Health Canada
Health Products and Food Branch

OUR MANDATE:

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

Guide

Process Validation :
Gaseous Sterilization for Pharmaceuticals

Supersedes

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1. INTRODUCTION

Gaseous sterilization processing technology has been available for many years and has been developed to the current "state of the art", with progress being still maintained on several fronts, particularly with reference to vapor phase hydrogen peroxide and ozone.

Most of the literature pertaining to gaseous sterilization has been written with reference to applications for foods, medical devices, medical instruments and pharmaceutical product containers.

This document is intended to provide guidance to establish the scientific effectiveness of ethylene oxide sterilization procedures. It describes the procedures to evaluate the elements of ethylene oxide sterilization procedures which require confirmation by scientific tests. This guideline describes approaches to accomplish this goal in a way that is acceptable to the Health Products and Food Branch Inspectorate of Health Canada.

This guideline describes the documentation necessary to provide the written evidence that gaseous sterilization procedures have been evaluated and are under control. Such documentation is essential for both the user of the gaseous sterilization procedure and the specialists of the Health Products and Food Branch Inspectorate for the purposes of inspection and drug submission evaluation. This guideline is applicable only to gaseous sterilization procedures. Some principles described in the guideline may be shared with other sterilization procedures. These other sterilization procedures are the subjects of other guidelines and require different validation protocols.

It is not the intent of this document to provide details of specific procedures that may be used, nor to elaborate the mathematical principles of Sterility Assurance Levels (SALs) or Microbiological Safety Indices (MSIs). Such information is readily available from other references.

As with any sterilization procedure, the use of current Good Manufacturing Practice (GMP) and control of the manufacturing environment are essentials in the maintenance of barriers against microbial contamination.

To provide maximum benefit, gaseous sterilization procedure validation should be carried out as early as possible in the development of a new or modified procedure or new drug or device product.

This approach, often called prospective validation is preferred by the Inspectorate since it gives an indication of a well thought out production flow. It can also be cost effective as data can be collected while carrying out work which is required for reasons other than validation.

It is assumed that the reader has some familiarity with gaseous sterilization procedures in general, their application and restrictions on use, as well as effect on the items to be sterilized.

Gaseous sterilization procedures are the exposure of items (either components or products) to a chemical sterilant in a gaseous phase in a controlled manner to ensure that a pre-determined lethal effect is delivered to the items being processed with the objective of eliminating the pre-treatment bioburden and providing a satisfactory margin of safety.

It is emphasized that sample based, end product testing does not guarantee a consistent or high quality product but can only effectively identify and statistically quantify the incidence of substandard product. The gaseous sterilization procedure in conjunction with the remainder of the manufacturing process, must be designed to maximize the probability of the product being suitable for its intended use.

Before a gaseous sterilization procedure program is commenced the following items should be in existence or have been carried out:

1. Product definition, in terms of physical, chemical, microbial and pharmacological properties, where appropriate

2. Specifications for raw materials and components

3. Determination of required Sterility Assurance Level (SAL) based on the use of the items being treated

4. Compatibility of the process with the items to be treated

5. Determination of acceptable limits of the major residues after gaseous sterilization procedures

6. Validation of analytical methods used with adequate calibration and qualification of measuring equipment

Note: Validation "tests" should be repeated enough times to assure reliable and meaningful results.

In some circumstances a satisfactory demonstration that the gaseous sterilization procedure consistently produces the desired Sterility Assurance Level may eliminate the need to test every batch of items being treated, for sterility.

Validation of gaseous sterilization procedures involves, but is not restricted to, consideration of the following elements:

- Bioburden
- Manufacturing Area Environment
- Determination of Time and Humidity in the preconditioning area
- Determination of Temperature, Pressure, Time and Humidity in the chamber, ventilation of load after sterilization
- Loading Patterns
- Biological indicator survival
- Vendor Certification (if the gaseous sterilization treatment is carried out by an external contractor).

2. VALIDATION GENERAL TERMINOLOGY

2.1 In the context of this guide, Process Validation is defined as:

The action taken to demonstrate, and to provide documented evidence that a process will, with a high degree of assurance, consistently achieve the desired and intended results.

2.2 Before Process Validation can commence there must be what may be termed an essential Prevalidation phase. This phase, in addition to such considerations as equipment specification, equipment design and equipment purchase, requires attention to Equipment Qualification.

2.3 Equipment Qualification in turn has two main phases:

2.3.1 Installation Qualification, that is demonstrating and certifying that a piece of equipment is properly installed, is provided with all necessary services, subsidiary equipment and instruments, and is capable of performing in accordance with its basic design parameters.

2.3.2 Operational Qualification, consists of demonstrating that the equipment will perform consistently, and within pre-defined limits, as specified and installed.

2.4 None of these various phases need to be considered as entirely "water-tight" compartments. The divisions have been defined as a matter of convenience in discussion. In practice there is likely to be some overlap, or merging, between the various components of Validation/Qualification. In addition, there are quite wide-spread variations in terminology and conception. Some consider "Qualification" and "Validation" as two separate, yet related activities. Others use the term "Validation" to embrace the overall activity of Prevalidation/Qualification PLUS Process Validation.

The relationships between these various phases may be summarized as follows:

<table>
<tr><td rowspan="2">SPECIFICATION

DESIGN

PURCHASE</td><td colspan="2">EQUIPMENT QUALIFICATION</td><td rowspan="2">PROCESS QUALIFICATION</td></tr>
<tr><td>INSTALLATION QUALIFICATION</td><td>OPERATIONAL QUALIFICATION</td></tr>
</table>

Sometimes termed "PREVALIDATION"

The overall activity of Validation

2.5 Validation has also been considered to have three aspects, or possible strategies - Prospective Validation, Concurrent Validation, and Retrospective Validation.

2.5.1 Prospective Validation applies to new processes and new equipment, where studies are conducted and evaluated, and the overall process/equipment system is confirmed as validated before the commencement of routine production.

2.5.2 Concurrent Validation applies to existing processes and equipment. It consists of studies conducted during normal routine production and can only be considered acceptable for processes which have a manufacturing and test history indicating consistent quality production.

2.5.3 Retrospective Validation applies to existing processes and equipment, and is based solely on historical information. Unless sufficiently detailed past processing and control records are available, retrospective validation studies are unlikely to be either possible or acceptable. For example, it would be necessary to establish that the process had not been modified and that the equipment was still operating under the same conditions of construction and performance as documented in the historical records. Maintenance records and process change control documentation would be necessary to support any such claim. Furthermore, the incidence of process failures, and records of rejects and/or reworking would need to be carefully evaluated for evidence of inconsistency in the process. Manufacturing, maintenance, testing and calibration data would all need to demonstrate process uniformity, consistency and continuity.

2.5.4 Concluding Note on Validation Terminology. While there is considerable variation in the understanding and use of the various terms discussed above, there is general agreement that the critical validation concepts are the following:

- the overall process is understood
- equipment is appropriately specified and designed
- equipment is properly installed and maintained and is demonstrably operating as specified and designed
- the process is validated to ensure that it does achieve the desired and intended result

3. DEFINITIONS SPECIFIC TO GASEOUS STERILIZATION

Sterilization cycle: Treatment comprising conditioning (if used) exposure to ethylene oxide in a sealed chamber, removal of ethylene oxide and flushing if used.

Preconditioning: Treatment of product prior to the sterilization cycle to attain a predetermined temperature and relative humidity throughout the load.

Preconditioning area: The area in which preconditioning occurs. This may be a chamber or room. A room is considered to be an enclosed space capable of holding more product than can be accommodated in the sterilizer at any one time. A chamber is an area which will only accommodate sufficient product to fill the sterilizer.

Conditioning: Treatment of product within the sterilization cycle, but prior to ethylene oxide admission to attain a predetermined temperature and relative humidity throughout the load.

Gas up time: The time elapsed from the start of ethylene oxide injection into the sterilization chamber until the desired gas concentration is attained.

Cycle completion: That point after completion of the sterilization cycle at which the load may be removed from the chamber.

Fault indication system: An audible or visual signal to indicate to the operator a failure of an operating system.

Permit to work: Authorization to use a sterilizer based upon the fact that it and associated equipment have been validated, maintained and calibrated according to agreed schedules.

Total sterilizer chamber volume: The total internal volume of the sterilizer.

Usable sterilizer chamber volume: The volume inside the sterilizer chamber which may be occupied by a full load including any pallets or other restraining materials which may be used, but excluding clearance space, space for pallet rollers etc).

Sterilization load: The contents of a sterilizer chamber during one complete cycle. It may include more than one manufacturing batch lot, or during qualification may be a partial (defined) load.

Reference load: A defined load made up of one or more products which, as constituted, is the most difficult to sterilize.

Worst case: The position at which it is most difficult to achieve the desired conditions.

Biological indicator (BI): A preparation incorporating a known number of viable bacterial spores of selected resistance to the sterilization process.

In addition throughout this Guideline the words must/shall and should are to be interpreted in the following manner:

Must/Shall: Indicates that this is expected to be done in order to comply with the principles of Good Manufacturing Practice (GMP).

Should: Expresses the need for careful judgement and justification before a decision is made not to comply.

4. OUTLINE OF GASEOUS STERILIZATION PROCEDURES

4.1 Ethylene Oxide (ETO) Sterilization

4.1.1 This guideline is based on the assumption that, except under very carefully defined and controlled conditions, each cycle will be monitored using biological indicators. lternative systems which base assessment of the adequacy of the cycle on continuous monitoring of all the physical and chemical parameters affecting the efficacy of the cycle require additional provision.

4.1.2 Each stage of the evaluation of the adequacy and consistency of an ethylene oxide sterilization process, including any pre-humidification shall be based on a pre-established and approved detailed written protocol.

4.1.3 Before the studies commence, a written change control procedure shall be established to prevent unauthorized change to the protocol and process and restrict change during any phase of the studies until all relevant data is evaluated.

4.1.4 The protocol should be written in accordance with the validation approach chosen and outlined in section 2.

4.1.5 The protocol should specify in detail:

4.1.5.1 The process objectives in terms of type of material, including any packaging, the chamber content and probability of survival (or micro-biological safety index MSI) desired from the process.

4.1.5.2 Pre-established details and or ranges for the process parameters which include pre-humidification time and relative humidity, temperature, loading pattern(s), relative humidity, partial pressure of ethylene oxide (and any carrier gas), exposure time, and degassification procedures.

4.1.5.3 A description of all of the equipment and any support or ancillary equipment in terms of type, model, operational range and characteristics.

4.1.5.4 The performance characteristics of each system, sub-system or equipment described in 3.1.4.3. These characteristics should include, but not necessarily be restricted to pressure gauge accuracy and sensitivity, valve operations, alarm system functions, timer responses and accuracy, gas and water vapor flow rates and pressures, jacket cooling.

4.1.5.5 For new equipment: installation qualification, for all systems, sub-systems, equipment and monitors and computerized systems is a requirement of the overall validation activity.

4.1.5.6 For existing equipment: any necessary improvements to equipment or other compensatory procedures, with appropriate justification shall be adequately qualified.

4.1.5.7 The methods and procedures for monitoring the performance of equipment systems and sub-systems and the process.

4.1.5.8 All laboratory tests, including validation of the testing procedures.

4.1.5.9 The training and qualification of personnel responsible for the evaluation and certification of each stage of the protocol and for the final approval of the entire validation procedure.

5. PERSONNEL

5.1 All personnel involved in the validation study are required to have sufficient experience and training to carry out the tasks assigned to them. This experience and training should be described in written form.

5.2 Personnel with the necessary training and experience should ensure that all documentation is developed within a sound engineering, technical and scientific basis, and that all studies carried out are fully evaluated and certified.

5.3 Only personnel with the necessary training and experience should operate equipment and measuring devices as described in this guideline.

5.4 All personnel involved should have the necessary training and expertise in the theory and practice of the operation, maintenance and microbiological principles of sterilizers and sterilization.

6. DATA REVIEW AND STUDY CERTIFICATION

6.1 All information and data generated in the course of a study to validate a gaseous sterilization procedure, should be evaluated by competent, appropriately qualified individuals and should be assessed against the protocol criteria to determine whether they are, or are not, in compliance with the pre-established criteria.

6.2 Full documentation for the rationale for these decisions must be available.

6.3 If the evaluation shows that any pre-established criterion is not met, the impact of this failure, on the entire process should be investigated. This investigation should be thoroughly documented.

There should also be an additional assessment of the appropriateness of the criterion, or criteria, with which compliance was not established.

6.4 The final certification of the validation study should specify the process parameters established during the course of the study.

7. GENERAL LABORATORY CONSIDERATIONS

7.1 All laboratory tests should be performed by a competent laboratory.

7.2 Detailed procedures for all laboratory operations should be available in writing.

7.3 An audit system to determine the competence of contract testing laboratories should be described in writing and be carried out.

8. CHEMISTRY LABORATORY REQUIREMENTS

8.1 If the protocol defines the acceptance criteria for the presence of residual ethylene oxide and by-products of the process, a competent laboratory furnished with the necessary equipment and personnel should carry out the determinations using appropriately validated analytical methods.

8.2 While gas analysis is not absolutely essential, it may provide useful additional information. Where the analysis is carried out the conditions of section 6.4.1.1 must be complied with.

9. MICROBIOLOGICAL CONSIDERATIONS

9.1 Biological Indicators

9.1.1 All biological indicators used in the validation study or used as part of post-validation monitoring or in a requalification study must be calibrated.

9.1.2 Indicators should be used on or before their declared expiry date and stored in such a way that their quality is unimpaired.

9.1.3 Indicators should be tested according to a written procedure for quantitation of the challenge organism and for their response to exposure to the stated critical parameters.

9.1.4 For commercially obtained indicators a certificate of calibration indicating the 'D' value of the lot under carefully defined conditions must be obtained and the suppliers count verified at selected periods during the shelf life of the indicator.

9.1.5 For "in-house" prepared indicators "D" value determination, quantitation and identity verification are required. In carrying out "D" value determinations, the choice of medium, electrolytes, carbohydrate and other physiological components, including the nature of the carrier of the indicator must be clearly defined.

9.1.6 Records of any indicator qualification must be retained in writing.

9.2 Microbiological qualification studies

9.2.1 Microbiological qualification studies must be carried out under cycle conditions equivalent to, or marginally inferior to, the minimum acceptable conditions on a production cycle. Ideally the studies should be carried out at or below the minimum acceptable rH, EO concentration and temperature. However it is acceptable to carry out the qualification studies with just two of these factors at or below the minimum acceptable level provided the other factor is maintained at or below the midpoint of the acceptable range.

9.2.2 Biological monitors or inoculated product should be evenly distributed in the load but shall include those locations where sterilization conditions are assumed most difficult to achieve. The number used must be a minimum of 20 for chambers up to 5000 liters of usable chamber volume. (For a pallet of $2.5m^3$ these should be distributed as a minimum of 10 per pallet). For larger chambers this must be increased by 2 for each 1000 liters or part thereof for the next 5000 liters, plus 2 per 2000 liters of usable chamber volume thereafter.

9.2.3 Biological monitors should be placed in that part of the product which is most difficult to sterilize. Product should be packaged as it will normally be presented to the sterilizer. Where the design of the product is such that a biological monitor cannot be accommodated in the part most difficult to sterilize, the product should be inoculated with a know spore suspension to provide a known number of viable spores. If a test piece designed to simulate the product is to be used for routine monitoring it must be validated concurrently with the product.

9.2.4 Biological monitors and spore suspension used to inoculate product must be specified.

9.2.5 The preferred method of microbiological qualification is to determine with a reference load the lethality of the cycle by construction of a survivor curve.

An alternative method also using a reference load is to determine the minimum exposure time at which there are no survivors. The routine cycle exposure time must be at least double this.

9.2.6 For initial validation three cycles should be run for each test.

9.3 Acceptance of Biological Controls

9.3.1 Biological monitors should be removed from the load and cultured as quickly as possible. Ideally removal from the load should be completed within four hours of cycle completion, and culture commenced within a further four hours.

9.3.2 If these time periods are exceeded biological monitors should be stored refrigerated prior to culture. The effects of delayed recovery, and in particular exposure to residual EO requires validation.

9.3.3 Recovery media, culture conditions etc, for biological monitors should be subject to control. It should be demonstrated that the culture conditions used are capable of recovering low level of spores.

9.3.4 Biological monitors should be incubated at a temperature of 30-35 ^{0}C. Positive controls e.g. an indicator which has not been exposed to EO, and negative controls e.g. an uninoculated sample of the media used for the test should be set up and incubated with the test samples.

9.3.5 Ideally monitors should be examined daily. The Positive control must show growth/turbidity within 48 hours.

9.3.6 Microbiological records should show when growth (if any) is first detected.

9.3.7 Any confirmed growth of the test organisms on the biological monitor must be interpreted as a failed cycle.

9.4 Method to Demonstrate Acceptability

9.4.1 To demonstrate acceptability it is recommended that triplicate sublethal cycles should be run at each of two sublethal cycle times. The times of the sublethal cycles should be chosen so as to expect survival of 30% to 80% of the monitors (i.e. test positive). The minimum acceptable number of cycles at each time point is three.

9.4.2 The study may be performed during routine validation or using suitable laboratory equipment under controlled conditions.

9.4.3 The recommended numbers of biological monitors (BMs) per validation run should be used (Section 6.4.5). For example if 20 BMs used per validation run then:

- To compare alternative BMs, 20 of each type under examination should be used. These should be located one of each type, in 20 positions within the chamber.

- To compare alternative recovery systems 40 BMs for each parameter being examined should be located in pairs in 20 positions within the chamber. On completion of the cycle one of each pair should be incubated under each condition being examined.

10. INSTRUMENTS AND INSTRUMENT CALIBRATION

10.1 Calibration

10.1.1 Equipment used to sterilize products should be provided with recording devices and/or indicators which should be calibrated initially and checked at specific intervals by adequate methods according to a planned maintenance schedule.

10.1.2 Calibration of gauges should be traceable to national standards. The minimum frequency of calibration should be specified, and, in any case, the period between calibration should not be greater than 6 calendar months.

10.1.3 The rH sensors should be "degassed" and recalibrated at a minimum of two points, as necessary.

10.1.4 All calibration procedures must be recorded and documented. An indication that the machine equipment is in a known state of calibration should be displayed.

10.1.5 Instruments requiring calibration include but are not restricted to:

- Temperature recorders and sensors
- Thermocouples
- Pressure Sensors
- Timers
- Gas analyzers
- Scales (for weighing amounts of gas used)

10.2 Leak tests should be performed on all chambers irrespective of the cycle employed. For subatmospheric pure ethylene oxide machines, the leak rate should not exceed 6mm Hg in 10 minutes. Tests shall be performed at least monthly.

10.3 Air filters must be bacterial retentive. Replacement should be included in the planned preventative maintenance scheme, and at the minimum, the frequency for changing filters is every 6 months.

10.4 The internal surfaces of the vaporizer should be cleanable. Cleaning/replacement should be included in a planned preventative maintenance scheme.

11. RECOMMENDED SERIES OF ACTIVITIES

11.1 Equipment Specification and Design

- Definition of system and equipment
- Drawings of sterilizer, pipings and sensors
- Specifications for sensors

11.2 System Function

- Does system function according to specification and design?
- temperature profile of empty precondition room and empty sterilizer
- rH profile
- Leak Test
- Evaluation of ethylene oxide supply system and vaporizer
- Test cycle runs with critical parameters evaluation

11.3 Calibration

- Calibration Procedures
- Documentation of Results
- "Permit to Operate" for Equipment.

11.4 Qualification

11.4.1 Operational Qualification

- Determination of temperature profile in preconditioning and sterilizer with selected loading patterns
- Sensor placement at "most difficult to sterilize" locations
- Determination of rH and gas concentration profile
- "Contamination" of "worst case" product at "most difficult to sterilize" locations
- Use of fully loaded chamber with "worst case" product mix
- Sterilization time definition
- Residue dissipation curves

11.5 Process Qualification

11.5.1 Evaluation and documentation of ALL test results.

11.5.2 Creation of Validation report when assurance is obtained that the cycle is consistently achieving the desired effect and is operating within previously defined parameters.

11.6 Validation Acceptance

The final act of validation is acceptance (or rejection) of the results. Documentation for sign off should include:

- the protocol
- reference to the specification of the sterilizer involved
- details of products used (including packaging and load patterns in the sterilizer)
- the cycle specification
- the inspection and testing programme (including reference to methods)
- reference to training manuals and records for all personnel involved
- the records, physical and biological, of all validation runs
- all maintenance and calibration procedures, and an indication that all gauges, recorders etc. were calibrated at the time of the validation runs
- all written operating procedures including process control limits
- provision for future review and revalidation

11.7 Routine Operation and Control

11.7.1 The chamber cycle specification should typically include the following points:

- maximum permissible loading time
- initial vacuum level and time taken to achieve it
- holding time under vacuum, when used
- steam addition, pressure, temperature or time, when used
- steam holding time
- Gas injection, specifying pressure rise and time to achieve it
- gas hold time (minimum)
- gas concentration in chamber
- weight of EO used
- chamber temperature (minimum and maximum) during entire cycle
- details of air washing at the end of the cycle
- relative humidity
- number of biological monitors and their locations

11.7.2 Sufficient data should be recorded to demonstrate that the specification has been achieved for each routine cycle.

11.7.3 Routine temperature monitoring from within the load is not essential following performance qualification to a standard described in previous section. A minimum of two probes measuring chamber temperature are required. At least one probe should be positioned within the chamber at the coldest location as determined during commissioning.

11.7.4 A system is required to positively identify whether products have been processed.

12. PRODUCT QUALIFICATION

Packaging materials and methods should be selected which are compatible with the proposed ethylene oxide sterilization process and which maintain sterility and quality of the contained product. These performance requirements should be achieved through suitable design and verified according to prescribed validation procedures. The following guidance concerns aspects of packaging which are important to sterilization by ethylene oxide and is not intended to detail all requirements of packaging for sterile product.

12.1 Design

12.1.1 Materials which demonstrate adequate physical properties necessary for maintaining package integrity and product quality should be chosen for the unit container. Physical properties such as tensile strength, wet and dry tear strength, burst strength and air permeability should be considered.

12.1.2 When sealed together these materials should demonstrate adequate seal strength.

12.1.3 The materials should be compatible with the contained product and the assembled pack should withstand the chosen ethylene oxide sterilization process including preconditioning. This should include stability of inks and intended printing materials.

12.1.4 All other levels of packaging such as shelf containers and outer containers should be capable of providing adequate protection during transit and storage and should be compatible with the sterilizing process including preconditioning. Consideration should be given to ink, print and label stability.

12.1.5 Where possible product should be sterilized in the fully packaged state with sealed unit, shelf and outer containers. It is important that materials are chosen which allow adequate moisture penetration during preconditioning and ethylene oxide penetration during sterilization.

12.1.6 Reference should be made to relevant published standards such as ***"Specifications for papers used in Medical Packaging to be sterilized by Ethylene Oxide or Irradiation"*** - EUCOMED.

12.1.7 All material and packaging requirements should be detailed in written draft specifications.

12.2 Validation

12.2.1 A written validation protocol should be available and should detail the validation requirements.

12.2.2 Performance criteria for materials and packaging specified during design should be measured according to standards methods of test. These include tensile strength, wet and dry tear strength, burst strength, air permeability, seal strength and integrity. These criteria should be checked before and after sterilization.

12.2.3 Consideration should be given to microbial and physical challenge test procedures in order to determine the ability of the unit container to maintain sterility.

12.2.4 Humidity and gas penetration and success in achieving sterilizing conditions within the unit container will be determined during the sterilization process validation procedure.

12.2.5 After sterilization suitable journey hazard trials should be considered for the product with all levels of packaging and physical testing repeated to determine ability to withstand such treatment.

12.2.6 Each level of packaging should be subjected to expected storage conditions in order to demonstrate adequate performance, throughout the expected shelf life.

12.2.7 The ability to withstand more than one sterilization cycle should be established for each layer of packaging in order that reprocessing through sterilization may be carried out when necessary.

12.3 Specification

12.3.1 Requirements for validated materials and packaging should be detailed in written and approved specifications.

13. DESIGN CRITERIA FOR STERILIZERS AND RELATED EQUIPMENT

13.1 Ethylene Oxide Supply.

13.1.1 Ethylene Oxide storage areas should be secure, ventilated and comply with local safety regulations.

13.1.2 Storage areas for the container of Ethylene Oxide in use must include provision for temperature control where ambient conditions are subject to temperature variation greater than the range recommended by the Ethylene Oxide supplier.

13.1.3 Where the Ethylene Oxide supply to the sterilizer is from a bulk storage tank which is periodically replenished, the tank should be equipped with means to remove samples for analysis, means to empty the tank completely, and provision for cleaning in the event of inadvertent contamination or excessive accumulation of polymers of Ethylene Oxide.

13.1.4 The gas admission system must be equipped with a vaporizer to ensure that liquid Ethylene Oxide is not admitted to the sterilizer chamber.

13.1.5 Ethylene Oxide should be filtered before admission to the vaporizer to ensure the removal of particles of dirt, rust, and polymerized Ethylene Oxide.

13.1.6 The vaporizer should be designed so that the heat transfer surfaces are discardable or demountable to allow cleaning of the internal surfaces. (Polymers of Ethylene Oxide may form and accumulate on the internal surfaces with consequent impairment of heat transfer and/or blockage of the vaporizer).

13.1.7 Provision should be made for continuous measurement of the temperature of the Ethylene Oxide gas between the vaporizer and the sterilizer chamber.

Wherever possible this should control an automatic shut off valve to interrupt the supply of Ethylene Oxide when the temperature falls below a predetermined value to prevent liquid Ethylene Oxide from entering the sterilizer chamber.

13.1.8 The design and construction of the sterilizer and/or gas admission system must allow the amount of gas admitted to be monitored by at least two of the following:

- pressure rise in the sterilizer
- sampling from the sterilizer chamber (for subsequent chemical analysis)
- weight difference of the gas cylinder
- volume of gas delivered.

Whichever primary method is used the measuring equipment should have sufficient sensitivity to allow recording of quantities of gas which may be admitted throughout the sterilization holding period.

13.1.9 Homogeneity of cycle conditions is best achieved by forced circulation.

13.2 Sterilizer Control and Instrumentation.

13.2.1 All measuring instruments and controls fitted to any one sterilizer, and preferably to all sterilizers on any one site, should provide readings in the same system of units. The minimum acceptable is that the reading for any particular variable are in the same units.

13.2.2 The controller and recorder must be separate.

13.2.3 Manual control of an Ethylene Oxide sterilizer does not provide consistently reproducible conditions from cycle to cycle. The variations in cycle conditions make validation of the process difficult and therefore manual control is normally unacceptable.

13.2.4 Each sterilizer should be equipped with the following instruments, located at the loading end of the sterilizer or in a separate control room so that they may be readily viewed by the operator:

- chamber pressure gauge or indicator
- chamber pressure recorder
- chamber temperature indicator
- chamber temperature recorder
- chamber rH indicator
- chamber rH recorder
- gas admission temperature indicator
- chamber jacket temperature indicator

13.2.5 The use of a single data recorder to replace the three separate recorders listed is acceptable.

13.2.6 In addition to an operating cycle stage indicator, a fault indication system should be fitted. The recording instruments should clearly indicate sensor malfunction.

13.2.7 For maintenance purposes a cycle counter may be of value.

13.2.8 Ethylene Oxide sterilization is commonly carried out within the temperature range 20-60 ^{0}C with cycle times from 2-18 hours. Table 1 gives recommendations for temperature indicators and recorders for monitoring cycles in this range.

Single sensors which indicate the average temperature throughout the length of the chamber e.g. long bulb mercury in steel Bourbon type instruments are not acceptable as the sensor for temperature recorders or controllers.

13.2.9 Three principle categories of Ethylene Oxide cycle are commonly used:

- Pure Ethylene Oxide or Ethylene Oxide with diluent gas at sub-atmospheric pressure
- Ethylene Oxide with a diluent gas such as fluorinated hydrocarbons or nitrogen at pressures up to 2 bar
- Ethylene Oxide with a diluent gas such as carbon dioxide at pressures up to 6 bar.

The recommendations for pressure indicators and recorders used in these cycle are given in Table 1.

13.2.10 The recommendations for humidity indicators are given in Table 1.

TABLE 1 Recommendations for Indicators and Recorders

Indicator / Recorder	Range	Minimum Scale Length	Error Limit	Chart mm/min
Temperature	0-100^{0}C	150 mm	+/- 0.5 % full scale	>1
Pressure (subatmospheric cycles)	-1 to 0 bar or equivalent	150 mm	+/- 1% full scale	>1
Pressure (positive up to 2 bar)	-1 to 4 bar or equivalent	150 mm	+/- 1% full scale	>1
Pressure (positive up to 6 bar)	-1 to 10 bar or equivalent	150 mm	+/- 1% full scale	>1
Relative Humidity	0-100%	100 mm	+/- 2.5% full scale	>1

13.2.11 Direct monitoring of rH is preferred but the use of temperature or pressure rise is also acceptable. Whichever method is used it must be reproducible.

NOTE: The rH as perceived by sensor at a low pressure may be different from that measured at a higher pressure.

13.2.12 Depending on the type of rH sensor chosen, it may be necessary either to isolate the sensor from the chamber atmosphere immediately prior to admitting the Ethylene Oxide or to remove the sensor for degassing and recalibration as appropriate. If necessary, provision should be made in the design and construction of the sterilizer to facilitate whichever of these methods is used.

13.2.13 Provision should be made to allow the integrity of the vessel to be tested under vacuum and pressure conditions as appropriate.

13.2.14 Air admitted to the sterilizer chamber at the end of the cycle should be filtered through a microbial retentive filter. Although the packaging normally used for sterile products is designed to prevent the ingress of micro organisms, the filtration efficiency of the material is affected by the air flow rate across the material. At the high flow rates associated with air replacement at the end of the cycle unfiltered air may compromise the sterility of the product.

13.2.15 Provision should be made in the design and construction of the sterilizer chamber to allow additional temperature and rH sensors to be positioned throughout the chamber for testing during commissioning and performance qualification.

13.3 Design Criteria of the Preconditioning room or chamber where separate from the sterilization chamber.

13.3.1 The preconditioning should be separate from assembly and packaging areas.

The standard of finish should be similar to that of environmentally controlled areas e.g. easily cleanable and durable finish.

13.3.2 The design and construction of the preconditioning area should ensure that product held within the area is secure. This will require adequate facilities for segregation and identification of different production batches, and facilities for controlling ingress and egress of product and personnel. The preconditioning area should be located in close proximity to the sterilizer(s) to facilitate rapid transfer of the product.

13.3.3 The temperature and relative humidity (rH) of the area should be related to the conditions employed in the sterilization cycle. These should be such that the temperature and rH of the load going into the sterilizer are neither so low that problems of long heat up and condensation occur, nor so high that temperature control of the cycle is compromised.

13.3.4 The area shall have forced air flow. Consideration should be given to the effect the load will have on the air flow patterns within the area. The dynamics and pattern of air flow should be designed to uniform conditions of temperature and rH throughout the preconditioning area.

13.3.5 The maintenance of uniform conditions within the preconditioning area may be compromised unless means are provided to control the length of time that access doors are left open. Where separate doors are provided for personnel access theses should be self closing. Consideration should be given to providing means to alert the operator when the doors have been left open e.g. by means of an audible and visual alarm activated after a pre-determined delay.

13.3.6 Provision should be made for continuous monitoring of the temperature and rH from a reference position as determined during validation. Additional sensors may be required at other positions to confirm uniformity throughout the area.

13.3.7 The design and operation of humidifiers used in the area must be such that the possibility of increases in microbial contamination is minimized.

Humidification by steam injection is preferred. Humidifiers which operate by dispersion of unheated water into an aerosol e.g. spinning disc humidifiers or nebulizers are potent sources of microbial contamination and are unlikely to be suitable.

13.3.8 rH should be controlled by direct monitoring. Interpolation from temperature rise due to steam admission is rarely satisfactory.

14. PRODUCT PROCESS CLAIMS

14.1 The Microbiological Safety Index (MSI) is set on the indicated or anticipated use of the final product.

14.2 The MSI can be established from bioburden studies on the items before sterilization and to calculate the MSI the organism with the highest determined 'D' value should be used.

14.3 Where products are required to be pyrogen free (or specified as containing lower than a particular level of bacteria endotoxin as determined by the Limulus Amebocyte Lysate Test), consideration must be given to the environment in which the items are manufactured or assembled, to the bioburden of components and careful control should be established over critical parameters in these respects.

14.4 It is essential to establish that initial levels of endotoxin are low and that if micro-organisms are present, the opportunities for growth are minimized by such restrictions as limitation of time between assembly and sterilization or maintenance of the items at low temperature. It has to be recognized however that the conditions experienced by the items during many types of preconditioning are conducive to microbial growth.

15. REQUALIFICATION

15.1 Requalification is indicated when a significant change occurs or on a periodic basis to detect any inadvertent process changes. A single requalification run may typically be made on an annual basis for each cycle. Significant changes in any of the following may lead to complete requalification unless the change can be shown not to increase the difficulty of sterilization or diminish the MSI;

a) Packaging
b) Product design
c) Loading configuration or density
d) Sterilizing equipment or process cycle

Significant maintenance work may require recommissioning of the sterilizer which may, in turn, lead to requalification.

In addition, trends in biological indicator failure not attributable to process specification failures should be examined and may lead to requalification.

15.2 All changes to the sterilization system or process must be pre-authorized through the approved Change Control Procedure.

15.3 Requalification is the activity which establishes that changes to parts of the sterilization system have not invalidated the initial total validation process.

15.4 Requalification is performed according to detailed written procedures that require the original parameters and limits to be used in a critical evaluation of the data obtained.

15.5 Requalification studies must be documented to the same extent as the original total validation process. If the results are satisfactory the process(es) may be recertificated. If the results are not satisfactory the modified system or process will require a total validation study to assess its (their) suitability.

16. EXPERT EVALUATION

16.1 An evaluation of the total validation study against the protocol requirements should be prepared and conclusions drawn at each stage stated.

The final conclusions should indicate whether the total validation study requirements were met.

In addition, all the parameters used to describe the process to be used for routine ethylene oxide sterilization to ensure that qualified sterilization processes are obtained routinely, should be stated.

16.2 The Expert Evaluation should be signed by duly authorized officers of the organization who were members of the team establishing and authorizing the Validation Study Protocol. These officers should have the necessary experience, qualification and expertise to understand the study and its implications.

16.3 Overall responsibility for the Approval Process is lodged with the most senior person in the Validation Study Team and the most senior person responsible for the Quality Assurance within the organization.

17. DOCUMENTATION

17.1 All documentation should be signed and dated. Only authorized signatures should be accepted.

17.2 Procedures for and records of calibration of equipment should be maintained.

17.3 For each sterilizing cycle, a record should be maintained of product(s) processed through that cycle.

17.4 Date and time of initiation and completion of cycle should be recorded.

17.5 For each batch processed legible records of the physical values achieved during the sterilization cycle must be retained, e.g. gas control factors, temperature, pressure, humidity. These must be reviewed, signed and dated to confirm the values achieved are within those specified.

17.6 The operation of the sterilizer should be on a "permit to work" basis.

17.7 No product labeled as sterile shall be released for distribution until any prescribed microbiological control procedures have been satisfactorily completed and so approved by the microbiologist.

17.8 Batch manufacturing records should include sterilization and associated microbiological records or reference to them.

Legible copies of the original recording of the cycle variables should be retained.

17.9 Batch manufacturing records must contain a dated signed statement that the batch has been approved for release or has been rejected.

17.10 For the purposes of inspection by the inspectors of the Health Products and Food Branch Inspectorate and for submission for pre-marketing evaluation, there should be:

a) An outline of the protocol followed which should indicate:

- the approach taken
- the justification for the approach
- description of any equipment modifications description of any protocol modifications made in light of results obtained

b) Process Documentation which indicates:

- process development
- product/packaging suitability

- final process parameters
- details of partial exposure processes
- details of partial load configurations
- details of full load configurations
- rationale for "worst case" decisions

c) Microbiology including:

- bioburden studies, with D value determinations
- biological indicator studies, including location selection
- product sterility tests
- microbiological method validation

18. OTHER GASEOUS STERILIZATION PROCEDURES

18.1 Other processes involving gaseous chemical sterilization procedures are in use. These include but are not restricted to:

- Low Temperature Steam Formaldehyde(LTSF)
- Ozone
- Vapor Phase Hydrogen Peroxide(VPHP)

18.2 The validation requirements for these processes are similar to those for Ethylene Oxide sterilization processes and the information in this guideline may be extrapolated for use in the validation of such processes.

18.3 None of the other gaseous sterilization procedures described above have been used to the extent to which ethylene oxide sterilization has been used and in many cases their use may be considered experimental.

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* Bureau of Compliance and Enforcement changed to Health Products and Food Branch Inspectorate (HPFBI).
** Bureau of Pharmaceutical Assessment now part of Therapeutic Products Directorate (TPD).
*** Bureau of Biologics and Radiopharmaceuticals changed to Biologics and Genetic Therapies Directorate (BGTD).
**** Office of Compliance, Planning and Coordination now National Coordination Centre (NCC).

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