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Technical Information Report

AAMI TIR14:1997

Contract sterilization for ethylene oxide

AAMI Association for the Advancement of Medical Instrumentation

AAMI TIR No.14—1997

Contract Sterilization for Ethylene Oxide

Approved 24 February 1997

Abstract: This AAMI Technical Information Report (TIR) provides additional guidance to augment ANSI/AAMI/IS0 11135, *Medical devices—Validation and routine control of ethylene oxide sterilization* for both medical device manufacturers that use contract sterilization facilities and contract sterilization operations. The TIR addresses how ANSI/AAMI/ISO 11135 applies to ethylene oxide sterilization operations for devices marketed in the United States.

Keywords: documentation, medical device manufacturing, product sampling, validation program,

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COMMITTEE REPRESENTATION

This technical information report was developed by the AAMI Industrial Ethylene Oxide Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee.

The **AAMI Sterilization Standards Committee,** which authorized the distribution of this report, has the following members:

Cochairs:
William E. Young
Virginia C. Chamberlain, PhD

Members:
Carl W. Bruch, PhD, Consultant, Hudson, WI
Virginia C. Chamberlain, PhD, Quintiles Quality Regulatory Alliance, Inc.
Neal E. Danielson, D's Enterprise, Wichita, KS
Judith C. Dowler, Medical Devices Bureau, Health Canada, Ottawa, ON
Frank B. Engley, Jr., PhD, University of Missouri, Columbia, MO
Victoria Hitchens, PhD, U.S. Food and Drug Administration
Collette P. Keyser, RN, Colonel, U.S. Army (Retired), Alexandria, VA
Robert F. Morrissey, PhD, Johnson & Johnson
Richard Nusbaum, Pennsylvania Engineering
Barry F.J. Page, Consultant, Garner, NC
Marimargaret Reichert, RN, MA, Reichert Consulting, Olmsted Falls, OH
Janet K. Schultz, RN, Jan Schultz & Associates, Allison Park, PA
James Whitbourne, Sterilization Technical Services
James L. Whitby, MA, MB, FRCP, Univ. of Western Ontario, London, ON
William E. Young, Baxter Healthcare Corporation

The **AAMI Industrial Ethylene Oxide Sterilization Working Group** has the following members:

Cochairs:
James M. Gibson, Jr.
William E. Young

Members:
Lauren Andersen, H.W. Andersen Products, Inc.
Krisann Anderson, St. Jude Medical, Inc.
Thomas A. Augurt, PhD, Propper Manufacturing, Inc.
Richard H. Bean, Zimmer
Anne F. Booth, MS, Booth & Associates, Barrington, IL
William C. Bradbury, PhD, Consultant, Sugarloaf, FL
Lloyd Brown, U.S. Surgical Corp.
Vincent A. Caputo, Quality Solutions, Inc.
Virginia C. Chamberlain, PhD, Quintiles Quality Regulatory Alliance, Inc.
Gary N. Cranston, Consulting & Technical Services
Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
Douglas D. Davie, Sterilization Validation Services
Richard J. DeRisio, MF, Sorin Biomedical, Inc.
Randal S. Fitzgerald, Ethox Corp.
James M. Gibson, Jr., JM Gibson Associates*
Joel Gorski, PhD, North American Science Associates, Inc.
Gary S. Graham, PhD, Abtox, Inc.

* At the time this TIR was drafted, Mr. Gibson represented Special Process Services.

Arthur C. Harris, Chicago Sterilization Services
Deborah Havlik, Griffith Micro Science, Inc.
Paul A. Honan, Getinge International, Inc.
Clark W. Houghtling, Cosmed Group, Inc.
Steve Kahn, Depuy, Inc./Boehringer Mannheim Corp.
Carolyn Kinsley, Becton Dickinson
Michael S. Korczynski, PhD, Abbott Labs
Mary S. Mayo, CR Bard, Inc.
Sarah Mowitt, U.S. Food and Drug Administration
John Nygard, Advanced Bio-Control Technologies
Gerry A. O'Dell, Johnson & Johnson
Stacey Paetschow, Pfizer Hospital Products Group
Daniel L. Prince, PhD, Gibraltar Biological Labs
Robert Reich, Pharmaceutical Systems, Inc.
Zenius V. Seliokas, Sherwood, Davis & Geck
Jon Seulean, Cobe Labs Inc.
Charles P. Truby, PhD, Isomedix
James Whitbourne, Sterilization Technical Services
C. C. Woltz, Allied Signal, Inc.
William E. Young, Baxter Healthcare Corp.

Alternates:

Paul Bombardier, Valleylab Inc./Pfizer Hospital Products Group
James E. Conner, Zimmer
Stephen A. Conviser, Allied Signal, Inc.
Zory Glaser, PhD, MPH, U.S. Pharmacopeial Convention, Inc.
Joyce Hansen, Baxter Healthcare Corp.
Thomas L. Hansen, Sherwood, Davis & Geck
Monica R. Kenyon, Cosmed Group, Inc.
Ralph Makinen, CIH, Griffith Micro Science, Inc.
John Masefield, Isomedix, Inc.
Anna M. McLernon, PhD, Ethicon, Inc./Johnson & Johnson
George Mills, MSC, U.S. Food and Drug Administration
Dave Parente, MBA, North American Science Associates, Inc.
Paul Sordellini, Quality Solutions, Inc.
Thelma Wilcott, Becton Dickinson
James D. Wilson, Pharmaceutical Systems, Inc.

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

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Chair:	Gary Cranston, Consulting & Technical Services
Members:	Susan Carpenter, CR Bard, Inc.
	Joyce Hansen, Baxter Healthcare Corp.
	Arthur C. Harris, Chicago Sterilization Services
	Monica R. Kenyon, Cosmed Group, Inc.
	Sue Kuhnert, Sterilization Technical Services
	Sarah Mowitt, U.S. Food and Drug Administration
	Robert Reich, Pharmaceutical Systems, Inc.
	Bill South, Isomedix, Inc.

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CONTRACT STERILIZATION FOR ETHYLENE OXIDE

Introduction

The medical device industry is using contract sterilization operations at an increasing rate. The resulting rise in the percentage of medical devices that are sterilized under contract calls for additional guidance to support this trend. A direct impact of using contract sterilization facilities is downsizing of the sterilization support and technical knowledge within the medical device manufacturer's resources. Experience indicates that contract sterilization procedures require enhanced communications between the manufacturer and the contractor to ensure a well-controlled sterilization process. As the contract sterilization industry continues to grow, it is increasingly evident that responsibility for sterility is shared by the medical device manufacturer and the contract sterilization facility. Furthermore, it is essential that the division of responsibilities be clearly defined and understood by both parties.

NOTE 1 This technical report is considered "informative," and use of the terms "shall," "should," etc., should be considered within the context of this technical report only. That is, if the decision is made to use a particular method presented in this technical report, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical report.

1 Scope

This AAMI Technical Information Report (TIR) provides additional guidance to augment ANSI/AAMI/IS0 11135, *Medical devices—Validation and routine control of ethylene oxide sterilization* for both medical device manufacturers that use contract sterilization facilities and contract sterilization operations. This TIR addresses how ANSI/AAMI/ISO 11135 applies to contract ethylene oxide sterilization operations for devices marketed in the United States.

Ethylene oxide contract sterilization guidance for health care providers is not specifically covered in this TIR.

2 Definitions

For the purposes of this Technical Information Report, the following definitions apply:

2.1 bacteriostasis/fungistasis test: Test performed with selected microorganisms to demonstrate the presence of substances that inhibit their multiplication.

2.2 calibration: Comparison of a measurement system or device of unknown accuracy to a measurement system or device of a known accuracy (traceable to national standards) to detect, correlate, report, or eliminate by adjustment any variation from the required performance limits of the unverified measurement system or device.

2.3 contract sterilizer: Any facility that offers to provide a contractual service intended to sterilize medical devices that are manufactured by another establishment.

NOTE 2 The definition may include any facility that sterilizes products manufactured by another establishment that may be within the same corporation. This establishment may sterilize its own devices as well as provide contractual services.

2.4 finished device: Device, or any accessory to a device, which is suitable for use, whether or not packaged or labeled for commercial distribution.

2.5 manufacturer: Any establishment, including any repacker and/or relabeler, that manufactures, fabricates, assembles, or processes a finished device.

2.6 process challenge device (PCD): Object that simulates the worst case of conditions as they are given for the sterilizing agent(s) in the items of the goods to be sterilized.

NOTE 3 The process challenge device is so constituted that a biological indicator can be arranged in the place most difficult for the sterilizing agent(s) to reach.

NOTE 4 The design of the process challenge device depends on the kind of goods to be sterilized and the sterilization procedure. The biological indicator should not interfere with the function of the test body.

NOTE 5 In some process challenge devices an inoculated carrier may be used instead of a biological indicator.

2.7 qualification: Documented evidence that all prescribed design and performance requirements are met.

2.8 validation: Documented procedure for obtaining, recording, and interpreting the results required to establish that a process will consistently yield a product complying with predetermined specifications.

NOTE 6 Validation is considered as a total program that consists of commissioning and performance qualification.

2.9 verification: Evaluation that is performed to assure current operation or applicability for use of a system.

NOTE 7 For ethylene oxide sterilization, a single point evaluation of thermocouples in the range of use may be performed prior to and after performing qualification to assure correct functioning of the equipment. Verification may also be used for other pieces of monitoring equipment depending upon their use. For example, if a secondary measuring device, such as a pressure transducer, is added to a sterilization vessel prior to performing qualification, the device should be calibrated prior to use and may be verified after use and prior to removal from the vessel.

3 Selection of sterilization facility

3.1 Initially, an evaluation is required to determine whether sterilization should be performed by a contract facility or if the capabilities exist for in-house processing. The manufacturer's selection of a location for sterilization should be well thought-out. Once this evaluation has been performed and it has been determined that contract sterilization is the choice, a number of factors require assessment to identify a contractor that best suits the manufacturer's needs.

Some of the issues affecting the choice of location include

a) proximity of the facility to the manufacturer;

b) size(s) and available capacity of chambers in relation to the expected volume of manufactured material;

c) processing capability of the facility with respect to preconditioning room(s), sterilization chambers, and aeration room(s);

d) cost of processing (includes sterilization and shipping);

e) OSHA, EPA, and safety compliance;

f) availability/proximity of laboratory services to the contractor; and

g) facility's regulatory compliance history.

3.2 To adequately determine the contractor's acceptability, the manufacturer or a designate should perform an audit of the contract sterilization facility under consideration. Due to the importance of the audit, the personnel performing the audit should be knowledgeable of the sterilization method being considered. The audit should cover issues such as

a) maintenance and calibration programs;

b) installation/commissioning qualifications of the vessels and environmental chambers (if used);

c) operational qualifications of the vessels and environmental chambers (if used);

d) personnel training;

e) management education and/or experience;

f) change control and documentation procedures;

g) use of quality systems;

h) software validation; and

i) OSHA, EPA, and safety compliance.

3.3 To facilitate the audit procedure, it is often helpful to have a predetermined audit document that reflects the domestic and international regulatory requirements. This enables the auditor to make an appropriately informed decision with regards to the contractor's compliance. Once the audit has been completed, the auditor should provide a written report stating acceptability of the contractor. This report should list corrective actions that need to be taken, if any. It is then the contractor's responsibility to address and document these corrective actions and to provide them to the auditor enabling closure of the audit process. If no corrective action is identified, a report should be issued stating an audit has been performed. Upon completion of corrective action, a letter should be issued by the manufacturer to the contractor closing the audit. If the corrective action can not be completed within a short period of time, a timetable outlining the anticipated completion date(s) should be provided to the auditor. The audit of the sterilization facility under consideration, in conjunction with logistical concerns, provide the manufacturer with sufficient information to make a well-informed selection. The final requirement for the acceptance of the location is to document the logic and criteria used in the selection process.

4 Written agreement between product manufacturer and contract sterilizer

Before starting contract sterilization processing, a written agreement that outlines the services and procedures to be supplied and followed by both parties shall be developed and signed. Requirements for the

contract between the two parties are found in 21 Code of Federal Regulation 801.150(e). This section of the regulation requires a written contract when interstate shipping is involved. For intrastate services, a contract is recommended to ensure compliance with GMP requirements for device master records (21 CFR 820.181). The regulation specifies the contents of the agreement, including a requirement for a detailed delineation of the sterilization process. It is necessary to examine the contract sterilizer's compliance with this regulation. In addition to the requirements of 21 CFR 801.150, good business practices may require other inclusions in the written agreement to clarify the division of responsibilities.

The written agreement may be in the form of a contract or Standard Operating Procedure (SOP) that is signed by both parties. The written agreement shall, directly or by reference to existing documents, indicate the responsibilities of each party for assuring the completion of all GMP requirements related to the sterilization process. For ethylene oxide sterilization, the written agreement should contain, or reference, at least the following:

a) Information transfer—The agreement should specify the individuals at each facility responsible for coordinating the flow of information between establishments and for approving procedural changes.

b) Records—The agreement should specify all required documentation (for example: procedures, processing records) to be used and maintained. Both parties should agree on the manner in which documentation changes are to be made.

c) Process validation—The written agreement should specify all parameters to be qualified by the contractor and the criteria for requalification.

d) Loading configuration—The agreement should specify the pallet patterns, vessel loading configuration, packaging (e.g., cartons or pieces), and whether the load is prewrapped or shrink wrapped for each product or product family.

e) Biological indicators (BIs) and product test samples—The agreement should specify responsibility for placement, retrieval, handling, processing, and maximum time intervals before shipment of BIs and product test samples. It should include instructions for packaging and shipment of BIs and product test samples to test laboratories for analysis.

f) Cycle parameters and process control—The agreement should specify the process parameters that should be achieved for sterilization once the sterilization process has been validated.

g) Post sterilization handling—The agreement should specify procedures for post sterilization quarantine of the product before release for distribution.

h) Batch records and review—The agreement should specify procedures and responsibility for approving sterilization batch records prior to release.

NOTE 8 The manufacturer is responsible for reviewing documentation before releasing the product for commercial distribution.

i) Finished product release—The agreement should specify product release procedures and identify the individuals who are responsible for approving release for distribution.

j) Audits—The agreement should specify the scope of audits, corrective actions, documentation of audit, and confidentiality.

NOTE 9 It is the responsibility of the manufacturer to assure that the audits are performed in accordance with the manufacturer's quality system.

k) Control of changes, process deviations, and product damage—The agreement should specify the individuals to be notified of any changes or deviations in the manufacturing or sterilization process. It should also specify the individual at the manufacturer or manufacturing plant that should be contacted when product is damaged to determine how the product should be handled at the contract sterilizer.

l) Reprocessing of loads—The agreement shall specify how reprocessing procedures are established, implemented, and controlled to assure that the reprocessing steps and product meet the validation and routine processing specification criteria.

m) Material handling and documentation—Adherence to Title 21, CFR, Part 801.150 is required for label control. The agreement should specify how adherence is to be controlled/conducted.

n) Contract agreement criteria—The written agreement shall specify all shipping arrangements including labeling for shipping and should identify laboratories to be used for sample testing.

5 Validation program

5.1 Responsibilities

Validation of the cycle is the responsibility of the device manufacturer. Responsibility for the validation tasks may be delegated to the contract sterilizer through the contract. If the contract sterilizer has assumed responsibility for validation, the manufacturer is still ultimately responsible for the safety and efficacy of those devices it produces. Contract sterilizers are considered an extension of the device manufacturer's operation and are responsible for the elements of the manufacturing operations that they perform.

5.2 Validation program outline

An outline of a typical validation program is given in Table 1.

Table 1—Outline of typical validation program

Pre-Assessment Product Qualification
Determine sterilization criteria (SAL, feasibility)
Determine sterilizability (penetration, venting, packaging)
Determine compatibility (temperature, humidity, pressure, chemical, cycle design)
Determine maximum repetitive sterilizations
Product Qualification
Determine postexposure performance (product and package functional, physical, effectivity)
Determine residual acceptability (limits, hold time, product deliverability)
Sterilizer and Product Validation
Conduct qualification studies (fractional exposures for lethality)
Evaluate success of sterilizability (penetration, venting, packaging
Ascertain compatibility (cycle design) (temperature, humidity, pressure, chemical)
Evaluate postexposure performance (product and package functional, physical, effectivity)
Ascertain residual acceptability (limits, hold time)
Validation Maintenance Program
Full Cycle Sterilization

5.3 Product families for sterilization

Product families are defined and established at the initiation of the validation program by a manufacturer. A family of products is typically composed of numerous products that possess common features, i.e., similar product design and functions, similar packaging, similar bioburden, similar materials and similar impact on chamber temperature distribution. During sterilization, these products may be contained within a given sterilizer load. If a manufacturer has several product families, these may also be sterilized together if the validation program so allows.

It is not recommended that a contract sterilizer mix products from different manufacturers in processing cycles unless validation studies have proven the effectiveness of the cycle for those mixes or worst case mixes, and the customers are informed and agree to the practice.

6 Handling of product samples and BI test samples

A document that details and defines methods to be employed for coordination of test sample selection, preparation, load placement or retrieval, shipment, and final testing should be reviewed with all parties responsible for handling of product.
The document should specify

a) preparation of samples (quantity, test method, identification);

b) presterilization storage (location and shelf life);

c) placement of samples;

d) removal and accountability;

e) storage of samples following sterilization (location and length of time); and

f) shipment of samples to laboratory.

A summary of the test categories for which a group of samples is commonly required and their associated technical references is provided in Table 2.

Table 2—Test descriptions and associated technical references

Doc No.*	Reference Document	Test Description
[11]	ANSI/AAMI/ISO 11737-1	Bioburden
[14] [29]	ANSI/AAMI/ISO 11737-2 USP<71>	Sterility—Natural product
[23] [29]	ISO 11138-2 USP<71>	Bacteriostasis/Fungistasis Sterility—Challenge device process
[5] [7] [9] [4] [29]	ANSI/AAMI/ISO 10993-1 ANSI/AAMI/ISO 10993-6 ANSI/AAMI/ISO 10993-9 ANSI/AAMI/ISO 10993-11 USP <161>	Biocompatibility—General
[8]	ANSI/AAMI/ISO 10993-7	EO residuals
[28]	FDA proposed rule 06/23/78	Proposed rule for maximum residual limits
[15] [29]	CDC Guideline (12-87) USP <161> & <85>	LAL test—Pyrogen
[13]	ANSI/AAMI/ISO 11607	Functionality—Product and packaging
[18]	HIMA Packaging	Packaging

*For full citations to the referenced document, see Annex C, Bibliography. Document numbers are keyed to the listings in Annex C.

A documented control system should be designed to maintain control over test samples through the sterilization process and analysis. A description of the test sample and quantity, sample ID, sample preparation and handling, and reconciliation should be included as part of the documented control system.

Traceability of samples should be monitored throughout preparation and analysis. Documentation of the various sample handling stages shall be clear and concise in order to avoid errors that commonly occur during validation. One approach that can be used to enhance control over sample handling while effectively documenting sample disposition is to construct a sample flow diagram that includes sample reconciliation form(s) for the various types of testing. The diagram and form(s) can be presented as attachments to the protocol. A sample location diagram that depicts the location of individual samples within the load should be included in the protocol.

7 Sterilization processing documentation

7.1 Validation documentation

The following is a list of documentation that, at minimum, should be included in the validation package.

a) Sterilization process

1) Preconditioning (if used), vessel and aeration (if used) identification, and facility location.
2) Commissioning information.
3) Calibration and/or verification information (for equipment used to monitor/control the sterilization process).

b) Documents

1) Validation protocol written procedures.
2) Final validation report.
3) Written agreement(s) between manufacturer and contractor.

c) Product and BI information

1) List of products or product families included in the validation.
2) Pallet or loading configurations to include sample placement location.
3) Lots and quantity of products used in the validation.
4) Description of product and BI test samples.
5) Description of dunnage (if used), i.e., rejected material, simulated material, product, etc.
6) Rationale for development of product families (if used).
7) Rationale for selection of process challenge device (if used). (The standard is referenced in the description section.)
8) Rationale for selection of most-difficult-to-sterilize location within the device.
9) Rationale for selection of sample location within the sterilizer load.
10) BI label information (manufacturer, Lot #, expiration date, spore population and D-value).
11) Date(s) BIs are placed in device or process challenge device.
12) Time and date of placement and retrieval of samples within the load.

d) Temperature, relative humidity and pressure information

1) List of thermocouples, humidity sensors, and pressure transducers used.
2) Locations within the product loads.
3) Temperature profile information for preconditioning (if used), vessel and aeration (if used), and relative humidity profile for preconditioning and until gas injection in the vessel.

4) Temperature of load prior to preconditioning (if used).
5) Time in and out of preconditioning (if used), vessel and aeration (if used), and transfer times (if used).
6) Rationale for selection of sensor placement within the sterilizer load.

e) Parameter information

1) Preconditioning records (if used).
2) Sterilization cycle printouts or records.
3) Aeration records (if used).
4) Amount and lot number of gas used.
5) Gas certification.

f) Other information

1) Bioburden information.
2) EO residual data.
3) Product and packaging functionality testing.
4) BI laboratory test results.
5) Product sterility test results.
6) Statement of acceptance.
7) Biocompatibility.
8) Pyrogen test result (if appropriate).
9) Bacteriostasis/fungistasis testing.

7.2 Cycle development documentation

For sublethal cycles, all the information listed in 7.1 a) through e), and f) 1), 4), 5), 6), and 9) should be included in the cycle development documentation package if applicable.

7.3 Routine processing documentation

The following is a list of documentation that, at a minimum, should be included for routine processing.

a) Routine information

1) Routine specifications including BI placement and retrieval information.
2) Sample transmittal.
3) Lot number, catalog number, and quantity of product received, sterilized, and shipped.
4) Product temperature and/or hold time, if applicable, to accommodate cold product conditions prior to or at the start of preconditioning (if used) or sterilization.
5) Times and dates in and out of preconditioning (if used), sterilization, and aeration (if used).
6) Records for conditions in preconditioning (if used), sterilization, and aeration (if used).
7) BI information (e.g., lot and preparation information).
8) BI results.
9) Written release or acceptance of the sterilization processing records.

b) Other information

1) Documentation of damage.
2) Deviation information.

3) Change control.

8 Controls for routine processing

8.1 Product load configuration

The diagram of loading configuration(s) for each product or product family should be specified. The routine product load configuration should conform to the validated load configuration. The loading parameters to be specified should, at minimum, include a pallet diagram or pattern to include

a) shrink wrap and strapping;

b) the minimum and maximum number of units per pallet;

c) the minimum and maximum number of pallets per chamber;

d) identification of the specific chambers that are qualified for the specific product or product family; and

e) the location and quantity of test samples used, e.g., process challenge devices and samples for sterility, pyrogenicity, and residual testing, if used.

8.2 Shipping and receiving product for processing

8.2.1 The device manufacturer is responsible for assuring that

a) the products are packed to maintain product integrity and cleanliness;

b) the written agreement is developed and signed before shipping;

c) the quantity of product and test samples, if used, is documented;

d) each pallet, carton, or designated shipping unit is conspicuously marked to show its nonsterile nature, e.g., "Nonsterile: Shipped for Further Processing";

e) products shipped have a validated process and are included in the written agreement; and

f) the contract sterilizer is provided with instructions about handling products that are damaged.

NOTE 10 Any product that is not processed (sterilized) by the contract sterilizer because of damage shall not be shipped without a label that indicates its nonsterile status.

8.2.2 The contractor is responsible for assuring that

a) the quantities of product and test samples received are documented and discrepancies are resolved with the manufacturer;
b) products processed are included in a written agreement;

c) material is segregated to avoid mixing sterile and nonsterile product; and

d) damaged material is documented and handled according to the written agreement.

8.2.3 Process control

The contractor should assure and demonstrate through process documentation that the process specifications are routinely achieved. Each qualified cycle for a specified product and manufacturer shall be documented, implemented, and monitored. The flow of materials to and from the sterilization area should be controlled to prevent mixing of processed and unprocessed product.

8.2.4 Process documentation review

Prior to release of product to the manufacturer, the contractor should review and approve all documentation for each sterilization load to assure that processing specifications have been met. Likewise, prior to release for distribution of the product, the manufacturer shall review processing documentation received from the contractor to assure that the agreed-upon process specifications have been achieved. These reviews shall be performed by personnel with the necessary education and experience.

The ultimate responsibility for the release of product as "sterile product" rests with the manufacturer. While certain tasks related to the release may be delegated to the contract sterilizer, the responsibility remains with the manufacturer. The manufacturer shall develop procedures for approving the release of the product. The manufacturer shall approve the release of the product based on the release criteria, which may include, but are not limited to: process parameters, sterility test results, biological indicator test results, bacterial endotoxins (LAL tests), residual results, and product/package functionality.

8.2.5 Indicators and test samples

Standardized operating procedures shall be generated in order to define routine storage, load placement, removal, shipping, and testing of samples. In addition, the standard operating procedures should include documentation required for each handling stage.

8.2.6 Change controls and process deviations

A procedure should be developed to respond to changes in the manufacturing or sterilization process. The manufacturer and the contractor should agree to inform each other of any changes or deviations that may have an impact on the effectiveness of the sterilization process or product and therefore may require cycle requalification. Examples of such occurrences include, but are not limited to

a) microbiological or physical failures;

b) control system or calibration problems;

c) equipment modifications;

d) changes to the material or configuration of the product and/or its packaging; and

e) changes to the manufacturing or sterilization environment.

The written agreement should include a mutual notification procedure to notify designated contractor and manufacturer representatives of such changes.

8.7 Resterilization

The effects of resterilization, if applicable, on product/packaging degradation and EO residuals should be known, a specific provision should be made for these effects. The written agreement shall address the manufacturer's and contractor's responsibilities for resterilization criteria.

8.8 Shipment of product following processing

8.8.1 The contractor is responsible for

a) reconciliation of the quantity of product shipped; and

b) identifying product status—if the manufacturer's release for quarantined shipment is obtained, each pallet, carton, or designated shipping unit is conspicuously marked, e.g., "Sterilized— Awaiting Test Results."

8.8.2 The manufacturer is responsible for documenting the quantity of product and test samples received and resolving any discrepancies with the carrier or contractor.

9 Maintenance of contract relationship

Maintenance of the relationship between the product manufacturer and the contract sterilizer is essential. Open lines of communication between both parties will enhance the understanding of the needs of the product manufacturer and enhance the service provided by the contract sterilizer. In addition to communication on a routine basis, activities such as the following should be conducted on a periodic basis:

a) perform audits of the contract sterilization facility;

b) review the annual requalification documentation (to include calibration; testing of the preconditioning room (if used), vessel, and aeration room (if used); comparison of vessel equivalency (if used); and comparison to original facility qualification data);

c) review requalification documentation of each product or product family, process parameters;

d) review process deviation trend analysis; and

e) review the written agreement to assure that it is current.

Annex A
(informative)

Sensor monitoring tables

A.1 Commissioning (Empty)

Table A.1—Preconditioning

AREA VOLUME		ANSI/AAMI/ISO 11135		EN 550	
M^3	FT^3	# TEMP PROBES	# HUMIDITY SENSORS	# TEMP PROBES	# HUMIDITY SENSORS
2.5	90	4	2	5*	2
5	175	4	2	4	2
10	350	4	4	4	4
15	530	6	6	6	6
25	885	10	10	10	10
35	1235	14	14	14	14
40	1410	16	16	16	16
50	1765	20	20	20	20
100	3500	20	20	20	20

Rules for determining number of probes—
ANSI/AAMI/ISO 11135 and *EN 550*
M^3=2.5 to 5, then 4 temperature probes and 2 humidity sensors.
M^3>5 and <50, then (M^3 x 0.4) = temperature probes and humidity sensors.
$M^3 \geq 50$, then 20 temperature probes and 20 humidity sensors.

*This number is correct as per *EN 550*.

Table A.2—Sterilization

CHAMBER VOLUME		ANSI/AAMI/ISO 11135	EN 550
M^3	FT^3	# TEMP PROBES	
2.5	90	10	10
5	175	10	10
10	350	15	15
15	530	20	20
20	705	20	25
25	885	20	30
30	1060	20	35
35	1235	20	40
50	1765	20	55
100	3500	20	105

Rules for determining number of probes—

ANSI/AAMI/ISO 11135

$M^3<5$, then 10 temperature probes.
$M^3 \geq 5$ and <10, then ($M^3 + 5$) = temperature probes.
$M^3 \geq 10$, then 20 temperature probes.

EN 550

$M^3>5$, then ($M^3 + 5$) = temperature probes.

Aeration: Same number of temperature probes as used above for preconditioning.

A.2 Performance qualification (with product)

Table A.3—Preconditioning and/or conditioning

PRODUCT LOAD VOLUME		ANSI/AAMI/ISO 11135		EN 550	
M^3	FT^3	# TEMP PROBES	# HUMIDITY SENSORS	# TEMP PROBES	# HUMIDITY SENSORS
2.5	90	5	2	5	2
5	175	4*	2	4	2
10	350	8	4	8	4
15	530	12	6	12	6
25	885	20	10	20	10
35	1235	28	14	28	14
50	1765	40	20	40	20
100	3500	40	20	40	20

Rules for determining number of sensors—

ANSI/AAMI/ISO 11135 and *EN 550*

M^3<2.5, then 5 temperature probes and 2 humidity sensors.

M^3≥5 and < 50, then (M^3 x 0.8) = temperature probes and (M^3 x 0.4) = humidity sensors.

M^3≥50, then 40 temperature probes and 20 humidity sensors.

*While 4 is correct, it is recommended that 5 temperature number probes be used for compliance with the nominal volume less than or equal to 2.5 M^3.

Table A.4—Sterilization

PRODUCT VOLUME		ANSI/AAMI/ISO 11135		EN 550	
M^3	FT^3	# TEMP PROBES	# BIs	# TEMP PROBES	# BIs
2.5	90	10	20	10	20
5	175	10	20	10	20
10	350	15	30	15	30
15	530	20	35	20	35
20	705	20	40	25	40
25	885	20	45	30	45
30	1060	20	50	35	50
35	1235	20	55	40	55
50	1765	20	70	55	70
100	3500	20	120	105	120

Rules for determining number of probes—

ANSI/AAMI/ISO 11135
M^3<5, then 10 temperature probes.
$M^3 \geq 5$ and <10, then (M^3 + 5) = temperature probes.
$M^3 \geq 10$, then 20 temperature probes.

EN 550
M^3>5, then (M^3 + 5) = temperature probes.

Rules for determining number of BIs—

ANSI/AAMI/ISO 11135 and *EN 550*
M^3<5, then 20 BIs.
M^3>5 and <10, then [(M^3 - 5) 2] + 20 = BIs.
M^3>10, then M^3 + 20 = BIs.

Aeration: No guidance for number of temperature probes. Because probes are in product for sterilization, it would be the same number as above.

Table A.5—Routine sterilization

PRODUCT VOLUME		ANSI/AAMI/ISO 11135	EN 550
M^3	FT^3	# BIOLOGICAL INDICATORS	
2.5	90	10	10
5	175	10	10
10	350	15	15
15	530	18	18
20	705	20	20
25	885	23	23
30	1060	25	25
50	1765	35	35
100	3500	60	60

Rules for determining number of BIs—

ANSI/AAMI/ISO 11135 and *EN 550*
$M^3 < 5$, then 10 BIs.
$M^3 \geq 5$ and < 10, then $(M^3 + 5)$ = BIs.
$M^3 \geq 10$, then $\frac{(M^3 - 10)}{2} + 15$ = BIs.

Annex B
(informative)

Protocol written procedure preparation

B.1 General

To ensure all aspects of commissioning, cycle development and/or process validation are addressed, a written action plan should be developed in the form of a protocol. The protocol should be reviewed and approved by qualified personnel prior to its execution.

Following execution and data analysis, a summary document should be prepared that assures protocol closure and provides a means of documenting the results in a fashion that is presentable to other parties of interest.

NOTE 11 Care should be exercised to establish a protocol scope that can be completed within a reasonable time frame.

B.2 Protocol format

The following protocol format may be used when developing an action plan.

B.2.1 Protocol title page

The title page of a protocol should contain specific information that will allow the reviewer to identify its purpose and contents. A unique means of protocol identification should be established to facilitate data management and tracking during protocol execution. Reviewers of the protocol should be identified and a means provided to document reviewer actions and approvals.

B.2.2 Objective/background

A brief description should be provided that gives the reviewer the information required to understand the circumstances which necessitated the protocol and establishes the end objective.

B.2.3 Scope

The scope section should establish the range and extent of the protocol written procedure.

B.2.4 Normative references

Normative references should identify all sources of requirements and guidelines utilized in the design of the protocol.

B.2.5 Definitions

The definitions section should list and present meanings for all terms in the protocol that may be unfamiliar to the reviewer.

B.2.6 Responsibilities

The responsibilities section should list all parties involved with the design, execution, and analysis of the protocol and their specific areas of responsibility.

B.2.7 Equipment/materials

The equipment and materials section should list all materials and equipment involved in the execution of the protocol and reference the calibration or certification requirements.

B.2.8 Procedures

The procedures section should describe in a structured manner all testing actions to be utilized in the execution of the protocol. All test methodologies should be addressed in a clear and concise manner in the order in which they will occur. The requirements for documentation of all activities should be established and forms provided as necessary to ensure an accurate and complete documentation trail.

B.2.9 Acceptance/rejection criteria

The acceptance/rejection criteria should be listed and utilized as review criteria during data analysis. Specific references to the established regulations, specifications, and guidelines may be included for clarification and reference purposes.

B.2.10 Documentation

The documentation section should list all required documentation and maintenance of all data associated with the protocol including distribution and filing.

B.3 Protocol closure

Once all testing has been performed and the results analyzed, a statement of closure should be prepared. Within the closure, the protocol findings should be summarized and any deviations to the testing plan and/or unexpected results should be addressed. Protocol closure should be reviewed and approved by those identified and responsible for approval of the testing protocol.

Annex C
(informative)

Bibliography

[1] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.* ANSI/AAMI/ISO 10993-3. Arlington (VA): AAMI, 1993.

[2] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 4: Selection of tests for interactions with blood.* ANSI/AAMI/ISO 10993-4. Arlington (VA): AAMI, 1993.

[3] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 5: Tests for cytotoxicity: In Vitro methods.* ANSI/AAMI/ISO 10993-5. Arlington (VA): AAMI, 1993.

[4] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 11: Tests for systemic toxicity. ANSI/AAMI 10993-11*. Arlington (VA): AAMI, 1993.

[5] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 1: Guidance on selection of tests.* ANSI/AAMI 10993-1. Arlington (VA): AAMI, 1994.

[6] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Medical devices—Validation and routine control of ethylene oxide sterilization.* ANSI/AAMI/ISO 11135. Arlington (VA): AAMI, 1994.

[7] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 6: Tests for local affects after implantation.* ANSI/AAMI/ISO 10993-6. Arlington (VA): AAMI, 1995.

[8] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 7: Ethylene oxide sterilization residuals.* ANSI/AAMI/ISO 10993-7. Arlington (VA): AAMI, 1995.

[9] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 9: Degradation of materials related to biological testing.* AAMI TIR 10993-9. Arlington (VA): AAMI, 1995.

[10] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 10: Tests for irritation and sensitization.* ANSI/AAMI/ISO 10993-10. Arlington (VA): AAMI, 1995.

[11] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of medical devices—Microbiological methods—Part 1: Estimation of population of microorganisms on products.* ANSI/AAMI/ISO 11737-1. Arlington (VA): AAMI, 1995.

[12] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 12: Sample preparation and reference materials.* ANSI/AAMI/ISO/CEN 10993-12. Arlington (VA): AAMI, 1996.

[13] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Packaging for terminally sterilized medical devices.* ANSI/AAMI/ISO 11607. Arlington (VA): AAMI, 1997.

[14] ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of medical devices—Microbiological methods—Part 2: Tests of sterility performed in the validation of a sterilization process.* ANSI/AAMI/ISO 11737-2. Arlington (VA): AAMI, (in preparation).

[15] CENTERS FOR DISEASE CONTROL AND PREVENTION. *Guideline on validation of the limulus amebocyte lysate test as an end-product endotoxin test for human and animal parenteral drugs, biological products, and medical devices.* Atlanta, GA: CDC, 1987.

[16] ENVIRONMENTAL PROTECTION AGENCY. National emission standards for hazardous air pollutants for ethylene oxide commercial sterilization and fumigation operations. *Code of Federal Regulations, Title 40, Parts 9 and 63.* Washington, DC: EPA, 1992.

[17] EUROPEAN COMMITTEE FOR STANDARDIZATION. *Sterilization of medical devices—Validation and routine control of ethylene oxide sterilization.* EN 550. Brussels: CEN, 1994.

[18] HEALTH INDUSTRY MANUFACTURERS ASSOCIATION. *Reference on Sterile Packaging.* HIMA Report No. 93-7. Washington, DC: HIMA, 1993.

[19] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Sampling procedures for inspection by attributes—Part 1: Sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection.* ISO 2859-1. Geneva: ISO, 1989.

[20] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Quality systems—Model for quality assurance in design, development, production, installation and servicing.* ISO 9001. Geneva: ISO, 1994.

[21] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Quality systems—Model for quality assurance in production, installation and servicing.* ISO 9002. Geneva: ISO, 1994.

[22] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Sterilization of health care products—Biological indicators—Part 1: General.* ISO 11138-1. Geneva: ISO, 1994.

[23] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Sterilization of health care products—Biological indicators—Part 2: Biological indicators for ethylene oxide sterilization.* ISO 11138-2. Geneva: ISO, 1994.

[24] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Quality management and quality system elements—Part 1: Guidelines.* ISO 9004-1. Geneva: ISO, 1994.

[25] OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION. Occupational exposure to ethylene oxide. *Code of Federal Regulations, Title 29, Part 1910.1047.* Washington, DC: OSHA, 1994.

[26] U.S. FOOD AND DRUG ADMINISTRATION. Medical devices—processing, labeling, or repacking. *Code of Federal Regulations, Title 21, Part 801.150.* Washington, DC: FDA, 1976.

[27] U.S. FOOD AND DRUG ADMINISTRATION. Good manufacturing practices for medical devices—General. *Code of Federal Regulations, Title 21, Part 820.* Washington, DC: FDA, 1978.

[28] U.S. FOOD AND DRUG ADMINISTRATION. Ethylene oxide, ethylene chlorohydrin, and ethylene glycol: Proposed maximum residue limits and maximum levels of exposure. HEW/FDA. *Federal Register*. Washington, DC: 43 (122) 1978.

[29] UNITED STATES PHARMACOPOEIA. United States Pharmacopeial Convention. In*: United States Pharmacopoeia* (23rd ed.). Easton, PA: Mack Publishing Co., 1994.

