocompatibility testing shall be available as part of the qualification of the material.

12.8.3 When marking the medical device, the passivation process and validation of such process shall be performed to ensure corrosion resistance.

12.8.4 The Manufacture of these Medical Devices may be carried out in Gray Areas free of classification in accordance with Appendix A of this Standard.

12.8.5 If the purpose of use of the Medical Device requires the sterility feature:

12.8.5.1 Prior to primary packaging of the product, specific processes for Bioburden control shall be established and shall be carried out in at least Class D (ISO Class 8) areas in accordance with Appendix A of this Standard.

12.8.5.1.1 Primary packaging areas shall have a minimum classification of ISO Class 8.

12.8.6 In cases where moisture is a risk factor for the product, controls shall be established to maintain this conditionwithin the requirements established based on risk management.

12.8.7 Areas where mercury is handled shall consider safety conditions for personnel.

12.8.8 When the Medical Device requires a specific condition for its transfer, in order to preserve the passivation, acontainer that guarantees such preservation shall be used.

12.8.9 In the case of implanted medical devices that do not have an expiration date, the manufacturing records should be retained for at least the time of use recommended by the manufacturer.

12.8.10 Retention samples shall be retained for each lot of Raw Material used in manufacture, in sufficient quantityfor at least two complete analyses under the Storage Conditions indicated in the Specifications.

12.8.10.1 For medical devices that are custom manufactured, it shall not be necessary to retain retention samples ofthe finished product.

12.8.11 In the manufacture of some of the products in this line, highly toxic materials are used that require special handling; handling conditions for these materials shall be established in accordance with the applicable provisions.

12.9 Textiles.

12.9.1 The processes considered for this manufacturing line are, among others: weaving, cutting, boiling, making up,washing, drying, pleating, etc. Some of the medical devices considered for this manufacturing line, including but not limited to cotton, masks, gauze, surgical garments, X-ray fields, surgical fields, compression stockings, surgical sponges, bandages, etc.

12.9.2 The manufacture of these medical devices may be carried out in gray areas free of classification in accordancewith Appendix A of this Standard.

12.9.3 If the purpose of use of the Medical Device requires the sterility feature:

12.9.3.1 Prior to primary packaging of the product, specific processes must be established for the control of Bioburden,which must be carried out at a minimum in clean areas, free of classification in accordance with Appendix A of this Standard.

12.9.3.2 When water is used for bioburden control, it shall be purified water level 1 or specific procedures shall be established for bioburden control of that input.

12.9.3.3 Primary packaging areas shall be at least clean areas, free of classification in accordance with Appendix A of this Standard.

12.9.4 For the management of wastes and nonconforming products containing radiopaque compounds, handling conditions for these materials shall be established in accordance with the applicable provisions.

12.9.5 Retention Samples of each Lot of Medical Device bearing the Sterility characteristic must be kept for at least one year after the Expiration Date indicated on the final packaging, stored under the conditions indicated on the label.

12.10 Assemblies.

12.10.1 In this production line are all establishments that receive as inputs the parts necessary for the assembly of any Medical Device, such as: catheters, hemodialysis equipment, venoclysis equipment, transfusion equipment, drainage equipment, feeding equipment, urostomy equipment, catheters, blocking equipment, syringes, sutures, hyperbaricchamber, thermal cradles, facial and body stimulators, circumcision chambers, autoclaves, ovens, respirators, electrosurgical units and defibrillators, microscopes, anesthesia circuits, baumanometers, stethoscopes, pacemakers, valves, incubators, ultrasound equipment, X-rays, lithotripters, vital sign monitors, medical device kits, etc. This list is notexhaustive. This list is enunciative but not limitative.

12.10.2 Assembly of non-sterile medical devices may be performed in gray areas free of classification in accordancewith Regulatory Appendix A of this Standard.

12.10.3 Assembly of medical devices to be sterilized shall be performed in Class D (ISO Class 8) areas in accordancewith Appendix A of this Standard.

12.10.4 When compressed air is used as part of assembly activities and is in contact with the product, it shall bedefined and qualified as a critical system, when the level of risk and the intended use of the medical device warrants it.

12.10.5 When solvents, adhesives or other chemical agents are used in assembly activities on parts that are in contactwith the patient, it shall be demonstrated based on validation that they do not leave residues that compromise the safetyof the product and/or that they do not modify the chemical composition of the supplies to be assembled.

12.10.6 Areas where solvents, adhesives or other chemical agents are used shall consider safety conditions for personnel.

12.10.7 For assembled heart valves, the hydrodynamic function test shall be performed on each valve.

12.10.8 The assembly of mass-produced medical equipment shall have functional testing of each piece of medical equipment assembled.

12.10.9 Retention samples of each Lot of Medical Devices bearing the sterility characteristic should be retained for atleast one year after the Expiration Date indicated on the final packaging, stored under the conditions indicated on the label.

12.10.10 In the case of probes and sutures, assembly resistance tests shall be carried out in accordance with FEUM.

12.10.10.1 When assembly is performed semi-automatically or automatically, they shall qualify the equipment and based on the result of the qualification, implement sampling criteria for the assembly strength test.

12.10.11 For medical electronic equipment, the supplies to be assembled may be approved with the certificate issuedby the manufacturer of the part, as long as there is no laboratory that performs the test in national territory and the certificate issued by the manufacturer of the part refers to the international technical standard used, and the result obtained in the test.

12.10.12 When the Medical Device has software for its operation or functioning, the software shall be validated together with the Medical Device, in accordance with the FEUM.

12.10.12.1 The national and international guides described in the bibliography of this Standard may be used as supportfor validation.

12.10.13 The validation of the Software considered as Medical Device shall be performed, according to the FEUM or subsection 11.17.

12.10.13.1 Analytical/technical validation of software as Medical Devices shall include as a minimum:

12.10.13.1.1 Technical documentation of the design and development of the software, i.e., the manner in which itwas constructed (at least, input data, operating systems, programming language, databases used, etc.).

12.10.13.1.2 Documentary evidence that the software processes input data correctly and reliably and generatesaccurate, complete, and precise output data.

12.10.13.1.3 Execution of tests that demonstrate that the software complies with the specifications established for the intended medical purpose.

12.10.14 Validation must be performed for mobile applications that are considered medical devices, in accordance with the FEUM or subsection 11.17.

12.10.15 Medical equipment *remanufacturing* and *refurbishing/rehabilitation* activities shall be carried out in specific areas for these processes.

12.10.15.1 They shall have procedures that establish the activities and criteria for receiving equipment, as well as theformats for recording these activities.

12.10.15.2 They shall have formats for reviewing and recording the activities carried out on the equipment in order to maintain traceability.

12.10.15.3 For *remanufacturing* and *refurbishing* activities, they shall ensure that the parts or systems replaced are ofthe same type or specification as stated in the previously authorized condition.

12.10.15.4 Remanufacturing (*remanufacturing*) and Refurbishment/Rehabilitation (*refurbished*) shall be carried out by the manufacturer, or an establishment authorized by the manufacturer.

12.11 Biological processes.

12.11.1 This production line includes all establishments that involve the handling of tissues or cells of human or animal origin. The processes considered for this manufacturing line are cutting, tissue cleaning, centrifugation, immersion, milling, molding, drying, lyophilization, demineralization, cryopreservation, radio preservation, incubation, sterilization, fixation, culture, propagation, purification, etcetera. Some of the medical devices considered for this manufacturing line include grafts, valves, implants, etc. This list is enunciative but not limitative.

12.11.2 Personnel.

12.11.2.1 Personnel involved in the manufacture of these products should receive specific training in the processes inwhich they are involved and in biosafety techniques, including personnel not directly involved in the production of the device, for example: cleaning, maintenance, and quality control personnel.

12.11.2.2 Personnel shall be under the supervision of a person who is qualified in techniques used in the manufacture of these products and who possesses scientific knowledge in their manufacture and handling. Personnel shall include specialists in histology, immunology, bacteriology, genetics, or other areas of knowledge that are required according to the nature of the product and processes.

12.11.2.3 There should be a training program for personnel in biosafety and biological containment practices according to the nature of the product.

12.11.3 Facilities.

12.11.3.1 For the production and packaging of biological medical devices, they shall have at least ISO-Class 7 classifiedareas for those that are sterilized by a terminal method.

12.11.3.1.1 The water used for the manufacture of medical devices shall be at least level 1 purified water or establishspecific procedures for Bioburden control.

12.11.3.2 Sterile biological medical devices that do not have a terminal sterilization method shall be manufactured inClass A (ISO-Class 5) areas. The environment for such Areas shall meet at least Class B.

12.11.4 Production.

12.11.4.1 Inputs of animal origin or those used for their manufacture derived from animal origin must present the certificate indicating that they are free of TSE, BSE, foot, and mouth disease, bovine leukosis and others that represent a health risk.

12.11.4.2 In the case of grafts of human origin, all products obtained from the same donor may be considered as oneLot and may be sub-lotified as long as traceability with a Lot of origin is maintained.

12.11.4.3 The Raw Material of human origin for the production and development of implants must come from tissue banks with sanitary license according to the applicable dispositions and must be evaluated with criteria that allow reducing the risks of disease transmission to the receptor, which shall be fully identified and traceable to the donor.

12.11.4.3.1 There shall be procedures describing the handling, storage, and transportation of raw materials of humanor animal origin, bulk products, and finished product, in order to maintain the cold chain.

12.11.4.3.1.1 All equipment for storage shall be qualified.

12.11.4.3.1.2 The cold chain must be validated.

12.11.4.3.1.3 A continuous temperature monitoring system must be in place to demonstrate that the cold chain has been maintained and to establish in writing the characteristics of the containers, the configuration of the packaging and the responsibilities of the persons involved in this process.

12.11.4.3.1.4 The time that the product can remain out of refrigeration should be established based on stability studies to ensure that it remains within specifications.

12.11.4.3.1.5 Temperature excursions should be investigated and corresponding CAPAs should be established.

12.11.4.3.1.6 A backup system and contingency plan should be in place to ensure that in emergency situations the storage conditions required for the product are maintained.

12.11.4.4 The processes of preparation and procurement of implants derived from human tissue shall ensure inactivation and sterilization, such processes shall be validated.

12.11.4.5 Depending on the origin of the Raw Material for the manufacture of biological Medical Devices, it must be guaranteed to be free of nucleic acids (by NAT) of Human Immunodeficiency Virus (HIV) 1 and 2, Hepatitis A Virus

(HAV),Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), parvovirus B19 or any other pathogenic microorganism.

12.11.4.6 Tissues and cell banks should be kept separately from other materials, under storage conditions designed to maintain their viability and avoid contamination.

12.11.4.7 They shall make continuous temperature records of freezers, refrigerators and/or incubators in which tissues and/or cells, or any other biological product, are kept.

12.11.4.8 Tissues may be conserved for a maximum of 5 years, as long as the conservation of viability, purity and bioburden characteristics is evaluated.

12.11.4.9 In the case of cell banks, their origin, genotypic and phenotypic characterization must be documented.

12.11.4.10 Manufacturing records should be retained for at least one year after the Expiry Date of the product.

12.11.4.11 Retention Samples of each lot manufactured shall be kept at least one year after the Expiry Date indicatedon the final packaging, stored under the conditions indicated on the label and in sufficient quantity according to the natureof the fabrics.

12.11.4.12 When the diagnostic agent requires a particular storage condition, such as refrigeration or freezing, appropriate controls and records should be established.

12.11.4.13 In the case of grafts, specific protocols should be developed based on scientific knowledge in order to determine the type of retention sample according to each raw material (tissue/cells), the quantity and the critical tests to be performed if required.

12.11.4.14 When the Medical Device is classified of biological origin in accordance with article 229 of the General Health Law and is administered to the patient, its release shall be carried out in accordance with the provisions of article 230 and 231 of the General Health Law.

12.11.4.15 Before disposal, biological products and materials shall be inactivated and handled according to Section 6of the Mexican Official Standard mentioned in Section 2.12 of this Standard.

12.12 Ceramics/glass.

12.12.1 The processes considered for this manufacturing line are melting, curing, blowing, molding, compression, firing, polishing, etc. Some of the medical devices considered for this manufacturing line are prosthesis, ceramic implants, intraocular lenses, etcetera. This list is enunciative but not limitative.

12.12.2 The manufacture of these medical devices may be carried out in gray areas free of classification in accordancewith Normative Appendix A of this Standard.

12.12.3 In the case of prostheses, if they are marked, the polishing process shall be carried out and validated in orderto avoid roughness.

12.12.4 If the purpose of use of the Medical Device requires the sterility feature:

12.12.4.1 Prior to primary packaging of the product, specific processes for Bioburden control shall be implemented and this process shall be carried out in Class D (ISO Class 8) areas in accordance with Appendix A of this Standard.

12.12.4.2 Primary Packaging Areas shall have a minimum Class D (ISO Class 8) classification in accordance withAppendix A of this Standard.

12.12.5 Manufacturing records for these ceramic and glass devices should be retained for at least the time of userecommended by the manufacturer.

12.12.6 Retention Samples shall be kept for each Batch of Raw Material used in the Manufacture in sufficient quantityfor at least two complete analyses under the required Storage Conditions.

12.12.6.1 For medical devices that are custom manufactured, it shall not be necessary to retain Retention Samples ofthe finished product.

12.13 Medicated Medical Devices.

They are those devices that include as an integral part a medicine that exerts on the human body a secondary or additional action to that of the Medical Device, consequently, in addition to this Standard, the generalities of medicines in accordance with the Mexican Official Standard NOM-059-SSA1-2015, good manufacturing practices of medicines, the corresponding monographs of the FEUM and other applicable provisions shall apply to them.

12.14 Radiopharmaceuticals.

12.14.1 General.

12.14.1.1 The manufacture and handling of radiopharmaceuticals are potentially hazardous. The level of risk

depends,in particular, on the types of radiation, radiation energy, half-life and radiotoxicity of the radionuclides. Particular attention should be paid to the prevention of cross-contamination, retention of radionuclide contaminants and waste disposal.

12.14.1.2 Due to the short half-life of their radionuclides, some radiopharmaceuticals may be released before the completion of all quality control tests. In this case, accurate and detailed description of the entire release procedure including the responsibilities of the personnel involved and continuous evaluation of the effectiveness of the QA system is essential.

12.14.1.3 Manufacturing procedures used by industrial manufacturers, Nuclear Centers/Institutes and Positron Emission Tomography Centers for the production and quality control of the different types of products according to the following table:

Manufacturing Type	NO GMP * NO	GMP**		GMP***	
Radiopharmaceuticals Positron emitting radiopharmaceuticals Radioactive and non-radioactive precursors for the production of radiopharmaceuticals	Reactor / Cyclotron Production	Chemical Synthesis	Purification stages	Processing, Formulation and Dispensing	Final or aseptic sterilization
Radionuclide generators	Reactor / Cyclotron Production	Processing			

The target and the transfer system from the cyclotron to the synthesis preparation can be considered as the first stages of the active substance manufacture.

The GMP principles to be followed in the chemical synthesis part, refer to the Mexican Official Standard NOM-164-SSA1-2015, Good Manufacturing Practices for Pharmaceuticals.

For processing, formulation and dispensation refer to section 12.5.1 and the provisions of this section.

12.14.1.4 The final manufacturer of the Radiopharmaceutical should describe and justify in a risk management the steps for the manufacture of the active substance and the final product in which GMPs apply at the specific process/manufacturing steps.

12.14.1.5 The preparation of radiopharmaceuticals implies compliance with the regulations applicable to radiation protection, the General Regulations on Radiation Safety, and other applicable provisions.

12.14.1.6 Radiopharmaceuticals administered parenterally shall comply with the sterility requirements for parenteral routes and, if applicable, with the aseptic working conditions for the manufacture of sterile formulations described in Section 12.5 of this Standard and with the provisions of the Critical Systems chapter of the FEUM.

12.14.1.7 Specifications and quality control test methods for the most commonly used radiopharmaceuticals are specified in the FEUM Medical Device Supplement or in the marketing authorization.

12.14.1.8 Clinical trials.

12.14.1.8.1 Radiopharmaceuticals intended for use in clinical trials in drug research must also be produced in accordance with the GMP principles of this Standard.

12.14.2 Quality Assurance.

12.14.2.1 Quality assurance is even more important in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and, in some circumstances, the need to distribute or administer the product before quality control testing for release and use is completed.

12.14.2.2 As with all pharmaceutical products, products should be well protected against contamination and cross-contamination. However, the environment and operators must also be protected against radiation. This means that the role of an effective quality assurance system is of paramount importance.

12.14.2.3 It is important that data generated from facility and process monitoring be recorded and evaluated as partof product release.

12.14.2.4 Risk management, focusing on a combination of GMP and radiation protection, should be performed to establish the scope of qualification/validation in the manufacture of radiopharmaceuticals.

12.14.3 Personnel.

12.14.3.1 All manufacturing operations should be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in the production, analytical control and release of

radiopharmaceuticals should be properly trained in radiopharmaceutical specific aspects of the Quality Management System. The authorized person must have full responsibility for the release of the products.

12.14.3.2 All personnel (including those related to cleaning and maintenance) employed in areas where radioactive products are manufactured shall receive additional training related to the handling of this class of products.

12.14.3.3 When production facilities are shared with research institutions, research personnel should be trained in GMP and quality control standards and should review and approve research activities to ensure that they do not presenta hazard to the manufacture of radiopharmaceuticals.

12.14.4 Facilities and equipment.

12.14.4.1 Radioactive products shall be manufactured in Controlled Areas (environmental and radioactive). All manufacturing steps shall be carried out in dedicated radiopharmaceutical and self-contained facilities.

12.14.4.2 Measures should be established and implemented to prevent cross-contamination by personnel, materials,radionuclides, etcetera. Contained or closed equipment should be the first choice when cross-contamination risks exist. Where open equipment is used or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the proposed level of environmental cleanliness is appropriate for the type of product being manufactured.

12.14.4.3 Access to the manufacturing areas shall be through an airlock and shall comply with clothing requirementsaccording to the cleanliness and radiological protection class. Access to these areas shall be restricted to unauthorized personnel.

12.14.4.4 Workstations and their environment shall be monitored for radioactivity, particulate matter and microbiological quality as required by the EC.

12.14.4.5 Preventive maintenance, calibration and qualification programs should be carried out to ensure that all facilities and equipment used in the manufacture of radiopharmaceuticals are adequate and qualified. These activities should be carried out by competent personnel and logbooks should be kept and properly safeguarded.

12.14.4.6 Precautions should be taken to avoid radioactive contamination within the facility. Controls should be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through routine smear testing.

12.14.4.7 The equipment should be constructed in such a way that the surfaces that come into contact with the product are not reactive, additive, or absorptive, in order not to alter the quality of the radiopharmaceutical.

12.14.4.8 Re-circulation of exhaust air from the area where radioactive products are handled should be avoided unlessjustified. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases andmeasures should be taken to protect controlled areas from microbial and particulate contamination.

12.14.4.9 In order to contain radioactive particles, it may be necessary for the air pressure where products are exposed to be lower compared to surrounding areas. However, it is still necessary to protect the product from environmental contamination. This can be achieved, for example, by using barrier technology or air locks, acting as pressure wells.

12.14.4.10 Sterile production.

12.14.4.10.1 Sterile radiopharmaceuticals can be divided into those that are aseptically manufactured, and those that are terminally sterilized. The facility should maintain the level of environmental cleanliness for the type of operation being performed. For the manufacture of sterile products, the work area where the products or containers may be exposed to the environment, the cleanliness requirements must comply with those described in paragraph 12.5 of this Standard.

12.14.4.10.2 For the manufacture of radiopharmaceuticals, a risk assessment may be applied to determine appropriatepressure differentials, air flow direction and air quality.

12.14.4.10.3 In the case of use of closed, automated systems (chemical synthesis, purification, in-line sterile filtration) a grade C environment will be appropriate (usually "radiation containment chambers"). Radiation containment chambersshould comply with a high degree of air cleanliness, with filtered feed air. Aseptic activities should be performed in a gradeA area.

12.14.4.10.4 Prior to the start of manufacturing, assembly of sterile and consumable equipment (tubes, sterile filtersand sealed and closed sterile vials in counter flow path) should be performed under aseptic conditions.

12.14.5 Documentation.

12.14.5.1 All documents related to the manufacture of radiopharmaceuticals shall be prepared, reviewed, approved, and distributed according to written procedures.

12.14.5.2 Specifications should be established and documented for raw materials, labeling and packaging materials, critical intermediates, and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as processing aids, gaskets, sterile filtration kits, that could have a critical impact on quality.

12.14.5.3 Acceptance criteria should be established for the radiopharmaceutical including release criteria, as well as

half-life specifications (examples: chemical identity of the radionuclide, radioactive concentration, purity, and specific activity).

12.14.5.4 Records of the main equipment used, cleaning, disinfection, sterilization, and maintenance shall show the name of the product and Batch Number, in addition to the date, time and signature of the persons involved in these activities.

12.14.5.5 Records shall be retained for at least 3 years.

12.14.6 Production.

12.14.6.1 The production of different radioactive products at the same time, and/or in the same work area, should beavoided to minimize the risk of cross-contamination or confusion.

12.14.6.2 Special attention should be given to validation, including validation of computer systems to be carried outin accordance with 10.14 of this Standard. New manufacturing processes should be validated prospectively.

12.14.6.3 Critical parameters shall be identified before or during validation and the necessary intervals shall be definedto ensure that the operation is reproducible.

12.14.6.4 Membrane filter integrity testing should be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.

12.14.6.5 Due to radiation exposure, it is acceptable that most of the labeling of the primary container be done prior to manufacture. Empty closed sterile vials may be marked with partial information prior to filling, provided that this procedure does not compromise sterility or prevent visual inspection of the filled vial.

12.14.7 Quality control.

12.14.7.1 Some radiopharmaceuticals may be released and used based on an evaluation of batch documentation, even if all chemical and microbiological tests have not been completed. Release of the radiopharmaceutical may be carriedout in two or more stages, before and after full analytical testing.

12.14.7.1.1 Evaluation of production records and analytical testing of the batch shall be reviewed by a person designated by the health officer prior to permitting transport of the radiopharmaceutical in quarantine status to the clinical department.

12.14.7.1.2 Evaluation of final analytical data, ensuring that all deviations from regular procedures are documented, justified, and properly released prior to documented certification by the sanitary officer. Where certain test results are not available prior to product use, the sanitary officer should conditionally certify the product prior to use and, finally, shouldcertify the product after all test results are obtained.

12.14.7.2 Most radiopharmaceuticals are for use within a short time and the period of validity with respect to the radioactive shelf life shall be clearly indicated.

12.14.7.3 Radiopharmaceuticals with radionuclides with long half-lives shall be tested to show that they meet all relevant acceptance criteria prior to release and certification by the authorized person.

12.14.7.4 Before testing is performed, samples may be stored to allow sufficient time for radioactivity to decay. All tests, including the sterility test, should be performed in a time frame determined by the quality unit that ensures that the samples do not pose a risk to personnel handling them.

12.14.7.5 A written procedure should be established detailing the evaluation of production and analytical data to be considered prior to batch release.

12.14.7.6 Products that do not meet the acceptance criteria shall be rejected. If the material is reprocessed, pre-established procedures should be followed, and the finished product should meet the acceptance criteria prior to release. Returned products should not be reprocessed and should be confined and treated as radioactive waste, taking into account the applicable nuclear regulations.

12.14.7.7 A procedure should also describe the actions to be taken by the authorized person (sanitary manager) if unsatisfactory (out-of-specification) results are obtained after the product has been dispensed and prior to expiration. Such events should be investigated to include relevant corrective and preventive actions taken to prevent future events. This process should be documented.

12.14.7.8 Information should be given to clinically responsible persons. To facilitate this, a traceability system shouldbe implemented for radiopharmaceuticals.

12.14.7.9 A system for verifying the quality of starting materials shall be in place at the site. Supplier approval should include an evaluation that provides assurance that the material consistently meets specifications. Starting materials, packaging materials and critical process aids should be purchased from suppliers previously approved by the quality unit.

12.14.8 Reference and Retention Samples.

12.14.8.1 Sufficient samples of the bulk formulated product (non-radioactive pharmaceutical formulation,

containingthe chemical reagents necessary for the preparation of radiopharmaceuticals) should be retained for at least six months after the expiration of the finished product unless otherwise justified through risk management.

12.14.8.2 Samples of starting materials other than gases, solvents or water used in the manufacturing process shall be retained for at least two years after the release of the radiopharmaceutical; this period may be shorter if the stability period of the material indicated in its specification is shorter.

12.14.9 Distribution.

12.14.9.1 Distribution of finished product should be carried out under controlled conditions to ensure product qualityand to avoid any type of contamination.

12.14.9.2 Before all relevant test results are available, receipt of the radiopharmaceuticals by the receiving unit (such as hospital, clinic and/or radio pharmacy) is acceptable provided that the product is not administered until such results are satisfactory and have been received and evaluated by the health officer.

12.15 *Remanufacturing* and Refurbishment/Rehabilitation

12.15.1 Medical device *remanufacturing* and *refurbishment/rehabilitation* activities shall be carried out in areas specific to these processes.

12.15.1.1 They should have procedures that establish the activities and criteria for the reception of medical devices, as well as the formats for recording these activities.

12.15.1.2 They shall have formats for reviewing and recording the activities carried out on medical devices in order tomaintain traceability.

12.15.1.3 For *remanufacturing* and *refurbishing* activities, they shall ensure that the parts or systems replaced are ofthe same type or specification as stated in the previously authorized condition.

12.15.1.4 *Remanufacturing* and Refurbishment/Rehabilitation shall be performed by the manufacturer or by an establishment approved by the manufacturer.

12.15.1.4.1 The approval of the alternate establishment to carry out such activities must be established in writing; thisestablishment shall comply with the requirements set forth in this Standard.

12.16 The holder of the sanitary registration, distributors and persons designated by the manufacturer may carry outrepair activities, these activities must be carried out in specific areas, separate from the distribution area, and must be carried out following the processes, procedures and records implemented for such purpose.

12.17 Compatibility of turns.

12.17.1 Authorization must be requested to the Ministry of Health for the shared use of facilities and equipment for the manufacture of medical devices, following the requirements established in this Standard; and presenting the corresponding risk management.

12.17.2 The shared use of facilities and equipment for the manufacture of classified products with other businesses shall be evaluated by the Secretariat of Health on a case-by-case basis, at the request of the interested party.

13. Quality control laboratory

13.1 General.

The quality control function comprises the organization, documentation, and procedures to ensure that GLP-compliant testing is carried out in accordance with current methods and specifications, so that inputs and outputs are not released for use or sale until their quality has been assessed.

13.2 Each manufacturer shall have a quality control laboratory independent from the Production Area and under the authority of a qualified person, with academic background and experience verifiable through his/her curriculum vitae.

13.3 The control laboratory areas must meet the requirements established in Section 10.2.4 of this Standard.

13.4 The personnel, areas and equipment used in the quality control laboratory shall be qualified, as indicated in 9.2.

13.5 There should be standardized procedures for cleaning, maintenance, and operation of laboratory areas, measuring instruments and equipment with appropriate records.

13.6 They shall have a calibration program for measuring instruments used in the laboratory.

13.7 In the case of pharmacopeial methods, system suitability studies must be carried out.

13.8 They should have specifications, sampling procedures, test procedures and records, analytical or conformity certificates and records of environmental monitoring.

13.9 Laboratory documentation must comply with the provisions of paragraph 6.2 of this Standard.

13.10 Sample containers should have an identification indicating at least: the name and/or description of the input, the Lot Number, the date of sampling, the storage conditions, and the containers from which the samples have been taken.

13.11 Retention samples of each finished product Lot must be kept at least one year after the expiration date of the Medical Device, in its final packaging and stored under the conditions indicated on the label, according to the provisions of Chapter 7.

13.12 Retention samples of raw materials should be retained for at least one year after the expiry of the last batch of product in which it was used and stored according to the conditions indicated on the label, in accordance with the provisions of Chapter 7.

13.13 Holding samples of solvents, gases and water used in the manufacture of medical devices shall not be retained.

13.14 When the primary or secondary packaging site declared in the sanitary registration is different from the medical device manufacturing site, the packaging sites shall keep retention samples of the materials used in accordance with Chapter 7.

13.15 Records of test results shall include at least the following data:

13.15.1 Name and/or description of the product, presentation and, when applicable, concentration.

13.15.2 Lot/Serial Number.

13.15.3 Name of manufacturer or supplier.

13.15.4 References to specifications and analytical methods.

13.15.5 Test results, including observations, calculations, equipment output printouts.

13.15.6 When the test is performed by an authorized external laboratory, reference should be made to the original Certificate of Analysis.

13.15.7 The date on which the tests are to be carried out.

13.15.8 The initials or names of the persons who performed the tests.

13.15.9 The initials or names of the persons reviewing the data and/or calculations.

13.16 There should be procedures describing the handling and storage of reagents, solutions, strains, and culturemedia used in the laboratory.

13.17 Reagent solutions and culture media shall be prepared in accordance with FEUM and applicable supplements.

13.17.1 In the absence of a pharmacopeial reference, a method validated by the manufacturer may be used.

13.18 The expiration date of reagents and culture media should be indicated on the label along with the storage conditions. For volumetric solutions, the date of titration, actual concentration and the initials of the person who prepared it should be indicated.

13.19 Primary and secondary reference substances should be dated, stored, handled, and used in a manner that doesnot affect their quality. At least the following should be recorded: origin, lot and identification and expiration date.

13.20 When animals are used for laboratory testing in the analysis of raw materials or products, they shall be purchased from qualified suppliers as indicated in 6.6.4.2.2.2 and quarantined prior to use.

13.20.1 They shall be maintained and controlled in a manner that ensures their suitability for their intended use.

13.20.2 They shall be identified upon receipt, and records shall be kept of their receipt, history of use and final disposal.

13.21 All in-process control tests shall be performed in accordance with methods approved by the quality unit.

13.21.1 All in-process control tests shall be performed at the manufacturing site.

13.22 There should be a procedure indicating the actions to be taken in the case of out-of-specification or out-of-trend analytical results.

13.22.1 The analysis of the same sample should not be repeated when any of the results is out of specification without first having carried out the corresponding investigation, and neither can they be averaged when one of them is out of specification.

13.22.2 The procedure for analytical results out of specification must contemplate at least the following:

13.22.2.1 Verification of results to rule out clearly identified analytical errors, this investigation should be documented and reported.

13.22.2.2 If an analytical error is ruled out, it must be justified as part of the investigation.

13.22.2.2.1 An investigation shall be initiated involving all Areas related to the Manufacture of the product, and a test plan shall be established considering repeat sampling or re-analysis of Samples to confirm the result.

13.22.2.3 The evaluation and interpretation of the results obtained shall be established considering all the findings of the investigation, re-analysis, or re-sampling to determine the acceptance or rejection of the investigated Lot.

13.22.3 Investigations and conclusions of out-of-specification analytical results must be approved by the sanitary officer.

13.23 The use of external quality control laboratories must comply with the provisions of Chapter 17 of this Standard and may be accepted for special causes but must be reflected in the quality control records.

13.24 Sampling should be performed and recorded in accordance with written procedures approved by the health officer, describing:

13.24.1 Sampling method.

13.24.2 Equipment and/or utensils to be used.

13.24.3 The amount of sample to be taken.

13.24.4 Instructions for possible subdivision of the sample.

13.24.5 Type and conditions of the container to be used for the sample.

13.24.6 Identification of sampled containers.

13.24.7 Any special precautions to be taken, particularly in relation to sampling of sterile or harmful materials.

13.24.8 Storage conditions.

13.24.9 Instructions for cleaning and storage of sampling equipment.

13.25 Upon authorization by the Secretariat of Health, the holder of a Sanitary Registration may carry out a reduction in the frequency and/or in the analytical tests for Inputs for the manufacture of Medical Devices.

13.25.1 For the analytical reduction of Supplies, the Holder of the Sanitary Registration of the manufactured Medical Device shall submit to the Secretariat of Health the following information:

13.25.1.1 The Annual Product Report for 3 years prior to the application.

13.26.1.2 That there are no major changes in the manufacturing process of the medical device.

13.25.1.1 Copy of the current Health Registration Office of the Medical Device in which the Input is used.

13.25.1.2 Current GMP certificate of the applicant's manufacturing site.

13.25.1.3 Qualification report of the manufacturer and supplier(s) involved in the supply chain.

13.25.1.4 Risk assessment containing the technical and scientific justification supporting the request for frequency and analytical tests to be reduced.

13.25.1.5 Statistical study performed between the results obtained by the manufacturer of the Input and those obtained at the Medical Device Manufacturing site, with a minimum of 20 consecutive Batches of the Input used in the Manufacture of the Medical Device, to demonstrate that there is no statistically significant difference. Analytical certificates supporting the study batches should be included.

13.26 Transfer of analytical methods.

13.26.1 Prior to transferring an analytical method, the transferring laboratory should verify that the analytical methods comply with those reported in the corresponding technical dossier.

Only previously validated methods can be transferred.

13.26.2 Any modifications to the original validation that were made prior to initiating the transfer process shall be documented and evaluated.

13.26.3 Types of analytical method transfer, including:

13.26.3.1 From the analytical development unit to the quality control laboratory.

13.26.3.2 From the development unit or quality control laboratory of a foreign plant to a subsidiary in Mexico or to an authorized third party.

13.26.3.3 From the manufacturer to a maquiladora.

13.26.4 The following factors should be considered for an analytical transfer:

13.26.4.1 The receiving unit must have qualified facilities, equipment, instruments, and personnel, as indicated in 9.2,for the methods to be transferred.

13.26.4.2 Protocols and analytical methodologies of the methods to be transferred must be available.

13.26.4.3 The transfer protocol must include, at least:

13.26.4.3.1 Description of the test to be performed and the relevant analytical methods to be transferred.

13.26.4.3.2 Identification of any additional requirements.

13.26.4.3.3 Identification of reference standards and samples to be analyzed;

13.26.4.3.4 Description and identification of any special transport and preservation conditions of the products, standards, and reagents to be used.

13.26.4.3.5 Acceptance criteria, which should be based on the validation study of the analytical methodology.

13.27 When animals are used in laboratory tests and have a biotheriums, they must comply with the provisions of theOfficial Mexican Standard mentioned in paragraph 2.10 of the Normative References chapter of this Standard.

14. Release of finished product

14.1 Release of Imported Medical Devices.

14.1.1 The health officer shall determine the release of Medical Devices.

14.1.2 There should be a procedure for the inspection of imported medical devices and a record of such activity should be made.

14.1.3 The medical device inspection shall include at least: review of the analytical certificate and/or certificate of conformity, physical review of the condition of the product, the number of samples to be evaluated shall be determined based on statistical criteria.

14.1.4 Each facility shall define, in accordance with its Quality Management System, how documentation shall be handled, and the minimum requirement is established in this section.

14.1.5 For the release of condoms, in addition to the above items, the following must be complied with:

14.1.5.1 Perform the analysis in the country for each imported Lot according to the provisions of the FEUM, these analyses may be performed in the importer's quality control laboratory or with an authorized third-party laboratory.

14.1.5.2 Submit a report every six months or every 30 batches, whichever comes first to the Ministry of Health containing the analytical certificates of origin, copy of the results of the analysis performed in the country, comparative statistical study, and trends, copy of the current sanitary registration, simple copy of the current GMP certificate or its equivalent from the manufacturer of the medical device.

14.1.6 Retention samples shall be kept at the manufacturer's facilities.

14.2 Release of Medical Devices of national manufacture.

14.2.1 The health officer or the person authorized by the health officer who determines the release of the medical devices shall have the academic training, knowledge, and experience according to the provisions of subsection 9.1.3.

14.2.2 There shall be a procedure describing the batch file review and product release process.

14.2.3 The validation of the cold chain does not exempt the routine monitoring that must be carried out to guarantee the conditions required by the product, it should be noted that this only applies to certain types of DM and not to all.

14.2.4 In addition to the Lot file, the following must be taken into consideration as a minimum:

14.2.4.1 The change control system to check that there are no open changes that impact the Lot to be released.

14.2.4.2 The results of the Environmental Monitoring Program to review that they do not impact the lot to be released, in accordance with Chapter 12.

14.2.4.3 That the corresponding retention samples have been taken.

14.2.4.4 Any other documents related to product quality, including deviation or nonconformancereports.

14.3 For products requiring cold chain maintenance, there should be evidence of temperature monitoring during transportation from the manufacturing site to the distribution site. Excursions should be investigated and evaluated.

14.3.1 Lot Release should consider cold chain compliance review.

15. Stability studies

15.1 General considerations.

15.1.1 Stability or aging studies should be performed for those medical devices that, due to their characteristics and purpose of use, require an expiration date and should be demonstrated by the manufacturer through scientific evidence that supports the expiration date or shelf life assigned to them. These studies make it possible to assign/confirm the periods, number of sterilization cycles, bulk storage times during the process, establish the storage and transport conditions, based on risk management, as well as guarantee the container-closure system.

15.1.2 Stability studies for formulated medical devices containing a drug must be performed according to the Mexican Official Standard mentioned in paragraph 2.11 of this Standard; in the case of formulated medical devices not containing a drug, they must be performed according to the FEUM or applicable international guidelines.

15.1.3 When stability or accelerated aging studies are carried out to demonstrate the expiration date or tentative shelf life, they should be performed on representative samples of the production process in the primary container proposed for storage and distribution, under extreme storage conditions, in a minimum of three batches.

15.1.4 Real-time (long-term) stability or aging studies shall be carried out on representative samples of the production process in the primary container or package proposed for storage and distribution under the conditions established by the manufacturer, in a minimum of three batches.

15.1.5 The manufacturer shall consider all evaluation parameters that correspond to the type of product to ensure that the medical device is stable/functional during its useful life.

15.1.6 Written protocols specifying how the study will be conducted should contain at least the following information:

15.1.6.1 Name and/or description of the Medical Device, as well as presentation and concentration.

15.1.6.2 Lot number and size, or serial number.

15.1.6.3 Description and composition of the primary container or packaging.

15.1.6.4 Storage conditions (temperature, % RH, light, etc.) of the study.

15.1.6.5 Sampling and analysis times.

15.1.6.6 Test Parameters.

15.1.6.7 Acceptance criteria or specifications.

15.1.6.8 Reference of analytical or test methods by parameter and their validation.

15.1.7 There shall be written reports that demonstrate traceability with the corresponding protocol and shall include:

15.1.7.1 Results obtained by storage condition and date of analysis.

15.1.7.2 Statistical methods and formulas used.

15.1.7.3 Observed deviations.

15.1.7.4 Statistical evaluation of data; include graphs.

15.1.7.5 Results of statistical analysis and conclusions.

15.2 Real time (long term) stability or aging studies of the lots submitted in the registration dossier must be the same until the requested shelf life is covered.

15.2.1 The shelf life or tentative expiration date should be confirmed with stability or real time (long term) aging studies.

15.3 An annual stabilities program should be implemented based on statistical criteria that considers the number of manufactured batches to guarantee the expiration period of the medical device, which should be endorsed or authorized by the sanitary responsible.

15.4 Batches manufactured for Stability Studies shall be subject to standard production procedures.

15.5 When a Batch of products is reprocessed or reworked it must be subjected to Stability Studies.

15.6 The stability of the medical device should be confirmed with at least three batches of product, when available:

15.6.1 A change of additives or excipients and that does not impact the condition of registration.

15.6.2 A change in the analytical or test method during the Stability Study, previously demonstrating the equivalenceof the methods.

15.6.3 A change in the Primary Packaging, according to the characteristics and risk of the product.

15.7 Stability Studies may be extended to those products belonging to the same family, provided that the composition, formulation, container or packaging, or characteristics are the same in all cases.

16. Recall of product from the market

16.1 There should be a system for timely and effective withdrawal of products from the market and for products known or suspected to be out of specification or where their safety, quality and efficacy are compromised, which should be notified to the Ministry of Health through COFEPRIS.

16.2 There must be a SOP that describes:

16.2.1 That the sanitary manager is in charge of coordinating the product recall and its execution.

16.2.2 Product recall activities, allowing them to be initiated quickly at all levels.

16.2.3 Storage instructions for the recalled product.

16.2.4 Notification to health authorities in accordance with applicable regulations.

16.2.5 Review of product distribution records that allow for effective product recall.

16.2.6 Continuous verification of the withdrawal process.

16.2.7 The final report shall include a reconciliation between the amount distributed and the amount recovered, the actions to be taken to avoid recurrence, the final destination of the product and the corresponding conclusion.

17. Subcontracted activities

Fundamentals.

Any activity included in this Standard that is subcontracted must be defined, agreed upon and controlled to avoid inaccuracies that could result in an unsatisfactory product or operation.

It must be formalized in a written contract between the contracting agent and the contracted agent that clearly establishes the responsibilities of each party.

The contracting agent's Quality Management System must clearly reflect the way in which the health manager, or person authorizing the release of each batch of product, contemplates the subcontracted activities in his/her responsibility.

17.1 General.

17.1.1 A written contract shall be drawn up covering the subcontracted activities, the related products or operations and any related Technical Agreements.

17.1.2 All agreements for subcontracted activities, including any proposed technical or other modifications, must be in accordance with the applicable provisions and with the conditions authorized in the sanitary registration of the product in question.

17.1.3 When the Health Registration Holder and the manufacturer are not the same, agreements should be in place that take into account the principles described in this chapter.

17.2 Contracting Agent.

17.2.1 The contractor's Quality Management System shall include the control and review of any subcontracted activities and shall consider the principles of risk management.

17.2.2 The following is the responsibility of the Contracting Party:

17.2.2.1 Evaluate the legality, suitability, and competence of the contracted party to successfully carry out the subcontracted activities; as well as ensure through the contract that the principles and guidelines of this Standard are followed.

17.2.2.2 If external laboratories are used, they must be authorized as authorized third-party laboratories, issued by the Health Authority.

17.2.3 The contracting party must provide the contracted party with all the information and knowledge necessary to perform the contracted operations correctly in accordance with the applicable provisions and with the conditions authorized in the sanitary registration of the product in question.

17.2.4 The contractor shall monitor and review the employee's performance and the identification, implementation and control of any improvements made.

17.2.5 The contractor shall be responsible for the review and evaluation of records and results related to subcontracted activities.

17.3 Contracted agent.

17.3.1 The contractor must be capable of satisfactorily performing the work commissioned by the principal, having Facilities, equipment, knowledge, experience, and competent personnel.

17.3.2 The contractor shall ensure that all products, materials, and information delivered to it are fit for their intendedpurpose.

17.3.3 The contractor shall not subcontract to a third party any part of the work entrusted to it in respect of the contract without prior assessment and approval by the principal. Agreements entered into between the contractor and any third party shall ensure that information and knowledge, including that of the assessment of the suitability of the third party, is available in the same manner as it is between the original principal and the contractor.

17.3.4 The contracted party shall not make changes without the authorization of the contracting agent, outside the terms of the contract, that may adversely affect the quality of the activities subcontracted by the principal.

17.3.5 Subcontracted activities, including contract review, may be subject to Inspection by the competent authorities.

17.4 Contract.

17.4.1 A contract should be drawn up between the contractor and the subcontractor specifying their respective

responsibilities and forms of communication in relation to the subcontracted activities. The technical aspects of the contract should be drawn up by competent persons with adequate knowledge of the subcontracted activities and GMP. All agreements for subcontracted activities should be in accordance with current regulations and the conditions authorized in the sanitary registration of the product in question and be approved by both parties, both by the legal representative and the sanitary responsible.

17.4.2 The contract shall clearly describe who assumes responsibility for each stage of the outsourced activity, such as: knowledge management, technology transfer, supply chain, subcontracting, materials quality and procurement, materials analysis and release, production responsibility and quality controls (including in-process controls, sampling, andanalysis).

17.4.3 The contractor shall keep or have available all records related to subcontracted activities, such as: production, analysis, and distribution records, as well as reference samples. Any data important for assessing the quality of a product in case of complaints or suspected defects, or for investigating suspected counterfeit product, shall be accessible and specified in the contractor's procedures.

17.4.4 The contract shall allow the principal to audit the subcontracted activities, either by the contractor or by mutually agreed subcontractors.

17.5 Subcontracted Services.

17.5.1 All contractors for medical device manufacturing process services such as analytical laboratory services, Critical Systems services, and equipment that impact product quality shall be evaluated and qualified as suppliers.

17.5.2 There should be a procedure that describes the criteria for evaluating contractors prior to approval by the contracting agent's quality unit.

17.5.3 The Contractor shall not subcontract medical device manufacturing process toll manufacturing services or analytical laboratory services.

17.6 Maquilas.

17.6.1 When it is required to machine a process, the corresponding maquila notice must be submitted to COFEPRIS, attaching at least the following:

17.6.1.1 Notice of operation of the maquiladora establishment.

17.6.1.2 Technology Transfer.

17.6.1.3 Validation of the process to be carried out.

17.6.2 The maquiladoras of medical device manufacturing processes are obliged to comply with this Standard and with the other applicable provisions.

17.6.3 The manufacturer must ensure the transfer of technology to the contractor, which must be attached to the maquila notice to be submitted to COFEPRIS.

17.6.3.1 Medical device sterilization process assembly plants are required to have a current good manufacturing practices certification, which must be attached to the assembly plant notice.

17.6.3.2 The sterilization processes should be validated at the facilities of the assembly plant.

17.6.3.3 The quality of the medical device is the responsibility of the holder of the sanitary registration.

17.6.4 The stages to be machined shall be validated at the Maquiladora's facilities.

17.6.5 Product quality shall be the responsibility of the Sanitary Registration Holder.

17.6.6 The Health Registration Holder or manufacturer of the device must supervise the manufacture of the device and audit the operations of the maquiladora as described in the applicable regulations.

17.6.7 The maquiladora must deliver the maquiladora product to the Sanitary Registration Holder, together with the original documentation of the maquiladora stages including the Records of In-Process Controls. The maquiladora must keep a copy of this documentation for the time indicated in section 6.2.3.2 of this Standard.

17.6.8 It is the responsibility of the Sanitary Registration Holder to ensure that the complete analysis is carried out for the release of the finished product.

17.6.9 The Sanitary Registration Holder must guarantee that the product to be manufactured will be manufactured under the same conditions in which the sanitary registration was granted.

17.7 Analytical laboratory services.

17.7.1 The Sanitary Registrant must ensure the analytical transfer to the contracted laboratory.

17.7.2 A system for the transfer of samples shall be established to ensure the integrity of the samples.

17.8 Critical Systems and Equipment Services.

17.8.1 The facility shall evaluate the academic background, technical training and experience of the personnel providing this type of service.

18. Final destination of waste

18.1 A system documented in an SOP must be in place to ensure compliance with applicable environmental and sanitary regulations for the final destination of polluting and/or hazardous waste, notifying the corresponding authorities.

19. Good Storage and Distribution Practices

This chapter applies to medical device warehouses and distribution warehouses.

19.1 General.

19.1.1 Medical device distribution is the set of activities of procurement, storage, transportation, supply and, where appropriate, marketing of medical devices and is important in the overall management of the supply chain. Today's medical device distribution network is increasingly complex. Having BPAD in place assists distributors in performing their activities, prevents counterfeit medical devices from entering the supply chain, ensures control of the distribution chain and maintains the quality, safety, and integrity of medical devices.

19.2 Quality Management System.

19.2.1 Distributors shall maintain a Quality Management System that establishes the organizational structure, responsibilities, and processes in relation to their activities, for which they shall consider the following:

19.2.1.1 Quality Manual.

19.2.1.2 Audit System.

19.2.1.3 Complaint Management.

19.2.1.4 Handling of out-of-specification or nonconforming product.

19.2.1.5 Deviation Management and CAPA system.

19.2.1.6 Withdrawal of product.

19.2.1.7 Change Control.

19.2.1.8 PMV.

19.2.1.9 Risk Management.

19.2.1.10 Document Control.

19.2.1.11 Returns.

19.2.2 The size, structure and complexity of the distributor's activities shall be taken into account when designing or modifying the Quality Management System.

19.2.3 All distribution activities shall be clearly defined in procedures and systematically reviewed.

19.2.3.1 Import and export activities must be carried out in accordance with the applicable provisions.

19.2.4 All critical stages of the storage and distribution processes, significant changes and, where applicable, validation shall be identified, controlled, and documented.

19.2.5 The Quality Management System shall ensure that:

19.2.5.1 Medical Devices are procured, held, supplied, exported, or imported in accordance with the requirements ofthe BPADs described in this chapter.

19.2.5.2 Products are delivered to their recipients ensuring their quality and preservation conditions.

19.2.5.3 Records shall be kept in accordance with paragraph 6.2.4.

19.2.5.4 Deviations from documented procedures are documented and investigated.

19.2.5.5 Corrective and Preventive Actions (CAPA) are taken to correct and prevent Deviations in accordance with risk management principles.

19.2.6 Complaints.

19.2.6.1 There shall be a procedure for handling complaints, which shall include:

19.2.6.1.1 One person responsible for complaint handling.

19.2.6.1.2 Mandatory attention and documentation of all complaints.

19.2.6.1.3 The research process including the impact on product quality, safety, and efficacy/functionality.

19.2.6.1.4 Definition of the CAPAs to be carried out with respect to the problem.

19.2.6.1.5 The manner and time of response to the client.

19.2.6.2 Perform classification of complaints; pointing out those related to the quality of the medical device and those related to distribution.

19.2.6.3 Complaints related to Medical Device Quality and/or a possible product defect should be reported to the manufacturer and/or Sanitary Registration Holder.

19.2.6.4 The cases that are required to be notified to the health authority and how to do so, in accordance with the applicable regulations.

19.2.6.5 Complaint records should at a minimum have the following:

19.2.6.5.1 Medical device name, presentation, Lot/Serial Number, and date of receipt.

19.2.6.5.2 Quantity involved.

19.2.6.5.3 Reason.

19.2.6.5.4 Name and address of the person generating it.

19.2.6.5.5 Result of the investigation.

19.2.6.5.6 Actions taken.

19.2.6.6 A review of complaints should be conducted on a periodic basis, based on a risk assessment, to identify increasing trends in specific or recurring problems and take appropriate action.

19.2.7 Returns.

19.2.7.1 There should be a procedure for the control of returned products, indicating:

19.2.7.1.1 To be placed in temporary holding/quarantine and evaluated by the quality unit to determine if they should be released or destroyed.

19.2.7.1.2 Specific storage requirements.

19.2.7.1.3 Receipt, identification, evaluation, and destination records.

19.2.7.2 They shall have a report of the returned product which shall indicate at least the following:

19.2.7.2.1 Product name, presentation, Lot/Serial Number and Expiration Date.

19.2.7.2.2 Date of return, amount returned.

19.2.7.2.3 Time elapsed since the Medical Device in question was originally shipped.

19.2.7.2.4 Date and reason for return.

19.2.7.2.5 Name and address of returning party.

19.2.7.2.6 Inspection of returned product for integrity, safety, quality, based on risk management should include description of the distribution route, conditions of transfer of the returned product, decision, and final destination of the product.

19.2.7.3 Recovery of returned product is not permitted if, during inspection of the condition of the container, cartons or boxes, or labeling text, the integrity, safety, identity, concentration, quality, or purity of the product is compromised.

19.2.7.3.1 Stolen products that have been recovered cannot be returned to saleable stock.

19.2.8 Withdrawal of product.

19.2.8.1 Product withdrawal shall be carried out in accordance with Chapter 16 of this Standard.

19.2.9 Audits.

19.2.9.1 Audits shall be carried out according to a program, which are classified as follows: Internal Audits (self-inspections) and Supplier Audits.

19.2.9.2 There must be procedures that establish the process for the execution of an audit that contains at least:

19.2.9.2.1 The scope of each type of Audit.

19.2.9.2.2 The qualification of the audit group including:

19.2.9.2.2.1 Experience, training, skills, availability, and independence of the Audited Area.

19.2.9.2.3 Execution process: planning, responsibilities, requirements, records, and reporting.

19.2.9.2.4 Frequency for each type of audit.

19.2.9.3 Internal audits (self-inspections).

19.2.9.3.1 A self-inspection system shall be in place to evaluate the implementation and application of the BPADs and propose the necessary corrective actions.

19.2.9.3.2 Self-inspection audits shall be conducted by personnel independent of the audited area. They may also be conducted by external personnel.

19.2.9.3.3 All self-inspections shall be recorded. Reports shall include all observations made during Inspections and, where appropriate, proposals for Corrective and/or Preventive Actions shall be recorded in the facility's CAPA system.

19.2.9.3.4 The results of self-inspections shall be communicated to the personnel involved.

19.2.9.4 Supplier audits.

19.2.9.4.1 Facilities shall determine based on a risk assessment those suppliers of Supplies/Services that have an impact on the quality, safety, and efficacy/functionality of Medical Devices.

19.2.9.4.2 There shall be a procedure for the execution of audits for input suppliers, and subcontracted activities or technical agreements.

19.2.9.4.3 There shall be a periodic audit program, as well as documentary evidence to demonstrate compliance.

19.2.9.4.4 The periodicity of supplier audits shall be established based on the level of risk in the input or service provided, the impact and on previous qualification reports.

19.2.9.4.5 Supplier audit reports shall be part of the supplier qualification file.

19.2.10 Management shall have a formal process to review, at least annually, the Quality Management System. The review shall include:

19.2.10.1 Measurement of compliance with the objectives of the Quality Management System.

19.2.10.2 Evaluation of Quality Management System performance indicators, such as complaints, product recalls, returns, deviations, CAPA, process changes, feedback on contracted activities, technical agreements, audits, and risk management.

19.2.10.3 Standards, guidelines, and quality issues that arise and may impact the Quality Management System.

19.2.10.4 Innovations that may improve the Quality Management System.

19.2.10.5 Changes in target and business environment.

19.2.11 The outcome of each Quality Management System review shall be documented in a timely manner and effectively communicated internally.

19.3 Risk management.

19.3.1 Risk management is a systematic process and shall be carried out in accordance with Chapter 7 of this Standard.

19.4 Personnel.

19.4.1 According to the size of the establishment and the activities carried out, it shall have the number of qualified personnel, as indicated in subsection 9.2.

19.4.2 There shall be a personnel profile and job description that defines the requirements to be met by personnel and their responsibilities.

19.4.3 The owner of the establishment or legal representative shall designate a sanitary manager in accordance with paragraphs 9.1.3 and 9.1.3.1 of this Standard and the provisions of the Supplement for establishments dedicated to the sale and supply of medicines and other health inputs of the FEUM, as well as provide adequate resources and assign the necessary responsibility for the fulfillment of their functions.

19.4.4 The sanitary officer may delegate the functions in accordance with 9.1.3 in his/her absence to ensure activities under the BPADs.

19.4.5 The health officer shall, among other things:

19.4.5.1 Ensure that the Quality Management System is implemented and maintained.

19.4.5.2 Ensure that initial and ongoing training programs are implemented and maintained.

19.4.5.3 Coordinate product withdrawal operations, in accordance with the procedure.

19.4.5.4 Ensure that customer complaints or grievances are addressed.

19.4.5.5 Ensure that suppliers are approved and that warehouses and/or pharmacies have a notice of operation and a health officer's notice.

19.4.5.6 Approve all subcontracted activities that may have an impact on BPADs.

19.4.5.7 Ensure that internal audits are conducted according to a pre-established program and that the necessary

corrective actions are taken.

19.4.5.8 Maintain records of any activities delegated in accordance with subsection 9.1.3 of this Standard.

19.4.5.9 Decide jointly with the Sanitary Registration Holder on the final destination of returned, rejected, withdrawn or counterfeit products in accordance with the provisions of the Quality Manual and procedures or in the case of subcontracted services, in accordance with the provisions of the applicable legal framework, with the applicable quality and distribution contracts, technical agreements and/or equivalent documents.

19.4.5.10 Ensure compliance with any additional requirements according to medical device characteristics or classification.

19.4.6 Personnel that impact product quality shall receive initial and ongoing training according to their role, based on written procedures and in accordance with a documented training program. All personnel shall ensure competency in GHPPs through ongoing training.

19.4.7 Training should include aspects such as product identification to detect counterfeit medical devices from entering the supply chain.

19.4.8 Personnel handling products requiring more stringent conditions should receive specific training, such as temperature sensitive and sterile products.

19.4.9 Training Records shall be kept.

19.4.10 Personal hygiene and safety procedures shall be established for the activities being carried out, covering health, hygiene, and clothing.

19.5 Facilities and equipment.

19.5.1 Distributors shall have buildings, facilities, and equipment to ensure the storage and distribution of medical devices. The facilities shall be clean, dry, and maintained within the temperature and humidity ranges in accordance withthe conditions authorized in the sanitary registrations and/or labels of the Medical Devices.

19.5.2 Facilities.

19.5.2.1 Facilities shall be designed to ensure that the storage conditions required for the preservation of medical devices are maintained.

19.5.2.2 They shall be secure, structurally sound and of sufficient capacity in accordance with the quantity of products, to allow for the safe storage and handling of medical devices.

19.5.2.3 They shall have areas for the reception, storage, and shipment of medical devices.

19.5.2.4 When performing counter-labeling activities, they must have a specific, identified, and delimited area for thisactivity.

19.5.2.5 They shall be designed and equipped in such a way as to prevent the entry of insects, rodents, or other animals.

19.5.2.5.1 A preventive pest control program shall be in place.

19.5.2.5.1.1 The authorized pest control service provider shall have a current sanitary license.

19.5.2.5.2 Pest control records shall be kept.

19.5.2.6 Buildings and Storage Areas shall be clean and free of trash and dust.

19.5.2.6.1 There shall be a procedure for cleaning, including a cleaning schedule, instructions, and records.

19.5.2.6.2 Equipment and cleaning agents that are not a source of contamination should be chosen and used.

19.5.2.7 They must have a potable water supply for personnel needs.

19.5.2.8 The electrical installation must be protected and identified to avoid the risk of accidents.

19.5.2.9 Rest or dining rooms and workers' toilets should be separate from storage areas.

19.5.2.10 Maintenance activities should be carried out at the Facilities under a program to maintain storage conditions.

19.5.2.11 Food, beverages, and tobacco shall be prohibited in the Storage Areas.

19.5.2.12 Storage Areas shall be equipped with lighting and ventilation to allow all operations to be carried out accurately and safely.

19.5.2.12.1 The furniture used for storage should be made of material resistant to cleaning agents and should be placed in such a way as to facilitate cleaning.

19.5.2.13 Access shall be restricted to authorized personnel, by means of a control established in the corresponding procedure. Visitors must be accompanied at all times by authorized personnel.

19.5.2.14 Medical devices should be stored in clearly identified areas. Any electronic inventory control system should be validated.

19.5.2.15 Receiving and shipping areas should protect products from the weather and be properly equipped to maintain the conditions required for the review (inspection) process.

19.5.2.15.1 They shall have pallets, easy to move, clean and avoid harmful fauna.

19.5.2.16 There shall be a separation between receiving, shipping and storage areas.

19.5.2.17 Products awaiting a decision as to their disposition or products that have been returned shall be segregated either physically or through an equivalent electronic system.

19.5.2.18 Counterfeit, expired, recalled, rejected medical devices shall be identified, physically separated and in segregated areas.

19.5.2.19 Products that present a special safety risk of fire or explosion must be stored in one or more special areas subject to the safety and protection measures indicated in accordance with subsection 2.3 of the Normative References chapter of this Standard.

19.5.2.20 They must have a design that allows monitoring and control of temperature and RH through natural ventilation or air conditioning systems.

19.5.2.21 They shall have calibrated instruments to monitor and record temperature and RH conditions, according to the conditions required by the device.

19.5.2.21.1 They shall have a calibration program for the instruments used.

19.5.2.22 Initial temperature and RH mapping should be carried out in the storage area prior to use, under representative conditions, to determine the points of greatest fluctuation and to place temperature and RH monitors at these points.

19.5.2.22.1 If the results of temperature and RH mapping show that the conditions in the storage area do not meet the authorized storage requirements for Medical Devices, temperature control measures should be implemented which may include the placement of air conditioning.

19.5.2.22.2 The mapping exercise should be repeated when there are modifications that impact product storage conditions or environmental condition monitoring equipment.

19.5.2.23 When the Facilities are not directly operated by the distributor, a written contract must be established, in accordance with the provisions of Section 17.5 of this Standard.

19.5.3 Equipment.

19.5.3.1 Equipment used for the storage and distribution of medical devices shall be designed, placed, and maintainedin a condition that ensures the purposes for which it was intended.

19.5.3.2 They shall have an alternative electric power plant or service to maintain the operation of refrigeration chambers, freezers, or air conditioning systems, during contingencies to guarantee the conservation of the medical devices.

19.5.3.3 They shall have equipment for the storage of medical devices that require a specific temperature condition, such as refrigeration and freezing.

19.5.3.3.1 They shall have an alarm system to indicate any excursion of the storage conditions required for the conservation of the Medical Devices.

19.5.3.4 Equipment maintenance activities should be carried out under a program in order to maintain the required conditions for the preservation of medical devices.

19.5.3.5 Repair and/or maintenance of equipment shall be performed in accordance with an SOP so that the quality and integrity of the products is not compromised.

19.5.3.6 Equipment and instrument repair and/or maintenance records shall be kept.

19.6 Qualification and Validation.

19.6.1 Equipment involved in the storage of medical devices shall be qualified in the 4 consecutive stages indicated in clause 11.7 of this Standard.

19.6.2 Computerized systems used in the storage, reception, packaging, and transportation processes shall be validated in accordance with Section 11.15 of this Standard.

19.6.3 An evaluation of the equipment should be carried out to determine if a new qualification is necessary or to establish the periodicity with which the alarm systems in the refrigeration chambers should be evaluated, based on the risk assessment.

19.7 Legal and technical documentation.

19.7.1 The development and management of documentation shall be carried out in accordance with clause 6.2 of this Standard, the scope of the system shall be based on the size and complexity of the organization, and shall consider as a minimum:

19.7.1.1 Updated operating and health officer's notices, according to the establishment's line of business.

19.7.1.2 Warehouse layout plan or diagram showing the flow of material and personnel, updated, and authorized by the sanitary officer.

19.7.1.3 Updated list of equipment and instruments used in the warehouse, as well as SOPs, use, maintenance and/or calibration logs.

19.7.1.4 Records of all health verification visits received procedures, trades, or follow-up with the Ministry of Health.

19.7.1.5 Invoices covering the receipt and delivery of the medical devices issued by the supplier or documentation covering the legal possession of the medical devices, including donations and transfer between warehouses of the same corporation, indicating at least:

19.7.1.5.1 Date.

19.7.1.5.2 Distinctive and/or generic name.

19.7.1.5.3 Quantity.

19.7.1.5.4 Presentation.

19.7.1.5.5 Lot/Serial Number.

19.7.1.5.6 Name and address of supplier.

19.7.1.5.7 Client or recipient.

19.7.1.6 They should have procedures for the acquisition, reception, and registration of health inputs, which clearly establish that only approved products may be received.

19.7.1.7 There shall be procedures to maintain control of incoming and outgoing medical devices, complying with the criterion of first expiration-first out or first in-first out.

19.7.1.8 When performing relabeling of imported medical devices, procedures should be in place detailing the activities to be performed, responsibilities and records to be kept.

19.7.1.9 The place of storage of all documents related to the back labeling, release and/or distribution of medical devices must be clearly defined.

19.7.1.9.1 Control measures shall be implemented to ensure the integrity of the documents during the entire storage period, the storage period shall be based on the useful life of the product plus an additional period of at least one year.

19.7.1.10 When the store is independent of the manufacturer, it must have a current edition of the supplement for establishments dedicated to the sale and supply of medicines and other health supplies.

19.8 Operations.

All operations performed must ensure traceability, the distributor must use all available means to minimize the risk of counterfeit medical devices entering the supply chain.

19.8.1 Acquisition.

19.8.1.1 Distributors must obtain medical devices from medical device manufacturers or medical device warehouses and distribution depots that have a current notice of operation or equivalent document.

19.8.1.1.1 When the medical devices are acquired abroad, they must have the legal documentation that covers their manufacture and importation.

19.8.2 Receipt.

Receiving activities must ensure that the medical device received is the correct one, that it comes from an approved supplier and that it has not been visibly damaged in transit.

19.8.2.1 Each medical device, lot or group of containers shall be checked for completeness, identified with at least name, quantity, lot/serial number and originating facility data.

19.8.2.1.1 Medical Devices that require special handling, storage or security measures should be given priority, once the review has been completed, they should be moved to the Storage Areas.

19.8.2.2 The operator or person responsible for the transport must present documentation supporting possession and transportation, such as invoices, transfers, or remissions.

19.8.2.3 Medical Device containers should be cleaned upon receipt prior to storage.

19.8.2.4 Medical Devices shall not be made available for distribution until the product file review and release in accordance with Chapter 14 of this Standard.

19.8.2.5 If a counterfeit product is suspected, the Lot must be segregated and reported to the Secretariat of Health.

19.8.3 Back labeling.

19.8.3.1 There must be a back-labeling file for each Lot/Serial Number or family of the medical device.

19.8.3.2 They must issue an order for back labeling by Medical Device Lot/Serial Number, indicating the following:

19.8.3.2.1 Distinctive and/or generic name.

19.8.3.2.2 Lot/Serial Number.

19.8.3.2.3 Lot number and quantities of packing materials.

19.8.3.2.4 Reconciliation of packaging materials and labels to ensure quantity used, sent for destruction and/or materials returned.

19.8.3.2.5 Copy of the back label affixed.

19.8.3.2.6 Records of the controls established in the back labeling procedure.

19.8.3.2.7 Date and time of start and end of back labeling.

19.8.3.2.8 Final yield obtained during such activity.

19.8.3.2.9 Name and signature of the person who performed the activities.

19.8.3.2.10 Name and signature of the person who supervised the activities.

19.8.3.3 Prior to beginning back-labeling activities, the work area must be cleared and included as part of the back-labeling order.

19.8.3.4 Any deviation from the back labeling instructions must be recorded, investigated, and evaluated. Theinvestigation must be completed for Lot Release.

19.8.3.5 Each back labeling file must be signed by the sanitary officer or qualified person to ensure that the activity was carried out in compliance with the corresponding procedures.

19.8.4 Storage.

19.8.4.1 Medical Devices should be stored separately from other products that may alter them and should be stored at appropriate light, temperature, RH conditions. Attention should be given to products requiring specific storage conditions.

19.8.4.2 A system shall be established to allow control of the location of each medical device during storage, whether manual or computerized.

19.8.4.3 Stock rotation must be carried out in such a way as to follow the control procedure in accordance with 19.7.1.7 of this Standard.

19.8.4.4 Medical Devices shall be handled and stored in a manner that prevents spills, breakage, contamination, and mixing.

19.8.4.5 There shall be precise instructions for inventory control.

19.8.4.5.1 Irregularities detected in inventories should be investigated and documented.

19.8.5 Distribution.

19.8.5.1 Must establish a system, either manual or computerized, that allows the correct distribution of medical devices.

19.8.5.1.1 If a medical device using UDI is distributed, systems shall be in place to provide tracking of each device to the end user. The tracking system should be reviewed and audited to confirm that it is effective and should contain at a minimum: lot number, device model number or serial number or other identifier to provide effective tracking of devices.

19.8.5.2 An SOP should be established for the control of the distribution of Medical Devices, describing:

19.8.5.2.1 Data to be recorded for each shipment such as: medical device name, lot/serial number, quantity, and purchase order or equivalent document.

19.8.5.2.2 The form and conditions of transport.

19.8.5.2.3 Storage instructions throughout the distribution chain.

19.8.5.3 It must be guaranteed that the product at the time of distribution has a remaining shelf life that ensures that it can be used without the risk of expiration in the distribution process.

19.8.5.4 Medical Devices shall be transported in containers that have no effect on the quality of the products, and that offer protection from external influences, including contamination.

19.8.5.5 The container and packaging should be selected according to the transportation requirements of the medical devices; the space according to the quantity of medical devices, outside temperatures; the estimated maximum time for transportation, transit time through customs, as well as all controls that have an impact on the quality of the product.

19.8.5.5.1 They shall perform cold chain validation.

19.8.5.6 Containers should be labeled to provide information on handling and storage requirements and precautions to ensure that products are handled and protected at all times.

19.8.5.7 A document (e.g., delivery note/packing list, invoice) must be attached to all shipments indicating the date; name of the Medical Device; the Batch/Serial Number; quantity; name and address of the supplier; the name and address of delivery.

19.8.5.8 Product identification and integrity must be ensured.

19.8.5.8.1 A procedure shall be in place for the investigation and handling of deviations during transportation and delivery of product.

19.8.5.9 Distribution records of each product Lot or Serial Number shall be retained to facilitate recall in accordance with Chapter 16 of this Standard.

19.8.5.10 Transportation for distribution must guarantee the conditions of conservation and cleanliness of the medical devices.

19.8.5.10.1 The required temperature and % RH conditions should be maintained during the transport of medical devices.

19.8.5.10.2 They must have instruments for measuring and recording temperature and % RH during transportation and delivery of the products, which must be calibrated.

19.8.5.10.3 There shall be written procedures for the operation, cleaning and maintenance of all conveyances and equipment used for the distribution process.

19.8.5.10.4 When the transportation is carried out by a third party, the contract must cover the requirements foreseen in clause 17.5 of this Standard.

19.8.5.10.4.1 Transport providers shall be instructed and trained in the conditions applicable to Medical Devices for temperature, RH, Cleanliness and Safety, including loading and unloading activities.

19.8.6 Medical devices destined for destruction shall be identified, segregated, and handled according to a written procedure. It should be carried out by a company authorized by the Ministry of Environment and Natural Resources.

19.8.6.1 Records of all destroyed medical devices shall be retained for a period of 5 years.

19.9 Counterfeit medical devices.

19.9.1 A procedure should be in place whereby distributors immediately inform COFEPRIS and the Health Registration Holder of any counterfeit or suspected counterfeit medical device and act on the instructions as specified by the authority.

19.9.2 Any counterfeit medical devices found in the supply chain shall be physically segregated and stored in a specific area separate from other medical devices. All relevant activities in relation to such products should be documented and Records kept.

19.9.3 Upon confirmation that a Medical Device was counterfeited, the Health Registration Holder must notify COFEPRIS so that it may order the withdrawal of such product from the market.

20. Conformity with international and Mexican standards

This Standard is partially consistent with the following standards:

20.1 ISO13485:2016 Medical Devices-Quality management systems-Requirements for regulatory purposes.

20.2 ISO 14969:2004 Medical Devices-Quality Management Systems-Guidance on the application of 13485:2003.

20.3 ISO 9000:2015 Quality management systems-Fundamentals and vocabulary.

20.4 ISO 9001:2015 Quality management systems-Requirements.

20.5 NMX-CC-9000-IMNC-2000 Quality Management Systems - Fundamentals and Vocabulary.

20.6 NMX-CC-9001-IMNC-2000 Quality Management Systems-Requirements.

20.7 Guide to good manufacturing practice for medicinal products. Annex 3 Manufacture of radiopharmaceuticals, PIC/S.

21. Bibliography

21.1 General Health Law.

21.2 General Law of Ecological Balance and Environmental Protection.

21.3 Federal Law on Metrology and Standardization.

21.4 Regulation of Health Supplies.

21.5 Regulation of the Federal Law on Metrology and Standardization.

21.6 Pharmacopoeia of the United Mexican States, 12th Ed. Ed. Mexico (2018).

21.7 Medical Device Supplement to the Pharmacopoeia of the United Mexican States, 4th Ed. Mexico (2017).

21.8 ISO 11135-1:2014. Sterilization of health care products-Ethylene Oxide-Part 1: Requirements for development, validation, and routine control of sterilization process for medical devices.

21.9 ISO/TS 11135-2:2014 Sterilization of health care products-Ethylene Oxide-Part 2: Guidance on the application of ISO 11135-1.

21.10 ISO 11137-1:2013. Sterilization of health care products--Radiation-Part 1: Requirements for validation and routine control of a sterilization process for medical.

21.11 ISO 11137-2:2006 Sterilization of health care products-Radiation-Part 2: Establishing the sterilization dose.

21.12 ISO 11137-3:2006 Sterilization of health care products-Radiation-Part 3: Guidance on dosimetric aspects.

21.13 ISO 19011:2011. Guidelines for quality and /or environmental management systems auditing.

21.14 ISO 14644-1:2015. Cleanrooms and associated controlled environments--Part 1: Classification of air cleanliness.

21.15 ISO 14644-2:2015. Cleanrooms and associated controlled environments--Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.

21.16 ISO 14644-3:2005. Cleanrooms and associated controlled environments--Part 3: Test methods.

21.17 ISO 14644-4:2001. Cleanrooms and associated controlled environments--Part 4: Design, construction and start--up.

21.18 ISO 14644-5:2004. Cleanrooms and associated controlled environments--Part 5: Operations.

21.19 ISO 14971:2007. Medical devices--Application of risk management to medical devices.

21.20 ISO 4074:2015. Natural rubber latex male condoms - Requirements and test methods.

21.21 ANSI/ASQC 01-1988. Generic guidelines for auditing of quality systems.

21.22 ASTM F 1980 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

21.23 Code of Federal Regulations Title 21; Part 820, Medical Device Good Manufacturing Practices Manual - Washington, Food and Drug Administration, 2001.

21.24 Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing--Current Good ManufacturingPractice--Washington, D.C., Food and Drug Administration, September 2004.

21.25 Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice; European Commission, Brussels,2015.

21.26 European Commission, Guide to Good Manufacturing Practice Annex I.

21.27 European Commission, Guide to Good Manufacturing Practice Annex 1, Manufacture of Sterile MedicinalProducts, June 2008.

21.28 European Commission, Guide to Good Manufacturing Practice Annex 15, Qualification and validation, July 2001.

21.29 Manufacture of Sterile Medicinal Products, January 1997.

21.30 Points to Consider for Aseptic Processing, PDA Journal of Pharmaceutical Science and Technology, 2015, Part 1.Points to Consider for Aseptic Processing, PDA Journal of Pharmaceutical Science and Technology, 2016, Part 2.

21.31 U.S. Foods and Drug Administration. Guidance for Industry Process Validation: General Principles and

Practices.Washington, January 2011.

21.32 European Medicines Agency, Guideline on process validation for finished products-information and data to beprovided in regulatory submissions, United Kingdom, 27 February 2014.

21.33 ISPE. GAMP 5, A Risk-Based Approach to Compliant GxP Computerized Systems. 2008.

21.34 IMDRF/SaMD WG/N10FINAL:2013. Software as a Medical Device (SaMD): Key Definitions. December 2013.

21.35 IMDRF/SaMD WG/N12FINAL:2014. Software as a Medical Device (SaMD): Possible Framework for Risk Categorization and Corresponding Considerations. September 2014.

21.36 IMDRF/SaMD WG/N41FINAL:2017. Software as a Medical Device (SaMD): Clinical Evaluation. June 2017.

21.37 Guidance for Industry and Food and Drug Administration Staff. Mobile Medical Applications: Guidance for Foodand Drug Administration Staff. February 2015.

22. Compliance with the standard

Compliance with this Standard is the responsibility of the Ministry of Health and the governments of the Federal Entities, within the scope of their respective competencies, whose personnel will carry out the necessary verification and surveillance.

23. Conformity assessment

The Conformity Assessment may be requested at the request of the party responsible for health, the legal representative or the person empowered to do so before the competent authority or the persons accredited or authorized for such purposes.

23.1 Establishments that manufacture products that are not considered health inputs under the agreement listed below are not required to comply with the conformity assessment of this Standard.

23.1.1 Agreement announcing the list of health inputs considered as low risk for the purposes of obtaining sanitary registration, and those products that due to their nature, characteristics and use are not considered as health inputs and therefore do not require sanitary registration, published in the Official Gazette of the Federation on December 22, 2014.

24. Validity

This standard will become effective 180 calendar days after its publication in the Official Gazette of the Federation.

TRANSITORY

ONLY. - The entry into force of this Standard will render ineffective the Official Mexican Standard NOM-241-SSA1-2012, Good Manufacturing Practices for establishments dedicated to the manufacture of medical devices, published in the Official Journal of the Federation on October 11, 2012.

Mexico City at --- from --------de--- 2021