DOF: 20/12/2021

Official Mexican Technical Regulation NOM-241-SSA1-2021, Good manufacturing practices for medical devices.

On the margin a seal with the National Coat of Arms, which reads: Mexican United States - HEALTH – Ministry of Health.

ALEJANDRO ERNESTO SVARCH PÉREZ, Federal Commissioner for Protection against Sanitary Risks and Chairman of the National Advisory Committee for Standardization of Health Regulation and Promotion, based on the provisions under Articles 39 of the Organic Law of the Federal Public Administration; 4 of the Federal Law of Administrative Procedure; 3, sections XXIII and XXIV, 13, section 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 in connection with the Fourth Transitory Provision of the Decree enacting the Law on Quality Infrastructure and repealing the Federal Law on Metrology and Standardization, published in the Official Journal of the Federation on July 1, 2020; 28 and 33 of the Regulation 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 Protection against Sanitary Risks; and

CONSIDERING

That on June 14, 2019, in compliance with the agreement of the National Advisory Committee for Standardization of Health Regulation and Promotion and the provisions of Article 47, Section I, of the Federal Law on Metrology and Standardization, it was published the Draft of this Technical Regulation in the Official Journal of the Federation, so that within 60 calendar days following the mentioned publication, the interested parties could submit their comments to the Committee.

That previously, the response to the comments received by the aforementioned Committee was published in the Official Journal of the Federation, under the terms of Article 47, Section III of the Federal Law on Metrology and Standardization, and

In view of the above considerations, and with the approval of the National Advisory Committee for the Standardization of HealthRegulation and Promotion, I have been pleased to issue and order the publication in the Official Journal of the Federation of the

OFFICIAL MEXICAN TECHNICAL REGULATION NOM-241-SSA1-2021,
GOOD MANUFACTURING PRACTICES FOR MEDICAL DEVICES

PREFACE

The following participated in the development of this Technical Regulation:

MINISTRY OF HEALTHFederal 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 Supplies.

INSTITUTE OF SECURITY AND SOCIAL SERVICES FOR STATE EMPLOYEES.
Infrastructure Sub-directorate.

NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO.
School 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, C.A.MEXICAN

PHARMACEUTICAL

ASSOCIATION, C.A.

MEXICAN PHARMACEUTICAL ASSOCIATION OF THE WEST, C.A.

NATIONAL COLLEGE OF CHEMISTS PHARMACISTS

BIOLOGISTS OF MEXICO, C.ACHEMICAL PHARMACEUTICAL

PRODUCTION, C.A.

MEXICAN ASSOCIATION OF PHARMACEUTICAL LABORATORIES, C.A.
MEXICAN ASSOCIATION OF INNOVATIVE INDUSTRIES OF

MEDICAL DEVICE, C.A.COLLEGE OF BIOMEDICAL

ENGINEERS OF MEXICO, C.A.

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0. Introduction

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

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 health control in the manufacturing facilities, packaging warehouses and distribution of medical devices following the criteria established in this Mexican Official Technical Regulation.

1. Objective and scope

1.1 Objective

The purpose of this Technical Regulation is to establish the minimum requirements for the processes of design, development, manufacture, storage, and distribution of medical devices, based on their risk level, to guarantee that they consistently meet the requirements of quality, safety, and functionality to be used by the final consumer or patient.

1.2 Scope

This Technical Regulation is mandatory in the national territory, for all the facilities dedicated to the manufacture of medical devices,packaging warehouses, storage, and distribution of medical devices.

2. Regulatory references

For the correct application of this Technical Regulation, it is necessary to refer to the following Official Mexican Technical Regulations in force or thosethat may replace them, as applicable:

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

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

2.3 Official Mexican Technical Regulation NOM-005-STPS-1998, Relative to safety and hygiene conditions in work centers for handling, transportation, and storage of hazardous chemicals.

2.4 Official Mexican Technical Regulation NOM-007-NUCL-2014, Radiological safety requirements to be met for permanent implants of radioactive material for therapeutic purposes in humans.

2.5 Official Mexican Technical Regulation NOM-011-STPS-2001, Safety and hygiene conditions in work centers where noise is generated.

2.6 Official Mexican Technical Regulation NOM-017-STPS-2008, Personal protective equipment-selection, use and management in work centers.

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

2.8 Official Mexican Technical Regulation NOM-026-STPS-2008, Safety and hygiene colors and signs, and identification of risks due to fluidsconducted in pipelines.

2.9 Official Mexican Technical Regulation NOM-028-NUCL-2009. Management of radioactive waste in radioactive facilities using open sources.

2.10 Official Mexican Technical Regulation NOM-030-STPS-2009, Preventive occupational health and safety services - functions and activities.

2.11 Official Mexican Technical Regulation NOM-036-1-STPS-2018, Ergonomic risk factors at Work-Identification, analysis, prevention, andcontrol. Part 1: Manual handling of loads

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

2.13 Official Mexican Technical Regulation NOM-059-SSA1-2015, Good manufacturing practices for medicines.

2.14 Official Mexican Technical Regulation NOM-062-ZOO-1999, Technical specifications for the

production, care, and use of laboratory animals.

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

2.16 Official Mexican Technical Regulation NOM-087-SEMARNAT-SSA1-2002, Environmental health, Biological and infectious hazardous waste, classification, and handling specifications.

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

2.18 Official Mexican Technical Regulation NOM-164-SSA1-2015 Good manufacturing practices for drugs.

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

3. Terms and definitions

For the purposes of this Technical Regulation, the following is defined as:

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

3.2 Corrective action, to the activity that is planned and executed to eliminate the cause of a deviation or nonconformity whit the aim of preventing its recurrence.

3.3 Preventive action, to 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 Packaging, to all the operations to which a bulk product must undergo until it is presented as a finished product. Primary packaging are the elements that are in direct contact with the medical device and secondary packaging is considered to include the medical device in its primary packaging.

3.5 Technical agreement, to the document formalizing and detailing the conditions under which activities or services will be carried out between the parties and clearly defining the obligations and responsibilities of each party, especially regarding quality aspects and GMP and GSDP.

3.6 Wastewater, to the water discharged because of activities related to manufacturing, in the terms indicated in the Official Mexican Technical Regulation mentioned in section 2.1 of this Technical Regulation.

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

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

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

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

3.11 Clean area, to the place where 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, to the set of planned and systematic activities performed by an organization to provide confidence thata product or service meets the specified quality requirements.

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

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

3.15 Animal facilities, to the set of facilities, furniture and buildings intended for the housing and maintenance of laboratory animals during one or more phases of their life cycle, i.e., birth, development, reproduction, and death.

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

3.17 Good manufacturing practices (GMP), to the set of guidelines and interrelated activities aimed at guaranteeing 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 Practices (GLP), to the set of rules, operational procedures and practices established to assure the quality and integrity of the activities performed in the laboratory and of the analytical data obtained from tests or trials.

3.19 Calibration, to 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 compliance of established specifications to guarantee the suitability of use.

3.21 Qualification, to 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 (PQ), to the documented evidence that the facilities, systems, and equipment perform in compliance with previously established acceptance criteria.

3.23 Design qualification (DQ), to the documented evidence demonstrating that the proposed design of the facilities, systemsand equipment is suitable for the intended purpose.

3.24 Installation qualification (IQ), to the documented evidence that facilities, systems, and equipment have been installed inaccordance with previously established design specifications.

3.25 Operational qualification (OQ), to the documented evidence that the equipment, facilities, and systems operate consistently in accordance with established design specifications.

3.26 Training, to those activities aimed at generating or reinforcing knowledge in personnel.

3.27 Certificate of analysis, to the document indicating the tests, specifications and results obtained in the evaluation of the medical device, according to the type of product and its risk level. It must include the name, description of the product, batch or serial number, manufacturing and/or expiration date.

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

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

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

3.31 Dynamic conditions, to those in which the facility is operating in the defined operating mode and with the specified numberof personnel.

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

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

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

3.35 Contaminant, to the undesirable impurities of a chemical or microbiological nature, or foreign matter, present in a supply,intermediate product and/or finished product.

3.36 Change control, to the evaluation and documentation of changes impacting the quality, performance, or operation of themedical device.

3.37 In-process control, to the verifications performed during manufacturing to monitor and, if necessary, adjust the process.

3.38 Acceptance criteria, to predefined conditions, specifications, standards, or ranges that must be met under pre- establishedtest conditions.

3.39 Quarantine, to the state of supplies and products preventing their disposition for further processing and/or release, that canbe evidenced by physical separation or other means.

3.40 Deviation or non-conformity, to the failure to comply with a previously established requirement.

3.41 Medical device, to the instrument, apparatus, appliance, tool, machine, *software*, implantable

product or material, diagnostic agent, material, substance, or similar product, to be employed, alone or in combination, directly or indirectly, in humans; for any of the following purposes of use:

— Diagnosis, prevention, surveillance, or monitoring, and/or aiding in the treatment of diseases;

— Diagnosis, surveillance or monitoring, treatment, protection, absorption, drainage, or aid in the healing of a wound;

— Substitution, modification, or support of the anatomy or of a physiological process;

— Life support;

— Contraception;

— 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, to the authorized document containing the information to perform and control the operations of theprocesses and activities related to the manufacture of a product.

3.43 Container or Primary packaging, to the elements of the packaging system that come in direct contact with the medicaldevice.

3.44 Container or secondary packaging, to the elements that are part of the packaging in which the medical device is marketedand that do not come in direct contact with the medical device.

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

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

3.47 Sterility, to the absence of viable microorganisms.

3.48 Stability studies, to the tests performed on a medical device for a certain period, under the influence of temperature, humidity, or light in its container, to demonstrate the shelf life of the device and determine its expiration date.

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

3.50 Accelerated aging studies, to 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 storage conditions.

3.51 Real-time (long-term) stability studies, to 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 conditions and expiration date of a medical device, through a program of sampling and evaluation of the physical, chemical, and biological requirements, verifying the preservation of their propertiesduring its shelf life.

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

3.53 Label, to any label, heading, inscription, mark, or graphic image that has been written, printed, stenciled, marked, embossed, or engraved, affixed, or sealed on any material likely to contain the medical device, including the container itself.

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

3.55 Legal dossier, to the set of documents demonstrating that the medical device complies with the regulations issued by theMinistry of Health.

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

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

3.58 Electronic signature, to 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 handwritten signature.

3.59 Quality Risk Management, to the systematic process for the assessment, control, communication, and review of risks to the quality of medical devices throughout their life cycle.

3.60 Inspection, to the evaluation of conformity by means of measurement, assay/testing or comparison with standards accompanied by a judgement.

3.61 Facility, to the set of areas, equipment and utilities intended to perform a specific operation or process.

3.62 Work instruction, to the detailed, sequential, and specific description of a task.

3.63 Supplies, to those raw materials, components for assembly, primary packaging material, packaging material and productthat are received in a facility.

3.64 Concurrent release, to the release for distribution of a batch of the manufactured device following a process qualification protocol that meets the criteria for release established before the protocol has been completed.

3.65 Batch/lot release, to the judgement indicating the disposition of the product based on a systematic review to guaranteethe quality from all aspects, particularly those of the GMP.

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

3.67 Batch, to the specific quantity of any raw material or supply (for health), which has been produced in a production cycle,under equivalent operating conditions and during a determined period.

3.68 Quality manual, to the document describing the quality management system of a facility, in accordance with the qualitypolicy and objectives established in the manual.

3.69 Contract manufacturing, to the process or stage of a process involved in the manufacture of a medical device, conductedby a facility other than the Health Registration Holder or manufacturer; it may be national or international; temporary or permanent.

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

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

3.72 Sample, to the quantity of material which composition is representative of the batch to be examined.

3.73 Retention sample, to enough raw materials or product to perform two complete analyses, except for sterility test.

3.74 Batch or serial number, to the numeric or alphanumeric combination that specifically identifies a batch.

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

3.76 Production order, to a copy of the master production order or formula with an assigned batch number, used fordispensing and recording the supplies to produce a batch of medical device.

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

3.78 Worst case, to the condition or set of conditions encompassing upper and/or lower limits and circumstances of a process, within standard operating procedures, having the greatest opportunity for

process failure when compared to ideal conditions. Such conditions do not necessarily lead to product or process failure.

3.79 Validation Master Plan (VMP), to the document specifying 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 must be established.

3.80 Packaging procedure, to the document containing detailed instructions for processing a bulk product into a finished product.

3.81 Production procedure, to the document containing the detailed instructions for processing raw materials, materials, or components into bulk medical devices prior to their packaging in the package intended for their commercialization.

3.82 Standard Operating Procedure (SOP), to the document containing the instructions necessary to reproducibly perform anoperation.

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

3.84 Semi-finished product, to the product in its primary packaging and that will undergo subsequent stages to become afinished product.

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

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

3.87 Protocol, to the written work plan establishing the objectives, procedures, methods, and acceptance criteria to conduct astudy.

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

3.89 Complaint, to any observation of non-satisfaction from an internal or external customer, related to the quality, safety, andfunctionality of the product.

3.90 Traceability or Tracking, to the ability to reconstruct the history, location of an element, a component, or an activity, usingrecords as evidence.

3.91 Repackaging, to the change of packaging of any medical device, if the quality of the device is guaranteed.

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

3.93 Record, to the document including the evidence of the implemented actions to demonstrate compliance with activities orinstructions.

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

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

3.96 Final yield, to the quantity of finished medical device obtained at the end of the manufacturing process.

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

3.98 *Refurbishment/Rehabilitation*, to the restoration of the medical device to a condition of safety and effectiveness comparable to the condition 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 ofnon-functioning components or parts outside of routine or periodic maintenance for the current owner of the device.

3.100 Reprocessing, to the submission of a total or partial batch, to one or more defined stages of the validated manufacturingprocess due to non-compliance with the specifications.

3.101 Rework, to the submission of a total or partial batch to one or more undefined stages of the validated manufacturingprocess due to non-compliance with the specifications.

3.102 Annual Product Review (APR) or Annual Product Quality Review (APQR), to the historical analysis of the quality of aproduct, which takes as a reference all current regulatory documents applicable to medical devices, usually recognized internationalcriteria, as well as the internal guidelines of each company.

3.103 Robustness, to the ability of a process to be insensitive, to a known extent, to factors that could affect the process underthe established conditions.

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

3.105 Safety, to the assessment of the benefit that a medical device produced against its potential risks at a given time.

3.106 Computerized system, to the 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), to the way the organization directs and controls the activities associated with quality.

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

3.109 Software as a medical device, that used for one or more medical purposes, whose main characteristic is that it does notneed to be part of the medical device hardware to meet the intended medical purpose; it can run 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 according to this definition are considered software as a medical device. Software that operates the physical medical device is excluded from this definition.

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

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

3.112 Technology transfer, to the systematic process that is followed to transfer the knowledge and experience during development and/or commercialization to another responsible and authorized unit. This process includes the transfer of documentation and the demonstrated capacity 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, to the documented 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, to the documented evidence that a cleaning procedure for areas and equipment used in the manufacture of medical devices reduces the cleaning agent and processed product residues to a pre-established level.

3.115 Validation of software as a medical device, to the documented evidence generated through the collection and evaluation of the ability of a software to generate with accuracy, integrity, and precision the intended functions from the input data.

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

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

4. Symbols and abbreviations

When the following symbols or abbreviations are referred to in this Technical Regulation, it shall be understood as:

4.1 Symbols

4.1.1	ºC	Degree Celsius.
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 Abbreviations

4.2.1	GDP	Good Documentation Practices.
4.2.2	BSE	Bovine Spongiform Encephalopathies
4.2.3	CAPA	Corrective Action and Preventive Action
4.2.4	DQ	Design qualification
4.2.5	IQ	Installation qualification
4.2.6	OQ	Operational Qualification
4.2.7	PQ	Execution or performance qualification
4.2.8	COFEPRIS	Federal Commission for Protection against Sanitary Risks.
4.2.9	FEUM	Pharmacopoeia of the United Mexican States.
4.2.10	HEPA	High Efficiency Particulate Air Filter
4.2.11	RH	Relative Humidity.
4.2.12	HVAC	Heating, Ventilation and Air.
4.2.13	N.A.	Not applicable.
4.2.14	NAT	Nucleic Acid Test.
4.2.15	m/s	Meter per second
4.2.16	m^3	Cubic meter.
4.2.17	µm	Micrometer.
4.2.18	Pa	Pascals.
4.2.19	TSE	Transmissible Spongiform Encephalopathies
4.2.20	UDI	Unique Device Identifier
4.2.21	CFU	Colony Forming Units.
4.2.22	HIV	Human Immunodeficiency Virus.
4.2.23	VMP	Validation Master Plan
4.2.24	HAV	Hepatitis A virus.
4.2.25	HBV	Hepatitis B virus.
4.2.26	HCV	Hepatitis C virus.

5. Classification of medical devices

5.1 Based on the risk associated to their use, medical devices are classified as follows:

5.1.1 Class I: medical devices known in medical practice whose 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 which they are produced or in their concentration and, generally, are introduced into the organism and remain in the body 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 organism and remain in the body for more than thirty days.

5.2 Medical devices considered in the General Health Law are:

5.2.1 Medical equipment: devices, 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 conducting biomedical research activities.

5.2.2 Prostheses, orthoses, and functional aids: devices intended to replace or supplement a function, an organ, or a tissueof 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 can be used as an aid 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 injuries or their annexes.

5.2.6 Hygienic products: materials and substances applied to the surface of the skin or body cavities having 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 guarantee that medical devices are of the required quality for their intended use. Quality management therefore incorporates GMP, GDP, GSDP, GLP, and Risk Management principles. Including the use of appropriate tools.

6.1.2 The facility must design, implement, document, and maintain the Quality Management System, as well as maintain its effectiveness in accordance with the requirements of this Technical Regulation, 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 Facility management should have a formal process for reviewing the Quality Management System at least once a year.

6.1.4 The manufacture of medical devices must be performed following a Quality Management System supported by:

6.1.4.1 A quality policy and a documentation system that is designed, planned, implemented, maintained, and subjected to continuous improvement, so that products can only be marketed or supplied once 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 entire life cycle of the product.

6.1.4.3 The design, development and/or technology transfer of medical devices considering GMP requirements.

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

6.1.4.5 The responsibilities of the personnel in the Quality Management System, which must be referenced in the quality manual.

6.1.4.6 Implementing timely measures to assure the correct manufacture, supply, use of raw materials, packaging materials, andthe selection and follow-up of suppliers, and to verify that each delivery comes from the supply chain approved by the quality assurance area.

6.1.4.7 Procedures and/or technical quality agreements to assure the management of outsourced activities, according to their risk level.

6.1.4.8 The establishment and maintenance of a state of control of process execution and product quality through monitoring measures and the results of those measures, which are considered for batch release, investigation of deviations and for implementation of corrective actions to avoid recurrence.

6.1.4.9 Conduct 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 the prospective evaluation of planned changes.

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

6.1.4.13 Root cause analysis applied during the investigation of deviations or nonconformities, complaints, nonconforming product, audit findings, returns, recalls, adverse event reports, suspected product defects or other 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 must be identified and implemented 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 manager and/or in accordance with subsection 9.1.3, prior to the sale or supply of each manufacturing batch or unit, to assure that the medical device has been produced and controlled according to the requirements established in the marketing authorization and any other regulations regarding the production, control, and release of devices.

6.1.4.15 Adoption of measures to assure that medical devices are stored and distributed in such a way that quality ismaintained throughout the validity period, shelf life and/or expiration date.

6.1.4.16 Self-inspection and/or quality audit procedure evaluating the effectiveness and implementation of the QualityManagement System.

6.1.5 The minimum elements to be included in the Quality Management System are as follows:

6.1.5.1 Quality manual.

6.1.5.2 Audit system.

6.1.5.3 Complaint management.

6.1.5.4 Handling of out-of-specification or non-conforming product.

6.1.5.5 Deviation management and CAPA system.

6.1.5.6 Recall.

6.1.5.7 Change control.

6.1.5.8 VMP.

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 must be defined and adhered in accordance with the provisions of the Quality Management System. The requirements apply equally to all forms of documentation media. Electronic document generation systems impacting product quality need to be understood, well documented, available, and validated.

6.2.1.2 Documents of the Quality Control System must be written in Spanish. When documents are in two or more languages, the Spanish version must 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 must 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 must be established in the document control system for both hybrid and homogeneous systems.

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

6.2.2.3 Documents must be designed, prepared, reviewed, authorized, modified, distributed and/or cancelled in accordance withthe provisions of the Quality Management System.

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

6.2.3 Document safeguarding.

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

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

6.2.3.2.1 For medical devices without an expiration date or shelf life, the average lifetime that the device will remain in use mustbe considered; the period determined must be justified.

6.2.3.3 For other types of documents, the retention period will depend on the activity the documentation supports. Critical documentation, including primary data (e.g., related to validation or stability), supporting the information in the health registration ormarketing authorization should be retained if 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 newdata package

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

6.2.3.4 Any type of storage other than the time must be based on the applicable legal provisions.

6.2.4 GDP.

6.2.4.1 Documents containing instructions must be approved, signed, and dated. All types of documents must be defined and conform to the provisions of 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 must be reviewed in accordance with their validity and kept up to date.

6.2.4.3 Quality Management System documents should not be handwritten; however, when documents require data entry, blanksshould be left to allow for those entries to be made.

6.2.4.3.1 Handwritten records on documents must be made in a clear, legible, and indelible manner.

6.2.4.3.2 Recording of activities must be done at the time of the activity respecting the chronological order.

6.2.4.4 Any correction to an activity record or document must 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 must be documented; records must contain the dateand identify the person who performed the activity.

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

6.2.5 Types of documents.

This Technical Regulation addresses different types of documents, however, the manufacturer must design the documentation accordingto the products and processes, particularly those that do not use the

batch concept.

The documents comprising the documentation system include, but are not limited to:

6.2.5.1 Quality manual.

There must be a quality manual or document containing the description of the Quality Management System, including management responsibilities. The manual must establish and assure 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 supplies, bulk product and finished product, the certificate of analysis and/or certificate of conformity must comply with the characteristics indicated in section 3.27 or 3.28 of this Technical Regulation, as appropriate.

6.2.5.2.2 Specifications for raw materials, containers and packaging materials should 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 supplier of materials.

6.2.5.2.2.3 A sample and/or a faithful 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 Re-analysis period and number of re-analyses, if applicable.

6.2.5.2.2.8 Material handling precautions.

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

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

6.2.5.2.4.1 Product name and assigned internal code.

6.2.5.2.4.2 Sampling Instructions

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 Expiration period, expiration date or shelf life of the product.

6.2.5.2.4.7 Precautions for handling the product.

6.2.5.3 Production Master Order.

6.2.5.3.1 There must be a written order and master production instructions for each product, these master documents will beused to generate the work documents.

6.2.5.3.2 The production order must include at least:

6.2.5.3.2.1 Product name and an assigned internal code.

6.2.5.3.2.2 Batch size and/or serial number.

6.2.5.3.2.3 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 yield with acceptance limits for each stage of the process.

6.2.5.3.3 Production instructions must include at least:

6.2.5.3.3.1 Area in which each stage of the process takes place.

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 for 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 assure that it is free of previous products,equipment, and unnecessary materials.

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

6.2.5.3.3.6 Detailed instructions on how to perform each step of the process, including critical process parameters such astime, temperature, and speed.

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 product handling and storage, according to the nature of the product.

6.2.5.3.4 For medical device assembly processes, there must be an instruction manual detailing how toperform the process.

6.2.5.4 Master Packaging Order.

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

6.2.5.4.2 The Master Packaging Order must include at least the following:

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

6.2.5.4.2.2 Batch or serial number of the bulk product.

6.2.5.4.2.3 Final presentation.

6.2.5.4.2.4 Complete list of all materials required for product packaging, including codes, quantities, and cross reference tospecifications, if appropriate.

6.2.5.4.2.5 Theoretical yield with acceptance limits for each stage of the process.

6.2.5.4.3 The Packaging Order must include at least the following:

6.2.5.4.3.1 Graphical representation of product packaging or cross reference as appropriate.

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

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

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

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

6.2.5.4.3.6 Instructions for the reconciliation of printed materials.

6.2.5.4.3.7 Storage conditions for the finished product.

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

6.2.5.4.4 For medical devices that only require packaging, there must be an instruction manual that clearly details how to performthis process, the label must indicate at least the product, the health registration, and precautions for handling.

6.2.5.5 Medical device record.

6.2.5.5.1 For each type of medical device or family of medical devices, the facility must generate and maintain one or more fileseither containing or referencing documents generated to demonstrate compliance with the requirements of this Technical Regulation.

6.2.5.5.2 Records should 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 for use.

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, in accordance with the conditions authorized in the health registration and contain the order and instructions for production and packaging with the record of the activities.

6.2.5.6.2 This record must contain the following:

6.2.5.6.2.1 Production order and instructions.

6.2.5.6.2.2 Batch or Serial number of the product.

6.2.5.6.2.3 Batch numbers or item identifier and dispensed quantities of all materials included in the manufacturing process.

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 the operator who executed the operation with the initial of the first name and first surname, this information must be traceable to an operators and supervisors record of the production areas.

6.2.5.6.2.6 Supervision records.

6.2.5.6.2.7 Record of in-process controls including the results obtained and the individuals 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 must be recorded, investigated, and evaluated. The investigationmust be completed to release the batch.

6.2.5.6.2.10 Each production file must be signed by the sanitary responsible or qualified quality assurance person certifyingthat the product was produced in compliance with GMP.

6.2.5.6.3 Packaging Record.

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 conditionsauthorized in the health registration, contain the instructions and the record of the activities performed for packaging.

6.2.5.6.3.2 The packaging record must be integrated with the product manufacturing record and must contain at least the following:

6.2.5.6.3.2.1 Order and instructions or packaging procedure.

6.2.5.6.3.2.2 Batch or serial number of the product.

6.2.5.6.3.2.3 Batch numbers or item identifier and quantities of bulk product, container 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 thereturned materials.

6.2.5.6.3.2.5 Start and end dates and times of the packaging stages.

6.2.5.6.3.2.6 Identification of the operator who executed the operation with the initial of the first name and first surname, thisinformation must be traceable to a record an operators and supervisors record of the packaging areas.

6.2.5.6.3.2.7 Supervision records.

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

6.2.5.6.3.2.9 Final yield obtained during the different stages of packaging.

6.2.5.6.3.2.10 Any deviation from the packaging instructions or procedure must be recorded, investigated, and evaluated. Theinvestigation must be completed to release the batch.

6.2.5.6.3.2.11 Each packaging file must be signed for compliance by the Health Manager or qualified person in the quality assurance area to guarantee the release of the product complies with GMP.

6.2.5.7 Analytical and test methods.

6.2.5.7.1 There must be written procedures describing the methods, equipment and instruments used for the analysis or evaluation of supplies and products at different stages of manufacture.

6.2.5.7.2 A record of the analyses and evaluations performed must be kept.

6.2.5.8 Other documents related to GMP compliance.

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

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

6.2.5.8.3 There must be written documentation for the following activities or processes, this list is not limiting 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 in GMP and technical topics relatedto 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 thequality 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 non-conformities.

6.2.5.8.3.10 Complaint report.

6.2.5.8.3.11 Change Control Report.

6.2.5.8.3.12 Product returns.

6.2.5.8.3.13 Recall.

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

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

6.2.5.8.3.16 Supplies reception.

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 sections 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 health license and notice of Health Manager.

6.2.5.8.3.23.2 Current GMP certificate.

6.2.5.8.3.23.3 Current copy of the FEUM supplement for medical devices. **6.2.5.8.3.23.4** Original health registration, certified copy or validated digital file.
6.2.5.8.3.23.5 Instructions or indications for use

Change control.

6.3.1 There must be a documented change control system including Risk Management for the evaluation and impact of the proposed change on processes, suppliers, critical systems, computer systems, areas, utilities, equipment, analytical methods, specifications, documentation, regulatory provisions, and product quality.

6.3.2 Unplanned changes should be considered as deviations or nonconformities.

6.3.3 A committee or technical group integrated by representatives of the areas involved and the person in charge of the qualityunit should be formed to review, evaluate, and approve the proposed change.

6.3.4 The implementation of the approved changes must be followed up and their closure must be assured in accordance with the provisions previously established.

6.4 Purchasing management.

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

6.4.2 The event of non-compliance with purchasing requirements must be discussed with the supplier according to the risk associated with the purchased supplies and compliance with approved specifications.

6.4.3 Purchase information.

6.4.3.1 The purchase information must refer to the purchased supply and must include:

6.4.3.1.1 Supply specifications.

6.4.3.1.2 Requirements for supply acceptance.

6.4.3.1.3 Requirements for supplier qualification.

6.4.3.1.4 Quality Management System requirements.

6.4.4 It must be assured that the purchase requirements or specifications are in force before they are communicated to thesupplier.

6.4.5 A technical agreement must be in place, through which the supplier notifies the buyer before the implementation of any change impacting the characteristics of the purchased supply to comply with the purchase requirements.

6.4.6 Records and purchasing documents must be maintained in accordance with Section 6.2 of this Technical Regulation.

6.4.7 Verification of the purchased supply.

6.4.7.1 Inspection or other activity necessary to assure that the purchased supply complies with the purchase requirements shallbe established and implemented. The scope of the verification activities shall be based on the results of the supplier's evaluation, considering the associated risks.

6.4.7.2 When any change in the purchased supply is detected or reported, it must be determined whether these changes havean impact in the manufacturing process of the product.

6.4.7.3 When the company intends to conduct the evaluation at the supplier's facility,

the planned verification activities and the method of product release shall be indicated in the purchase agreement.

6.4.7.4 Assessment records must be maintained in accordance with subsection 6.2 of this Technical Regulation.

6.5 Returns.

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

6.5.1.1 That the products should be placed in quarantine and evaluated by the quality unit to determine whether they should bereleased or destroyed.

6.5.1.2 Reception, identification, evaluation, and final disposal records. The report must contain at least the following:

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

6.5.1.2.2 Return date, quantity returned.

6.5.1.2.3 Reason for return.

6.5.1.2.4 Name and location of the person who returns.

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

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

6.6 Measurement, analysis, and improvement.

6.6.1 Overview.

The organization must plan and implement monitoring, measurement, analysis, and improvement to demonstrate productconformity; guarantee 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 the specifications of supplies, products and processes must be collected andcontrolled. The methods for obtaining and using this information must be documented.

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

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

6.6.3 Complaints management.

6.6.3.1 There must be a person responsible for the management of complaints.

6.6.3.2 There must be a procedure for complaints management, which must include:

6.6.3.2.1 The mandatory nature of attention and documentation of all complaints.

6.6.3.2.2 The investigation process and judgement of the type of complaint including the impact to the quality, safety, andefficacy of the product.

6.6.3.2.3 Definition of the CAPA to be implemented regarding the problem.

6.6.3.2.4 The way and time of response to the customer.

6.6.3.2.5 Indicate in which cases the product will be recalled and notify the Ministry of Health, through COFEPRIS.

6.6.3.3 As part of the investigation of a complaint of a defective batch or unit of product, prospective and retrospectiveevaluation should be extended to other batches to determine if they are also affected.

6.6.3.4 Complaint records should at least contain the following:

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

6.6.3.4.2 Reception date of the complaint by the Health Register Holder.

6.6.3.4.3 Quantity involved.

6.6.3.4.4 Reason.

6.6.3.4.5 Name and location of the person who generates the complaint.

6.6.3.4.6 Complaint date.

6.6.3.4.7 Investigation results.

6.6.3.4.8 Implemented actions.

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

6.6.3.5 A review of complaints must be conducted to identify trends in specific or recurring problems and to implement thenecessary 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 theMexican Official Technical Regulation mentioned in paragraph 2.19 of this Technical Regulation.

6.6.4 Audits.

6.6.4.1 There must be procedures establishing the process for the execution of an audit containing at least the following information:

6.6.4.1.1 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 from the audited area.

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

6.6.4.1.2.3 Frequency of audits and the establishment of a permanent audit program.

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

6.6.4.2.1 Internal audits (self-inspections):

There must be a self-inspection system for the evaluation of the Quality Management System and the level of GMPcompliance.

6.6.4.2.1.1 Self-inspection audits must be conducted by personnel independent from the audited area. They can also beconducted by external personnel.

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

6.6.4.2.1.2.1 All self-inspections must be recorded. Reports shall include all observations made during inspections and, whereappropriate, proposed corrective actions must be recorded in the facility's CAPA system.

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

6.6.4.2.2 Supplier audits.

6.6.4.2.2.1 Facilities must determine based on a risk assessment those suppliers of supplies that have an impact on thequality, safety, and efficacy of medical devices.

6.6.4.2.2.2 Criteria must be established for the evaluation and selection of suppliers including:**6.6.4.2.2.2.1** Supplier's ability to provide products that meet the organization's requirements. **6.6.4.2.2.2.2** Supplier performance.

6.6.4.2.2.2.3 The impact of the purchased product on the quality of the medical device.

6.6.4.2.2.2.4 The risk associated with the medical device.

6.6.4.2.2.3 There must be a procedure for the execution of audits for suppliers of materials, analytical service providers,service providers to critical systems and equipment and contract manufacturers.

6.6.4.2.2.4 A periodic audit program must be in place and documented evidence shall be available to demonstrate compliance.

6.6.4.2.2.4.1 The schedule of supplier audits should be established based on the level of risk in the process, the impact andprevious qualification reports.

6.6.4.2.2.5 Supplier audit reports must be part of the Supplier' qualification file.

6.6.5 Process monitoring and measurement.

6.6.5.1 The facility must have a formal process to review at least once a year the Quality Management System. The reviewshall 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 the processes within theQuality Management System, includes at least:

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

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

6.6.5.5 Innovations that can improve the Quality Management System.

6.6.5.6 Objectives changes and business environment.

6.6.6 Product monitoring and measurement.

6.6.6.1 There must be an annual systematic review of the quality of each product. The health manager must assure 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, and from trend analysis and risk assessment, the need for changes in the manufacturing process, process controls and specifications can be determined.

6.6.6.3 There must be a procedure to perform the product monitoring and measurement containing the objectives to determine and justify the areas selected for review, as well as the possible extent of the review.

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

6.6.6.5 There must be a record of the Annual Product Review (APR) or the Annual Product Quality Review (APQR); 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 during the year, number of approved batches with deviations or nonconformities andnumber of rejected batches.

6.6.6.5.3 Review of starting materials.

6.6.6.5.4 Summary of critical operations data, in-process controls and finished product allowing trend analysis.

6.6.6.5.5 Recording of deviations or non-conformities, out-of-specification results, change control, returns, complaints, recalls including the investigation report and conclusions of the implemented actions.

6.6.6.6 The APR 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 during the year, number of approved batches, number of approved batches with deviations or non-conformities and number of rejected batches;

6.6.6.6.3 Review of starting materials;

6.6.6.6.4 Summary of critical operations, in-process controls and finished product data allowing trend analysis, and

6.6.6.6.5 Recording of deviations or non-conformities, out-of-specification results, change control, returns, complaints, recallsincluding investigation report and conclusions of implemented actions, summary of stabilities and maintenance of validated status.

6.6.6.7 The APQR must contain at least the following information:

6.6.6.7.1 Name, period of shelf life;

6.6.6.7.2 Serial/identification numbers of products manufactured during 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 allowing trend analysis, and

6.6.6.7.5 Recording of deviations or non-conformities, out-of-specification results, change control, returns, complaints, recalls including the investigation report and conclusions of the implemented actions.

6.6.7 Control of non-conforming product.

6.6.7.1 Deviations or non-conformities.

6.6.7.1.1 Products at any stage not complying with the established specifications or 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 must be issued to define the level and extent of the nonconformance and establish corrective actions to determine if the product can be repackaged, recovered, reprocessed, reworked, or rejected.

6.6.7.1.3 There must be an investigation of deviations or nonconformities to determine the root cause analysis. This analysis canbe determined based on Risk Management principles.

6.6.7.1.3.1 A methodology must be established for the investigation of deviations, nonconformities or increasing trends includingthe 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) should be considered and addressed. The depth of the investigation should be commensurate with the significance and associated risk.

6.6.7.2 Handling of non-conforming product.

6.6.7.2.1 There must be a procedure describing:

6.6.7.2.1.1 Identification of non-conforming product.

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

6.6.7.2.1.3 Actions to be implemented in cases of repackaging, 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 health manager or his or her designee.

6.6.7.3.2 The health manager or authorized person must establish the final disposition of the product.

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

6.6.7.3.4 Recovered batches must be subjected to quality analysis and documentation must demonstrate that the quality of therecovered batch is equivalent to that of the original process.

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

6.6.7.3.6 A specific rework, recovery or reprocessing order and instructions must be issued for each batch or batch series.

6.6.7.3.7 In the case of reprocessing, rework and/or repackaging, a batch/serial number different from the original must beassigned, which must be authorized by the Health Manager.

6.6.7.3.8 The release of a reworked, recovered, or reprocessed batch must follow the steps described in the section 14 of thisTechnical Regulation and be authorized by the Health Manager or his/her designee.

6.6.8 Data analysis.

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

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

6.6.8.3 Data analysis must include information generated because of monitoring and measurement and from other relevantsources and include, at a minimum, the following information:

6.6.8.3.1 Feedback: complaints, recalls, returns, deviations, CAPA, process changes; process and product trends, feedbackon 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 must use thisanalysis as input for improvement as indicated in section 6.6.9 of this Technical Regulation.

6.6.9 Improvement.

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

6.6.10 CAPA.

6.6.10.1 A system should be in place for the implementation of CAPA's resulting from nonconformities, complaints, returns, out-of-specification results, audits, trends, and those defined by the system itself.

6.6.10.2 A methodology must be established for the investigation of deviations, nonconformities or increasing trends includingthe use of technical and/or statistical tools to determine the root cause, the definition of responsible parties and commitment dates.

6.6.10.3 The CAPA's 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 must be verified that any newrisks are assessed according to 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 implement actions toeliminate the cause of the nonconformity or deviation to prevent its recurrence. All necessary corrective actions should be implemented immediately or justify their delay. The type of corrective actions should be proportional to the impact of nonconformitiesfound.

6.6.10.5.2 Verify that the corrective action does not adversely affect the ability to meet authorized specifications or registration conditions, 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 must determine the actionto eliminate the causes of the nonconformity or deviation, to prevent its recurrence. Preventive actions should be proportional to thepotential impact 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 ofthe medical device.

6.7 Facilities having certification under ISO13485 standard in force issued by organizations authorized by national accreditation bodies or internationally recognized accreditation bodies shall be recognized in the conformity assessment as equivalent to the requirements established in section 6 of this Technical Regulation.

6.7.1 During the conformity assessment of this Technical Regulation, the inspection shall be conducted under a reduced approach except for section 6 and its subsections.

7. Quality Risk Management

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

7.2 Methodology for Risk Management in systems, operations and processes must be supported by proven analysis tools and according to their risk level, to assure the effective and logical management of priorities and strategies for Quality Risk Management.

7.3 There must be a set of procedures evidencing the implementation, training, and qualification of the personnel responsible for the Quality Risk Management System and its application.

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

7.5 There must be an efficient communication method to assure 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 guarantee its validity and the robustness of the Quality Management System.

7.7 For implementing the Quality Risk Management, refer to the Appendix "Application of Risk Management to Medical Devices"of the FEUM Supplement for Medical Devices.

8. Design and development

8.1 Overview.

8.1.1 The person responsible for the development area must document the design and development procedures.

8.2 Design and development planning.

8.2.1 The person responsible for the development area should plan and control the design and development of the product. As appropriate, design and development planning documents must be maintained and updated as design and development progresses.

8.2.2 During design and development planning, the following must be documented:

8.2.2.1 Design and development stages.

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

8.2.2.3 Appropriate design verification, validation, and transfer activities at each stage of design and development.

8.2.2.4 Responsibilities and authorizations for design and development.

8.2.2.5 Methods assuring traceability of design and development inputs and outputs.

8.2.2.6 Necessary resources, including the required personnel expertise.

8.3 Design and development inputs.

8.3.1 Records of inputs related to product requirements must be determined and maintained.

8.3.2 These inputs shall include:

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

8.3.2.2 Applicable requirements and provisions.

8.3.2.3 Applicable Risk Management Result(s).

8.3.2.4 Information from previous similar designs.

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

8.3.3 Design and development input records will be reviewed by the development area manager for appropriate use andapproval.

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

8.4 Design and development products.

8.4.1 Design and development products must:

8.4.1.1 Meet the input requirements for design and development.

8.4.1.2 Provide adequate information for purchase, production, and service delivery.

8.4.1.3 Contain or refer to product acceptance criteria.

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

8.4.2 Design and development results must be in a form suitable for verification against design and development inputs. Theymust be approved by the development manager and the health manager prior to implementation.

8.4.3 Design and development products records must be kept.

8.5 Design and development review.

8.5.1 Systematic design and development reviews must be conducted in accordance with pre-established and documentedplans for:

8.5.1.1 Assess the ability of design and development deliverables to meet requirements.

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

8.5.2 Participants in the reviews should include representatives of functions related to the design and stage of developmentbeing reviewed.

8.5.3 Records of the results of reviews and any necessary action should be kept and include identification of the design underreview, the participants involved and the review date.

8.6 Design and development verification.

8.6.1 Design and development verification must be performed as planned and documented to assure that the design anddevelopment products have met the input requirements.

8.6.2 The person responsible for the development area must document verification plans including methods, acceptancecriteria such as statistical techniques with a justification for sample size.

8.6.3 If the intended use requires the medical device to be connected or interface with other medical device(s), verificationshall 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 must be retained.

8.7 Design and development validation.

8.7.1 Design and development validation must be performed as planned and documented to assure that the resulting productis able to meet the requirements for the specified application or intended use.

8.7.2 The facility must document validation plans including methods, acceptance criteria such as statistical techniques with ajustification for sample size.

8.7.3 Design validation shall be performed on a representative product. The representative product includes initial productionunits, batches, or their equivalents. The rationale for the selecting the product used for validation must be recorded.

8.7.4 As part of the design and development validation, the person responsible for the development area must perform clinicalor performance evaluations.

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

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

8.7.7 Validation must be completed prior to product release or implementation for commercialization.

8.7.8 Records of the results, and the conclusion of the validation, and the necessary actions must be retained.

8.8 Design and development transfer.

8.8.1 The person responsible for the development area must document procedures for the transfer of products from design and development to manufacturing. These procedures shall assure 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 Results and conclusions of the transfer must be recorded.

8.9 Design and development change control.

8.9.1 The person responsible for the development area must document the procedures to control design and development changes.

8.9.2 The person in charge of the responsible for the development area must determine the significance of the change based on the performance, functionality, safety, and regulatory requirements for obtaining the medical device's health registration and its intended use.

8.9.3 Design and development changes should be identified before implementation. Changes shall be:

8.9.3.1 Reviewed.

8.9.3.2 Verified.

8.9.3.3 Validated.

8.9.3.4 Approved.

8.9.4 Review of design and development changes should include evaluation of the impact of changes on components, products in process or already delivered, Risk Management inputs or outputs, and manufacturing processes.

8.9.5 Records of changes, their review and any necessary action should be retained.

8.10 Design and development record.

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

9. Personnel

9.1 There must be an authorized and updated organization chart that clearly establishes the levels of authority and the 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 must be completely independent within the organizational structure, not depending on or reporting to each other.

9.1.2 The health manager must have the highest hierarchical level in the quality area of the facility, reporting directly to the highest position in the facility.

9.1.2.1 The health manager must have at least a bachelor's degree in the pharmaceutical, chemical, biological, medical, biomedical, biochemical or other profession, as long as it is related to the process; 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, allowing decision making in GMP or GSDP aspects.

9.1.2.2 The health manager is responsible for the quality of the product, together with the highest authority of the organization, he/she is responsible for assuring that a Quality Management System is in place.

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

9.1.3 Delegation of functions.

9.1.3.1 The health manager shall designate in writing the person(s) who will oversee various tasks, including the signing of operational documents, when the health manager is absent or under special circumstances, e.g., concurrent projects and workload.

9.1.3.2 The designated person(s) will have to comply with the requirements established in the applicable provisions for health managers.

9.1.4 The health manager must authorize the master documents that guarantee compliance with the GMP and the basic documents of the Quality Management System. The documents generated from these documents may be signed in accordance with the declarations of the documentation system.

9.1.5 For manufacturing plants established in Mexico, the owner of the facility shall be responsible together with the health manager for compliance with this Technical Regulation and other applicable provisions.

9.1.5.1 For manufacturing plants established abroad, the Health Registration Holder and/or his/her legal representative in Mexico, together with the health manager (responsible for the quality unit), shall be responsible for compliance with this Technical Regulation.

9.2 There must be a selection, training, evaluation, and qualification system in place to guarantee that

personnel have the necessary academic background, knowledge, and experience to perform their functions and responsibilities in accordance with thejob profile.

9.3 There must be an annual training program including GMP or GSDP topics, job-specific operations, hygiene and safety, andevidence of its implementation should be maintained. Training must include specific topics for personnel working in areas where there are risks of contamination or handling of highly active, toxic, or sensitive materials orproducts.

9.3.1 The effectiveness of training must be evaluated at least once a year, through proficiency tests demonstrating the ability orexpertise of the personnel in the assigned tasks.

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

9.4.1 The clothing requirements for each manufacturing area will depend on the classification of the area based on the risk level of the medical device and should 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 the health status of the person does not compromise the quality of the products.

9.6 Periodic medical evaluation requirements for manufacturing and quality personnel will depend on the type of product and manufacturing process they participate on.

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

9.7 Any personnel showing a possible illness or overt injury, as determined by medical examination or physical supervision, that may adversely impact 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 of the finished product, during the period taken to determine the health condition by competent medical personnel. All personnel shall be instructed to report to supervisory personnel any disease condition that may have adverse impact on medical device manufacturing processes.

9.8 If the personnel in the manufacturing areas where the medical device or supplies are exposed must leave the area, they shallchange 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 itsmaterials are exposed.

9.11 External personnel providing technical advice, consulting, as well as contractors, for any of the sections included in this Technical Regulation, 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 medical devices manufactured.

9.11.1 Records should be maintained indicating the name, experience and type of service provided by the external personnel orconsultant.

9.11.2 Temporary personnel or consultants should not define the final judgment of the medical device.

9.12 Personnel must not eat or store food or beverages of any kind in the manufacturing areas, laboratory, and warehouse areas, nor smoke in any area of the facility except in those areas designated for these purposes.

9.13 Temporary operative personnel must comply with the same requirements as permanent personnel, after an induction courseon the activity to be performed.

9.14 Newly hired personnel, both temporary and permanent, must work under the supervision of qualified personnel until they demonstrate their qualification to perform their functions.

10. Facilities and equipment

10.1 General.

10.1.1 The facility must be designed, built, and maintained in accordance with the operations performed therein, based on the risk level of the medical device. Its design and construction must allow cleaning, order, maintenance, and prevention of contamination, and personnel and materials flow must follow a logical

sequence.

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

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

10.1.4 Areas and equipment must be located, designed, constructed, installed, and maintained in conditions allowing their correct operation.

10.1.5 Critical areas, manufacturing equipment and systems directly impacting product quality must be qualified and validated.

10.1.6 There must be alternate power supply systems to maintain the conditions of the 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, to implement the necessary measures in accordance with the corresponding SOP.

10.2 Facilities.

10.2.1 Considerations.

10.2.1.1 There must be manufacturing areas, laboratory and other rooms involved in manufacturing, which must be constructed using materials allowing cleaning, keep them free of dust, insects, pests and facilitate their maintenance, to minimize the risk of contamination.

10.2.1.2 Activities for the prevention, control and eradication of harmful fauna must be carried out in accordance with an established program.

10.2.1.3 Maintenance activities must be carried on facilities and buildings under a program to assure that repair and maintenanceoperations do not represent a risk to product quality.

10.2.1.4 In case of construction or remodeling works, the required measures must be applied based on Risk Management to avoid contamination of areas and/or products.

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

10.2.1.6 Lighting, temperature, humidity, and ventilation must be adequate for the activities performed in each area and must notdirectly or indirectly affect the product, equipment, and personnel.

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

10.2.1.8 Manufacturing areas must be identified and separated for each of the manufacturing processes; in the case of processesin which more than one operation is carried out continuously, Risk Management must be performed and the design of the areas must be justified.

10.2.2 Production areas.

10.2.2.1 There must be specific areas for: reception, inspection and/or sampling, weighing and/or dispensing of materials; production, bulk product storage and packaging.

10.2.2.2 The design and location of the areas must allow personnel, materials, product in process, finished product and waste flow 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 Technical Regulation.

10.2.2.3 Production areas shall be classified based on regulatory Appendix A of this Technical Regulation.

10.2.2.3.1 There must be environmental monitoring of the classified areas.

10.2.2.4 Design of the production areas must include rooms for personnel access, change of working clothes according to the classification of the regulatory Appendix A of this Technical Regulation.

10.2.2.4.1 Access to production areas must be restricted and controlled.

10.2.2.5 According to the classification of the manufacturing area and the risk level of the product, the ventilation duct installations, electrical power lines and other services inherent to the production areas must

be hidden or outside of them. Their location and design must allow maintenance, and in cases where volatile liquids are used in the production areas, there must be anti-explosion facilities and systems that maintain the concentrations allowed in the applicable standards.

10.2.2.6 Fixed piping must be identified according to the code of the Official Mexican Technical Regulation mentioned in section 2.6 of this Technical Regulation, and in those cases where the direction of flow is applicable.

10.2.2.7 Pipelines through which raw materials, intermediate or bulk products are transferred must be built using inert, non- contaminating material and must be identified.

10.2.2.8 If the manufacture of medical devices requires the use of water, Risk Management must be performed to determine thetype 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 must be designed, installed,qualified, and monitored in accordance with FEUM.

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

10.2.2.10 Drains must have traps or some device to prevent backflow or contamination. In Class A/B areas (see Appendix A ofthis Technical Regulation) used for aseptic production, drainage is prohibited.

10.2.2.11 There must be areas for the storage of manufacturing equipment accessories.

10.2.2.12 There must be specific areas or cabinets, duly identified to store tools, substances or materials required for the maintenance of manufacturing equipment, which must comply with the same sanitary conditions according to the area in which theyare located.

10.2.2.13 Areas, manufacturing equipment and processes must have the required critical systems such as: HVAC, compressedair, pharmaceutical water, and pure steam.

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

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

10.2.2.16 HVAC system shall be designed and configured in accordance with the minimum considerations established in FEUMto meet the required area classification in accordance with regulatory Appendix A of this Technical Regulation.

10.2.2.17 Areas must have a monitoring system for critical variables in accordance with FEUM to comply with the classification of regulatory Appendix A of this Technical Regulation.

10.2.2.18 The formulated product areas where dusts are generated must have dust extraction and collection systems designedto avoid cross-contamination and environmental contamination.

10.2.2.19 For aseptic processes, facilities should also consider the following:

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

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

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

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

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

10.2.2.20 It must be assured 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 The storage areas must be designed and constructed to assure GSDP's, they must comply with cleanliness, temperature and RH conditions required by the type of supplies and/or products and must be

monitored and verified.

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

10.2.3.3 The reception area for supplies and products must be designed and constructed to protect them from the outsideenvironment, allowing inspection and cleaning.

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

10.2.3.5 They must have delimited areas for the storage of supplies and recovered or returned products. Rejected productsshould be in segregated and identified areas.

10.2.3.6 Printed packaging materials must be stored in an area with controlled and restricted access.

10.2.3.7 There must be specific areas with storage conditions for holding samples of raw materials and/or finished medicaldevices, 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 must be physically separated from the production areas and warehouses and haveenough rooms and space for testing and analyses carried out there.

10.2.4.1.1 If the laboratory is intended for microbiological analysis, it must have an air injection system, the characteristics ofwhich 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 the nature ofthe tests.

10.2.4.2 Instruments sensitive to vibration, electrical interference, humidity or requiring special conditions must be installed inseparate rooms or in rooms that provide the conditions recommended by the manufacturer for their protection.

10.2.4.3 Laboratory must have a specific area for receiving samples of supplies 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 andcomply with the technical specifications, in terms of the Official Mexican Technical Regulation mentioned in section 2.10 of this Technical Regulation.

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

10.2.5 Auxiliary areas.

10.2.5.1 Areas destined for medical service and dining rooms must be separated from manufacturing areas.

10.2.5.2 Areas for dressing rooms, locker rooms, laundry and sanitary services should be easily accessible, and their sizemust correspond to the number of workers.

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

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

10.2.5.5 There must be a specific area, separate from the manufacturing areas, to store the waste generated during themanufacture and/or analysis of the products.

10.3 Equipment.

10.3.1 Overview.

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

10.3.1.2 The location of the manufacturing equipment shall not obstruct the movement of personnel, nor the ventilation system grids, they should facilitate the flow of materials, assure 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 must 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 conducted, it must be considered that the materials of the manufacturingequipment and accessories that are in direct contact with the product must be inert and non-absorbent or non-adsorbent.

10.3.1.4.1 Lubricants, refrigerants, or other substances required for the operation of manufacturing equipment shall not be indirect 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 incontact with the product, they must be at least food grade, be purchased under a specification and establish their handling.

10.3.1.5 Gears and moving parts must be protected to avoid contamination of the medical device in process and for operatorsafety.

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

10.3.1.7 Damaged equipment awaiting maintenance must be identified and not represent a risk to personnel and operation.

10.3.1.8 Manufacturing equipment, accessories, utensils, and all piping must be cleaned and maintained in accordance withwritten procedures detailing the activities to be performed.

10.3.1.9 To maintain traceability and functionality, a record of the use and inspection of the condition of the accessories mustbe maintained.

10.3.1.10 Filters used in the production or primary packaging of products must be made of materials that do not release fibersor other foreign bodies.

10.3.1.11 Instruments used in the monitoring and control of critical process parameters must be calibrated and inspectedaccording to a written program designed to assure 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 device is in direct contact with the patient, the water generation and distribution system or, if applicable, the water generation equipment, must be treated as a critical system and its design, construction, qualification, and monitoring must be performed in accordance with FEUM.

10.4.2 The HVAC system shall be designed, constructed, and maintained in accordance with the FEUM to assure theclassification required in regulatory Appendix A of this Technical Regulation.

10.4.2.1 HVAC corresponding to Class A (ISO-Class 5), B and C (ISO-Class 7) must have at least 99.97% HEPA terminal filtersof 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 they must have at least 85% efficiency filters, in accordance with the provisions of Appendix A of this Technical Regulation.

10.4.3 The compressed air generation and distribution system must be designed, constructed, and maintained in accordancewith FEUM.

11. Qualification and validation

11.1 Overview.

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 assure device quality.

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

11.2 Scope of validation.

11.2.1 The scope of validation must 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 VMP.

11.4.1 There must be a written VMP for the development of the qualification and validation activities, which must be authorized by the highest hierarchical level of the organization and by the health manager, and the scope, responsibilities and priorities of the qualification and validation must be established.

11.4.2 The VMP 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 its equivalent.

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

11.4.2.6 Forms 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 impacting product quality.

11.4.2.12 Critical systems.

11.4.2.13 Production and packaging equipment.

11.4.2.14 Cleaning and/or sanitizing procedure or methods.

11.4.2.15 Production and packaging processes.

11.4.2.16 Maintenance of the validated status.

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

11.5 Technology transfer must have a planned and documented approach using Risk Management, considering trained personnel, qualification and validation requirements, manufacturing systems and quality control, and must 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 performed, specifying the critical stages, and including the acceptance criteria.

11.6.1 Qualification and validation reports.

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

11.7 Qualification.

Qualification must be performed through the following four consecutive stages:

11.7.1 They must have DQ based on user requirements, including functional and regulatory requirements.

11.7.2 They must have IQ according to DQ and manufacturer's requirements.

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

11.7.4 They must have PQ demonstrating that the equipment and system comply with the previously established requirements under routine use conditions and within the permitted working intervals for each product.

11.7.5 To proceed to the next stage of qualification, the previous stage must be satisfactorily completed. Next stage can be started only when there are no open major non-conformities and a documented

assessment demonstrating no significant impact on the next stage is available.

11.7.5.1 Measuring instruments involved in the qualification must be calibrated with traceability to national and/or international standards.

11.7.6 When the manufacture of medical devices involves manual processes, and controls must be established to assure 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 qualification.

11.8.1 The HVAC system must be qualified according to FEUM, considering at least the following parameters: temperature andRH% of the Areas it feeds, air injection volume, pressure differentials between areas, number of air changes, particle counts, air flows, cleanliness levels, flow rate 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 used in the manufacture of medical devices must be in accordance with FEUM.

11.10 Qualification of the compressed air system.

11.10.1 The qualification of the compressed air generation and distribution system must be conducted in accordance with FEUM.

11.11 Process validation.

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

11.11.2 Process validation must be completed prior to distribution and sale of the product.

11.11.3 Process validation should be performed with a Quality Risk Management approach.

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

11.11.3.2 The implemented approach must be based on scientific knowledge, level of understanding and demonstrable controlon the manufacturer side.

11.11.4 Process qualification. This stage can be conducted with a prospective or concurrent release approach:

11.11.4.1 Facilities, equipment, critical systems, and utilities must be qualified.

11.11.4.1.1 Each of these elements can be qualified with individual plans or all together with a general plan.

11.11.4.2 Process PQ.

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

11.11.4.2.2 At this stage, the manufacturing conditions must be defined and confirmed. This stage is integrated by the manufacturing process to produce commercial batches, of all the previously qualified elements, including qualified personnel, control procedures and supplies.

11.11.4.2.3 Objective measurement methods must be established using statistical tools.

11.11.4.2.4 Additional sampling, testing, and scrutiny of process performance than would be typical in commercial production must be performed during this phase.

11.11.4.2.5 The level of monitoring and testing must guarantee uniformity of product quality throughout the batch.

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 process qualification batches.

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 health emergency, this decision must be previously justified and

approved from the protocol by the health manager or authorized person. Documentation requirements must be the same as for prospective validation.

11.11.5.2 This allows that, even if the validation with the minimum number of batches necessary to complete it has not been concluded, the release of these batches can be done, 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 the 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 health registration.

11.11.5.4 Any non-conformance report or event from customers must be documented in the validation report for each batch andinvestigated immediately to determine the root cause for correction.

11.11.5.5 Concurrently released batches 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 intended to be sterile and not subjected to terminal sterilization, each of the unit operations involved must be validated independently and confirmed as a whole.

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

11.13 Cleaning validation.

11.13.1 Cleaning validation must be performed to demonstrate the effectiveness of the cleaning procedures.

11.13.2 Cleaning procedures must be consistent with the nature of the products.

11.13.2.1 There must be a program for the use of sanitizers including a sporicidal agent.

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

11.13.2.3 Interactions between the different sanitizing agents must 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 must 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 can be used for validation or "worst case" criteria. This selection can 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 must 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 must be established based on the validation results.

11.13.8 A periodic program for trace determination of products included in the cleaning validation shall be established. This periodicity must 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 FEUM requirements.

11.14.2 When pharmacopeial methods are used, the applicability to the product must be demonstrated, under the laboratory operating conditions and according to the desired analytical method.

11.15 Validation of computer systems.

11.15.1 Computer systems impacting product quality and data integrity must be validated.

11.15.2 There must be an inventory of all computer systems available.

11.15.3 Computer systems must consider software components, instruments, equipment, and information technology infrastructure.

11.15.3.1 There must be a system of protection, integrity, and backup of the information, which must be determined based on the risk assessment documentation of the computer system. Data access and readability must be assured during the entire retentionperiod.

11.15.3.2 Access to data must be controlled.

11.15.3.2.1 Physical and/or logical controls must 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 must lock a user after a defined number of unsuccessful login attempts.

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

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

11.15.3.3.2 If it is determined that a system generates and maintains regulated electronic data, there must be documentaryevidence to assure traceability, easy access, and data integrity.

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

11.15.3.5 Data must 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 during validation andmonitored 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 alteration of the data 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 assure accuracy, integrity, and consistency in the expected performance of the computer systems.

11.15.4.1 Risk Management must be applied to the entire validation cycle, including the planning, specification, testing, systemrelease, maintenance, and system retirement phases.

11.15.4.2 Components of the information technology infrastructure and any relevant tools or equipment must 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 recordsdelivered by the supplier shall not substitute the validation tests performed by the company, equipment, and personnel, such as validation plan, user requirements, risk analysis, PQ, and validation report.

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

11.15.5 There should be a traceability matrix documenting the multiple stages of specification (including revisions) and testing upon satisfactory completion.

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

11.15.5.2 Control procedures must be implemented to assure the review of data audit on a regular basis; the frequency and method shall be determined according to the risk.

11.15.5.3 Systems with data auditing functionality must output information allowing 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 the review confirming data is notaltered in value and/or definition during the migration process.

11.15.6 For electronic signatures:

11.15.6.1 Electronic signatures 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 andequivalent to the handwritten signatures must be established.

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

11.15.6.4 Electronic signatures shall be linked to their respective electronic records to assure that the signatures have notbeen altered, copied, or otherwise transferred to an electronic record to be falsified by ordinary means.

11.15.6.5 In case the electronic signature is made by means of *tokens* or biometric devices, the system must ensure that itcannot be used by another person and that control measures have been implemented.

11.15.7 Warehouses using software for inventory control shall have protocols for access controls and procedures for use thatguarantee data integrity.

11.16 Maintenance of the validated status.

11.16.1 Maintenance of facilities, equipment and systems is another important aspect to assure the process is maintained undercontrol. Once qualified/validated status has been achieved it must be maintained through routine monitoring, maintenance, procedures, and calibration programs.

11.16.2 A review at a frequency determined by means of a risk assessment, of the facilities, systems and equipment must be performed to determine if re-qualification is required. This must be documented as part of the

maintenance of the validated status.

11.16.2.1 If the facilities, systems, and equipment have not undergone significant changes, documentary evidence that they meet

the predefined requirements is sufficient as evidence of their maintenance of the validated status.

11.16.3 When a change affects the quality or characteristics of the product, or its components and/or process, a new qualificationand/or validation must be performed.

11.17 Qualification and validation guidelines.

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

12. Manufacturing Systems

12.1 Medical device manufacturing systems must follow written procedures to assure compliance with GMP. The characteristicsof each system will be conditioned by Risk Management, the nature of the processes and the quality specifications of each product.

12.2 Control of supplies.

12.2.1 Overview.

12.2.1.1 There must be written procedures for the reception, identification, sampling, storage, control, and handling of all suppliesused in the manufacture of medical devices.

12.2.1.2 It shall be assured that certificates of analysis or conformity of the supplies are those issued by the manufacturer.

12.2.1.3 Supplier qualification and approval must be performed prior to the purchase of any supply.

12.2.1.4 Supplies at any stage of manufacture must be handled and stored to prevent contamination and alteration.

12.2.1.5 Supplies must be identified with a batch number to prove traceability.

12.2.1.5.1 When different batches are received in a shipment, each batch must be considered separately for sampling, analysisor evaluation and release.

12.2.1.5.2 Supplies must be analyzed or evaluated by the quality unit at the medical device manufacturing site.

12.2.1.5.3 In the case of a consignment of a batch already received, the criteria for evaluating or analyzing the supplies must beestablished.

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

12.2.1.7 A system must be in place to assure that supplies are used under the criteria of First expiration- First-out or First-in-First-out.

12.2.1.8 Supplies, bulk product, semi-finished and finished products must be placed a location avoiding direct contact with thefloor.

12.2.1.8.1 When computer systems are used to control supplies, they must be validated.

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

12.2.1.10 Rejected supplies must be identified and segregated to prevent their use in manufacturing.

12.2.2 Reception.

12.2.2.1 Each container or group of containers must be verified for integrity and identified with at least name, quantity, andbatch number.

12.2.2.2 Supplies must be identified for storage indicating at least the following information:

12.2.2.2.1 The name and the international denomination.

12.2.2.2.2 Batch/serial number.

12.2.2.2.3 Quantity and number of containers.

12.2.2.2.4 Status.

12.2.2.2.5 Expiration or re-analysis date.

12.2.2.2.6 When the nature of supplies does not consider any of these general characteristics, it must be justified based on RiskManagement.

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

12.2.3 Sampling.

12.2.3.1 Supplies must be stored in quarantine until they have been sampled, analyzed, or evaluated and released for use bythe quality unit.

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

12.2.3.3 Samples taken must be identified.

12.2.3.4 The sampled containers must indicate this in their identification.

12.2.4 Dispensing.

12.2.4.1 Traceability of supplies per batch of quantities received versus quantities delivered, must be verified.

12.2.4.2 Supplies should be weighed or measured according to written procedures and this activity must be verified by asecond person.

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

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

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

12.2.4.4 When adjustments to the quantity of supplies a medical device to be manufactures are required, they must besupplied and verified by authorized personnel and documented in the

production order.

12.2.4.5 If a supply is removed from the original container to another, the new container must be identified in the same way.

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

12.2.4.7 Dispensed supplies for manufacturing must be separated by product batch they will be used for.

12.3 Control of manufacturing operations.

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

12.3.2 Access to manufacturing areas must be restricted and controlled.

12.3.3 Controls must be in place to prevent cross contamination. The cleaning validation protocol must be prepared based onRisk Management.

12.3.4 Manufacturing areas shall be maintained to the appropriate degree of cleanliness and sanitization in accordance withRisk Management, nature of the processes and area classification indicated in Regulatory Appendix A of this Technical Regulation.

12.3.4.1 There must be a SOP describing:

12.3.4.1.1 The procedure 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 qualityarea may be used.

12.3.5 Before starting the manufacturing process, the cleanliness of areas and equipment must be verified, and there should beno raw material, product, product residue or documents from the previous operation not required for the operation.

12.3.6 Medical device manufacturing areas shall maintain conditions consistent with Risk Management, nature of theprocesses and classification in accordance with Regulatory Appendix A of this Technical Regulation.

12.3.7 Operations of different products or batches shall not be carried out simultaneously in the same room, except when thereis no risk of cross-contamination.

12.3.8 Supplies flow must be carried out in a logical sequence to prevent the risk of cross- contamination.

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

12.3.10 Production or assembly order must remain available during the process.

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

12.3.12 Addition and ordering of supplies during manufacture shall be conducted and supervised according to themanufacturing instructions. Recording of the fabrication must be performed at the time of execution.

12.3.12.1 Production procedure must indicate the critical operations that require supervision.

12.3.13 Performance of in-process controls during production must not affect the process or jeopardize the quality of theproduct and personnel.

12.3.14 Results of testing and analyses performed for process control must be recorded or attached to the production orpackaging file.

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

12.3.16 If maintenance is required during manufacturing, procedures must be established describing measures to prevent affecting the quality characteristics of supplies, products, and area conditions.

12.3.17 When the medical device is sterilized, the validation of the process must be conducted in accordance with FEUM.

12.3.17.1 To release a batch of sterile product, satisfactory sterility test results must be available.

12.3.17.2 For sterile medical devices, retention samples must be retained 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.

12.3.18 Finished product storage and distribution areas.

12.3.18.1 The finished product is considered in quarantine until all its analyses have been performed and it is released by the quality unit.

12.3.18.2 All distribution activities must 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 A system must be established, either manual or computerized, allowing the correct distribution of medical devices.

12.3.18.5 A SOP must be established for the control of medical device distribution, describing:

12.3.18.5.1 Data to be recorded for each shipment such as: medical device name, Batch/serial number, quantity, purchaseorder, release file number.

12.3.18.5.2 The means and transport conditions

12.3.18.6 There must be storage instructions throughout the distribution chain available.

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

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

12.3.18.9 For products to be maintained under refrigerated conditions, packaging qualification and cold chain validation must beperformed.

12.3.18.10 A document (e.g., delivery note/packing list, invoice) must be attached to all shipments indicating the date; medical device name; batch/serial number; quantity; supplier's name and address; delivery name and address.

12.3.18.11 Product identification and integrity must be guaranteed.

12.3.18.12 A procedure shall be in place for the investigation and handling of deviations during transportation and delivery of theproduct, in accordance with section 6.6.7.1.3.1.

12.3.18.13 Distribution records for each product batch or serial number must be kept facilitating recall in accordance with section16 of this Technical Regulation.

12.3.18.14 The transportation for distribution must guarantee the conditions of conservation, cleanliness, and hygiene of the medical devices.

12.3.18.15 There must be written procedures for the operation, cleaning and maintenance of all transportation means and equipment used for the distribution process.

12.3.19 Production lines that may be involved in the manufacture of a medical device will be described below.

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

12.4 Formulated products.

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

12.4.2 The production and/or primary packaging processes must comply at least with ISO Class 8, considering Risk Management, as established in section 10.1.2.

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

12.4.3 Feeding and dosing systems must be designed to minimize exposure of supplies 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 bejacketed and have agitation control systems.

12.4.5 The type of water used for the final rinsing of equipment, accessories, and utensils in contact with the product must bedetermined based on Risk Management, the type of product and intended use of the medical device.

12.4.6 The quality of water used in production must comply with FEUM.

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

12.4.8 Retention samples of raw materials and finished product must be retained in accordance with sections 13.11 and 13.12of this Technical Regulation.

12.4.8.1 Retention samples of primary packaging materials and those that contribute to product integrity shall be retained for thesame length of time as the expiration date of the last batch of product they were used for.

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 ofthe Official Mexican Technical Regulation mentioned in section 2.9 of this Technical Regulation and the report of the Risk Management results of the product.

12.5.2 Retention samples of raw materials and finished product must be retained in accordance with sections 13.11 and 13.12of this Technical Regulation.

12.5.2.1 Retention samples of primary packaging materials and those that contribute to product integrity must be retained forthe same length of time as the expiration date of the last batch of product they were used for.

12.6 Plastics, polymers, and elastomers.

12.6.1 The processes considered for this manufacturing line include, 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 batch by batch, the execution of tests may be exempted such as systemic injection, intracutaneous reactivity, radiopacity and identification of the medical grade plastic, although these are referred to in the FEUM; provided that the type of plastic, polymer and/or elastomer has not changed with respect to the material authorized in the health registration, the supplier is qualified and they have evidence of compliance with these tests in at least 3 batches of the raw material, as part of the qualification of the material.

12.6.3 If FEUM requires systemic injection and intracutaneous reactivity tests for the release of finished product batch by batch,the execution of these tests may be waived, however, the results of these tests must be indicated on the certificate of analysis with reference to the original certificate of analysis and the date of execution of the tests, and not as tests performed batch by batch of product.

12.6.4 When the medical device does not come into direct contact with the patient, the manufacturing areas may be clean areaswithout classification in accordance with regulatory Appendix A of this Technical Regulation.

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

12.6.6 If the intended use of the medical device requires the sterility characteristic:

12.6.6.1 Manufacturing areas from the molding/forming/assembly process shall have Class D (ISO Class 8) and shall establishspecific procedures for bioburden control.

12.6.6.2 The water used for the final rinsing of the equipment or as an input in the manufacture of the medical device must bepurified water level 1 or demonstrate that specific procedures for the control of bioburden are in place.

12.6.7 Retention samples of each batch manufactured must be retained 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 forthe sterility test.

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

12.6.7.2 Manufacturing records must be retained for at least one year after the expiration date of the product.

12.6.7.2.1 For medical devices of this line, without an expiration date, the manufacturing records should be retained for at leastthe time of use recommended by the manufacturer.

12.6.8 An annual stability program must be implemented considering at least one batch per year of product manufacturedintended for commercialization, in accordance with FEUM.

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

12.7.1 Diagnostic supplies that can be used alone or in combination as an aid to other clinical or paraclinical procedures. Some of these include, but are not limited to agar plates and dehydrated culture media, anti-human globulin reagents, hemoclasifying 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 must be under the supervision of a person qualified in techniques such as strain management, allergen collection and possessing specialized scientific knowledge in immunology, microbiology, virology, or other according to thetype of product and processes to be performed.

12.7.2.2 All personnel involved in the manufacture of these products should receive specific training in the handling of strains, aseptic and/or hygiene and microbiology techniques or other areas of knowledge that may be required according to the nature of theproduct and processes.

12.7.2.2.1 Equivalent measures shall be implemented for temporary employees.

12.7.2.3 There must be a training program for personnel in biosafety and biological containment practices according to thetype of product and processes to be performed

12.7.3 Facilities.

12.7.3.1 Manufacture of non-sterile *in vitro* diagnostic agents may be performed in clean areas without classification inaccordance with Appendix A of this Technical Regulation.

12.7.3.2 The manufacture of *in vitro* diagnostic agents to be sterilized by a terminal method must be performed at least in classD areas (ISO-class 8).

12.7.3.3 For the manufacture of sterile *in vivo* diagnostic agents, facilities shall include:

12.7.3.3.1 Class C Areas (ISO Class-7) for products sterilized by a terminal method.

12.7.3.3.2 Class A areas (ISO Class-5) for products manufactured by aseptic processing. The environment around Class Aareas (ISO Class-5) shall be at least Class C (ISO-7).

12.7.3.3.3 Water system for the manufacture of injections according to 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 must be recorded and evaluated as part of the product release.

12.7.4.2 Temperature records of freezers and/or refrigerators where strains, sera and cultures are stored must be maintained.

12.7.4.3 Each reagent batch must be tested by all methods recommended by the manufacturer on the labels and in theinstructions for use, for release.

12.7.4.4 When the diagnostic agent requires a particular storage condition, controls should be established to maintain thiscondition and the corresponding records.

12.7.4.5 For diagnostic agents containing antibodies, the expiration date of a batch shall be greater than one year and must beestablished from the date of the last potency test.

12.7.4.6 Retention samples of each batch manufactured shall be retained 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. In case the retention time is less

than this period, it must be justified based on Risk Management.

12.8 Metal-mechanics.

12.8.1 The processes considered for this manufacturing line include, but are not limited to melting, casting, cutting, stamping, tempering, 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 materials and corrosion resistance, even though these are referred to in FEUM; provided that the type of metal has not changed with respect to the material authorized in the health registration, the supplier is qualified and there are 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 performed as part of the qualification of the material must be available.

12.8.3 When marking the medical device, the passivation process and validation of this process must be performed to assurecorrosion resistance.

12.8.4 The manufacture of these medical devices may be carried out in gray areas without classification in accordance with Regulatory Appendix A of this Technical Regulation.

12.8.5 If the intended use of the medical device requires the sterility characteristic:

12.8.5.1 Prior to primary packaging of the product, specific processes for bioburden control must be established and must be conducted in at least Class D (ISO Class 8) areas in accordance with Appendix A of this Technical Regulation.

12.8.5.1.1 Primary packaging areas must be at least ISO-class 8.

12.8.6 In cases where humidity is a risk factor for the product, controls must be established to maintain this condition within theestablished requirements based on Risk Management.

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

12.8.8 When the medical device requires a specific condition to be transferred, to preserve the passivation, a container that guarantees such preservation must be used.

12.8.9 In the case of implanted medical devices without an expiration date, the manufacturing records should be retained for atleast the time of use recommended by the manufacturer.

12.8.10 Retention samples must be maintained for each batch of raw material used in the manufacture, in sufficient quantity for at least two complete analyses under the storage conditions indicated in the Specifications.

12.8.10.1 In the case of custom-manufactures medical devices, it is not necessary to maintain retention samples of the finishedproduct.

12.8.11 In the manufacture of some of the products in this line, highly toxic materials are used that require special handling; thehandling conditions for these materials must 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 include, but are 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 performed in gray areas without classification in accordance with Regulatory Appendix A of this Technical Regulation.

12.9.3 If the intended use of the medical device requires the sterility characteristic:

12.9.3.1 Prior to primary packaging of the product, specific processes must be established for the control of Bioburden, which must be performed at a minimum in clean areas, without classification in accordance with Appendix A of this Technical Regulation.

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

12.9.3.3 Primary Packaging Areas must be at least clean areas, without classification in accordance with Appendix A of this Technical Regulation.

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

12.9.5 Retention samples of each batch of medical device bearing the Sterility characteristic should be retained for at least oneyear after the Expiration Date indicated on the final packaging and stored under the conditions indicated on the label.

12.10 Assemblies.

12.10.1 In this production line are all facilities receiving as supplies the necessary parts 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, hyperbaric chamber, 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 not exhaustive. This list is illustrative but not limiting.

12.10.2 Assembly of non-sterile medical devices may be performed in gray areas without classification in accordance with Regulatory Appendix A of this Technical Regulation.

12.10.3 Assembly of medical devices to be sterilized shall be performed in Class D (ISO Class 8) areas in accordance with Appendix A of this Technical Regulation.

12.10.4 When compressed air is used as part of assembly activities and is in contact with the product, it should be defined and qualified as a critical system, when it is justified by the level of risk and the intended use of the medical device.

12.10.5 When solvents, adhesives or other chemical agents are used in assembly activities, in parts coming into contact with the patient, it must be demonstrated based on validation that they do not leave residues that compromise the safety of 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 should consider safety conditions for personnel.

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

12.10.8 The assembly of medical equipment manufactured in series must have functional testing to each piece of medical equipment assembled.

12.10.9 Retention samples of each batch of medical devices showing the sterility characteristics must be retained for at least one year after the expiration date indicated on the final packaging and stored under the conditions indicated on the label.

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

12.10.10.1 When assembly is performed semi-automatically or automatically, the equipment must be qualified and based on theresult of qualification, the sampling criteria must be implemented for the assembly strength testing.

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

12.10.12 When the medical device includes software for its operation or functioning, Software validation must be performed in conjunction with the Medical Device, in accordance with FEUM.

12.10.12.1 The national and international guides described in the bibliography of this Technical Regulation may be used as support for validation.

12.10.13 Validation of the software considered as a medical device must be performed, according to FEUM or to the section 11.17.

12.10.13.1 Analytical/technical validation of the software as a medical device must include at a minimum:

12.10.13.1.1 Technical documentation of the design and development of the software, i.e., information of software construction(at least, input data, operating systems, programming language, databases used, etc.).

12.10.13.1.2 Documented evidence that the software processes input data correctly and reliably and generates accurate,complete, and precise output data.

12.10.13.1.3 Execution of tests demonstrating that the software complies with the specifications established for the intendedmedical purpose.

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

12.10.15 *Remanufacturing and Refurbishing/ Rehabilitation* of medical equipment must be carried out in specific areas for theseprocesses.

12.10.15.1 There must be procedures establishing the activities and criteria for receiving equipment, as well as the forms forrecording these activities.

12.10.15.2 There must be forms for reviewing and recording the activities carried out on the equipment to maintain traceability.

12.10.15.3 For *remanufacturing* and *refurbishment/rehabilitation* activities, the replaced parts or systems must be of the sametype or specification indicated in the previously authorized condition.

12.10.15.4 *Remanufacturing* and *refurbishment/rehabilitation* must be performed by the manufacturer or at a facility authorizedby the manufacturer.

12.11 Biological processes.

12.11.1 This production line includes all facilities performing 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, cultivation, propagation, purification, etc. Some of the medical devices considered for this manufacturing line include grafts, valves, implants, etc. This list isillustrative but not limiting.

12.11.2 Personnel.

12.11.2.1 Personnel involved in the manufacture of these products must receive specific training in the processes they are to beinvolved with 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 The personnel shall be under the supervision of a person 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 required according to the nature of the product and the processes.

12.11.2.3 There must 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, there must be at least ISO-Class 7 areas for devices sterilized by a terminal method.

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

12.11.3.2 Sterile biological medical devices not having a terminal sterilization method shall be manufactured in Class A (ISO- Class 5) areas. The environment around these areas shall meet at least Class B.

12.11.4 Production.

12.11.4.1 Supplies of animal origin or those used for their manufacture derived from animal origin must present the certificate indicating they are free of TSE, BSE, foot and mouth disease, bovine leucosis and others representing 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 one batch andmay be assigned with a sub-batch number if traceability with the batch of origin is maintained.

12.11.4.3 Raw material of human origin for the production and development of implants must come from tissue banks with healthlicense according to the applicable dispositions and must be evaluated with criteria allowing the reduction of the risks of disease transmission to the receptor, which will be fully identified and traceable to the donor.

12.11.4.3.1 There must be procedures describing the handling, storage and transportation of raw materials, bulk products and finished product of human or animal origin, to maintain the cold chain.

12.11.4.3.1.1 All equipment for storage must 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 the cold chain has been maintainedand to establish in writing the characteristics of the containers, the configuration of the packaging and the responsibilities of the personnel involved in this process.

12.11.4.3.1.4 The time for the product to remain out of refrigeration should be established based on stability studies to assure itremains within specifications.

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

12.11.4.3.1.6 A backup system and contingency plan must be in place to assure the maintenance of storage conditions requiredby the product in emergency situations.

12.11.4.4 The processes of preparation and procurement of implants derived from human tissue must assure inactivation and sterilization. Those processes must 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 that the device is free of nucleic acids (by NAT) of Human Immunodeficiency Virus (HIV) 1 and 2, Hepatitis A Virus (HAV), HepatitisB Virus (HBV), Hepatitis C Virus (HCV), parvovirus B19 or any other pathogenic microorganism.

12.11.4.6 Tissues and cell banks must be kept separately from other materials, under storage conditions designed to maintain their viability and avoid contamination.

12.11.4.7 Continuous temperature records of freezers, refrigerators and/or incubators in which tissues and/or cells, or anyother biological product, are stored, must be available.

12.11.4.8 Tissues may be preserved for a maximum of 5 years, if the conservation of viability, purity and bioburdencharacteristics 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 must be retained for at least one year after the expiration date of the product.

12.11.4.11 Retention samples of each batch manufactured must be maintained at least one year after the expiration date indicated on the final packaging and stored under the conditions indicated on the label and in sufficient quantity according to the nature of the tissues.

12.11.4.12 When the diagnostic agent requires a particular storage condition, such as refrigeration or freezing, appropriate controls and records must be established.

12.11.4.13 In the case of grafts, specific protocols based on scientific knowledge must be developed 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 performed in accordance with the provisions of Articles 230 and 231 of the General Health Law.

12.11.4.15 Before disposal, biological products and materials must be inactivated and handled according to section 6 of the Official Mexican Technical Regulation mentioned in section 2.12 of this Technical Regulation.

12.12 Ceramics/glass.

12.12.1 The processes considered for this manufacturing line are casting, 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 illustrative but not limiting.

12.12.2 The manufacture of these medical devices may be performed in gray areas without classification in accordance withRegulatory Appendix A of this Technical Regulation.

12.12.3 In the case of prostheses, if they are marked, the polishing process must be performed and validated to avoid roughness.

12.12.4 If the intended use of the medical device requires the sterility characteristic:

12.12.4.1 Prior to primary packaging of the product, specific processes for Bioburden control must be implemented and thisprocess must be carried out in Class D (ISO Class 8) areas in accordance with Appendix A of this Technical Regulation.

12.12.4.2 Primary Packaging Areas must be Class D (ISO-Class 8) as a minimum in accordance with Appendix A of this Technical Regulation.

12.12.5 The manufacturing records of these ceramic and glass devices must be retained for at least the time of userecommended by the manufacturer.

12.12.6 Retention samples must be retained for each batch of raw material used in the Manufacture in sufficient quantity for atleast two complete analyses under the required storage conditions.

12.12.6.1 In the case of custom-manufactured medical devices, it is not necessary to maintain Retention Samples of the finishedproduct.

12.13 Medicated medical devices.

They are those devices including as an integral part a drug that exerts on the human body a secondary or additional action to that of the medical device, consequently, in addition to this Technical Regulation, the generalities of drugs will be applied in accordance with the Official Mexican Technical Regulation NOM-059-SSA1-2015, Good Manufacturing Practices of Medicines, and the corresponding provisions in FEUM monographs and other applicable provisions.

12.14 Radiopharmaceuticals.

12.14.1 Overview.

12.14.1.1 The manufacture and handling of radiopharmaceuticals are potentially hazardous. The level of risk depends 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 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 quality assurance system is essential.

12.14.1.3 Manufacturing procedures used by industrial manufacturers, Nuclear Centers/Institutes and positron-emittingtomography centers for the production and quality control of the different types of products must be according to the following table:

Manufacturing Type	NOT GMP *	GMP**		GMP***	
Radiopharmaceuticals Positron-Emitting Radiopharmaceuticals Radioactive and non-radioactive precursors to produce radiopharmaceuticals	Reactor/ Cyclotron Production	Chemical Synthesis	Purification stages	Processing, Formulation and Dispensing	Final or aseptic sterilization

Radionuclide generators	Reactor/ Cyclotron Production	Processing

* The blank and the transfer system from the cyclotron to the synthesis preparation can be considered as the first stages of theactive substance manufacture.

** The GMP principles to be followed in the chemical synthesis part, refer to the Official Mexican Technical Regulation cited in the sectionof 2.18 of this Technical Regulation.

*** For processing, formulating, and dispensing refer to section 12.5.1 and the provisions in this section.

12.14.1.4 The final manufacturer of the radiopharmaceutical must describe and justify in a Risk Management the steps for the manufacture of the active substance and the final product in which GMPs are applicable in the specific process/manufacturing steps.

12.14.1.5 The preparation of radiopharmaceuticals implies compliance with the regulations applicable to radiation protection, theGeneral Regulations on Radiological Safety, and other applicable provisions.

12.14.1.6 Radiopharmaceuticals to be administered parenterally must comply with the sterility requirements for parenteral routesand, where applicable, the aseptic working conditions for the manufacture of sterile formulations as described in section 12.5 of this Technical Regulation and the provisions of the Critical Systems chapter of FEUM.

12.14.1.7 Specifications and quality control test methods for the most used radiopharmaceuticals are specified in FEUM Supplement for Medical Devices or in the marketing authorization.

12.14.1.8 Clinical trials.

12.14.1.8.1 Radiopharmaceuticals intended to be used in clinical trials in drug research must also be produced in accordancewith the GMP principles of this Technical Regulation.

12.14.2 Quality Assurance.

12.14.2.1 Quality assurance is even more important in the manufacture of radiopharmaceuticals, because of their characteristics, low volumes and, in some circumstances, the need to distribute or administer the product before quality control testing is completedfor release and use.

12.14.2.2 As with all pharmaceutical products, the products must 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 utmost importance.

12.14.2.3 It is important that data generated from facilities and processes monitoring be recorded and evaluated as part of productrelease.

12.14.2.4 To establish the scope of qualification/validation in the manufacture of radiopharmaceuticals, Risk Management mustbe performed, focusing on a combination of GMP and radiation protection.

12.14.3 Personnel.

12.14.3.1 All manufacturing operations shall 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 must be properly trained in radiopharmaceuticals 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 aremanufactured must 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 must be trained in GMP and quality control standards and must review and approve research activities to assure they do not represent a hazard to the manufacture of radiopharmaceuticals.

12.14.4 Facilities and equipment.

12.14.4.1 Radioactive products must be manufactured in controlled areas (environmental and radioactive). All manufacturing steps must be carried out in dedicated radiopharmaceutical and self-contained facilities.

12.14.4.2 Measures must be established and implemented to avoid cross-contamination by personnel, materials, radionuclides, etc. Contained or enclosed equipment should be the first choice when cross-contamination risks exist. Where open equipment is used or equipment is opened, precautions must 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 must be through an airlock and shall comply with clothing requirements according to the cleanliness and radiological protection class. Access to these areas must be restricted to unauthorized personnel.

12.14.4.4 Workstations and their environment must be monitored for radioactivity, particulate matter, and microbiological qualityas established in PQ.

12.14.4.5 Preventive maintenance, calibration and qualification programs must be carried out to assure all facilities and equipment used in the manufacture of radiopharmaceuticals are adequate and qualified. These activities must be performed by competent personnel and logbooks should be kept and properly safeguarded.

12.14.4.6 Precautions must be taken to avoid radioactive contamination within the facility. Controls must be in place to detect any radioactive contamination, either directly using radiation detectors or indirectly through routine smear testing.

12.14.4.7 Equipment must be constructed so as the surfaces that meet the product are not reactive, additive, or absorbing, to avoid impacting the quality of the radiopharmaceutical.

12.14.4.8 Re-circulation of exhaust air from the area where radioactive products are handled must be avoided unless justified. Air outlets must be designed to minimize environmental contamination by radioactive particles and gases and measures should be taken to protect controlled areas from microbial and particulate contamination.

12.14.4.9 To contain radioactive particles, it may be necessary for the air pressure where products are exposed to be lower compared to the 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 must 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 section 12.5 of this Technical Regulation.

12.14.4.10.2 For the manufacture of radiopharmaceuticals, a risk assessment can be conducted to determine appropriate pressure differentials, air flow direction and air quality.

12.14.4.10.3 In the case of use of closed and automated systems (chemical synthesis, purification, in-line sterile filtration) a grade C environment will be appropriate (usually "radiation containment chambers"). Radiation containment chambers must comply with a high degree of air cleanliness, with filtered feed air. Aseptic activities should be performed in a grade A area.

12.14.4.10.4 Prior to the start of manufacturing, the assembly of sterile equipment and consumables (tubes, sterile filters and sealed and closed sterile vials in counter-flow path) must be performed under aseptic conditions.

12.14.5 Documentation.

12.14.5.1 All documents related to the manufacture of radiopharmaceuticals must be issued, reviewed, approved, anddistributed according to written procedures.

12.14.5.2 Specifications must be established and documented for raw materials, labeling and packaging materials, critical intermediates and finished radiopharmaceuticals. Specifications should also be in place for any other critical items used in the manufacturing process, such as processing aids, gaskets, sterile filtration kits, which could have a critical impact on quality.

12.14.5.3 Acceptance criteria must be established for the radiopharmaceuticals 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 product name and batch number, as well as the date, time and signature of the persons involved in these activities.

12.14.5.5 Records must 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 be avoidedto minimize the risk of cross-contamination or confusion.

12.14.6.2 Special attention should be given to validation, including validation of computer systems that should be carried out inaccordance with the subsection of 10.14this Technical Regulation. New manufacturing processes should be validated prospectively.

12.14.6.3 Critical parameters must be identified before or during validation and the necessary intervals must be defined toassure the operation is reproducible.

12.14.6.4 Membrane filter integrity testing must be performed for aseptically filled products, considering the requirement 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 performed prior to manufacture. Empty closed sterile vials may be marked with partial information prior to filling if this procedure does not compromisesterility or prevent visual control of the filled vial.

12.14.7 Quality control.

12.14.7.1 Some radiopharmaceuticals may be distributed and used based on an evaluation of the documentation of the batch,

even if not all chemical and microbiological tests have been completed. The release of the radiopharmaceutical can be performed in twoor more stages, before and after the completion of analytical testing.

12.14.7.1.1 The evaluation of the production records and analytical tests of the batch must be reviewed by a person designatedby the health manager before allowing the radiopharmaceutical in quarantine status to be transported to the clinical department.

12.14.7.1.2 Evaluation of final analytical data, assuring that all deviations from regular procedures are documented, justified, and properly released prior to certification documented by the health manager.

Where certain test results are not available prior product use, the health manager must conditionally certify the product prior touse and, finally, must certify the product after all testing 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 shelflife must be clearly indicated.

12.14.7.3 Radiopharmaceuticals with radionuclides with long half-lives must be tested to show they meet all relevant acceptancecriteria prior to release and certification by the authorized person.

12.14.7.4 Before testing is performed, the samples may be stored to allow the radioactivity to decay sufficiently. All tests, including the sterility test must be performed within the time determined by the quality unit, which guarantees the samples do not represent arisk to the personnel handling them.

12.14.7.5 A written procedure must be established detailing the evaluation of production and analytical data, that must be considered prior to batch release.

12.14.7.6 Products not meeting the acceptance criteria must be rejected. If the material is reprocessed, pre-established procedures must be followed, and the finished product must meet the acceptance criteria prior to release. Returned products should not be reprocessed and should be confined and treated as radioactive waste, considering the applicable nuclear regulations.

12.14.7.7 A procedure must also describe the actions to be implemented by the authorized person (health manager) if non- satisfactory (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 must be documented.

12.14.7.8 Information should be given to the clinically responsible persons. To facilitate this, a traceability system for radiopharmaceuticals must be implemented.

12.14.7.9 A system for verifying the quality of starting materials must be in place at the site. Supplier approval should include an evaluation providing 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, containing the chemical reagents necessary for the preparation of radiopharmaceuticals) must be retained for at least six months after the expiration date of the finished product unless otherwise justified through Risk Management.

12.14.8.2 Samples of the starting materials other than gases, solvents or water used in the manufacturing process must 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 the specification is shorter.

12.14.9 Distribution.

12.14.9.1 The distribution of the finished product must be performed under controlled conditions to guarantee the quality of theproduct and to avoid any type of contamination.

12.14.9.2 Before all the corresponding test results are available, it is acceptable for the receiving unit (such as hospital, clinic and/or radio pharmacy) to receive the radiopharmaceuticals, provided that the product is not administered until the results are satisfactory and have been received and evaluated by the health manager.

12.15 *Remanufacturing* and *Refurbishment/Rehabilitation*

12.15.1 Medical device *remanufacturing* and *refurbishing* activities shall be performed in specific areas for these processes.

12.15.1.1 There must be procedures establishing the activities and criteria for the reception of medical devices, as well as the forms for recording these activities.

12.15.1.2 There should be forms for reviewing and recording the activities performed on medical devices to maintain traceability.

12.15.1.3 For *remanufacturing* and *refurbishment/rehabilitation* activities, the parts or systems replaced must be of the same type or specification as stated in the previously authorized condition.

12.15.1.4 *Remanufacturing* and *Refurbishment/Rehabilitation* must be performed by the manufacturer or by a facility approvedby the manufacturer.

12.15.1.4.1 The approval of the alternative facility to perform the activities must be established in writing; this facility shallcomply with the requirements established in this Technical Regulation.

12.16 The Health Registration Holder, distributors and persons designated by the manufacturer may carry out repair activities, these activities must be performed in specific areas, separate from the distribution area, and must be conducted following the processes, procedures and records implemented for that purpose.

12.17 Compatibility of business line.

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 Technical Regulation; and submitting the corresponding risk management.

12.17.2 The shared use of facilities and equipment for the manufacture of classified products with other business lines will be evaluated on a case-by-case basis by the Ministry of Health, at the request of the interested party.

13. Quality control laboratory

13.1 Overview.

The quality control function comprises the organization, documentation, and procedures to assure that GLP-compliant testing isperformed in accordance with current methods and specifications, so that supplies and products are not released for use or sale untiltheir quality has been assessed.

13.2 Each manufacturer must have a quality control laboratory independent from the Production Area and under the authority of a qualified person, with academic training 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 Technical Regulation.

13.4 The personnel, areas and equipment used in the quality control laboratory must be qualified, as indicated in section 9.2.

13.5 There must be standardized procedures for cleaning, maintenance, and operation of laboratory areas, measuringinstruments and equipment with corresponding records.

13.6 There must be a calibration program for measuring instruments used in the laboratory.

13.7 In the case of pharmacopeial methods, system suitability studies must be conducted.

13.8 There must be specifications, sampling procedures, testing procedures and records, analytical or conformity certificates and records of environmental monitoring.

13.9 Laboratory documentation must comply with the provisions of section 6.2 of this Technical Regulation.

13.10 Sample containers must have an identification indicating at least: the name and/or description of the supply, the batch number, the sampling date, the storage conditions, and the containers from which the samples have been taken.

13.11 Retention samples of each batch of finished product must be maintained at least one year after the expiration date of the medical device, in their final packaging and stored under the conditions indicated on the label, as established in section 7.

13.12 Retention samples of raw materials must be retained for at least one year after the expiration date of the last batch of product it was used for and stored according to the conditions indicated on the label, in accordance with the provisions of section 7.

13.13 No retention samples of solvents, gases and water used in the manufacture of medical devices should be retained.

13.14 When the primary or secondary packaging site declared in the health registration is different from the manufacturing site of the medical device, the packaging sites must maintain retention samples of the materials used in accordance with section 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 Batch/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 shall be made to the original Certificate of Analysis.

13.15.7 Testing date.

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 data and/or calculations.

13.16 There must be procedures describing the handling and storage of reagents, solutions, strains, and culture media used in the laboratory.

13.17 Reagent solutions and culture media must be prepared in accordance with FEUM and applicable supplements.

13.17.1 If there is no pharmacopeial reference, a method validated by the manufacturer may be used.

13.18 The expiration date of the reagents and culture media must 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 the solution must be indicated.

13.19 Primary and secondary reference substances should be dated, stored, handled, and used in a manner that does notaffect their quality. At least the following must be recorded: origin, batch and identification and expiration date.

13.20 When animals are used for laboratory testing in the analysis of Raw Materials or products they must be purchased fromqualified suppliers as indicated in section 6.6.4.2.2.2 and quarantined prior to use

They shall be maintained and controlled to assure their suitability for their intended use.

13.20.1 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 must be performed according to methods approved by the quality unit.

13.21.1 All in-process control tests shall be performed at the manufacturing site.

13.22 There must be a procedure indicating the actions to be implemented when out-of-specification or out-of-trend analyticalresults are obtained.

13.22.1 The analysis of the same sample shall not be repeated when any of the results are out of specification before the corresponding investigation has been performed, and neither can they be averaged when one of the results is out of specification.

13.22.2 The procedure for out of specification analytical results must include at least the following:

13.22.2.1 Verification of results to discard clearly identified analytical errors must be documented and reported.

13.22.2.2 If an analytical error is discarded, a rationale must be included as part of the investigation.

13.22.2.2.1 An investigation must be initiated involving all areas related to the manufacturing of the product, and a test planmust be established considering repeat sampling or re-analysis of the samples to confirm the result.

13.22.2.3 The evaluation and interpretation of the results obtained must be established considering all the investigationfindings, re-analysis, or re-sampling to determine the acceptance or rejection of the investigated batch.

13.22.3 Investigations and conclusions of out-of-specification analytical results must be approved by the health manager.

13.23 The use of external quality control laboratories must comply with the provisions of section 17 of this Technical Regulation and maybe accepted for special causes but must be reflected in the quality control records.

13.24 Sampling must be performed and recorded in accordance with written procedures approved by the health manager,including the following information:

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 considered, especially in relation to the 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 Ministry of Health, the Health Registration Holder may carry out a reduction in the frequencyand/or in the analytical tests for Supplies used to manufacture medical devices.

13.25.1 For the analytical reduction of Supplies, the Health Registration Holder of the manufactured medical device shallsubmit the following information to the Ministry of Health:

13.25.1.1 The Annual Product Report covering 3 years prior to the application.

13.26.1.2 Evidence of no major changes in the manufacturing process of the medical device.

13.25.1.1 Copy of the current Health Registration document of the medical device using the supply.

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 application to reduce the frequencyand analytical testing.

13.25.1.5 Statistical study performed between the results obtained by the manufacturer of the supply and those obtained at the manufacturing site of the medical device, with a minimum of 20 consecutive batches of the supply used in the manufacture of the device.

to demonstrate that there is no statistically significant difference. Analytical certificates supporting the study batches should beincluded.

13.26 Transfer of analytical methods.

13.26.1 Before transferring an analytical method, the transferring laboratory must verify that the analytical methods comply withthose reported in the corresponding technical file.

Only previously validated methods can be transferred.

13.26.2 Any modifications to the original validation performed before initiating the transfer process must 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 authorizedthird party.

13.26.3.3 From the manufacturer to a contract manufacturer.

13.26.4 The following factors must be considered to conduct an analytical transfer:

13.26.4.1 The receiving unit must have qualified facilities, equipment, instruments, and personnel, as indicated in section 9.2, forthe 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, based on the analytical methodology validation study.

13.27 When animals are used in laboratory tests and animal facilities are available, the provisions of the Official Mexican Technical Regulation mentioned in section 2.10 of the Regulatory References chapter of this Technical Regulation must be complied with.

14. Release of finished product

14.1 Release of imported medical devices.

14.1.1 The health manager must determine the release of medical devices.

14.1.2 There must be a procedure for the inspection of imported medical devices and a record should be kept of this activity.

14.1.3 The Medical Device Inspection should include at least: review of the analytical and/or conformity certificate, physical review of the product condition, the number of samples to be evaluated should be determined based on statistical criteria.

14.1.4 Each facility must define, in accordance with the Quality Management System, how documentation management shall becarried out, the minimum requirement is established in the 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 batch in accordance with the provisions of 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 health 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 domestically manufactured medical devices.

14.2.1 The health manager or the person authorized by the health manager who determines the release of the medical devices must have the academic training, knowledge, and experience according to the provisions of subsection 9.1.3.

14.2.2 There must be a procedure the process for reviewing the batch file and product release.

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 MD and not to all of them.

14.2.4 In addition to the batch file, the following must be taken into consideration as a minimum:

14.2.4.1 The change control system to verify there are no open changes impacting the batch to be released.

14.2.4.2 Results of Environmental Monitoring Program to review there is no impact to the batch to be released, in accordance with section 12.

14.2.4.3 That the corresponding retention samples have been taken.

14.2.4.4 Any other documents or letter related to product quality, including deviation or nonconformity reports.

14.3 For products requiring cold chain maintenance, there must be evidence of temperature monitoring during transportation from the manufacturing site to the distribution site. Excursions should be investigated and evaluated.

14.3.1 Batch release should consider cold chain compliance review.

15. Stability studies

15.1 General considerations.

15.1.1 Stability or aging studies must be performed for the medical devices requiring an expiration date due to their characteristics and intended use and the expiration date or shelf life assigned to the medical device must be demonstrated by the manufacturer through scientific evidence supporting. These studies allow assigning/confirming the periods, number of sterilization cycles, bulk storage times during the process, establishing the storage and transportation conditions, based on Risk Management, as well as guaranteeing the container-closure system.

15.1.2 Stability studies for formulated medical devices containing a drug must be performed according to the Official Mexican Technical Regulation mentioned in section 2.11 of this Technical Regulation; for formulated medical devices that do not contain a drug, studies must be performed according to 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 at least three batches.

15.1.4 Real-time (long-term) stability or aging studies must 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 at least three batches.

15.1.5 The manufacturer shall consider all the evaluation parameters corresponding to the type of product, to assure the medicaldevice is stable/functional during its shelf 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 Batch number and size, or serial number.

15.1.6.3 Description and composition of the primary container or package.

15.1.6.4 Storage conditions (temperature, % RH, light, etc.) of the study.

15.1.6.5 Sampling and analysis periods.

15.1.6.6 Test parameters.

15.1.6.7 Acceptance criteria or specifications.

15.1.6.8 Reference to analytical or test methods by parameter and their validation.

15.1.7 There must be written reports demonstrating traceability with the corresponding protocol including:

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 the statistical analysis and conclusions.

15.2 The Real-time (long-term) stability or aging studies of the batches submitted in the registration dossier must be the same until the requested shelf life is covered.

15.2.1 The tentative shelf life or expiration date must be confirmed through stability or real time (long term) aging studies.

15.3 An annual stabilities program must be implemented based on statistical criteria considering the number of batches manufactured to guarantee the expiration period of the medical device, that should be endorsed or authorized by the health manager.

15.4 Batches manufactured to conduct stability studies must be manufactured by using standard production procedures.

15.5 When a batch of product is reprocessed or reworked, it must undergo Stability Studies.

15.6 Stability of the medical device must be confirmed with at least three batches of product, when available:

15.6.1 A change of additives or excipients with no impact in registration conditions.

15.6.2 A change in the analytical or test method during the Stability Study, previously demonstrating the equivalence of the methods.

15.6.3 A change in the Primary Packaging, according to the characteristics and risk to the product.

15.7 Stability studies can 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

16.1 There must be a system to recall products from the market in a timely and effective manner and for products known or suspected to be out of specification or where the safety, quality and efficacy of the product is compromised, all of which must be notified to the Ministry of Health through COFEPRIS.

16.2 There must be a SOP describing the following:

16.2.1 The coordination of recall and its execution is the responsibility of the Health Manager.

16.2.2 Recall activities, allowing to start quickly at all levels.

16.2.3 Storage instructions for the recalled product.

16.2.4 Notification to the health authorities in accordance with applicable regulations.

16.2.5 Review of product distribution records allowing an effective recall.

16.2.6 Continuous verification of the recall process.

16.2.7 The final report must include a reconciliation between the distributed quantity and the recovered

quantity, the actions to be implemented to avoid recurrence, the destination of the product and the corresponding conclusion.

17. Outsourced activities

Fundamentals.

Any outsourced activity included in this Technical Regulation must be defined, agreed upon and controlled to avoid inaccuracies that mayresult in an unsatisfactory product or operation.

Activities must be formalized in a written contract between the contracting agent and the contracted agent that clearlyestablishes the responsibilities of each party.

The contracting agent's Quality Management System must clearly reflect how the health manager, or person authorizing therelease of each batch of product, considers the subcontracted activities in his/her responsibility.

17.1 Overview.

17.1.1 A written contract shall be formalized including the subcontracted activities, the related products or operations and any related Technical Agreements.

17.1.2 All agreements for outsourced activities, including any technical modification or other proposed agreements, must be in accordance with the applicable provisions and with the conditions authorized in the health registration of the involved product.

17.1.3 When the Health Registration Holder and the manufacturer are not the same, agreements must be in place considering the principles described in this chapter.

17.2 Contracting agent.

17.2.1 The contractor's Quality Management System must include the control and review of any outsourced activities and mustconsider the principles of Risk Management.

17.2.2 The following is the responsibility of the contractor:

17.2.2.1 Evaluate the legality, suitability, and competence of the contracted party to successfully perform the outsourced activities; as well as assuring through the contract that the principles and guidelines of this Technical Regulation are followed.

17.2.2.1.1 If external laboratories are used, the laboratory must be authorized as authorized third-party laboratory, 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 health registration of the involved product.

17.2.4 The contractor must control and review the contractor's performance and the identification, implementation and control ofany improvements made.

17.2.5 The contractor shall be responsible for the review and evaluation of the records and results related to the outsourced activities.

17.3 Contracted agent.

17.3.1 The contracted party must be able of satisfactorily performing the work commissioned by the contractor, having the necessary facilities, equipment, knowledge, experience, and competent personnel.

17.3.2 The contracted party must assure that all products, materials, and know-how delivered are suitable for their intendedpurpose.

17.3.3 The contracted party shall not subcontract to a third party any part of the work entrusted to his/her company regarding to the contract without the contracting party evaluation and approval|. Agreements between the contracted party and any third party shall assure that information and knowledge, including the assessment of the suitability of the third party, is available in the same way as they are between the original contracting and contracted party.

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 contracting party.

17.3.5 Outsourced activities, including contract review, may be subject to inspection by the competent

authorities.

17.4 Contract.

17.4.1 A contract should be developed between the contractor and the contracted party specifying their corresponding responsibilities and means of communication regarding the subcontracted activities. The technical aspects of the contract must be prepared by competent persons with adequate knowledge of the subcontracted activities and GMP. All agreements for outsourced activities shall be in accordance with current regulations and the conditions authorized in the health registration of the corresponding product and shall be approved by both parties, by the legal representative as well as the health manager.

17.4.2 The contract should clearly indicate the person responsible for each stage of the outsourced activity, such as: knowledge management, technology transfer, supply chain, outsourcing, quality and material procurement, material analysis and release, production responsibility and quality controls (including In-Process Controls, sampling, and analysis).

17.4.3 The contracting party shall keep or have available all records related to outsourced 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 products must be accessible and specified in the contractor's procedures.

17.4.4 The contract must allow the contractor to audit the outsourced activities, either by the contractor or by mutually agreed third parties.

17.5 Outsourced services.

17.5.1 All contractors for medical device manufacturing process services such as analytical laboratory services, critical systems services and equipment impacting product quality must be evaluated and qualified as suppliers.

17.5.2 There should be a procedure describing the criteria for evaluating contractors before they are approved by the quality unit of the contracting agent.

17.5.3 The Contractor shall not subcontract medical device manufacturing process services or analytical laboratory services.

17.6 Contract manufacturing.

17.6.1 When contract manufacturing is required, the corresponding contract manufacturing notice must be submitted to COFEPRIS, attaching at least the following:

17.6.1.1 Notice of operation of the contract manufacturing facility.

17.6.1.2 Technology transfer.

17.6.1.3 Process validation to be performed.

17.6.2 Contract manufacturing suppliers for medical devices are required to comply with this Technical Regulation and other applicable provisions.

17.6.3 The manufacturer must assure the technology transfer to the contracted party, which must be attached to the contract manufacturing notice to be submitted to COFEPRIS.

17.6.3.1 Contract manufacturers for medical device sterilization process are required to have current good manufacturing practices certification, which must be attached to the contract manufacturing notice

17.6.3.2 Sterilization processes must be validated at the contract manufacturer´s facilities.

17.6.3.3 The quality of the medical device is the responsibility of the health registration holder.

17.6.4 The stages to be processed must be validated at the contract manufacturer´s facilities.

17.6.5 The quality of the product will be the responsibility of the Health 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 contract manufacturer as described in the applicable regulations.

17.6.7 The contract manufacturer must deliver the product to the Health Registration Holder, together with the original documentation of the manufacturing stages including the In-Process Controls records. The contract manufacturer must retain a copy of this documentation for the period indicated in section 6.2.3.2 of this Technical Regulation.

17.6.8 It is the responsibility of the Health Registration Holder to assure that the complete analysis is performed for the release of the finished product.

17.6.9 The Health Registration Holder must guarantee that the product to be manufactured will be manufactured under the sameconditions described in the current health registration.

17.7 Analytical laboratory services.

17.7.1 The Health Registration Holder must assure the analytical transfer to the contracted laboratory.

17.7.2 A system for the transfer of samples shall be established to guarantee the integrity of the samples.

17.8 Critical Systems and Equipment Services.

17.8.1 The facility must evaluate the academic background, technical training and experience of the personnel providing this service.

18. Destination of waste

18.1 There must be a system documented in a SOP guaranteeing compliance with applicable ecological and health regulations for the destination of contaminating and/or hazardous waste, notifying the corresponding authorities.

19. Good Storage and Distribution Practices

This chapter is applicable to medical device warehouses and distribution centers.

19.1 Overview.

19.1.1 The distribution of medical devices is the set of activities of procurement, storage, transportation, supply and, where appropriate, marketing of medical devices and is important in the integrated management of the supply chain. Today's medical device distribution network is increasingly complex. Having GSDP in place assists distributors in carrying out their activities, prevents counterfeit medical devices from entering the supply chain, assures control of the distribution chain, and maintains the quality, safety, and integrity of medical devices.

19.2 Quality Management System.

19.2.1 Distributors must maintain a Quality Management System establishing the organizational structure, responsibilities, and processes in relation to their activities, considering 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 results or non-conforming product.

19.2.1.5 Deviation Management and CAPA system.

19.2.1.6 Recall.

19.2.1.7 Change Control.

19.2.1.8 VMP.

19.2.1.9 Risk Management.

19.2.1.10 Document control.

19.2.1.11 Returns.

19.2.2 When designing or modifying the Quality Management System, the size, structure, and complexity of the distributor's activities must be considered.

19.2.3 All distribution activities must be clearly defined in procedures and systematically reviewed.

19.2.3.1 Import and export activities must be performed in accordance with the applicable provisions.

19.2.4 All critical stages of the storage and distribution processes must be identified, controlled, and documented, significant changes must be validated as applicable.

19.2.5 The Quality Management System must assure the following:

19.2.5.1 Medical devices are purchased, maintained, supplied, exported, or imported in accordance with the requirements of theGSDP's described in this chapter.

19.2.5.2 Products are delivered to their recipients assuring their quality and conservation conditions.

19.2.5.3 Records are made in accordance with subsection 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 implemented to correct Deviations and prevent them according to RiskManagement principles.

19.2.6 Complaints.

19.2.6.1 There must be a procedure for handling complaints, including the following:

19.2.6.1.1 A person responsible for complaints management.

19.2.6.1.2 Mandatory attention and documentation of all complaints.

19.2.6.1.3 Investigation process including the impact on product quality, safety, and efficacy/functionality.

19.2.6.1.4 Definition of the CAPA to be implemented to solve the problem.

19.2.6.1.5 The means and response time to the customer.

19.2.6.2 Perform classification of complaints; pointing out those related to the quality of the medical device and those related todistribution.

19.2.6.3 Complaints related to the quality of the medical device and/or a possible product defect must be reported to themanufacturer and/or Health Registration Holder.

19.2.6.4 Cases 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 must at least include the following:

19.2.6.5.1 Medical device name, presentation, batch/serial number and reception date.

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 the complaint.

19.2.6.5.5 Investigation results.

19.2.6.5.6 Implemented Actions.

19.2.6.6 Complaints must be reviewed periodically, based on a risk assessment, to identify increasing trends in specific orrecurring problems and implement the necessary measures.

19.2.7 Returns.

19.2.7.1 There must be a procedure for the control of returned products, indicating that:

19.2.7.1.1 The product should be put on temporary hold/ quarantine and be evaluated by the Quality Unit to determine whetherthe product should be released or destroyed.

19.2.7.1.2 Specific storage requirements.

19.2.7.1.3 Reception, identification, evaluation, and destination records.

19.2.7.2 There must be a report of the returned product indicating at least the following:

19.2.7.2.1 Product name, presentation, batch/serial number and expiration date.

19.2.7.2.2 Return date, quantity returned.

19.2.7.2.3 Time elapsed since the medical device was originally shipped.

19.2.7.2.4 Date and reason for return.

19.2.7.2.5 Name and address of the person who returns the product.

19.2.7.2.6 Inspection of the returned product to indicate the conditions of integrity, safety, quality, based on risk managementshall include description of the distribution route, conditions returned product transfer, decision, and destination of the product.

19.2.7.3 Recovery of returned product is not allowed if during inspection of the container, cartons or boxes conditions, or thetexts of the labeling compromise the integrity, safety, identity, concentration, quality, or purity of the product.

19.2.7.3.1 Stolen products that have been recovered cannot be returned to saleable stock.

19.2.8 Recall.

19.2.8.1 Recall must be conducted in accordance with section 16 of this Technical Regulation.

19.2.9 Audits.

19.2.9.1 Audits must be performed according to a program. They are classified as follows: Internal Audits (self-inspections) andSupplier Audits.

19.2.9.2 There must be procedures establishing the process for executing an audit containing at least:

19.2.9.2.1 Scope of each type of audit.

19.2.9.2.2 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 There must be a self-inspection system for evaluating the implementation and application of GSDP´s and proposing the necessary corrective actions.

19.2.9.3.2 Self-inspection audits must be conducted by personnel independent of the audited area. They may also be conductedby external personnel.

19.2.9.3.3 All self-inspections must be recorded. Reports shall include all observations made during Inspections and, where appropriate, proposed Corrective and/or Preventive Actions shall be recorded in the CAPA system of the facility.

19.2.9.3.4 Results of self-inspections must be communicated to the involved personnel.

19.2.9.4 Supplier audits.

19.2.9.4.1 Facilities must determine, based on a risk assessment those suppliers of Supplies/Services having an impact on thequality, safety, and efficacy/functionality of medical devices.

19.2.9.4.2 There must be a procedure for the execution of audits for materials suppliers, and outsourced activities or technical agreements.

19.2.9.4.3 There must be a periodic audit program, as well as documented 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 supply or service provided, theimpact and previous qualification reports.

19.2.9.4.5 Supplier audit reports must be part of the supplier's qualification file.

19.2.10 Management shall have a formal process to review, at least annually, the Quality Management System. The review shallinclude:

19.2.10.1 Measuring of compliance with the objectives of the Quality Management System.

19.2.10.2 Evaluation of Quality Management System performance indicators, such as complaints, 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 arising and that may impact the Quality Management System.

19.2.10.4 Innovations that can improve the Quality Management System.

19.2.10.5 Changes in objectives and business environment.

19.2.11 Result 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 must be conducted in accordance with section 7 of this Technical Regulation.

19.4 Personnel.

19.4.1 According to the size of the facility and the activities performed, there must be the number of qualified personnel, as indicated in section 9.2.

19.4.2 There must be a profile and job description for the personnel, defining the requirements to be met by the personnel and their responsibilities.

19.4.3 The owner of the facility or legal representative must designate a health manager in accordance with subsections 9.1.3 and 9.1.3.1 of this Technical Regulation and the provisions in the supplement for facilities dedicated to the sale and supply of medicines and other health supplies of FEUM, also, the owner must provide adequate resources and assign the necessary responsibility for the compliance of his/her functions.

19.4.4 The health manager may delegate functions according to subsection 9.1.3 in his/her absence to assure the activities underthe GSDP's.

19.4.5 The health manager must, among other things:

19.4.5.1 Assure the Quality Management System is implemented and maintained.

19.4.5.2 Assure initial and ongoing training programs are implemented and maintained.

19.4.5.3 Coordinate product recall operations, in accordance with the procedure.

19.4.5.4 Assure customer claims or complaints are addressed.

19.4.5.5 Assure suppliers are approved and warehouses and/or drug distributors have notices of operation and health manager.

19.4.5.6 Approve all outsourced activities that may have an impact GSDP's.

19.4.5.7 Assure internal audits are conducted according to a pre-established program and the necessary corrective actions areimplemented.

19.4.5.8 Maintain records of any activities delegated in accordance with subsection 9.1.3 of this Technical Regulation.

19.4.5.9 Decide together with the Health Registration Holder on the destination of returned, rejected, recalled or counterfeit products in accordance with the provisions of the Quality Manual and procedures or in the case of outsourced 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 Assure compliance with any additional requirements according to characteristics or classification of medical devices.

19.4.6 Personnel impacting product quality must receive initial and ongoing training according to their role, based on written procedures and in accordance with a documented training program. All personnel must assure competency in the GSDP's through ongoing training.

19.4.7 Training must include aspects such as product identification to detect counterfeit medical devices from entering the supplychain.

19.4.8 Personnel handling products requiring more stringent conditions must receive specific training, such as temperature- sensitive and sterile products.

19.4.9 Training Records must be retained.

19.4.10 Personal hygiene and safety procedures must be established for the activities being performed, covering health, hygiene,and clothing.

19.5 Facilities and equipment.

19.5.1 Distributors must have buildings, facilities, and equipment to assure the storage and distribution of medical devices. Facilities must be clean, dry, and maintained within the temperature and humidity ranges in accordance with the conditions authorized in the health registration and/or medical device label.

19.5.2 Facilities.

19.5.2.1 Facilities must be designed to assure the storage conditions required for the preservation of medical devices are maintained.

19.5.2.2 They must be safe, structurally sound and of sufficient capacity in accordance with the quantity of products, to allow safe storage and handling of medical devices.

19.5.2.3 They must have areas for the reception, storage, and shipment of medical devices.

19.5.2.4 When counter-labeling activities are performed, they must have a specific, identified, and delimited area for the activity.

19.5.2.5 They must be designed and equipped to prevent the entry of insects, rodents, or other animals.

19.5.2.5.1 A preventive pest control program must be in place.

19.5.2.5.1.1 The authorized pest control service supplier must have a current health license.

19.5.2.5.2 Pest control records should be maintained.

19.5.2.6 Buildings and storage areas must be clean and free of trash and dust.

19.5.2.6.1 There must be a procedure for cleaning, including a cleaning schedule, instructions, and records.

19.5.2.6.2 Equipment and cleaning agents not being a source of contamination should be selected and used.

19.5.2.7 There must be a drinking water supply for the personnel needs.

19.5.2.8 Electrical installation must be protected and identified to avoid the risk of accidents.

19.5.2.9 Restrooms or dining room and workers' toilets must be independent from storage areas.

19.5.2.10 Maintenance activities must be carried out at the Facilities under a program to maintain storage conditions.

19.5.2.11 Food, beverages, and tobacco must be prohibited in storage areas.

19.5.2.12 Storage areas must be equipped with lighting and ventilation to allow all operations to be conducted accurately andsafely.

19.5.2.12.1 Furniture used for storage must be made of material resistant to cleaning agents and must be placed to facilitate cleaning.

19.5.2.13 Access must be restricted to authorized personnel, by means of a control established in the correspondingprocedure. Visitors must be always accompanied by authorized personnel.

19.5.2.14 Medical devices must be stored in clearly identified areas. Any electronic inventory control system must be validated.

19.5.2.15 Receiving and shipping areas must protect products from the weather and be properly equipped to maintain theconditions required for review (inspection) processes.

19.5.2.15.1 They must have pallets easy to move and clean and avoid harmful fauna.

19.5.2.16 There must be a separation between receiving, shipping and storage areas.

19.5.2.17 Products awaiting a decision regarding their disposition or products that have been returned must be segregatedeither physically or through an equivalent electronic system.

19.5.2.18 Counterfeit, expired, recalled, and rejected medical devices must be identified, physically separated and insegregated areas.

19.5.2.19 Products representing a special safety risk of fire or explosion must be stored in one or more special areas subject tothe safety and protection measures indicated in accordance with section 2.3 of the Regulatory References section of this Technical Regulation.

19.5.2.20 There must be a design allowing monitoring and control of temperature and RH, through natural ventilation or airconditioning systems.

19.5.2.21 There must be calibrated instruments to monitor and record temperature and RH conditions, according to theconditions required by the device.

19.5.2.21.1 There must be a calibration program for the instruments used.

19.5.2.22 An initial temperature and RH mapping of the storage area should be carried out prior to use, under representativeconditions, to determine the points of greatest fluctuation and to place the temperature and RH monitors at these points.

19.5.2.22.1 If the temperature and RH mapping results show that the storage area conditions 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 must be repeated when there are modifications impacting product storage conditions or environmental conditions monitoring equipment.

19.5.2.23 When Facilities are not directly operated by the distributor, a written contract must be established in accordance withthe provisions of Section 17.5 of this Technical Regulation.

19.5.3 Equipment.

19.5.3.1 Equipment used for storage and distribution of medical devices must be designed, placed, and maintained inconditions assuring the purposes for which they were intended.

19.5.3.2 There must be 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 medical devices.

19.5.3.3 There must be equipment for storage of medical devices requiring a specific temperature condition, such asrefrigeration and freezing.

19.5.3.3.1 There must be an alarm system to indicate any excursion from the storage conditions required for the conservationof medical devices.

19.5.3.4 Equipment maintenance activities must be carried out under a program to maintain the conditions required for theconservation of medical devices.

19.5.3.5 Repair and/or maintenance of equipment must be carried out in accordance with the provisions of a SOP, so thequality and integrity of the products is not compromised.

19.5.3.6 Equipment and instrument repair and/or maintenance records must be maintained.

19.6 Qualification and Validation.

19.6.1 Equipment involved in the storage of medical devices must be qualified in the 4 consecutive stages indicated in section

11.7 of this Technical Regulation.

19.6.2 Computerized systems used for storage, reception, packaging, and transportation processes must be validated inaccordance with section 11.15 of this Technical Regulation.

19.6.3 An evaluation of the equipment must be performed to determine if a new qualification is necessary or to establish theperiodicity to evaluate alarm systems in the refrigeration chambers, based on risk assessment.

19.7 Legal and technical documentation.

19.7.1 Preparation and management of documentation shall be performed in accordance with section 6.2 of this Technical Regulation. Thescope 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 manager notices, according to the business lines of the facility.

19.7.1.2 Distribution plan or diagram of the warehouse where material and personnel flows are indicated, updated, andauthorized by the Health Manager.

19.7.1.3 Updated list of equipment and instruments used in the warehouse, as well as SOPs, use, maintenance and/or calibrationlogs.

19.7.1.4 Records of all health verification visits received procedures, official documents, or follow-up with the Ministry of Health.

19.7.1.5 Invoices supporting the receipt and delivery of the medical devices issued by the supplier or documentation supporting 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 Brand name and/or generic name.

19.7.1.5.3 Quantity.

19.7.1.5.4 Presentation.

19.7.1.5.5 Batch/serial number.

19.7.1.5.6 Supplier's name and address.

19.7.1.5.7 Customer or recipient.

19.7.1.6 There must be procedures for purchasing, receipt and registration of health supplies that clearly state that onlyapproved product may be received.

19.7.1.7 There must be procedures to maintain control of incoming and outgoing medical devices, complying with the criterionof first expiration-first out or first in-first out.

19.7.1.8 When performing back labeling of imported medical devices, there must be procedures detailing the activities to beperformed, the responsibilities and the records to be maintained.

19.7.1.9 The place of storage of all documents related to the back labeling, release and/or distribution of medical devices mustbe clearly defined.

19.7.1.9.1 Control measures must be implemented to assure the integrity of the documents during the entire storage period,the storage period should be based on the shelf life of the product plus an additional period of at least one year.

19.7.1.10 When the warehouse is independent of the manufacturer, there must be a current edition of the supplement forfacilities dedicated to the sale and supply of medicines and other health supplies.

19.8 Operations.

All operations performed must guarantee traceability, the distributor must use all available means to minimize the risk ofcounterfeit medical devices entering the supply chain.

19.8.1 Acquisition.

19.8.1.1 Distributors must obtain medical devices from medical device factories or medical device warehouses and distribution centers having a current operation notice or equivalent document.

19.8.1.1.1 When medical devices are purchased abroad, they must have the legal documentation supporting their manufactureand importation.

19.8.2 Receipt.

Receiving activities must assure the medical device received is the correct one, it comes from an approved supplier, and ithas not been visibly damaged in transit.

19.8.2.1 Each medical device, batch or group of containers must be verified for integrity, and identified with at least name,quantity, batch/serial number and information on the facility of origin.

19.8.2.1.1 Priority should be given to medical devices requiring special handling, storage, or security measures, once theinspection 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 the documentation supporting the possession andtransportation, 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 should not be made available for distribution until the product file review and release is performed inaccordance with section 14 of this Technical Regulation.

19.8.2.5 If a counterfeit product is suspected, the batch must be segregated and reported to the Ministry of Health.

19.8.3 Back labeling.

19.8.3.1 There must be a back labeling file for each batch/serial number or family of the medical device.

19.8.3.2 An order must be issued for the back labeling by Batch/Serial number of the Medical Device, stating the following:

19.8.3.2.1 Brand name and/or generic name.

19.8.3.2.2 Batch/serial number.

19.8.3.2.3 Batch number and quantities of packaging materials.

19.8.3.2.4 Reconciliation of packaging materials and labels to assure the quantity used, sent for destruction and/or returnedmaterials.

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 Start and end date and time of back labeling.

19.8.3.2.8 Final yield obtained during this activity.

19.8.3.2.9 Name and signature of the person who executed the activities.

19.8.3.2.10 Name and signature of the person who supervised the activities.

19.8.3.3 Before starting 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. The investigationmust be concluded for Batch Release.

19.8.3.5 Each back labeling file must be signed by the health manager or qualified person to assure the activity was performedin compliance with the corresponding procedures.

19.8.4 Storage.

19.8.4.1 Medical devices must be stored separately from other products that may alter them and must be stored at thecorresponding light, temperature, and RH conditions. Attention should be paid to products requiring specific storage conditions.

19.8.4.2 A system must be established to control the location of each of the medical devices during storage, that can bemanual or computerized.

19.8.4.3 Stock rotation must be performed to follow the control procedure according to section 19.7.1.7 of this Technical Regulation

19.8.4.4 Medical devices must be handled and stored in a manner that prevents spillage, breakage, contamination, and mixing.

19.8.4.5 There must 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 A manual or electronic system must be established allowing the correct distribution of Medical Devices.

19.8.5.1.1 If a medical device using UDI is distributed, systems must be in place to provide tracking of each device to the end

user. The tracking system should be reviewed and audited to confirm it is effective and should contain at least: batch number, modelnumber or device serial number or other identifier to provide effective tracking of devices.

19.8.5.2 A SOP must be established for the control of medical device distribution, including the following information:

19.8.5.2.1 Data recorded for each shipment such as: medical device name, Batch/serial number, quantity, and purchase orderor equivalent document.

19.8.5.2.2 Means and transportation conditions.

19.8.5.2.3 Storage instructions throughout the entire distribution chain.

19.8.5.3 It must be guaranteed that the product at the time of distribution has a remaining shelf life that assures it can be usedwithout having the risk of expiring during the distribution process.

19.8.5.4 Medical devices must be transported in containers having no effect on the quality of the products, and offer protectionfrom external influences, including contamination.

19.8.5.5 The container and packaging to be selected according to the transportation requirements of the medical devices; the room according to the quantity of medical devices, the outside temperatures; the maximum estimated time for transportation, the transit time at customs, as well as all the controls having an impact on the quality of the product.

19.8.5.5.1 Validation of cold chain must be performed.

19.8.5.6 Containers must be labeled to provide information on handling and storage requirements and precautions to assureproducts are handled and always protected.

19.8.5.7 A document (e.g., delivery note/packing list, invoice) must be attached to all shipments indicating the date; name ofmedical device; batch/serial number; quantity; name and address of supplier; name and address of delivery.

19.8.5.8 The identification and integrity of the products must be guaranteed.

19.8.5.8.1 A procedure must be in place for the investigation and handling of deviations during transportation and delivery of theproduct.

19.8.5.9 Distribution records must be maintained for each product batch or Serial Number to facilitate the recall, in accordancewith the provisions of Section 16 of this Technical Regulation.

19.8.5.10 Transportation for distribution must guarantee the conditions of conservation and cleanliness of the medical devices.

19.8.5.10.1 Required temperature and % RH conditions must be maintained during the transportation of medical devices.

19.8.5.10.2 There must be instruments for measuring and recording temperature and % RH during transportation and deliveryof products, that must be calibrated.

19.8.5.10.3 There must be written procedures for the operation, cleaning and maintenance of all transport and equipment usedfor the distribution process.

19.8.5.10.4 When the transportation is carried out by a third party, the contract must cover the requirements established in section

17.5 of this Technical Regulation.

19.8.5.10.4.1 Transportation providers must be instructed and trained in the conditions applicable to medical devices fortemperature, RH, cleanliness, and safety, including loading and unloading activities.

19.8.6 Medical devices intended for destruction must be identified, segregated, and handled according to a written procedure. Itmust be performed by a company authorized by the Ministry of Environment and Natural Resources.

19.8.6.1 Records of all destroyed medical devices must be retained for a period of 5 years.

19.9 Counterfeit medical devices.

19.9.1 A procedure must be in place where distributors immediately inform COFEPRIS and the Health Registration Holder of anycounterfeit 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 areaseparate from other medical devices. All relevant activities in relation to these products must be documented and records maintained.

19.9.3 Upon confirmation that a medical device was counterfeited, the Health Registration Holder must notify COFEPRIS toorder the recall.

20. Agreement with international and Mexican standards

This Technical Regulation partially agrees 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. Mexico (2018).

21.7 Supplement for medical devices 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 ISO11135-1.

21.10 ISO 11137-1:2013. Sterilization of health care products--Radiation-Part 1: Requirements for validation and routinecontrol 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 andmonitoring 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

21.22 Code of Federal Regulations Title 21; Part 820, Medical Device Good Manufacturing Practices Manual - Washington,Food and Drug Administration, 2001.

21.23 Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing--Current Good Manufacturing Practice--Washington, D.C., Food and Drug Administration, September 2004.

21.24 Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice; European Commission, Brussels, 2015.

21.25 European Commission, Guide to Good Manufacturing Practice Annex I.

21.26 European Commission, Guide to Good Manufacturing Practice Annex 1, Manufacture of Sterile Medicinal Products, June2008.

21.27 European Commission, Guide to Good Manufacturing Practice Annex 15, Qualification and validation, July 2001.

21.28 Manufacture of Sterile Medicinal Products, January 1997.

21.29 Points to Consider for Aseptic Processing, PDA Journal of Pharmaceutical Science and Technology, 2015, Part 1. Pointsto Consider for Aseptic Processing, PDA Journal of Pharmaceutical Science and Technology, 2016, Part 2.

21.30 U.S. Foods and Drug Administration. Guidance for Industry Process Validation: General Principles and Practices.Washington, January 2011.

21.31 European Medicines Agency, Guideline on process validation for finished products-information and data to be providedin regulatory submissions, United Kingdom, 27 February 2014.

21.32 ISPE. GAMP 5, A Risk-Based Approach to Compliant GxP Computerized Systems. 2008.

21.33 IMDRF/SaMD WG/N10FINAL:2013. Software as a Medical Device (SaMD): Key Definitions. December 2013.

21.34 IMDRF/SaMD WG/N12FINAL:2014. Software as a Medical Device (SaMD): Possible Framework for Risk Categorizationand Corresponding Considerations. September 2014.

21.35 IMDRF/SaMD WG/N41FINAL:2017. Software as a Medical Device (SaMD): Clinical Evaluation. June 2017.

21.36 Guidance for Industry and Food and Drug Administration Staff. Mobile Medical Applications: Guidance for Food andDrug Administration Staff. February 2015.

22. Compliance with the Technical Regulation

Compliance with this Technical Regulation is the responsibility of the Ministry of Health and the governments of the federal entities, withinthe scope of their respective competencies, whose personnel will carry out the necessary verification and surveillance.

23. Conformity assessment

Conformity assessment may be requested the request of the health manager, the legal representative or the person empowered to do so before the competent authority or the persons accredited or authorized forsuch purposes.

23.1 Facilities manufacturing products not considered health supplies under the agreement listed below are not required to comply with the conformity assessment of this Technical Regulation.

23.1.1 Agreement announcing the list of health supplies considered as low risk for the purpose of obtaining health registration, and those products that because of their nature, characteristics and use are not considered as health supplies and therefore do notrequire health registration, published in the Official Journal of the Federation on December 22, 2014.

24. Validity

This Technical Regulation shall enter into force 18 months after its publication in the Official Journal of the Federation.

TRANSITORY

UNIQUE. - The entry into force of this Technical Regulation will supersede the Official Mexican Technical Regulation NOM-241-SSA1-2012, Good Manufacturing Practices for facilities dedicated to the manufacture of medical devices, published in the Official Journal of the Federation on October 11, 2012.

Mexico City, November 19, 2021.- The Federal Commissioner for Protection against Health Risks and President of the National Advisory Committee for Standardization of Health Regulation and Promotion, **Alejandro Ernesto Svarch Perez**. - Signature.

25. Regulatory Appendix A.

Manufacturing Areas.

Classification	Process examples [a]	Maximum allowed number of total particles[h] / m3:			Viable Particles[b]		Differential pressure and air flow	Air changes per hour j	Temperature and humidity	Clothing
		Static [g] / Dynamic Conditions		Monitoring frequency	(CFU)	Monitoring frequency				
		≥ 0.5 µm	≥ 5 µm							
Class A (ISO-Class 5)	Aseptic filling. Aseptic operations. Sampling, weighing, dispensing and preparation of sterile supplies.	3 520/3 520	20/20	CONTINUOUS / During the entire filling process	<1/plate [b.1] <1/m3 [b.2] <1/ plate [b.3] <1/glove [b.4]	CONTINUOUS / For the entire duration of the filling process	≥15 Pa with respect to adjacent rooms, applying a cascade concept [c]	na	18°C to 25°C 30 to 65% RH [f]	Sterile coverall, hood, goggles, shoes covers and gloves, for Aseptic Area.
Class B	Class A surrounding for sterile devices that are not subjected to terminal sterilization. Air locks to filling rooms. Dressing Rooms for Class A Areas	3,520 / 352,000	29/2 900	every 3 months[d]	<5/plate [b.1] <10/m3 [b.2] <5/plate [b.3] <5/glove [b.4]	Daily/ Production Shift	≥15 Pa with respect to non-aseptic areas, applying a cascade concept	20 a 50	18°C to 25°C 30 to 65% RH	Same as ISO-Class 5.
Class C (ISO-Class 7)	Preparation of solutions for sterilizing filtration, for terminal sterilization and elements of the container-closure system Storage of accessories for sterile pharmaceutical forms. Surrounding for the preparation of supplies for the manufacture of radiopharmaceuticals	352,000 / 3,520,000	2,900 / 29,000	every 6 months except for filling solutions with terminal sterilization that is carried out every 3 months[d]	<50/plate [b.1] <100/m3 b.2 <25/plate [b.3] -	Weekly	> 10 Pa	20 a 50	18°C to 25°C 30 to 65% RH	Clean plant uniform; hair, facial and body hair covered, mask and gloves.
Class D (ISO-Class 8) Class C surrounding (ISO-Class 7)	Manufacture of formulations Manufacture of plastics, polymers, and elastomers to be sterilized by terminal method (from molding / forming). Polishing / Blowing / Washing / Sanitizing Medical Devices to be sterilized by terminal method Primary packaging of Medical Devices to be sterilized by a terminal method. Assembly of Medical Devices to be sterilized. Manufacture of *in vitro* diagnostic agents to be sterilized by a terminal method.	3,520,000 / na	29,000 / na	every 6 months	<100/plate [b.1] <200/m3 b.2 <50/plate [b.3] -	Monthly	> 5 Pa Negative pressure where dust is generated with respect to adjacent rooms, and positive with respect to where no dust is generated.	10 to 20	18°C to 25°C 30 to 65% RH	Clean plant uniform; hair, facial and body hair covered, mask and gloves.
ISO-Class 9	Plastics, polymers, and elastomers processes that are in contact with the patient from molding/ forming.	35,200,000 / na	293,000 / na	Annually	na	na	Positive pressure with respect to unclassified areas.	na	18°C to 25°C	Clean plant uniform; covered hair.
Clean Area [i] (Free of classification)	Manufacture of plastics, polymers and elastomers that are not in direct contact with the patient. Manufacture of non-sterile diagnostic agents. Conditioning of textiles.	na	na	na	na	na	na	na	18°C to 25°C	Clean plant uniform; covered hair.
Gray Area (Freeof classification)	Metal-mechanical processes. Ceramic/ glass processes. Non-sterile Medical Device Assembly. Manufacture of textiles.	na	na	na	na	na	na	na	na	Uniform and Safety equipment.

NOTES:

a Examples given here are illustrative but not limiting.

b Microbiological monitoring should be performed using the following methods:

b.1 Sedimentation plate 90 mm in diameter, with exposure no less than 30 minutes and no longer than 4 hours.

b.2 Air sampling.

b.3 Contact plate 55 mm diameter.

b.4 Glove sampling in 5 fingers.

c The unidirectional flow zone must comply with the flow speed parameter 0.45 m/s ± 20%.

d It can be performed less frequently according to the maintenance of the validated status.

e It can be done at least in Class D provided there´s a support with validation studies.

f Class A rooms must meet these parameters, it does not apply to unidirectional flow modules.

g The particulate limits given in the table for Static Condition can be achieved after a short cleaning period, 15 to 20 minutes after completing the operation and without operators. The Dynamic Condition must be qualified based on design criteria established specifically for the type of process.

h Sample sizes taken for monitoring purposes are given as a function of the sampling system used and not necessarily the volume of the monitoring sample will be the same as the amount of air taken during the formal classification of the room.

i Clean area with sanitary finishes, and where cleaning and sanitization procedures are implemented as a minimum.

j This parameter can be an indicator of the adequate design of the system, therefore if there is no compliance with the range established in the table, it should be investigated and a technical justification should be made to prove that there are no inherent flaws in the design of the areas.
