I. PURPOSE

This quality policy manual defines the requirements of the Sterigenics quality management system. It includes:

- Senior management's quality assurance philosophy and operating requirements.
- Responsibility for their implementation and administration
- Requirements and controls, including references to documented procedures and technical procedures, to ensure compliance with customer requirements and all applicable regulations and standards.
- A description of the interactions between the processes of the quality management system.

II. REQUIREMENTS

1. Scope

To provide consistent quality service to our customers, this quality policy manual applies to all Sterigenics sites globally including processing facilities, laboratories and corporate offices.

It defines the quality management system and its implementation for processing, testing and supporting services provided by Sterigenics. This system is structured to comply with the standards listed in Section 2.0 Normative References.

Reduction in Scope

The following describes clauses that are excluded from the scope or non-applicable to Sterigenics at including identifying information about the affected sites.

Bridgeport Facility

The Bridgeport processing facility sanitizes one type of product for a single customer. Bridgeport does not process medical devices, drugs, or any other product that requires compliance with the regulations and standards that impact other Sterigenics sites, as defined in section 2 of this manual. For this reason, Bridgeport is excluded from the scope of this quality policy manual. Bridgeport will comply with certain aspects of the quality management system to continue to provide consistent quality service to their customer. Those portions of the quality management system that apply to Bridgeport will be documented in their facility-specific quality system documents.

ISO 9001:2008, ISO 13485:2003, and EN ISO 13485:2012 – Section 7.3, Design and Development

The SteriPro Consulting Services Groups located across the global Sterigenics' network, provide sterilization design services which assist Clients with the development of cost effective, long-term sterilization solutions, therefore Section 7.3, Design and Development, applies to the Consulting personnel and their related projects.

Sterigenics Rantigny manufactures kits and therefore Section 7.3, Design and Development applies to this site.

Sterigenics Americas (Gamma, EO and E-Beam processing sites) and EMEAA (Gamma, EO and E-Beam processing sites and laboratories) do not provide design services, and therefore Section 7.3, Design and Development, does not apply to these sites.

ISO 13485:2003 and EN ISO 13485:2012 – Sections 7.5.1.2.2, Installation activities, and 7.5.1.2.3, Servicing activities

Sterigenics Rantigny does not install or service medical devices. Therefore, Sections 7.5.1.2.2, Installation activities, and 7.5.1.2.3, Servicing activities, do not apply to this site.

Sterigenics Americas and EMEAA processing sites and laboratories do not manufacture medical devices. Therefore, Sections 7.5.1.2.2, Installation activities, and 7.5.1.2.3, Servicing activities, do not apply to these sites.

ISO 17025:2005

ISO 17025:2005 apples only to SteriPro laboratory or consulting locations that are accredited to ISO17025. Individual SteriPro locations may seek additional accreditations, such as ISO 17025, whenever those accreditations are consistent with the ISO 9001 & ISO 13485 requirements and are needed or required.

ISO 17025:2005 – Sections 5.6.2.1 Calibration

Sterigenics laboratories do not provide calibration services or calibration certificates. Therefore, Section 5.6.2.1 does not apply.

ISO 17025:2005 – Section 5.7 Sampling and Section 5.10.3.2 Test Reports

Sterigenics laboratories do not sample products for lab testing after processing. Sterigenics laboratories receive samples for testing from customers. Therefore, Sections 5.7 and 5.10.3.2 do not apply.

2. Regulations and Standards

Sterigenics quality management system will comply with the following regulations and standards:

Standard #	Title
ISO 9001:2008	Quality management systems – Requirements
ISO 13485:2003	Medical devices – Quality management systems – Requirements for regulatory purposes
EN ISO 13485:2012	Medical devices. Quality management systems. Requirements for regulatory purposes
ISO 11135-1:2007	Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
EN ISO 11135:2014	Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices NOTE: Sterigenics is currently in transition from the 2007 to the 2014 version of the standard. Compliance to 2007 will be maintained as all aspects of 2014 are adopted into the Sterigenics quality system.
EN ISO 11137-1:2006+A1:2013	Sterilization of health care products. Radiation. Requirements for development, validation and routine control of a sterilization process for medical devices
ISO 11137-2:2013	Sterilization of health care products -- Radiation -- Part 2: Establishing the sterilization dose
ISO 17025:2005	General requirements for the competence of testing and calibration laboratories
21 CFR Part 820	Quality System Regulation
21 CFR Part 210	Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
21 CFR Part 211	Current Good Manufacturing Practice for Finished Pharmaceuticals
MHLW Ministerial Ordinance #169, 2014	Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents (Including Revision by MHLW Ministerial Ordinance No. 87 Dated July 30, 2014)
Eudralex GMP Vol 4	EU Guidelines to GMP on Medicinal Products for Human and Veterinary Use
Eudralex GMP Vol 4, Annex 1	Manufacture of Sterile Medicinal Products
European Directive 93/42/EEC (*)	Medical Device Directive (COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices)
EN-556-1:2001 (*)	Sterilization of medical devices. Requirements for medical devices to be designated “STERILE”. Part 1: Requirements for terminally sterilized medical devices

(*) Only applicable to kits manufactured under the CE marking provisions for Sterigenics France (Rantigny)

Where other national standards or regulations require adherence, they too shall be applied, but only to the appropriate technology or facility. These standards may include, but are not limited to, EU GMP and Thai GMP (for Thailand).

21 CFR Part 211

Sterigenics processes finished pharmaceuticals as part of the manufacturing process of the pharmaceutical manufacturer. Sterigenics processing is subject to some of the regulations in 21 CFR Part 211. Sterigenics will comply with those regulations applicable to product processing operations per 21 CFR Part 210.2 (b).

ISO 13485:2003 & EN ISO 13485:2012

On August 31, 2012, EN ISO 13485:2012 *Medical Devices – Quality Management Systems Requirements for Regulatory Purposes*, became the European harmonized standard and replaced EN ISO 13485:2003 (which was considered obsolete as of the same date). EN ISO 13485:2012 is applicable only to manufacturers placing devices on the market in Europe. For the rest of the world, ISO 13485:2003 *Medical Devices – Quality Management Systems Requirements for Regulatory Purposes* remains the applicable standard.

In EN ISO 13485:2012, new Annex Z's provide greater clarity on the applicability and alignment of clauses of ISO 13485 to the quality systems requirements of the three European Medical Device Directives (MDD, AIMD and IVD). Each Annex Z covers a different Annex within one of the Medical Directives. For example, Annex ZB of EN ISO 13485:2012 shows the relationship between the MDD 93/42/EEC Annex II, Full Quality Assurance and the clauses of ISO 13485.

Changes to EN ISO 13485:2012 compared with the 2003 version are within the foreword and Annex Zs only. There has been absolutely no change to the Normative Text. The requirements clauses of the standard remain the same as the EN ISO EN ISO 13485:2003 and ISO 13485:2003 versions.

To reflect the global nature of our business, Sterigenics requested a reference to EN ISO 13485:2012 be added to our ISO 13485:2003 certificate. The certificate reflects ISO 13485:2003 and EN ISO 13485:2012.

Throughout this Quality Policy Manual, references to ISO 13485 indicate both ISO 13485:2003 and EN ISO 13485:2012.

3. Terms and Definitions

For the purpose of this quality manual, the terms and general definitions related to quality given in ISO 9000:2005 *Quality management systems – Fundamentals and vocabulary,* apply. Where different definitions related to laboratory accreditation are given in ISO 17000:2004, *Conformity assessment – vocabulary and general principles,* the definitions in ISO 17000 are preferred. Where specific definitions are required for 21 CFR Part 211, the definitions given in 21 CFR 210, *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General* are used.

Throughout this Quality Policy Manual,

- Wherever the term “product” occurs, it can also mean “service”.
- The term ‘management system’ is equivalent to ‘quality management system’

An “outsourced process” is a process that the organization needs for its quality management systems and which the organization chooses to have performed by an external party.

The term “procedure” means a documented procedure that is established, implemented and maintained. A single document may address the requirements for one or more procedures. A requirement for a documented procedure may be covered by one or more documents.

See Section III Definitions/Abbreviations

4. Quality Management System

4.1 Requirements

4.1.1 Quality Management System Requirements

Sterigenics shall establish, document, implement, and maintain a quality management system and maintain its effectiveness in accordance with the requirements of Section 2.0, Normative References. To implement and document the system, Sterigenics shall:

a) identify the processes needed for the quality management system and their application throughout the organization

b) determine the sequence and interaction of these processes

c) determine the criteria and methods required to ensure that both the operation and control of these processes are effective

d) ensure the availability of resources and information necessary to support the operation and monitoring of these processes

e) measure, monitor, analyze processes

f) implement actions necessary to achieve planned results and continually improve the effectiveness of these processes

The sequence and interaction of the key processes of the QMS system are illustrated in Appendix A.

Where Sterigenics chooses to outsource any process that affects product conformity with requirements, Sterigenics shall ensure control over such processes. Control of such outsourced processes shall be identified within the quality management system.

4.1.2 Laboratory Management System

Sterigenics shall ensure that the requirements for the laboratory management system appropriate to the scope of the laboratory activities are established, implemented and maintained in the quality management system. The laboratory shall document its policies, systems, programs, procedures, and instructions to the extent necessary to ensure the quality of the test results. The documentation shall be communicated to, understood by, available to, and implemented by the appropriate personnel.

The laboratory management system shall cover work carried out in the laboratory's permanent facilities, at sites away from its permanent facilities, or in associated temporary or mobile facilities.

4.2 Documentation Requirements

4.2.1 General

Quality management system documentation shall include, at a minimum:

a) documented statements of a quality policy and quality objectives

b) this quality policy manual

c) procedures necessary to implement requirements of Section 2.0, Normative References

d) documents needed to ensure the effective planning, operation, and control of processes

e) records required by Section 2.0 Normative References

f) any other documentation specified by national or regional regulations

The quality management system documentation is ordered hierarchically. This Quality Policy Manual is the topmost level. Each level in the hierarchy is supported by documents lower in the hierarchy. For example, an SOP may reference one or more work instructions that provide detailed requirements. Facility quality system documents are lower level work instructions and supporting documents that support facility-specific requirements set forth in the higher level documents. Documents lower on the quality system document hierarchy cannot violate the requirements of documents higher in the hierarchy.

The range and extent of quality management system documentation shall be dependent on the size and type of processing/testing in the facility; complexity and interaction of the processes, and methods used. The sequence and interaction of this documentation is illustrated in Appendix B.

4.2.2 Quality Policy Manual

This Quality Policy Manual is established and maintained and includes:

a) the scope of the quality management system, including details of and justification for any exclusion and/or non-application

b) reference to the procedures established to implement the quality system (including a procedure which describes the structure of the documentation)

c) a description of the interaction between elements of the quality management system.

4.2.3 Control of Documents

4.2.3.1 Document Approval and Issue

Sterigenics shall establish and maintain procedures to control all documents required by the quality management system. The procedures shall ensure that:

a) documents are reviewed and approved for adequacy prior to issue. Approvers will include representatives of the appropriate functional units and Quality Assurance personnel. For facility-specific documents, approvers will include the Quality Assurance Manager.

b) documents are reviewed, updated as necessary and re-approved;

c) changes and the current revision status of documents are identified

d) relevant versions of applicable documents are available at points of use

e) documents are legible, readily identifiable, and retrievable

f) documents are periodically reviewed and, where necessary, revised to

ensure continuing suitability and compliance with applicable requirements

g) documents are uniquely identified. Identification shall include the date of issue and/or revision identification, page numbering, the total number of pages, or a mark to signify the end of the document and the issuing authority(ies)

h) documents of external origin determined to be necessary for the planning and operation of the quality management system are identified and their distribution controlled

i) obsolete documents are removed from all points of issue and use, or otherwise controlled to prevent unintended use

j) obsolete documents retained for any purpose are suitably identified

k) indexes of documents or search functions are available to ensure documents can be located or retrieved by document number, topic, or other relevant criteria.

Documents may include policy statements, procedures, specifications, regulations, standards, other normative documents, test and/or calibration methods, drawings, software, specifications, instructions and manuals, charts, text books, posters, notices, memoranda, plans, or any other document (internally generated or from external sources) required by the quality management system .

Documents may be on various media, whether hard copy or electronic, and they may be digital, analog, photographic or written.

4.2.3.2 Document Changes

Sterigenics shall ensure that changes to documents are reviewed and approved either by the original approving function or by another designated function that has access to pertinent background information upon which to base its decisions related to review and approval.

Where practical, the altered or new text shall be identified in the document or the appropriate attachments.

Procedures shall be established to describe how changes in documents maintained in computerized systems are made and controlled.

Sterigenics shall define the period for which obsolete copies of documents are retained.

4.2.4 Control of Records

4.2.4.1 General

Sterigenics shall ensure that:

a) Records are established and maintained to provide evidence of conformance to specified requirements and of the effective operation of the quality management system.

b) Records remain legible, readily identifiable, and retrievable.

c) Records are stored and retained in such a way that they are readily retrievable in facilities that provide a suitable environment to prevent damage or deterioration and to prevent loss.

d) A procedure is established to define the controls needed for the identification, collection, access, filing, storage, maintenance, protection, confidentiality, retrieval, retention time and disposition of records.

e) Records are held securely and confidentially.

f) Records are readily available for authorized inspection throughout the record retention period. Access to records is based on confidentiality

requirements defined in procedures.

g) Written records for processing or testing of drug products shall be maintained so that the data therein can be used for evaluating, at least annually, the quality standards of the drug product to determine the need for changes in the drug product specifications or manufacturing or control procedures by the customer. Sterigenics facilities or laboratories participating in these evaluations with customers shall establish and follow written procedures for the evaluations including the following provisions:

1. A review of the representative number of batches whether approved or rejected, and, where applicable, records associated with the batch.
2. A review of complaints, recalls, returned or salvaged drug products, and investigations conducted as a result of processing history record or testing history record reviews.

When mistakes occur in records, each mistake shall be crossed out, not erased, made illegible, or deleted, and the correct value entered alongside or in proximity to the original entry. All such alterations to records shall be signed or initialed by the person making the correction. In the case of records stored electronically, equivalent measures shall be taken to avoid loss or change of original data.

Records may be in any media, such as hard copy or electronic media. Where records are stored electronically, Sterigenics shall have procedures in place to protect and back up the electronic records and to prevent unauthorized access or change of the records.

4.2.4.2 Laboratory Technical Records

The laboratory shall retain records of original observations, derived data, and sufficient information to establish an audit trail, calibration records, staff records and a copy of each test report for a defined period. The records for each test shall contain sufficient information to facilitate, if possible, identification of factors affecting the uncertainty and to enable the test to be repeated under conditions as close as possible to the original.

The records shall include the identity of personnel responsible for the performance of each test and checking the results.

Observations, data and calculations shall be recorded at the time they are made and shall be identifiable to the specific task.

4.2.5 Confidentiality

Sterigenics shall have policies and procedures to ensure the protection of confidential information, including customer's confidential information and proprietary rights. Procedures shall address protection of the electronic storage and transmission of results.

5. Management Responsibility

5.1 Management Commitment

Senior management shall demonstrate its commitment to the development and implementation of the quality management system and maintaining its effectiveness by:

a) communicating to the organization and maintaining awareness of the importance of meeting customer requirements, as well as regulatory and legal requirements;

b) establishing the quality policy

c) ensuring that quality objectives are established;

d) conducting management reviews;

e) ensuring the availability of resources.

5.2 Customer Focus

Senior management shall ensure that:

a) customer needs and expectations are determined and converted into requirements;

b) customer requirements are fully understood.

5.3 Quality Policy

Senior management shall ensure that the quality policy

a) is appropriate for the organization and our customers;

b) includes a commitment to comply with requirements and to maintain the effectiveness of the quality management system;

c) provides a framework for establishing and reviewing quality objectives;

d) is communicated and understood within the organization;

e) is reviewed for continuing suitability;

f) addresses the laboratory's commitment to good professional practice and to the quality of its testing in servicing its customers;

g) includes management's statement of the laboratory's standard of service

5.4 Planning

5.4.1 Quality Objectives

Senior management shall ensure that

a) Quality objectives, including those needed to meet requirements for product and services, are established at each relevant level and function within the organization.

b) The Quality Objectives are measurable and consistent with the quality policy and the commitment to continual improvement.

5.4.2 Quality Management System Planning

Senior management shall ensure that

a) the planning of the quality management system is carried out in order to achieve quality objectives and the quality system management requirements, and continual improvement of the quality management system;

b) the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented

5.5 Responsibility, Authority, and Communication

5.5.1 Responsibility and Authority

a) Organization

Senior management shall

i. Ensure that responsibilities and authorities are defined, documented, and communicated within the organization. This includes definition of the responsibilities of key personnel that have involvement or influence on the testing activities of the laboratory in order to identify potential conflict of interest.

ii. Establish the interrelation of all personnel who manage, perform, and verify work affecting quality.

iii. Ensure the independence and authority necessary to perform these tasks.

iv. Ensure that employees are aware of the relevance and importance of their activities and how they contribute to the achievement of the objectives of the

quality management system.

v. Appoint deputies for key managerial personnel as needed.

Organizational charts shall be used to define the responsibilities and authorities within the organization including the organization structure and relationships between quality management, technical operations, and support services. The organizational charts define the relationship of the various functions within the organization and business lines. For the laboratory, the organizational charts shall specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work affecting the quality of the tests. The organizational charts are available on the Sterigenics Intranet.

Facility organizational charts defining the relationship and various functions of the facility's specific organization shall be developed and maintained at each facility. The organizational chart will identify title and authority of personnel and define the relationship of the various functions within the facility and with other parts of the organization.

The laboratory organization shall carry out its testing activities in such a way as to satisfy the needs of the customer, the regulatory authorities, or organizations providing recognition.

b) Facility and Departmental Managers

Each member of management is ultimately responsible for:

i. implementing and communicating the quality policy and requirements of the quality management system throughout their respective departments;

ii. assuring that requirements of the quality management system are available and followed by each employee;

iii. ensuring that employees are provided with the proper training to perform the duties required of their position;

iv. initiating action to prevent the occurrence of product nonconformance;

v. initiating and providing solutions through designated channels

vi. providing adequate supervision of laboratory testing staff, including trainees, by persons familiar with methods and procedures, purpose of each test, and with the assessment of the test results

Specific responsibilities of managers are documented in job descriptions.

c) Quality Assurance Manager Authority

The Quality Assurance Manager is given the authority and responsibility to represent the facility/laboratory on all quality matters pertinent to the quality management system as established through customer and regulatory requirements and company quality policies and procedures. For this reason the Quality Assurance Manager, in addition to reporting directly to the General Manager or Director/General Manager, also reports, on a dotted line basis, to Quality Assurance management at the corporate level. Organizational charts are used to depict Quality Assurance reporting relationships.

Should a dispute occur between Operations, General Manager, Director/General Manager and the Quality Assurance Manager, in regard to the quality of a product, service or regulatory issue, the issue will be brought before VP level members of Global Quality Assurance for resolution.

d) Quality Control

Based on the size of the organization, responsibilities within each facility, and products processed, Sterigenics does not have separate functions for quality control and quality assurance. Quality control functions are the responsibility of the Quality Assurance Manager.

In some facilities, where required, there are individuals assigned quality control responsibilities. The organization charts for these facilities will define the individuals dedicated to quality control.

The heads of Quality Control and Operations must be independent from each other.

e) . Laboratory Organization

The laboratory shall have

i. Managerial and technical personnel who, irrespective of their other responsibilities, have the authority and resources needed to carry out their duties, including the implementation, maintenance and improvement of the management system, and to identify the occurrence of departures from the management system or from the procedures for performing tests and to initiate action to prevent or minimize such departures.

ii. Arrangements to ensure that its management and personnel are free from any undue internal and external commercial, financial or other pressures and influences that may adversely affect the quality of their work

iii. Policies and procedures to avoid involvement in any activities that would diminish confidence in its competence, impartiality, judgment or operational integrity.

iv. Technical management which has overall responsibility for the technical operations and the provision of the resources needed to ensure the required quality of laboratory operations.

5.5.2 Management Representative, Responsible Engineering Manager, and Quality Control Unit

Refer to Section III Definitions/Abbreviations for definitions of Management Representative, Responsible Engineering Manager and Quality Control Unit.

5.5.2.1 The Senior Vice President of Global Quality Assurance is given the responsibility of Management Representative and Responsible Engineering Manager for the overall quality program at the corporate level. The Management Representative has the responsibility and authority that includes:

a) ensuring that the processes needed for the quality management system are established, implemented, and maintained;

b) reporting to senior management on the performance of the quality management system and any need for improvement;

c) ensuring the promotion of awareness of regulatory and customer requirements throughout the organization.

5.5.2.2 The Quality Assurance Manager is given the responsibility of Management Representative and Responsible Engineering Manager at the facility level. The Quality Assurance Manager has the authority and responsibility to:

a) ensure that the processes needed for the quality management system are established, implemented, and maintained,

b) report to senior management on the performance of the quality management system and any need for improvement

c) ensure the promotion of awareness of regulatory and customer requirements throughout the organization/facility

5.5.2.3 The Quality Assurance Manager is given the responsibility of the quality control unit. In facilities where specific individuals are assigned quality control responsibilities, the individuals defined as quality control are responsible for executing the responsibilities below and the QA Manager is responsible for the quality control unit.

The quality control unit has the responsibility and authority to approve or reject all

processed drug products and the authority to review drug processing records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated.

Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

The quality control unit is responsible for approving or rejecting all processed drug products.

Quality Assurance approval is required on all procedures.

The quality control unit is responsible for approving or rejecting all facility procedures or specifications impacting the drug product.

The responsibilities and procedures applicable to quality control are in writing and the written procedures will be followed.

5.5.3 Internal Communication

Senior management shall ensure that appropriate communication processes are established within the organization including the laboratory and that communication takes place regarding the effectiveness of the quality management system.

5.6 Management Review

5.6.1 General

Senior management, at the corporate level, shall review the quality management system on an annual basis to ensure its continuing suitability, adequacy, and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system including the quality policy and quality objectives.

Facility/laboratory management shall review the quality management system on an annual basis to ensure its continuing suitability, adequacy, and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system including the quality policy and quality objectives. The results of this review will be utilized during the corporate management review.

Records from management reviews shall be maintained.

5.6.2 Review input

The input to management review shall include information on

a) results of audits, including assessments by external bodies,

b) customer feedback, including customer complaints,

c) process performance and product conformance,

d) for the laboratory, results of inter-laboratory comparisons or proficiency tests, if applicable

e) for the laboratory, changes in the volume and type of work

f) status of preventive and corrective actions,

g) follow-up actions from previous management reviews,

h) changes that could affect the quality management system,

i) recommendations for improvement,

j) new or revised regulatory requirements,

k) market strategies,

l) other relevant factors such as quality control activities, resources and staff training,

m) suitability of policies and procedures

5.6.3 Review output

The output from the management review shall include any decisions and actions related to information on

a) improvements needed to maintain the effectiveness of the quality management system and its processes,

b) improvement of product related to customer requirements,

c) resource needs

Findings from management reviews and the actions that arise from them shall be recorded. Management shall ensure that these actions are carried out within an appropriate and agreed timescale.

Management review results should feed into planning including the goals, objectives, and action plans for the coming year.

5.6.4 Product Quality Reviews

Facilities processing drug products may be requested to participate in a periodic quality review with the objective of verifying the consistency of the existing process, the appropriateness of the current specifications, to highlight trends and to identify process improvements. The reviews are required to be conducted at least annually. Customers may request the review and documentation of the following aspects of Sterigenics processes:

a) A review of critical in-process controls and finished product results.

b) A review of all batches that failed to meet established specification(s) and their investigation.

c) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.

d) A review of all changes carried out to the processes or analytical methods.

e) A review of all quality-related returns, complaints and recalls and the Investigations performed at the time.

f) A review of adequacy of any other previous product process or equipment corrective actions.

g) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

h) A review of any contractual arrangements to ensure that they are up to date.

6. Resource Management

6.1 Provision of Resources

Sterigenics shall determine and provide in a timely manner, the resources needed

a) to implement the quality management system and to maintain its effectiveness

b) to meet customer and regulatory requirements.

c) To ensure an adequate number of qualified personnel to perform and supervise product processing.

6.2 Human Resources

6.2.1 General

Personnel performing work affecting product quality shall be competent on the basis of appropriate education, training, skills and experience.

6.2.2 Competence, awareness and training

Sterigenics shall:

a) determine the necessary competence for personnel performing work affecting product quality;

b) provide training or take other actions to satisfy these needs;

c) evaluate the effectiveness of the actions taken;

d) ensure that employees are aware of the relevance and importance of their activities and how they contribute to the achievement of quality objectives and meeting customer requirements;

e) maintain appropriate records of education, training, skills, and experience.

6.2.3 Personnel Qualifications

Personnel shall have the education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be

a) in the particular operations that the employee performs

b) in good manufacturing practice as related to processing and testing, including the applicable good manufacturing practices and written procedures required by good manufacturing regulations as they relate to the employee's functions.

Training in good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

Each person responsible for supervising processing shall have the education, training, and experience, or any combination thereof, to perform the assigned functions in such a manner as to provide assurance that quality of the products processed will not be adversely affected by processing.

Certain pharmaceutical regulations define specific educational requirements for individuals releasing product. These requirements may include university or college degrees and may define specific areas of study. For facilities processing products required to comply with these regulations, Sterigenics ensures that the individuals responsible for releasing product meet the specific educational requirements.

In European facilities with a drug manufacturing authorization, the release of drugs from sterilization shall be approved by a registered Qualified Person.

6.2.4 Consultants

Consultants advising on processing of product or other aspects of the quality management system shall have sufficient education, training, and experience, or any combination thereof, to enable that person to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any such consultants and the type of service they provide.

6.3 Infrastructure (Facilities)

6.3.1 Facilities

Sterigenics shall determine, provide, and maintain the infrastructure needed to achieve conformity to product requirements. Infrastructure includes:

a) buildings, workspace, and associated utilities. Buildings will be of suitable design, size, construction, and location to perform operations, prevent mix-ups and product damage, and facilitate cleaning and maintenance. The flow of products through the buildings shall be designed to prevent contamination.

b) process equipment (both hardware and software);

c) supporting services (such as transport and communication)

6.3.2 Operations

Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas, or other control systems, as needed, to prevent contamination or mixups during the following procedures

- Storage of products awaiting processing or in process
- Processing operations
- Quarantine storage prior to product release
- Storage after release
- Control and laboratory operations;

6.3.3 Lighting

Adequate lighting shall be provided in all areas.

6.3.4 Ventilation, air filtration, air heating and cooling

a) Adequate ventilation shall be provided.

b) Equipment for adequate control over air pressure, humidity, and temperature shall be provided where appropriate during product processing.

6.3.5 Plumbing

a) Water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute to contamination of a product. As required, the quality of the water will be defined in work instructions.

b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

6.3.6 Sewage and refuse

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

6.3.7 Washing and toilet facilities

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

6.3.8 Sanitation

a) Any building used in the processing or storage of product shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects or other vermin. Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities. The written procedures shall be followed.

c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, or products and shall be followed. As required, regulatory requirements for rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents will be defined in work instructions.

d) Sanitation procedures will apply to work performed by contractors, temporary employees as well as work performed by employees during the ordinary course of operations.

6.3.9 Maintenance

Any building used in processing or holding product shall be maintained in a good state of repair. Sterigenics shall establish documented requirements for maintenance activities, including their frequency, when such activities or lack thereof can affect product quality.

Records of maintenance shall be maintained.

6.4 Work environment

Sterigenics shall determine and manage the work environment needed to achieve conformity to product requirements. The following requirements shall apply:

a) Sterigenics shall establish documented requirements for health, cleanliness, and clothing of personnel if contact between such personnel and the product or work environment could adversely affect the quality of the product.

   Any person at any time (either by medical examination or supervisory observation) to have an apparent illness, or open lesions that may adversely affect the safety or quality of products shall be excluded from direct contact with products until the condition is corrected or determined by competent medical personnel to not to jeopardize the safety or quality of the products.

b) If work environment conditions can have an adverse effect on product quality, Sterigenics shall establish documented requirements for the work environment conditions and documented procedures or work instructions to monitor and control these work environment conditions.

c) Sterigenics shall ensure that all personnel who are required to work temporarily under special environmental conditions within the work environment are appropriately trained or supervised by a trained person.

d) If appropriate, special arrangements shall be established and documented for the control of contaminated or potentially contaminated product in order to prevent contamination of other product, the work environment, or personnel.

e) Only personnel authorized by supervisory personnel shall enter those areas of the facilities designated as limited-access areas.

6.5 Personnel responsibilities

Personnel shall be responsible for complying with and shall be trained in procedures for

a) established work environment requirements.

b) practicing good sanitation and health habits.

c) reporting to supervisory personnel any health conditions that may have an adverse impact on quality of products.

7. Product Realization

7.1 Planning of Product Realization

Sterigenics shall plan and develop processes needed for product realization. Planning of product realization shall be consistent with the requirements of the other processes of the quality management system.

In planning product realization, Sterigenics shall determine the following, as appropriate:

a) quality objectives and requirements for the product, test or study;

b) the need to establish processes, documents, and provide resources specific to the product;

c) required verification, validation, monitoring, inspection, and test activities specific to the product and the criteria for product acceptance;

d) records needed to provide evidence that the realization processes and resulting product meet requirements.

The output of this planning shall be in a form suitable for Sterigenics method of operations.

Sterigenics shall establish documented requirements for risk management throughout product realization. Records arising from risk management shall be maintained.

7.2 Customer-Related Processes

7.2.1 Determination of Requirements Related to the Product

Sterigenics shall determine

a) requirements specified by the customer, including the requirements for delivery, and post-delivery activities;

b) requirements not stated by the customer but necessary for specified or intended use, where known;

c) regulatory and legal requirements related to the product;

d) any additional requirements determined by the organization

7.2.2 Review of Requirements Related to the Product

Sterigenics shall review the requirements related to the product. The review shall be conducted prior to Sterigenics commitment to process product to be released to market or conduct laboratory tests for the release of such product. . (e.g. submission of tenders, acceptance of contracts or orders, acceptance of changes to contracts or orders) and shall ensure that:

a) the requirements, including any laboratory methods to be used, are clearly defined, documented and understood;

b) contract or order requirements differing from those previously expressed are resolved;

c) the organization has the ability, capability, and resources to meet the defined requirements;

d) the appropriate test methods are selected and is capable of meeting the customer's requirements

For laboratory testing, the review shall also include any work that is subcontracted by the laboratory.

Records of the results of the review, including any significant changes, and actions arising from the review shall be maintained. For laboratory testing, records shall also be maintained of pertinent discussions with the customer relating to the customer's requirements or the results of the work during the period of execution of the contract.

Where the customer provides no written requirements, the customer requirements shall be confirmed before acceptance.

Where product requirements are changed, Sterigenics shall ensure that relevant documents are amended and that relevant personnel are made aware of the changed requirements.

If a contract needs to be amended after work has commenced, the same contract review process shall be repeated, if applicable, and any amendments shall be communicated to all affected personal.

7.2.3 Customer Communication

Sterigenics shall determine and implement effective arrangements for communicating with customers in relation to:

a) product and/or service information including deviations from the contract

b) inquiries, contracts, or order handling, including amendments

c) customer feedback including customer complaints and actions relating to nonconforming products or services;

d) advisory notices

7.2.4 Subcontracting of Laboratory Testing

7.2.4.1 When the laboratory subcontracts work, whether because of unforeseen

reasons (e.g., workload, need for further expertise or temporary incapacity) or on a continuing basis (e.g. through permanent subcontracting, agency, or franchising arrangements), this work shall be placed with a competent subcontractor. A competent subcontractor is one that, for example, complies with the testing procedures and Quality Requirements of SteriPro laboratories for the work in question.

7.2.4.2 The laboratory shall advise the customer of the arrangement in writing and, when using another SteriPro facility, the test methodology varies from the original agreement with the customers. In the case when an outside contractor is chosen to perform the testing the client must be notified. Accordingly as appropriate, the contracting facility may gain the approval of the customer, preferably in writing.

7.2.4.3 The laboratory is responsible to the customer for the subcontractor's work, except in the case where the customer or a regulatory authority specified which subcontractor is to be used.

7.2.4.4 The laboratory shall maintain a register of all subcontractors that it uses for tests and a record of the evidence of compliance with ISO 17025 for the work in question.

7.2.5 Laboratory Service to the Customer

7.2.5.1 The laboratory shall be willing to cooperate with customers or their representatives in clarifying the customer's request and in monitoring the laboratory's performance in relation to the work performed, provided that the laboratory ensures confidentiality with other customers. Cooperation may include

- providing the customer or the customer's representative reasonable access to relevant areas of the laboratory for the witnessing of tests performed for the customer
- preparation, packaging, and dispatch of test items needed by the customer for verification purposes

Communication with the customer, especially in large assignments, should be maintained throughout the work. The laboratory should inform the customer of any delays or major deviations in the performance of tests.

7.2.5.2 The laboratory shall seek feedback, both positive and negative, from its customers. The feedback shall be used and analyzed to improve the management system, testing and calibration activities and customer service.

7.3 Design and Development

For the purposes of process development (specifically sterilization cycle design) which is performed as part of a consulting project, the SteriPro Analytical Laboratory shall; plan, manage, and document all activities related to the design and development process.

7.3.1 Design and development planning

As part of the planning process for design and development projects, SteriPro Analytical Laboratory management shall define:

a) The design and development project phases from initial customer contact through approval of the Final Report.

b) The review, verification and validation that is appropriate for each phase of the project.

c) The responsibilities and authorities of all parties involved in the project.

The SteriPro Analytical Laboratory shall manage the interfaces between different groups involved in design and development to ensure effective communication and clear assignment of responsibility.

Planning output shall be documented and updated, as appropriate, as the design and development progresses,

7.3.2 Design and development inputs

Inputs related to the process development project shall be determined, recorded, reviewed and records maintained as part of the project file. These inputs shall include at a minimum

a) customer requirements

b) functional performance requirements

c) capability of the processing equipment

d) applicable statutory and regulatory requirements

e) where applicable, information derived from previous similar processes or related customer projects, and

f) other requirements essential to design and development

g) outputs of risk management

These inputs shall be reviewed for adequacy and approved.

Requirements shall be complete, unambiguous and not in conflict with each other.

7.3.3 Design and development outputs

The outputs of design and development shall be documented in the form of a Final Report that enables the verification against the design and development inputs and shall be approved by appropriate parties prior to implementation. The final report shall

a) show that the input requirements for the design and development project have been met

b) provide appropriate information for successful execution of the designed process including process specifications and tolerances

c) contain or reference the attainment of the project acceptance criteria

d) specify the characteristics of the process that are essential for its safe and proper use

Records of the design and development outputs shall be maintained.

7.3.4 Design and development review

At suitable stages, systematic reviews involving appropriate individual(s) representing the various functions involved in the design and development project shall be conducted

a) to evaluate the ability of the results of the design and development project to fulfill requirements and

b) to identify any problems and propose necessary actions

Results and necessary actions shall be documented and maintained.

7.3.5 Design and Development verification

Verification shall be performed through review of the Final Report to ensure that design and development outputs have satisfied the design and development input requirements. Records of the results of these reviews and any resulting actions shall be maintained.

7.3.6 Design and development validation

Validation activities shall be performed where required prior to delivery of the process to the customer or the processing facility and then at the facility prior to implementation of the process. Records and results of all validation activities and any necessary actions shall be maintained.

7.3.7 Control of design and development changes

Design and development changes shall be identified and records maintained. The changes shall be reviewed, verified and validated, as appropriate, and approved before implementation.

The review of design and development changes shall include evaluation of the effect of the changes on constituent parts or products involved in the delivered process.

Records of the results of the review of changes and any necessary actions shall be maintained.

7.4 Purchasing

7.4.1 Purchasing Process

Sterigenics shall establish procedures to ensure that purchased product conforms to specified purchase requirements. Procedures shall exist for the purchase, reception, and storage of reagents and laboratory consumable materials relevant for laboratory tests.

The type and extent of control applied to the supplier and the purchased product shall be dependent upon the effect of the purchased product or service on subsequent product realization, the final product, or laboratory tests.

Sterigenics shall evaluate and select suppliers based on their ability to supply product in accordance with the organization's requirements. Criteria for selection, evaluation, and re-evaluation shall be established. Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained. A list of approved suppliers will be maintained.

7.4.2 Purchasing Information

Purchasing information shall describe the product to be purchased, including, where appropriate

a) requirements for approval of product, procedures, processes, and equipment;

b) requirements for qualification of personnel;

c) quality management system requirements

Sterigenics shall ensure the adequacy of specified purchase requirements prior to their communication to the supplier. For items affecting the quality of laboratory output, purchasing requirements shall contain data describing the supplies and services ordered and shall be reviewed and approved for technical content prior to release.

Purchasing documents shall include, where possible, an agreement that the suppliers (including contractors and consultants) agree to notify Sterigenics of changes in the product or services so that Sterigenics may determine whether the changes may affect product processing or laboratory testing.

Sterigenics shall maintain relevant purchasing documents and records.

7.4.3 Verification of Purchased Product/Service

Sterigenics shall establish and implement inspection or other activities necessary for ensuring that purchased product or service meets specified purchase requirements. This includes purchased supplies, reagents and consumable materials that affect the quality of laboratory tests. The purchased product or service, if applicable, must be inspected or verified as complying with the purchase requirements, standard specifications, or requirements defined in laboratory methods prior to use of the purchased product or service. Records of the inspection or verification activities shall be maintained.

Where the customer proposes that verification activities be performed at the supplier's premises, the verification requirements shall be specified in the purchasing documents.

Records of the verification shall be maintained.

7.5 Production and Service Provision

7.5.1 Control of Production and Service Provision

7.5.1.1 General Requirements

Sterigenics shall plan and carry out production and service provision under controlled conditions. Controlled conditions shall include, as applicable

a) the availability of specifications that define the characteristics of service required; including any time limitations on processing steps required for processing drug, biotech, or other sensitive products

b) the availability of documented procedures, documented requirements, work instructions, and reference materials and reference measurement procedures as necessary;

c) the use of suitable equipment;

d) the availability and use of monitoring and measuring devices;

e) the implementation of monitoring and measurement;

f) the implementation of release, delivery, and post-delivery activities;

g) the implementation of defined operations for labeling and packaging, if applicable

Sterigenics shall establish and maintain a process history record (batch record) for each processing batch. Process history records shall be traceable to the batch and shall identify the amount processed and the amount approved for release. Each batch record shall be verified and approved.

7.5.1.2 Control of Production and Service Provision

7.5.1.2.1 Cleanliness of product and contamination control

Sterigenics shall establish documented requirements for maintaining the cleanliness of the product as it is presented to the facility for processing. Sterigenics will process the product as directed by the customer to help ensure the customer requirements for process cleanliness and removal of process agents are achieved.

7.5.1.3 Particular requirements for sterile medical devices

Sterigenics shall maintain records of the processing parameters for the process which was used for each processing batch. Process history records shall be traceable to each processing batch.

7.5.1.4 Laboratory Controls – General requirements

7.5.1.4.1 General requirements

The laboratory shall establish any specifications, standards, sampling plans, test procedures, or other laboratory control measures required including any changes in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms. These control mechanisms will be reviewed and approved by the quality control unit.

Requirements in the documented laboratory control mechanisms shall be followed and shall be documented at the time of performance. Any deviations from the written specifications, standards, sampling plans, test procedures, or other established laboratory control mechanisms shall be recorded and justified.

7.5.1.4.2 Required laboratory controls

Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the components, drug products containers, closures, in-process materials, labeling and

drug products conform to appropriate standards of identify, strength, quality, and purity, Required controls shall include:

a) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

b) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

c) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

d) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

7.5.1.4.3 Stability testing

Where Sterigenics laboratories perform stability testing on sterilized drug products, the laboratories will have procedures in place to meet the requirements of 21 CFR Part 211.66.

7.5.2 Validation of Processes

7.5.2.1 General Requirements

Sterigenics shall validate any processes for production and service provision where the resulting output cannot be fully verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the product is in use or the service has been delivered.

Validation shall demonstrate the ability of these processes to achieve planned results.

Sterigenics shall establish arrangements for these processes including, as applicable

a) Defined criteria for review and approval of the processes.

b) Approval of equipment and qualification of personnel

c) Use of specific methods and procedures

d) Requirements for records

e) Revalidation

Sterigenics shall establish procedures for the validation of the application of computer software (and changes to such software and/or its application) for production and service provision that affect the ability of the product to conform to specified requirements. Such applications shall be validated prior to use.

7.5.2.2 Particular requirements for sterile medical devices

Sterigenics shall establish procedures for the validation of sterilization processes. Sterilization processes shall be validated prior to initial use.

Records of validation shall be recorded.

7.5.3 Identification and Traceability

7.5.3.1 Identification

Sterigenics shall identify the product by suitable means throughout product realization and shall establish procedures for such product identification.

Where customers require product-specific labeling for pharmaceutical / drug products, the product specific labeling requirements will be implemented in work instructions at facilities processing the product.

Sterigenics shall establish procedures to ensure that nonconforming medical devices or other products returned to the organization are identified and distinguished from conforming product.

7.5.3.2 Traceability

7.5.3.2.1 **General**

Sterigenics shall establish procedures for traceability. Such procedures shall define the extent of product traceability and the records required.

Where traceability is a requirement, Sterigenics shall control and record the unique identification of the product.

7.5.3.2.2 **Particular requirements for active implantable medical devices and implantable medical devices**

Sterigenics shall maintain records of traceability of products and these records will be made available for inspection. Sterigenics shall record product shipping information including the name and address to which the product is shipped.

7.5.3.2.3 **Particular requirements for distribution of drug products**

Sterigenics shall record product shipping information including the product identification, date and quantity shipped, lot number, and name and address to which product is shipped.

For pharmaceutical products where agreed upon by the customer and Sterigenics, the lot number provided by the customer will be recorded. For other customers, the lot number recorded may be a purchase order, load number, product lot number, or other product identification depending on what the customer provides.

Where customers collect the shipment, Sterigenics retains records of the collection by the customer or customer-designated shipper.

7.5.3.3 Status Identification

Sterigenics shall identify the product status with respect to monitoring and measurement requirements.

The identification of product status shall be maintained throughout production, storage, installation, and servicing of the product to ensure that only product that has passed the required inspections and tests (or released under an authorized concession) is dispatched, used, or installed.

7.5.4 Customer Property

Sterigenics shall exercise care with customer property while it is under the organization's control or being used by the organization. Sterigenics shall identify, verify, protect and safeguard customer property provided for use or incorporation into a

product. If any customer property is lost, damaged, or otherwise found to be unsuitable for use, this shall be reported to the customer and records maintained. Customer property in the form of confidential information will remain confidential.

7.5.5 Preservation of Product

Sterigenics shall establish procedures or work instructions for preserving the conformity of product during internal processing and delivery to the intended destination.

This preservation shall include identification, handling, packaging, storage and protection. Preservation shall also apply to the constituent parts of a product.

Sterigenics shall establish procedures or work instructions for the control of product with a limited shelf-life or requiring special storage conditions. Such special storage conditions shall be controlled and recorded.

7.6 Control of Monitoring and Measurement Devices

Sterigenics shall determine the monitoring and measurement to be undertaken and the monitoring and measuring devices needed to provide evidence of conformity of product to determined requirements.

Sterigenics shall establish procedures to ensure that monitoring and measurement can be carried out and are carried out in a manner that is consistent with the monitoring and measurement requirements.

Where necessary to ensure valid results, measuring equipment shall be:

a) calibrated or verified at specified intervals, or prior to use against measurement standards traceable to international or national measurement standards; where no such standards exist, the basis used for calibration or verification must be documented;

b) adjusted or re-adjusted as necessary

c) identified to enable calibration status to be determined;

d) safeguarded from adjustments that would invalidate the measurement result

e) protected from damage and deterioration during handling, maintenance, and storage

In addition, Sterigenics shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The organization shall take appropriate action on the equipment and any product affected. Records of the results of calibration and verification shall be maintained.

When used in monitoring and measurement of specified requirements, the ability of computer software to satisfy the intended application shall be confirmed. This shall be undertaken prior to initial use and reconfirmed as necessary.

7.7 Equipment

7.7.1 Equipment design, size and location

Equipment used in product processing shall be of appropriate design, adequate, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. Equipment shall be appropriately identified to provide traceability and prevent mixups.

7.7.2 Equipment construction

Equipment shall be constructed so that surfaces that contact product are not reactive, additive or absorptive so as to alter the quality of the product beyond its established requirements.

Any substances required for operation, such as lubricants or coolants, shall not be allowed to come into contact with product so as to alter the quality of product beyond its established requirements.

7.7.3 Equipment cleaning and maintenance

a) Equipment shall be cleaned and maintained at defined intervals to prevent malfunctions or contamination that would alter the quality of the product beyond its established requirements.

b) Written procedures shall be established and followed for cleaning and maintenance of equipment used in product processing. The procedures shall include, but are not limited to, the following:

1. Assignment of responsibility for cleaning and maintenance
2. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations and the methods for disassembling and reassembling the equipment as necessary to assure proper cleaning and maintenance.
4. Protection of clean equipment from contamination prior to use
5. Inspection of equipment for cleanliness prior to use.

c) Records of cleaning and maintenance shall be retained.

7.7.3 Automatic, mechanical, and electronic equipment.

a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the processing of product. If such equipment is used, it shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of the calibration checks and inspections shall be maintained.

b) Appropriate controls shall be exercised over computer or related systems to assure that changes in processing records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances, a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems such as duplicates, tapes, or microfilm designed to assure backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

c) Such automated equipment used for performance of processing operations can satisfy requirements for performance of an operation by one person and checking by another if the equipment is used in conformity with this section and one person checks that the equipment properly performed the operations.

8. Measurement, Analysis and Improvement

8.1 General

Sterigenics shall plan and implement the monitoring, measurement, analysis and improvement processes needed to:

a) demonstrate conformity of the product;

b) ensure conformity of the quality management system;

c) maintain the effectiveness of the quality management system

This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

8.2 Monitoring and Measurement

8.2.1 Feedback

As one of the measurements of the performance of the quality management system, Sterigenics shall

- monitor information relating to whether the organization has met customer requirements
- monitor information relating to customer perception as to whether the organization has met customer requirements.
- seek feedback, both positive and negative, from customers.

The methods used for obtaining and using this information shall be determined based upon applicability.

Sterigenics shall establish a procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes. Customer feedback shall be used and analyzed to improve the management system, testing activities, and customer service.

If national or regional regulations require the organization to gain experience from the post-production phase, the review of this experience shall form part of the feedback system.

8.2.2 Internal Audit

The organization shall conduct internal audits at planned intervals to determine whether the quality management system

a) Conforms to the planned arrangements, to the requirements of this International Standard, and to the quality management system requirements established by Sterigenics

b) Is effectively implemented and maintained.

An audit program shall be planned, taking into consideration the status and importance of the processes and areas to be audited, as well as the results of previous audits. The audit criteria, scope, frequency, and methods shall be defined. Selection of auditors and conduct of audits shall ensure objectivity and impartiality of the audit process. Auditors shall not audit their own work.

Audits shall be conducted by qualified individuals that do not have direct responsibility for the location being audited.

The responsibilities and requirements for planning and conducting audits, and for reporting results and maintaining records shall be defined in a procedure.

The management responsible for the area being audited shall ensure that actions are taken without undue delay to eliminate detected nonconformities and their causes. Follow up activities shall include the verification of the actions taken and the reporting of the verification results.

When audit findings cast doubt on the effectiveness of the operations or on the correctness or validity of the laboratory's test results, the facility or laboratory shall take timely corrective action and shall notify customers in writing if investigations show that the processing or laboratory results may have been affected.

8.2.3 Measurement and Monitoring of Process, Process Control

8.2.3.1 General Requirements

Sterigenics shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes. These methods shall demonstrate the ability of the processes to achieve planned results. When planned results are not achieved, correction and corrective action shall be taken, as appropriate, to ensure conformity of the product.

The process will be implemented, measured and monitored for a state of control through the following:

a) documented procedures and work instructions;

b) approval of processes and process equipment;

c) suitable equipment, designed in a manner to perform maintenance, adjustments, and cleaning;

d) work performed by trained personnel and applicable criteria for workmanship defined;

e) compliance with applicable national reference standards/codes, regulations, documented procedures and quality plans;

f) processing and monitoring tasks documented at the time of performance

g) recording and justification for any deviation from documented procedures

h) monitoring, control, and inspection of the process through routine process data review and testing;

i) suitable environment, facilities, and environmentally controlled conditions to perform quality operations;

j) maintain procedures to prevent contamination of equipment or product by substances that could be reasonably expected to have adverse effect on product quality;

k) adequate buildings of suitable design and sufficient space to perform necessary operations;

l) ensure process integrity, prevent mix-ups, and preserve product condition;

m) preventive maintenance and inspection of equipment;

n) automated data processing systems and software, and any changes to said systems or software, used for production or quality system management, are validated for intended use;

o) compliance to all quality management system and safety requirements;

p) adequate health, cleanliness, and personal practices;

q) internal audits

All process inspections and testing shall be documented and retained as quality records.

8.2.3.2 Sampling and Testing of In-Process Materials

Ethylene oxide, propylene oxide, nitrogen, and steam are considered in-process materials in EO processing of pharmaceutical products.

a. If a facility performs sampling for pharmaceutical products, the facility shall establish and follow procedures that describe the in-process controls and tests to be conducted on appropriate samples of in-process materials of each batch.

b. Valid in-process specifications shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

c. Identity, strength, quality, and purity of ethylene oxide, propylene oxide, and nitrogen will be verified against Certificates of Analysis as appropriate, and approved or rejected by the quality control unit, during the production process.

Steam will be tested per established procedures or agreed upon customer specifications, and approved or rejected by the quality control unit, during the production processs.

d. Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

8.2.4 Measurement and Monitoring of Product and/or Service

8.2.4.1 General Requirements

Procedures shall be established for receiving, in process, and final inspection activities as they relate to processing and laboratory operations to assure that purchased supplies and services supplied to customers conform to specified acceptance criteria. Evidence of conformity to acceptance criteria shall be documented and records shall indicate the authority responsible for the release of the product or service. The Quality Control, Quality Assurance or Qualified Person is responsible for product release

Product release shall not proceed until all the specified activities have been satisfactorily completed, unless otherwise approved by the customer.

8.2.4.2 Particular requirements for active implantable medical devices and implantable medical devices

Records documenting any inspections or testing performed shall record the identity of personnel recording the inspection or testing.

8.3 Control of Nonconforming Product or Testing

8.3.1 Nonconforming Product

Sterigenics shall ensure that product that does not conform to product requirements is identified and controlled to prevent its unintended use or delivery. The procedures shall also define the controls and related responsibilities and authorities for dealing with nonconforming product shall be defined in procedures.

Controls shall be documented in established procedures to provide for the identification, documentation, evaluation, segregation and disposition of nonconforming product.

Sterigenics shall deal with nonconforming product by one or more of the following ways:

a) by taking action to eliminate the detected nonconformity

b) by receiving authorization from customer for acceptance, under concession, with or without correction or adjustment

c) by taking action to preclude its original intended use or application

d) by rejecting as unsuitable

Records of the nature of nonconformities and any subsequent actions taken, including concessions obtained, shall be maintained. Records of the identity of the person(s) authorizing the concession shall be maintained.

When nonconforming product is reworked it shall be subject to re-verification to demonstrate its conformity to requirements. The rework will be conducted according to written procedures defining a system for reworking batches that do not conform to specifications and the steps to be taken to insure that the reworked batches will conform to all established specifications. Rework will not be performed without the review and approval of the Quality Assurance Manager.

When nonconforming product is detected after delivery or use has started, the organization shall take action appropriate to the effects, or potential effects, of the nonconformity.

8.3.2 Nonconforming Testing

8.3.2.1 The laboratory shall have procedures that shall be implemented when any aspect of its testing work, or the results of this work, do not conform to its own procedures or the agreed requirements of the customer. The procedure shall ensure that:

a) the responsibilities and authorities for the management of nonconforming work are designated and actions (including halting of work and withholding of test reports, as necessary) are defined and taken when nonconforming work is identified

b) an evaluation of the significance of the nonconforming work is made

c) correction is taken immediately, together with any decision about the acceptability of the nonconforming work

d) where necessary, the customer is notified and the work is recalled

e) the responsibility for authorizing the resumption of work is defined

8.3.2.2 Where the evaluation indicates that the nonconforming work could recur or that there is doubt about the compliance of the laboratory's operations with its own procedures, the corrective action and preventive action procedures described in Section 8.5 shall be promptly followed.

8.4 Analysis of Data

The organization shall establish procedures to determine, collect, and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate if improvement of the effectiveness of the quality management system can be made.

This shall include data generated as a result of monitoring and measurement and from other relevant sources.

The analysis of data shall provide information related to:

a) customer feedback

b) conformity to product requirements;

c) characteristics and trends of processes and products including opportunities for preventive actions

d) supplier performance

Records of the results of the analysis of data shall be maintained.

8.5 Improvement

8.5.1 General

Sterigenics shall continually improve the effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions, and management review.

Sterigenics shall identify and implement any changes necessary to ensure and maintain the continued suitability and effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions, and management review.

Records of all customer complaints, investigations, and corrective actions taken shall be maintained. If investigation determines that the activities outside the organization contributed to the customer complaint, relevant information shall be exchanged between the organizations involved.

If any customer complaint is not followed by corrective and/or preventive action, the reason shall be authorized and recorded.

If national or regional regulations require notification of adverse events that meet specified reporting criteria, Sterigenics shall establish procedures for such notification to

regulatory authorities including written notification of Sterigenics senior management. Sterigenics senior management will also be notified in writing of reports of inspectional observations raised by FDA or any regulatory authority and any regulatory actions relating to good manufacturing practices brought by FDA or any regulatory authority.

Reference Section 9 for details regarding complaint files and reporting.

8.5.2 Corrective Action

Sterigenics shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered.

A procedure shall be established to define requirements for:

a) reviewing nonconformities (including customer complaints and departures from the policies and procedures in the quality management system or technical operations);

b) investigating to determine the root causes of nonconformities;

c) evaluating the need for action to ensure that nonconformities do not recur;

d) determining and implementing actions needed, including, if appropriate, updating documentation;

e) recording of the results of any investigation and of actions taken;

f) reviewing/monitoring corrective action taken and its effectiveness

Corrective actions shall be to a degree appropriate to the magnitude and the risk of the problem.

Where the identification of nonconformities or departures result in a serious issue or risk to the business and casts doubts on the facility's or laboratory's compliance with its own policies and procedures, the facility or laboratory shall ensure that the appropriate areas of activity are audited as soon as possible.

8.5.3 Preventive Action

Sterigenics shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems.

A procedure shall be established to define requirements for:

a) determining potential nonconformities and their causes;

b) evaluating the need for action to prevent occurrence of nonconformities;

c) determining and implementing action needed;

d) recording of the results of any investigation and of actions taken;

e) reviewing preventive action taken and its effectiveness

9. Complaint Filing and Control

Sterigenics shall establish procedures for the handling of all written and oral complaints to ensure:

a) complaints are processed in a consistent and timely manner;

b) oral complaints are documented upon receipt

c) complaints are reviewed the by Quality Assurance Manager or by the Quality Control Unit where required

d) complaints are evaluated to determine whether the complaint represents an event for medical devices and drug products that is required to be reported to FDA or other regulatory authorities.

e) complaints are reviewed and evaluated to determine whether an investigation is necessary. The results of the evaluation will be documented. Where no investigation is conducted, the

complaint record shall include the reason no investigation was made and the name of the individual responsible for decision not to investigate.

f) Any complaint that represents an event that is required to be reported to FDA or other regulatory authority is promptly reviewed, evaluated, and investigated by Corporate Quality Assurance and maintained in a separate portion of the complaint files. Investigations will include information about whether the processing or testing met specifications, whether the product processed or tested was being used for treatment or diagnosis, and the impact, if any, of the processing of testing on the reported incident or adverse event.

g) When an investigation is conducted, the investigation is documented. The investigation records include the findings of the investigation and follow up.

h) Complaint records include the following information:

- Name of the product
- Date complaint was received
- Any device identification(s) or control number(s) used (if the product was a medical device)
- Name and strength of the drug product and lot number (if the product was a drug product)
- Name, address and phone number of the complainant
- Nature and details of the complaint
- The dates and results of the investigation
- Any corrective actions taken
- Reply(ies) to the complainant

i) Complaint and investigation records are stored at the facility where the product was processed or tested. Complaints related to drug products are stored in a file designated for drug product complaints. If the records are stored at another location, they are readily available to the facility where the product was processed or tested.

j) Complaint information shall be trended to ensure continued improvement of the process and service, and to measure customer satisfaction. Trending information is reported to Sterigenics senior management and detailed complaint information is accessible to them.

10. Process/Test History Records and Release

Sterigenics shall establish procedures that ensure Process History Records (PHR's) for each processing run and Test History Records (THR's) for each laboratory test are maintained to demonstrate that the product was processed in accordance with the Customer Master Record or equivalent. These records shall include documentation that each significant step in the processing of the run or laboratory test was accomplished.

10.1 Process History Record

The Process History Record (Gamma, EO, EB) shall contain, at a minimum, the following information:

a) the dates of processing;

b) product ID and control numbers provided by the customer;

c) the lot number if required by pharmaceutical / drug product customers

d) the quantity processed;

e) the quantity released; records which indicate the product has been processed in accordance with the specified requirements;

f) the process run number

g) identity of individual major equipment used

h) For EO processing, specific identification of in-process material (EO, PO, nitrogen, steam) used

i) In process and laboratory control results

j) Complete labeling control records if required by pharmaceutical / drug product customers

k) Any sampling performed

l) Identification of the persons performing and directly supervising or checking each significant step in processing. If a significant step in processing is performed by automated equipment, the identification of the person checking the significant step performed by the automated equipment.

m) Any investigations performed as a result of process history record review

Process History Records are reviewed by the Quality Assurance Manager, Quality Control Unit or Qualified person, as appropriate, to determine compliance with customer specifications and procedures prior to release of the product. Any discrepancies or failures to meet specifications will be investigated whether or not the product or test result has been released. The investigation shall extend to other batches of the product that may have been associated with a specific failure or discrepancy. A written record of the investigation shall be produced including the conclusions and required follow up.

10.2 Test History Record

The Test History Record for the laboratory shall contain, at a minimum, the following information:

a) the dates of receipt, testing start, test completion;

b) product ID and control numbers provided by the customer;

c) the quantity tested;

d) the results of testing;

e) records which indicate the product has been tested in accordance with the specified requirements;

f) the laboratory test number

Where the laboratory performs testing on pharmaceutical / drug products, laboratory records shall also include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

a) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

b) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods,[1] or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

c) A statement of the weight or measure of sample used for each test, where appropriate.

d) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

e) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

f) A statement of the results of tests and how the results compare with established standards of

identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

g) The initials or signature of the person who performs each test and the date(s) the tests were performed.

h) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

i) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

j) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

k) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).

l) Complete records shall be maintained of all stability testing performed in accordance with 211.166.

11. Quality System Record

The Sterigenics Quality System Record is defined as follows.

11.1 Quality System Record

The Sterigenics quality system is a multi-tiered documentation system that defines the activities and documentation required to process medical devices for our customers. Corporate Quality Assurance is responsible for the quality system. Reference Appendix B for a diagram of the quality system.

The quality system includes the following document categories:

a) Quality Policy Manual

This Quality Policy Manual defines management's commitment to and requirements for delivering quality services and meeting customer requirements. This policy manual defines authority, responsibility and requirements of the Sterigenics quality management system.

b) Standard Operating Procedures and Quality System Procedures.

Standard Operating Procedures (SOPs) and Quality System Procedures (QSPs) define responsibilities, activities and record requirements for each element of the quality management system. Sterigenics is currently harmonizing the quality system and converting QSPs to SOPs.

c) Process Procedures

Process procedures define the quality management system and process requirements for each technology or laboratory. Sterigenics is currently harmonizing the quality system and converting process procedures to SOPs or work instructions.

d) Work Instructions

Work instructions define responsibilities for performing tasks including record requirements and timeframes. Work instructions are issued as corporate or facility work instructions.

e) Supporting Documents

In addition to the quality system document categories described above, additional document categories include forms, labels, tags, job aids, training manuals, and external reference documents. Additional categories may be added. These documents are issued as corporate or facility documents.

Facilities may issue additional quality system record components that define facility-specific quality system requirements. These include Facility Work Instructions, Facility Forms, Job Aids, Labels, and Tags and quality records.

11.2 Quality System Record Control

Indexes or master lists are maintained to identify current versions of the quality system documents. Copies of current approved documents are made available for viewing electronically.

This Quality System Record including all quality system documents are reviewed for adequacy and approved prior to issuance and distribution. Changes to documents are reviewed, approved and communicated to the appropriate personnel in a timely manner. Records of document changes are maintained. Refer to Section 4.2, Documentation Requirements, for additional information.

12. Laboratory Technical Requirements

12.1 General

Many factors determine the correctness and reliability of the tests performed by a laboratory. These factors include contributions from:

- human factors
- accommodation and environmental conditions
- test and calibration methods and method validation
- equipment
- measurement traceability
- sampling
- the handling of test items

The extent to which the factors contribute to the total uncertainty of measurement differs considerably between types of tests. The laboratory shall take account of these factors in developing test methods and procedures, in the training and qualification of personnel, and in the selection and calibration of the equipment used.

12.2 Personnel

12.2.1 Laboratory management shall ensure the competence of all who operate specific equipment, perform laboratory tests, evaluate test results, and sign test reports. When using staff that is undergoing training, appropriate supervision shall be provided. Personnel performing specific tasks shall be qualified on the basis of appropriate education, training, experience and/or demonstrated skills, as required.

If laboratory testing requires personnel certification, personnel performing these tasks shall be certified.

Personnel responsible for opinions and interpretation included in test reports should, in addition to the appropriate qualifications, training, experience, and satisfactory knowledge of the testing carried out, also have:

- relevant knowledge of the technology used for the manufacturing of the items, materials, products, etc. tested or the way they are used or intended to be used, and of the defects or degradations which may occur during or in service
- knowledge of general requirements expressed in legislation, regulations, and standards
- an understanding of the significance of deviations found with regard to the normal use of the items, materials, products, etc. concerned

12.2.2 Management of the laboratory shall formulate the goals with respect to the education, training, and skills of laboratory personnel. The laboratory shall have a policy and procedures for identifying training needs and providing training of personnel. The

training program shall be relevant to the present and anticipated tasks of the laboratory. The effectiveness of the training actions taken shall be evaluated.

12.2.3 The laboratory shall use personnel who are employed by, or under contract to, the laboratory. Where contracted and additional technical and key support personnel are used, the laboratory shall ensure that such personnel are supervised and competent and that they work in accordance with the laboratory's management system.

12.2.4 The laboratory shall maintain current job descriptions for managerial, technical, and key support personnel involved in tests. Job descriptions should define the following, at a minimum:

- Responsibilities with respect to performing tests
- Responsibilities with respect to planning tests and evaluation of results
- Responsibilities for reporting opinions and interpretations
- Responsibilities with respect to method modification and development and validation of new methods.
- Expertise and experience required
- Qualifications and training programs
- Managerial duties

12.2.5 Management shall authorize specific personnel to test, to issue test reports, to give opinions and interpretations and to operate particular types of equipment. The laboratory shall maintain records of the relevant authorization(s), competence, educational and professional qualifications, training, skills and experience of all technical personnel, including contracted personnel. This information shall be readily available and shall include the date on which authorization and/or competence is confirmed.

12.3 Accommodation and Environmental Conditions

12.3.1 Laboratory facilities for testing, including but not limited to energy sources, lighting and environmental conditions, shall be such as to facilitate correct performance of the tests.

The laboratory shall ensure that the environmental conditions do not invalidate the results or adversely affect the required quality of any measurement. Particular care shall be taken when tests are undertaken at sites other than a permanent laboratory facility. The technical requirements for accommodation and environmental conditions that can affect the results of tests shall be documented.

12.3.2 The laboratory shall monitor, control and record environmental conditions as required by the relevant specifications, methods and procedures or where they influence the quality of the results. Due attention shall be paid, for example, to biological sterility, dust, electromagnetic disturbances, radiation, humidity, electrical supply, temperature, and sound and vibration levels, as appropriate to the technical activities concerned. Tests shall be stopped when the environmental conditions jeopardize the results of the tests.

12.3.3 There shall be effective separation between neighboring areas in which there are incompatible activities. Measures shall be taken to prevent cross-contamination.

12.3.4 Access to and use of areas affecting the quality of the tests shall be controlled. The laboratory shall determine the extent of control based on its particular circumstances.

12.3.5 Measures shall be taken to ensure good housekeeping in the laboratory. Special procedures shall be prepared where necessary.

12.4 Test Methods and Method Validation

12.4.1 General

The laboratory shall use appropriate methods and procedures for all tests within its scope. These include handling, transport, storage and preparation of items to be

tested, and, where appropriate, an estimation of the measurement uncertainty as well as statistical techniques for analysis of test data.

The laboratory shall have instructions on the use and operation of all relevant equipment, and on the handling and preparation of items for testing, or both, where the absence of such instructions could jeopardize the results of tests. All instructions, standards, manuals and reference data relevant to the work of the laboratory shall be kept up to date and shall be made readily available to personnel. Deviation from test methods shall occur only if the deviation has been documented, technically justified, authorized and accepted by the customer.

For new test methods, procedures shall be developed prior to the test being performed and should contain the following information at a minimum:

a) Appropriate identification
b) Scope
c) Description of the type of item to be tested
d) Parameters of quantities and ranges to be determined
e) Apparatus and equipment, including technical performance requirements
f) Reference standards and reference materials required
g) Environmental conditions required and any stabilization period needed
h) Description of the procedure including
    - Affixing of identification marks, handling, transporting, storing and preparation of items
    - Checks to be made before the work is started
    - Checks that the equipment is working properly and, where required, calibration and adjustment of the equipment before each use
    - The method of recording the observations and results
    - Any safety measures to be observed
i) Criteria and/or requirements for approval/rejection
j) Data to be recorded and method of analysis and presentation
k) The uncertainty or the procedure for estimating uncertainty

International, regional, or national standards or other recognized specifications that contain sufficient and concise information on how to perform the tests do not need to be supplemented or rewritten as internal procedures if these standards are written in a way that can be used as published by laboratory staff.

12.4.2 Selection of Methods

The laboratory shall use test methods which meet the needs of the customer and which are appropriate for the tests it performs. Methods published in international, regional, or national standards shall preferably be used. The laboratory shall ensure that the latest version of a standard is used unless it is not appropriate or possible to do so. When necessary, the standard shall be supplemented with additional details to ensure consistent application.

When the customer does not specify the method to be used, the laboratory shall select appropriate methods that have been published either in international, regional, or national standards, or by reputable technical organizations, or in relevant scientific texts of journals, or as specified by the manufacturer of the equipment. Laboratory-developed methods or methods adopted by the laboratory may also be used if they are appropriate for the intended use and if they are validated. The customer shall be informed as to the method chosen. The laboratory shall confirm that it can properly

operate standard methods before introducing the tests. If the standard method changes, the confirmation shall be repeated.

The laboratory shall inform the customer when the method proposed by the customer is considered to be inappropriate or out of date.

12.4.3 Laboratory-developed Methods

The introduction of test methods developed by the laboratory for its own use shall be a planned activity and shall be assigned to qualified personnel equipped with adequate resources.

Plans shall be updated as development proceeds and effective communication amongst all personnel involved shall be ensured.

12.4.4 Non-standard Methods

When it is necessary to use methods not covered by standard methods, these shall be subject to agreement with the customer and shall include a clear specification of the customer's requirements and the purpose of the test. The method shall be appropriately validated prior to use.

12.4.5 Validation of Methods

12.4.5.1 Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled.

12.4.5.2 The laboratory shall validate non-standard methods, laboratory-designed/developed methods, standard methods used outside their intended scope and amplifications and modifications of standard methods to confirm that the methods are fit for the intended use. The validation shall be as extensive as is necessary to meet the needs of the given application of field of application, The laboratory shall record the result obtained, the procedure used for the validation, and a statement as to whether the method is fit for use.

Validation may include procedures for handling and transportation,

The techniques used for the determination of the performance of a method should be one of, or a combination of, the following

- Calibration using reference standards or reference materials
- Comparison of results achieved with other methods
- Inter-laboratory comparisons
- Systematic assessment of the factors influencing the result
- Assessment of the uncertainty of the results based on scientific understanding of the theoretical principles of the method and practical experience.

When changes are made in validated non-standard methods, the influence of such changes should be documented and, if appropriate, a new validation carried out.

12.4.5.3 The range and accuracy of the values obtained from validated methods (e.g., the uncertainty of the results, detection limit, selectivity of the method, linearity, limit of repeatability and/or reproducibility, robustness against external influences and/or cross-sensitivity against interference from the matrix of the samples/test object), as assessed for the intended use, shall be relevant to the customer's needs.

12.4.6 Estimation of Uncertainty of Measurement

12.4.6.1 A testing laboratory performing its own calibrations shall have and shall apply a procedure to estimate the uncertainty of measurement for all calibrations and types of calibrations.

12.4.6.2 Testing laboratories shall have and shall apply procedures for estimating uncertainty of measurement. In certain cases, the nature of the test method may preclude rigorous, metrologically and statistically valid, calculation of uncertainty of measurement. In these cases, the laboratory shall at least attempt to identify all the components of uncertainty and make a reasonable estimation, and shall ensure that the form of reporting of the result does not give a wrong impression of the uncertainty. Reasonable estimation shall be based on knowledge of the performance of the method and on the measurement scope and shall make use of, for example, previous experience and validation data.

12.4.6.3 When estimating the uncertainty of measurement, all uncertainty components which are of importance in the given situation shall be taken into account using appropriate methods of analysis.

12.4.7 Control of Data

Calculations and data transfers shall be subject to appropriate checks in a systematic manner.

When computers or automated equipment are used for the acquisition, processing, recording, reporting, storage or retrieval of test or calibration data, the laboratory shall ensure that:

a) Computer software developed by the user is documented in sufficient detail and is suitably validated as being adequate for use

b) Procedures are established and implemented for protecting the data; such procedures shall include, but not be limited to, integrity and confidentiality of data entry or collection, data storage, data transmission, and data processing

c) Computers and automated equipment are maintained to ensure proper functioning and are provided with the environmental and operating conditions necessary to maintain the integrity of test data.

12.5 Equipment

12.5.1 The laboratory shall be furnished with all items of measurement and test equipment required for the correct performance of the tests (Including preparation of test items, processing and analysis of test data). In those cases where the laboratory needs to use equipment outside its permanent control, it shall ensure that the requirements in this quality policy manual are met.

12.5.2 Equipment and its software used for testing and calibration shall be capable of achieving the accuracy required and shall comply with specifications relevant to the tests concerned. Calibration programs shall be established for key quantities or values of the instruments where these properties have a significant effect on the results. Before being placed into service, equipment shall be calibrated or checked to establish that it meets the laboratory's specification requirements and complies with the relevant standard specifications. It shall be checked and/or calibrated before use.

12.5.3 Equipment shall be operated by authorized personnel. Up to date instructions on the use and maintenance of equipment (including any relevant manuals provided by the manufacturer of the equipment) shall be readily available for use by the appropriate laboratory personnel.

12.5.4 Each item of equipment and its software used for testing and significant to the result shall, where practical, be uniquely identified.

12.5.5 Records shall be maintained of each item of equipment and its software significant to the tests performed. The records shall include at least the following:

a) The identity of the item of equipment and its software

b) The manufacturer's name, type of identification, and serial number or other unique identification

c) Checks that equipment complies with the specification

d) The current location, where appropriate

e) The manufacturer's instructions if available, or reference to their location

f) Dates, results and copies of reports and certificates of all calibration, adjustments, acceptance criteria, and the due date of the next calibration

g) The maintenance plan, where appropriate, and maintenance carried out to date

h) Any damage, malfunction or repair to the equipment.

12.5.6 The laboratory shall have procedures for safe handling, transport, storage, use and planned maintenance of measurement equipment to ensure proper functioning and in order to prevent contamination or deterioration.

If the equipment is used outside of the permanent laboratory for tests, additional procedures may be required.

12.5.7 Equipment that has been subjected to overloading or mishandling, gives suspect results, or has been shown to be defective or outside specified limits, shall be taken out of service. It shall be isolated to prevent its use or clearly labeled or marked as being out of service until it has been repaired and shown by calibration or test to perform correctly. The laboratory shall examine the effect of the defect or departure from specified limits on previous tests and shall address according to procedures for controlling nonconforming testing.

12.5.8 Wherever practicable, all equipment under the control of the laboratory and requiring calibration shall be labeled, coded, or otherwise identified to indicate the status of calibration, including the date when last calibrated and the date or expiration criteria when recalibration is due.

12.5.9 When for whatever reason, equipment goes outside the direct control of the laboratory, the laboratory shall ensure that the function and calibration status of the equipment are checked and shown to be satisfactory before the equipment is returned to service.

12.5.10 When intermediate checks are needed to maintain confidence in the calibration status of the equipment, these checks shall be carried out according to defined procedures.

12.5.11 Where calibrations give rise to a set of correction factors, the laboratory shall have procedures to ensure that copies (e.g., in computer software) are correctly updated.

12.5.12 Test and calibration equipment, including both hardware and software, shall be safeguarded from adjustments which would invalidate the test results.

12.6 Measurement Traceability

12.6.1 General

All equipment used for tests and/or calibrations, including equipment for subsidiary measurements (e.g. for environmental conditions) having a significant effect on the accuracy or validity of the result of the test, shall be calibrated before being put into service. The laboratory shall have an established program and procedure for the calibration of its equipment.

The calibration program shall include a system for selecting, using, calibrating, checking, controlling and maintaining measurement standards, reference materials used as measurement standards, and measuring and test equipment used to perform tests and calibrations.

12.6.2 Specific requirements

12.6.2.1 Testing

12.6.2.1.1 When using external calibration services, traceability of measurement shall be assured by the use of calibration services from laboratories

that can demonstrate competence, measurement capability and traceability. The calibration certificates issued by these laboratories shall contain the measurement results, including the measurement uncertainty and/or a statement of compliance with an identified metrological specification. The laboratory shall ensure that the equipment used can provide the uncertainty of measurement needed.

NOTE: The term "identified metrological specification" means that it must be clear from the calibration certificate which specification the measurements have been compared with, by including the specification or by giving an unambiguous reference to the specification.

12.6.2.2.2 Where traceability of measurements to SI units is not possible and/or not relevant, confidence shall be provided in measurements by establishing traceability to appropriate measurement standards such as:

- the use of certified reference materials provided by a competent supplier to give a reliable physical or chemical characterization of a material
- the use of specific methods and/or consensus standards that are clearly described and agreed by all parties concerned

Participation in a suitable program of inter-laboratory comparisons is required where possible.

12.6.3 Reference Standards and Reference Materials

12.6.3.1 Reference Standards

The laboratory shall have a program and procedure for the calibration of its reference standards. Reference standards shall be calibrated by a body that can provide traceability as described in section 12.6.2 Measurement Traceability. Reference standards of measurement held by the laboratory shall be used for calibration only and for no other purpose, unless it can be shown that their performance as reference standards would not be invalidated. Reference standards shall be calibrated before and after any adjustment.

12.6.3.2 Reference Materials

Reference materials shall, where possible be traced to SI units of measurement or to certified reference materials. Internal reference materials shall be checked as far as is technically and economically practicable.

12.6.3.3 Intermediate Checks

Checks needed to maintain confidence in the calibration status of reference, primary, transfer, or working standards and reference materials shall be carried out according to defined procedures and schedules.

12.6.2.4 Transport and Storage

The laboratory shall have procedures for safe handling, transport, storage and use of reference standards and reference materials in order to prevent contamination or deterioration and in order to protect their integrity.

If reference standards and reference materials are used outside the permanent laboratory for tests or calibrations, additional procedures may be necessary.

12.7 Handling of Test Items

12.7.1 The laboratory shall have procedures for the transportation, receipt, handling, protection, storage, retention and/or disposal of test items, including all provisions

necessary to protect the integrity of the item, and to protect the interests of the laboratory and the customer.

12.7.2 The laboratory shall have a system for identifying test items. The identification shall be retained throughout the life of the item in the laboratory. The system shall be designed and operated so as to ensure that items cannot be confused physically or when referred to in records or other documents. The system shall, if appropriate, accommodate a sub-division of groups of items and transfer of items within and from the laboratory.

12.7.3 Upon receipt of the test item, abnormalities or departures from normal or specified conditions, as described in the test method, shall be recorded. When there is doubt as to the suitability of an item for test, or when an item does not conform to the description provided, or the test required is not specified in sufficient detail, the laboratory shall consult the customer for further instructions before proceeding and shall record the discussion,

12.7.4 The laboratory shall have procedures and appropriate facilities for avoiding deterioration, loss or damage to the test items during storage, handling and preparation. Handling instructions provided with the item shall be followed. When items have to be stored or conditioned under specified environmental conditions, these conditions shall be maintained, monitored and recorded. Where a test item or a portion of an item is to be held secure, the laboratory shall have arrangements for storage and security that protect the condition and integrity of the secured items or portions concerned.

Where test items are to be returned into service after testing, special care is required to ensure that they are not damaged or injured during the handling, testing, or storing/waiting processes.

12.8 Assuring the Quality of Test Results

12.8.1 The laboratory shall have quality control procedures for monitoring the validity of tests undertaken. The resulting data shall be recorded in such a way that trends are detectable and, where practicable, statistical techniques shall be applied to the reviewing of the results. This monitoring shall be planned and reviewed and shall include, but not be limited to, the following:

a) regular use of certified reference materials and/or internal quality control using secondary reference materials

b) participation in inter-laboratory comparison or proficiency-testing programs/

c) replicate tests using the same or different methods

d) retesting of retained items

e) correlation of results for different characteristics of an item

Methods selected shall be appropriate for the type and volume of work undertaken.

12.8.2 Quality control data shall be analyzed and, where they are found to be outside pre-defined criteria, planned action shall be taken to correct the problem and to prevent incorrect results from being reported.

12.9 Reporting the Results

12.9.1 General

The results of each test or series of tests carried out by the laboratory shall be reported accurately, clearly, unambiguously and objectively, and in accordance with specific instructions in the test methods.

The results shall be reported, usually in a test report and shall include all the information requested by the customer and necessary for the interpretation of the test results and all information required by the method used as describe below.

In the case of tests performed for internal customers, or in the case of a written agreement with the customer, the results may be reported in a simplified way. All

required information shall be readily available in the laboratory which carried out the tests.

Test reports may be issued as hard copy or as electronic data transfer provided all requirements of this quality policy manual are met.

12.9.2 Test reports

Each test report shall include at least the following information, unless the laboratory has valid reasons for not doing so:

a) a title (e.g., “Test Report”)

b) name and address of the laboratory, and the location where the tests were carried out, if different from the address of the laboratory

c) unique identification of the test report (such as the serial number) and an identification on each page to ensure that the page is recognized as part of the test report, and a clear identification of the end of the test report

d) the page number and total number of pages when hard copies are used

e) name and address of the customer

f) identification of the method used

g) a description of, the condition of, and unambiguous identification of the item(s) tested

h) the date of receipt of the test item(s) where this is critical to the validity and application of the results, and the date(s) of performance of the test

i) reference to the sampling plan and procedures used by the laboratory or other bodies where these are relevant to the validity or application of the results

j) The test results with, where appropriate, the units of measurement

k) The name(s), function(s), and signature(s) or equivalent identification of person(s) authorizing the test report

l) Where relevant, a statement to the effect that the results relate only to the items tested.

12.9.3 Test reports – requirements necessary for interpretation of test results

In addition to the requirements listed in section 12.9.2, test reports shall, where necessary for the interpretation of the test results, include the following:

a) Deviations from, additions to, or exclusions from the test method, and information on specific test conditions, such as environmental conditions

b) Where relevant, a statement of compliance/non-compliance with requirements and/or specifications

c) Where appropriate and needed, opinions and interpretations

d) Additional information which may be required by specific methods, customers or groups of customers

12.9.4 Opinions and Interpretations

When opinions and interpretations are included, the laboratory shall document the basis upon which the opinions and interpretations have been made. Opinions and interpretations shall be clearly marked as such in a test report.

Opinions and interpretations in a test report may comprise, but not limited to, the following:

- An opinion on the statement of compliance/noncompliance of the results with requirements
- Fulfillment of contractual requirements

- Recommendations on how to use the results
- Guidance to be used for improvements.

When opinions and interpretations are communicated in direct dialog with the customer, the dialog shall be documented.

12.9.5 Testing Results Obtained from Subcontractors

When the test report contains results of tests performed by subcontractors, these results shall be clearly identified. The subcontractor shall report the results in writing or electronically.

12.9.6 Electronic Transmission of Results

In the case of transmission of test results by telephone, telex, facsimile, or other electronic or electromagnetic means, the requirements of ISO 17025 shall be met.

12.9.7 Format of Reports

The format shall be designed to accommodate each type of test carried out and to minimize the possibility of misunderstanding or misuse.

12.9.8 Amendments to Test Reports

Material amendments to a test report after issue shall be made only in the form of a further document, or data transfer, which includes the statement:
"Supplement to Test Report, serial number… [or as otherwise identified]",
or an equivalent form of wording.

Such amendments shall meet the requirements for test reports as defined in this quality policy manual.

When it is necessary to issue a complete new test report, this shall be uniquely identified and shall contain a reference to the original that it replaces.

III. DEFINITIONS/ABBREVIATIONS

Batch – means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture

Cfr. ISO9000:2005 *"Quality Management Systems – Fundamentals and vocabulary"*

CFR = Code of Federal Regulation

Drug product – A finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain and active ingredient but is intended to be used as a placebo. (21 CFR Part 210.3 (b) (4). For the purposes of this Quality Policy Manual, drug product may refer to drug product containers, closure systems, in-process materials, labeling and drug product. (21 CFR Part 210.3 (2).

E-Beam = Electron Beam

EMEAA = Europe, Middle-East, Asia, Africa

EO = Ethylene Oxide

FDA = Food and Drugs Administration

GMP = Good Manufacturing Practices

In process materials – in process materials at Sterigenics are ethylene oxide (EO), propylene oxide, nitrogen, and steam used in EO processing.

ISO = International Organization for Standardization

Lot number – any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of

a batch or lot of drug product or other material can be determined. (21 CFR Part 210.3 (11).

Management Representative = A member of management, appointed by senior management, with the responsibility and authority including ensure that quality management system (QMS) processes are established, implemented and maintained, reporting to top management on the performance of the QMS and need for improvement, and ensuring the promotion of awareness of regulatory and customer requirements throughout the organization. A Management Representative is required by ISO 13485 5.5.2. Management Representative is equivalent to Responsible Engineering Manager.

MHLW = Ministry of Health, Labour and Welfare

PAL (JPAL) = (Japan's) Pharmaceutical Affairs Law (Japan's Quality Management System Compliance – Japan's regulatory process for medical devices)

Quality control – Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the 47 organizations, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. (EudraLex Volume 4, Chapter 1, *Pharmaceutical Quality System*). The heads of Production and Quality Control must be independent from each other. (EudraLex Volume 4, Part 1, Chapter 2, *Personnel)*.

Quality control unit – any person or organizational element designated by the firm to be responsible for the duties relating to quality control (21 CFR Part 210.3 (15).

Responsible Engineering Manager = A member of management, appointed by senior management, with the responsibility and authority for duties that include ensuring that quality management system (QMS) processes are established, implemented and maintained, reporting to top management on the performance of the QMS and need for improvement, and ensuring the promotion of awareness of regulatory and customer requirements throughout the manufacturing site. A Responsible Engineering Manager is required by MHLW Ministerial Ordinance #169, 2004 Article 16. Responsible Engineering Manager is equivalent to Management Representative.

IV REVISION HISTORY

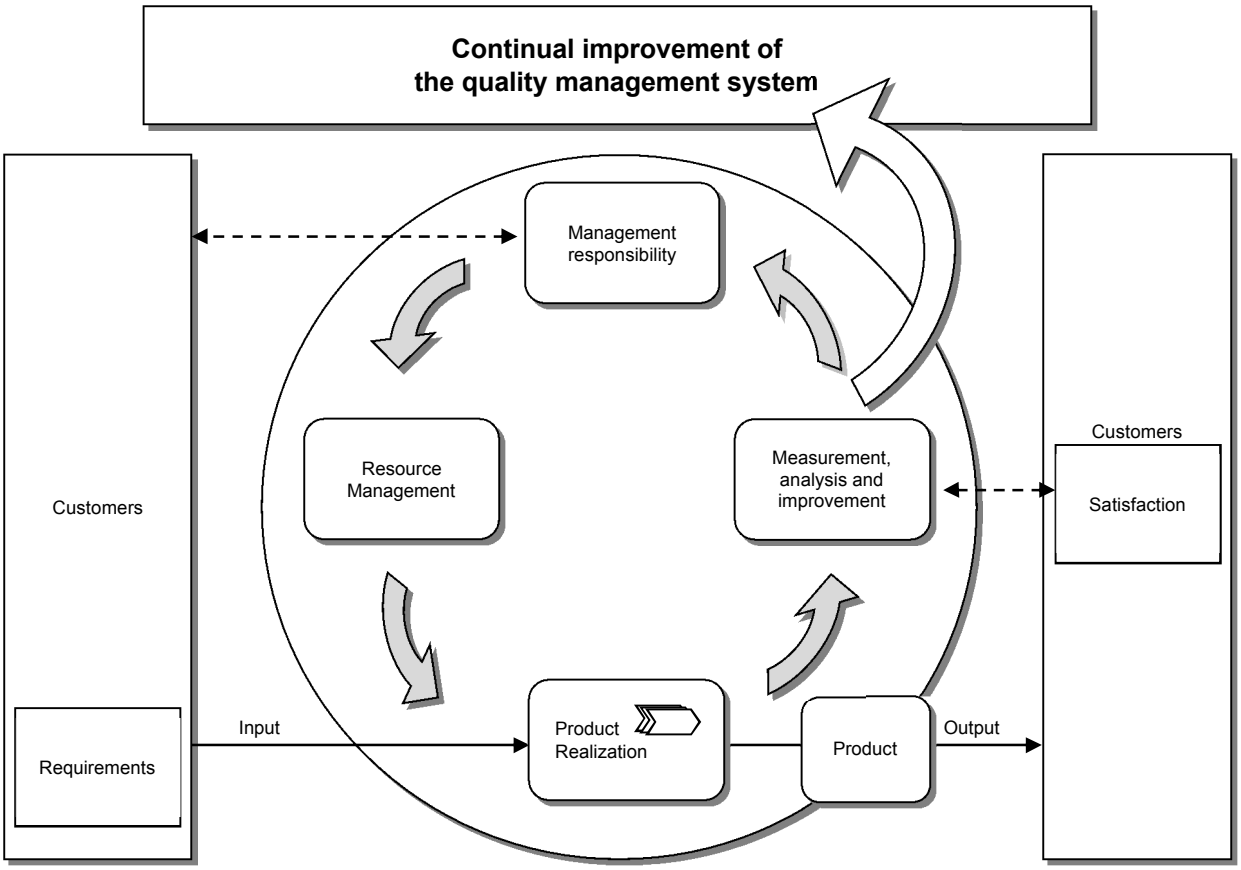
Revision	Section	Description of Change
29	2	Updated the title of the Japanese MHLW Ministerial Ordinance #169 to include a description of its revision by Ministerial Ordinance #87.
28	2	Added reference to ISO 11135-1:2007. Corrected formatting for ISO 11137-2:2013. Updated entry for MHLW 169 to reflect 2014 version.
	9	Corrected formatting to create point j.
27	1	Changed reference from sterilization facility to processing facility. Added Bridgeport as a Reduction in Scope.
	2	Changed section header to Regulations and Standards. Added references to EN ISO 11135:2007, EN ISO-11137-1:2006-Amd1:2013, ISO 11137-2:2013, EudraLex GMP Volume 4 and Annex 1, 21 CFR Part 210 & 211. Revised references as needed to correct document numbers and titles. Removed reference to ISO 11137-1:2006. Defined applicability of 21 CFR Part 211 to Sterigenics operations.
	3	Added reference and applicability of 21 CFR Part 210 definitions.
	4.2.1	Added a description of the quality management system document hierarchy including the requirement that documents lower in the hierarchy cannot violate requirements in documents at higher levels of the hierarchy.
	4.2.3.1.a	Defined approvers for documents at corporate and facility level.
	4.2.4.1.d	Added confidentiality to the list of records controls.
	4.2.4.1.f	Added requirements for readily available records for inspection throughout the retention period and access to records based on confidentiality requirements.
	4.2.4.1.g	Added requirements for maintaining data for participation in process quality reviews with the customer.
	5.5.21.d	Added requirements for quality control.
	5.5.2	Added Quality Control Unit responsibility.
	5.5.2.3	Added requirement to define responsibility for quality control unit. Added requirement for approving or rejecting all processed drug products. Added requirement for approving or rejecting procedures and specifications. Added requirement that adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products are available to the quality control unit. Added requirement that responsibilities and procedures applicable to the quality assurance manager are in writing and that procedures will be followed.
	5.6.4	Added new requirement for annual Product Quality Review conducted at request of customer processing drug products at a Sterigenics facility.
	6.1	Added requirement to ensure adequate number of qualified personnel to perform and supervise product processing.
	6.2.3	Added new section to define detailed personnel qualifications required by 21 CFR Part 211. Added requirement that release of drugs from sterilization be approved by a registered Qualified Person for European facilities with a drug manufacturing authorization.
	6.2.4	Added new section to define qualifications for consultants required by 21 CFR Part 211.
	6.3	Divided 6.3 into subsections 6.3.1 through 6.3.9 to infrastructure requirements defined by 21 CFR Part 211.

6.3.1	Added new section for facilities. Added new requirements that buildings are of suitable size, construction and location to facilitate cleaning and maintenance and flow of products through the building is designed to prevent contamination.
6.3.2	Added new section for operations with new requirements for separation of operations for storage, processing, quarantine pre-release and storage post-release.
6.3.3	Added new section for lighting.
6.3.4	Added new section for ventilation, air filtration, air heating and cooling
6.3.5	Added new section for plumbing.
6.3.6	Added new section for sewage and refuse.
6.3.7	Added new section for washing and toilet facilities
6.3.8	Added new section for sanitation.
6.3.9	Added new section for maintenance
6.4	Added new requirements for addressing persons with illness or lesions. Added new requirement for authorization of entry into limited access areas.
6.5	Added new section to define personnel responsibilities.
7.2.2	Clarified that review of requirements related to product is conducted prior to commitment to process product to be released to market and prior to conducting laboratory for the release of such product.
7.2.2.d	Change test method to test methods.
7.5.1.1.a	Added requirement that specifications will address any time limitations on processing steps required for processing drug, biotech or other sensitive products.
7.5.1.1	Changed reference from sterilization records to product processing records.
7.5.1.4	Added section defining requirements for laboratory controls including stability testing.
7.5.3.1	Added requirement for product specific labeling where required by customer will be implemented at facilities processing the product.
7.5.3.2.3	Added section for particular requirements for distribution of drug products.
7.7	Added new section for Equipment to address equipment requirements for product processing required by 21 CFR Part 211.
8.2.1	Added requirement for measuring information related to customer perception as to whether Sterigenics has met the customer requirements for clearer alignment with ISO 9001. Change laboratory customer feedback to customer feedback to ensure all feedback is used and analyzed to improve the management system.
8.2.2	Added facility and processing to sentence indicating that laboratory takes action when audit findings cast doubt on effectiveness of operations or validity of test results.
8.2.3	Added requirements for sampling and testing of in process materials
8.2.4.1	Removed reference to specific technologies from requirement for establishing procedures for processing. Added sentence defining QA/QC/QP as responsible for product release.
8.3.1	Added requirements for correcting nonconforming product required by 21 CFR Part 211.
8.5.1	Added requirement for notifying Sterigenics senior management in writing for adverse events that meet specified regulatory reporting criteria.
9	Complete revision of complaint filing and control section to more clearly reflect the requirements of 21 CFR Parts 211 and 820.

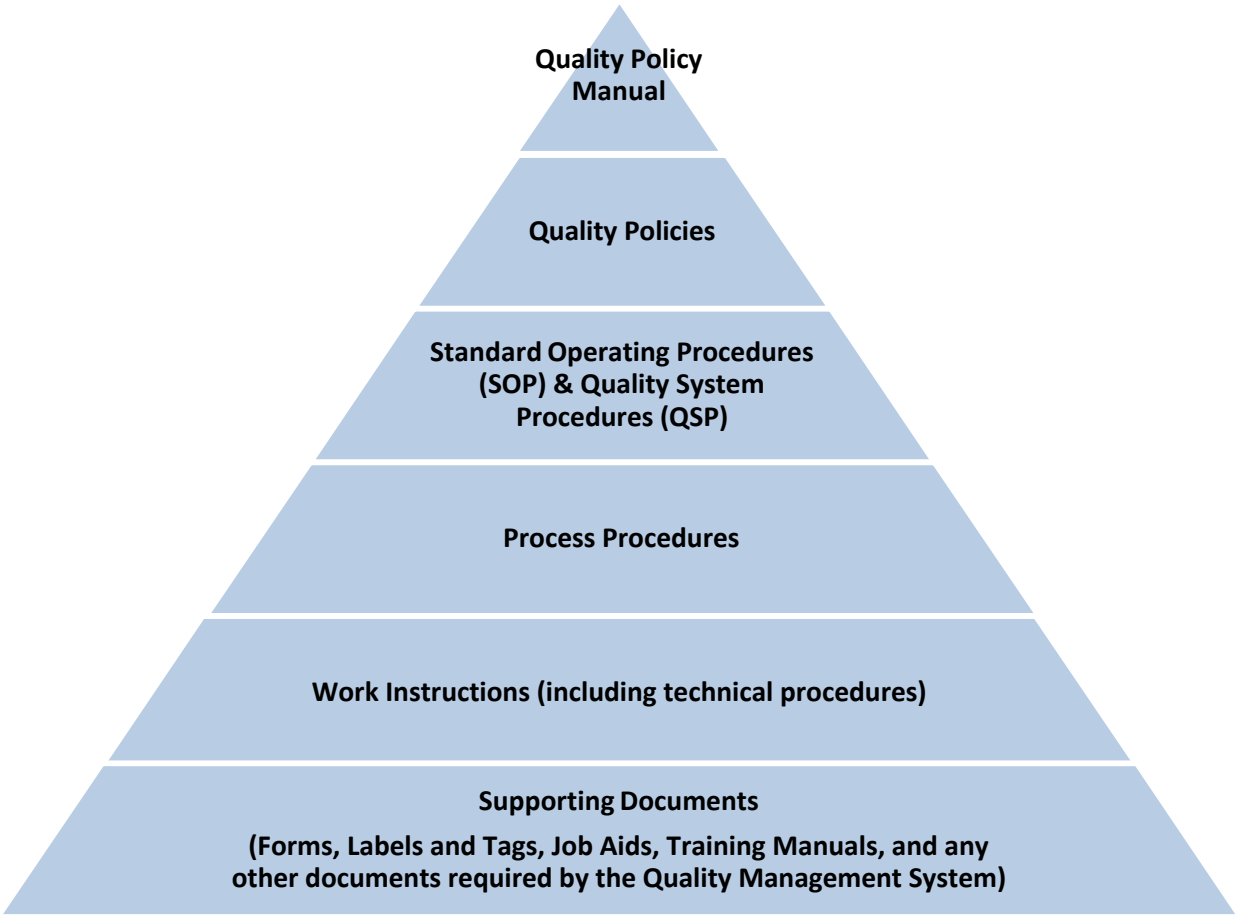
	10	Renamed section to include release. Removed technology specific references from process history records. Added 21 CFR Part 211 requirements for laboratory records. Added requirement for review of processing history records and test history records prior to release, handling of failures, investigations, and required records.
	11.1.c	Added information about global harmonization and resulting disposition of process procedures.
	III	Added definitions for drug product, in process materials, quality control, quality control unit, batch and lot number.
	Appendix C	Added 21 CFR Part 211 references to the cross reference table.
26	II.1	Replaced “Sterigenics SteriPro and/or Analytical Laboratories provide design services and therefore Section 7.3, Design and Development applies to these sites” with “Sterigenics SteriPro and/or Analytical Laboratories consulting groups provide design services and therefore Section 7.3, Design and Development, applies to these consulting personnel and their projects.”
	7.4.2	Added requirement that purchasing documents include an agreement that the suppliers (including contractors and consultants) notify Sterigenics of changes in the product or services so that Sterigenics may determine whether the changes may affect product processing or laboratory testing. This requirement is defined in G-SOP-013 but not clearly defined in this section.
	7.5.3.1	Changed ‘medical devices returned to the organization’ to ‘non-conforming devices returned to the organization’ in the second paragraph for clarity.
	Appendix C, Section 7.4.2	Added reference to 21 CFR Part 820.50 (b).
	Appendix C, Section 8.1	Added reference to 21 CFR Part 820.250. The requirement for statistical analysis is listed in section 8.1 of the document but the reference to 820.250 is not included in the cross reference table.
	Appendix C, Section 8.4	Added reference to 21 CFR Part 820.90.
	Appendix C, Section 8.4.2	Deleted this section as there is no corresponding section 8.4.2 in the manual. Moved reference to 21 CFR Part 820.50 (b) to section 7.4.2.
25	II.1	In Reduction in Scope, • Added an introductory paragraph that describes the exclusions and non-applicable. • Reorganized the exclusion for 7.3. Defined applicable facilities followed by non-applicable 50 Facilities. • Corrected the exclusion related to 7.5.1.2. The requirements of 7.5.1.2.1 apply to Sterigenics. The requirements of 7.5.1.2.2 and 7.5.1.2.3 do not apply to Sterigenics. • Removed exclusion for 7.5.3.2.2. Sterigenics does not manufacture implantable or active implantable devices. However, Sterigenics may sterilize these types of devices. Sterigenics complies with requirements for traceability between the customer product and sterilization batch and maintains records of product shipment. • Removed exclusion for 8.2.4.2. Sterigenics does not manufacture implantable or active implantable devices. However, Sterigenics may sterilize these types of devices. Sterigenics complies with requirements for identifying personnel inspecting or testing during processing. • Clarified scope of ISO 17025. The requirements of ISO 17025:2005 do not apply to Sterigenics Laboratories that are not accredited to ISO 17025.

	II.2	Added EN ISO 13485:2012, European Directive 93/42/Cee, and EN-556-1to the list of normative references. Added explanation of ISO 13485:2003 and EN ISO 13485:2012 and clarified referencing.
	4.1.1	Added a reference (hyperlink) to Appendix A for clarity.
	4.2.1	Added a reference (hyperlink) to Appendix B for clarity.
	7.2.4.1	Clarified requirements for competent subcontractors of laboratory testing.
	7.2.4.2	Clarified requirements for customer communication when • Test methodology varies from original agreement when using another SteriPro facility. • An outside contractor is chosen to perform testing Clarified requirements for contracting facility gaining customer approval.
	7.5.1	Added subsection header to clarify existing text in section described 7.5.1.1 General Requirements.
	7.5.1.1	To description of process history record (batch record), removed requirements for records of process parameters and traceability to production batch of medical devices. (These were added to 7.5.1.3). Added identification of the amount processed and the amount approved for release.
	7.5.1.2,	Added new section Control of Production and Service Provision.
	7.5.1.2.1	Added new section to define requirements for cleanliness of product and contamination control – removal of process agents from product during manufacture.
	7.5.1.3	Added new section to define particular requirements for sterile medical devices. Requirements include maintenance of records of the processing parameters for each sterilization batch and traceability of the sterilization records to the production batch of medical devices. This information was included in 7.5.1.1 in previous revisions.
	7.5.3.2.2	Added new section to define requirements for traceability between the customer product and sterilization batch and records of product shipment.
	8.2.4.2	Added section to describe requirements for identifying personnel inspecting or testing during processing.

Appendix A: Continual Improvement of the Quality Management System (Source ISO9001:2008)



Appendix B: Sterigenics Quality System



Facility Quality System Components

Appendix C: Cross References to Regulations and Standards

QPM Section	Regulations & Standards				
	ISO 13485:2003	ISO 9001:2008	ISO 17025:2005	21 CFR Part 820	21 CFR Part 211
I PURPOSE					
I			4.1.2		
II REQUIREMENTS					
1 Scope					
1	1	1	1		
1.1	1.1	1.1	-		
1.2	1.2	1.2	-		
2 Normative References					
2	2	2	2		
3 Terms and Definitions					
3	3	3	2, 3		
4 Quality and Laboratory Management Systems					
4.1	4.1	4.1	4.1, 4.2,		
4.1.2			4.2.1		
4.1.2			4.1.3		
4.2	4.2	4.2	4.3		
4.2.1	4.2.1	4.2.1	4.1.2		
4.2.1 c)			4.3.1, 4.8	820.20 (e)	
4.2.2	4.2.2	4.2.2	4.2.2, 4.2.5		
4.2.3	4.2.3	4.2.3	4.2.7, 4.3.1, 4.3.2, 4.3.3	820.40, 820.70 (b)	
4.2.3.1.a					211.100 (a)
4.2.4	4.2.4	4.2.4	4.13	820.180	
4.2.4.1					211.180 (d)
4.2.4.1.d					211.180 (a) (b)
4.2.4.1.f					211.180 (c)
4.2.4.1.g					211.180 (e)
4.2.5			4.1.5 c)		
5 Management Responsibility					
5	5	5	4		
5.1	5.1	5.1	4.2.3, 4.2.4	820.20 (a)	

QPM Section	Regulations & Standards				
	ISO 13485:2003	ISO 9001:2008	ISO 17025:2005	21 CFR Part 820	21 CFR Part 211
5.2	5.2	5.2	4.4.1		
5.3	5.3	5.3	4.2.2, 4.2.2 c)		
5.3 a)	5.3 a)	5.3 a)	4.2.2		
5.3 b)	5.3 b)	5.3 b)	4.2.2 e)		
5.3 c)	5.3 c)	5.3 c)	4.2.2		
5.3 d)	5.3 d)	5.3 d)	4.2.2 d)		
5.3 e)	5.3 e)	5.3 e)	4.2.2		
5.3 f)			4.2.2 a)		
5.3 g)			4.2.2 b)		
5.3 h)			4.2.2 d)		
5.4	5.4	5.4		820.20 (d)	
5.5	5.5	5.5			
5.5.1	5.5.1	5.5.1	4.2.6		
5.5.1 a)			4.1.4, 4.1.5 e), 4.1.5 f), 4.1.5 i), 4.1.5.j), 4.1.5 k)	820.20 (b)	
5.5.1 b)			4.1.5 g)		
5.5.1 d)			4.1.5 a), 4.1.5 b), 4.1.5 d), 4.1.5 h)		
5.5.2	5.5.2	5.5.2	4.1.5 i)	820.20 (b)	
5.5.2 a), d)	5.5.2 a)	5.5.2 a)	4.1.5 i)		
5.5.2 b), e)	5.5.2 b)	5.5.2 b)	4.11.1		
5.5.2 c), f)	5.5.2 c)	5.5.2 c)	4.2.4		
5.5.2.3					211.22 (a), (b), (c), (d)
5.5.3	5.5.3	5.5.3	4.1.6		
5.6	5.6	5.6	4.2.2, 4.15	820.20 (c)	
6 Resource Management					
6	6	6			
6.1	6.1	6.1		820.20 (b)	
6.1.c					211.25 (c)
6.2	6.2	6.2		820.20 (b), 820.25	
6.2.1	6.2.1	6.2.1			
6.2.2	6.2.2	6.2.2	4.1.5 k)		
6.2.3					211.25 (a), (b)
6.2.4					211.34

QPM Section	Regulations & Standards				
	ISO 13485:2003	ISO 9001:2008	ISO 17025:2005	21 CFR Part 820	21 CFR Part 211
6.3	6.3	6.3		820.70 (f), 820.70 (g)	
6.3.1.a					211.42 (a), (b)
6.3.2					211.42 (c)(3),(4), (5), (7), (8), (10)
6.3.3					211.44
6.3.4					211.46 (a), (b)
6.3.5					211.48
6.3.6					211.50
6.3.7					211.52
6.3.8					211.56
6.3.9					211.58
6.4	6.4	6.4		820.70 (c), 820.70 (d), 820.70 (e), 820.70 (h)	
6.4.a					211.28 (a), (d)
6.4.e					211.28 (c)
6.5.a					211.28 (a)
6.5.b					211.28 (b)
6.5.e					211.28 (d)
7 Product Realization					
7.1	7.1	7.1			
7.2	7.2	7.2			
7.2.1	7.2.1	7.2.1	4.4.1, 4.4.2, 4.4.3, 4.4.5		
7.2.2	7.2.2	7.2.2	4.4.1, 4.4.2, 4.4.3, 4.4.5		
7.2.2 a)			4.4.1 a)		
7.2.2 b)			4.4.1		
7.2.2 c)			4.4.1 b)		
7.2.2 d)			4.4.1 c)		
7.2.3	7.2.3	7.2.3	4.4.4		
7.2.4			4.5		
7.2.5			4.7		
7.3	7.3	7.3		820.30	
7.4	7.4	7.4			
7.4.1	7.4.1	7.4.1	4.6.1, 4.6.4	820.50 (a)	
7.4.2	7.4.2	7.4.2	4.6.3	820.50 (b)	

QPM Section	Regulations & Standards				
	ISO 13485:2003	ISO 9001:2008	ISO 17025:2005	21 CFR Part 820	21 CFR Part 211
7.4.3	7.4.3	7.4.3	4.6.2		
7.5	7.5	7.5			
7.5.1	7.5.1	7.5.1			211.142 (a)
7.5.1.1					211.111
7.5.1.4					Subpart I, 211.160 (a), (b) 211.166
7.5.2	7.5.2	7.5.2		820.70 (b), 820.70 (i), 820.75	
7.5.3	7.5.3	7.5.3		820.60, 820.65, 820.120	
7.5.3.1					Subpart G, 211.204
7.5.3.2.3					211.196
7.5.4	7.5.4	7.5.4			211.204
7.5.5	7.5.5	7.5.5		820.120, 820.140, 820.150	211.142 (b)
7.6	7.6	7.6		820.72	211.63, 211.65, 211.67, 211.68
7.7.1					211.63
7.7.2					211.65
7.7.3					211.67 (a), (b) (1), (2), (3), (5), (6), (c)
8 Measurement, Analysis, and Improvement					
8	8	8			
8.1	8.1	8.1		820.250	
8.2	8.2	8.2			
8.2.1	8.2.1	8.2.1			
8.2.2	8.2.2	8.2.2	4.11.5, 4.14	820.22	
8.2.3	8.2.3	8.2.3		820.70 (a), 820.70 (g)	211.100 (a), (b), 211.110 (a), (b), (c), (d)
8.2.4	8.2.4	8.2.4	4.5	820.80	
8.3	8.3	8.3	4.9		
8.3.1				820.90	211.115
8.4	8.4	8.4	5.9	820.90	

QPM Section	Regulations & Standards				
	ISO 13485:2003	ISO 9001:2008	ISO 17025:2005	21 CFR Part 820	21 CFR Part 211
8.5	8.5	8.5		820.100	
8.5.1	8.5.1	8.5.1	4.8 4.10		211.180 (f)
8.5.2	8.5.2	8.5.2	4.11		
8.5.3	8.5.3	8.5.3	4.12		
9 Complaint Filing and Control					
9				820.198	211.180 (f), 211.198
10 Process/Test History Records					
10				820.30 (j), 820.80, 820.184	211.111, 211.188, 211.192, 211.194
11 Quality System Record					
11				820.186	
12 Laboratory Technical Requirements					
12.1			5.1		
12.2			5.2		
12.3			5.3		
12.4			5.4		
12.5			5.5		
12.6			5.6		
12.7			5.8		
12.8			5.9		
12.9			5.10		

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