MILITARY STANDARD

MONITORING STERILIZATION SYSTEMS FOR MEDICAL DEVICES (INDUSTRIAL)

FSC 65GP

DEPARTMENT OF DEFENSE
WASHINGTON, DC 20301

Monitoring Sterilization Systems for Medical Devices (Industrial)

MIL-STD-966

1. This Military Standard is approved for use by all Departments and Agencies of the Department of Defense.

2. Recommended corrections, additions, or deletions should be addressed to: Defense Personnel Support Center, ATTN: Directorate of Medical Materiel, DPSC-ATT, Philadelphia, PA 19101.

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1. SCOPE

1.1 Scope. This standard covers systems to monitor the effectiveness of sterilization methods applied to medical devices during the manufacturing process.

2. REFERENCED DOCUMENTS

2.1 Issues of documents. The following documents of the issue in effect on date of invitation for bid or request for proposal form a part of this standard to the extent specified herein.

STANDARDS

MILITARY

MIL-STD-969 - Biological Indicators for Sterilization Processes.

(Copies of specifications, standards, and publications required by contractors in connection with specific procurement functions should be obtained from the procuring activity or as directed by the contracting officer.)

2.2 Other publications. The following documents form a part of this standard to the extent specified herein. Unless otherwise indicated, the issue in effect on date of invitation for bid or request for proposal shall apply.

LEA AND FEBIGER PUBLISHING COMPANY

Disinfection, Sterilization, and Preservation, 2nd edition, 1977 - Seymour S. Block, ed.

(Application for copies should be addressed to Lea and Febiger Publishing Co., 600 Washington Square, Philadelphia, PA 19106.)

3. DEFINITIONS

3.1 Decimal-reduction value (D-value). The number of survivors is a direct relation of the resistance of the organism to the sterilization process being used. One method for this determination is the D-value. A D-value is the time required at a given set of conditions (i.e., for steam, the parameters are temperature, pressure and time; for ethylene oxide, the parameters are temperature, relative humidity, gas concentration and time) to reduce the initial microbial population by 1 logarithm or 90 percent. The D-value must be determined from a straight line graph plot on semi-log graph paper of the log number of survivors versus time of exposure to a set of defined sterilization conditions, or from the mathematical statement $D=t/(\log N_o - \log N)$, where N_o is the initial homogenous microbial population, N is the surviving microbial population at any time (t), and D is the D-value for any specific set of conditions. The line shall be based on substantial statistical data.

3.2 Biological indicator (BI).

3.2.1 Inoculated product. A spore suspension-coated directly in, or on, the product. The population of spores per product and the recovery index of that population, and the resistance of that population to the mode of sterilization to be monitored must be known.

3.2.2 Inoculated carrier. Known spores coated in, or on, filter paper, glass, steel, etc. The population of spores per carrier, and the resistance of that population to the mode of sterilization to be monitored, and the manner used must be known.

3.3 Bioburden. The estimated number of micro-organisms present on a product before sterilization. The maximum shall be determined from culturing samples over various periods of time.

3.4 Subdivided. The test specimen of the sample unit which is divided into two parts of equal size. Each part shall be representative of the entire sample unit.

3.5 Unit package. The smallest unit of issue. The unit package may contain subunits.

3.6 Good manufacturing practice (GMP). Good manufacturing practice as established by regulatory agencies.

3.7 Sterile device system. Consists of the device, procedures to minimize its bioburden, sterilization process including equipment and monitoring instrumentation and controls, and packaging used to prevent recontamination.

3.8 Breakpoint. Intercept log "0" by the survival curve projection.

3.9 Seasonal effects. Seasonal effects include, but are not limited to, the variations of bioburden, temperature and humidity which are due to seasonal changes.

3.10 Contracting officer. The official representative of the procuring agency, responsible for award of the solicitation or administration of the resultant contract or purchase order.

3.11 Supplier. The contractor who supplies the device.

4. GENERAL REQUIREMENTS

4.1 Test methods. The test methods include alternate methods of sterility assurance monitoring for each individual sterilization system. For any sterilization process, the process monitoring methods are a vital key to assurance of effective sterilization and these methods must be defined and reevaluated on an established periodic basis. These test methods are:

a. Product testing only.

b. BIs and product testing.

c. BIs only:

(1) Inoculated carrier.
(2) Inoculated product.

d. Dosimetry.

4.2 Product knowledge. The test methods used for a specific product, using a specific sterilization system, shall be based on information such as, but not limited to, the following:

a. Product manufactured under GMP's for medical devices.

b. Previous sterilization experience on each product line evaluated by the quality assurance manager or by his designated individual and applied to an approved sterilization monitoring system.

c. Product bioburden.

d. Proper sample size for testing.

4.3 Bioburden control system. A system must be established and implemented which will assure that appropriate precautions are taken throughout the manufacturing process to minimize the product bioburden and reduce the possibility of micro-organisms occurring which are highly resistant to the sterilization system.

4.4 Sterile device system knowledge. The implementation of an effective program to attain sterility requires extensive knowledge of the device, the manufacturing environment, the sterilization process, the sterilization equipment and monitoring instrumentation, and packaging.

4.4.1 Establishing the system. When first implemented, the system must be validated by tests designed and supervised by individuals qualified by scientific training and experience in evaluating systems for attaining sterility. These tests shall cover the following:

a. Bioburden - Number and kind of organisms.

b. Bioburden resistance - Presence of organisms highly resistant to the sterilization process.

c. Effectiveness of process:

(1) Lethality.
(2) Establishing an appropriate safety factor.

d. Adequacy of packaging.

4.4.2 Periodic reevaluation. The system must be revalidated for any substantial change in the device, packaging, manufacturing, sterilization equipment or instrumentation. Revalidation must be performed after all sterilization failures, to the extent necessary to identify the reason for the failure and assure that it will not recur. Reevaluation must account for seasonal variation. The system shall be revalidated and documented at least annually.

5. DETAILED REQUIREMENTS

5.1 Test methods. The efficacy of the sterilization system shall be monitored by application of the applicable method cited in Table I.

TABLE I. Test methods.

Type of product sterilization	Test methods
Product not sterilized in final container, but sold sterile	Product only
Steam	BI and product or BI only (see 5.1.3)
Gas	BI and product or BI only (see 5.1.3)
Dry heat	BI and product or BI only (see 5.1.3)
Ionizing radiation	BI and product or BI only or dosimetry only, or dosimetry and BI

5.1.1 Product only. This method is used only for sterile products which are not sterilized in the final container. The following media-temperature combinations or alternate combination(s) for which there is documentation to prove at least equivalence in sterility test sensitivity shall be used. A minimum of 30 samples shall be tested at each of two incubation temperatures in liquid medium for a minimum of 14 days as follows:

Medium	Temperature
Fluid Thioglycollate	30^{o} - 35^{o}C
Soybean - Casein Digest	20^{o} - 25^{o}C

The culture medium shall be tested for growth potential and for freedom from contamination prior to use. Each sample unit may be subdivided for testing.

5.1.2 BI and product. This method, which includes an inoculated carrier, shall be used when existing or new products are sterilized in final package, and where little or no product data of bioburden and bioburden-resistance to the mode of sterilization or to the specific sterilization process cycle exists. This method is considered to be a minimum level of sterility assurance monitoring by utilization of not less than 10 BIs per product load and not less than one BI per 40 cubic feet of sterilization volume, and never less than 20 of each product for each test medium (media, incubation time and temperature, as described in 5.1.1.). The following shall be accomplished:

a. At least one positive control BI (inoculated carrier) shall be cultured.

b. BI shall be cultured in accordance with directions of the manufacturer of the BI.

c. The culture medium shall be tested for growth potential and for freedom from contamination prior to use.

5.1.3 BI only. Use of this method shall be based on substantial data of bioburden and bioburden-resistance to the mode of sterilization. Assurance of this system is developed in phases as follows, and must take into account any seasonal effects and various load sizes in the sterilizer:

a. Establish estimated bioburden on product.

b. Determine the resistance of product bioburden compared to BI to the mode of sterilization and to the parameters of the sterilization cycle used on the product.

c. Document the resistance of product bioburden compared to the resistance of the BI implanted in the most difficult to sterilize sites in product.

d. Project the developmental cycle for actual industrial sterilization cycle and load size, and validate previous experimental resistance and breakpoint knowledge results.

e. Calculate from the above data the exposure time parameters of the sterilization process of the production sterilization cycle which gives a level of probability of less than one-in-one-million units being nonsterile.

f. The bioburden shall be determined periodically so that it can be established that the bioburden is within process control limits. The bioburden-resistance relative to the resistance of the BIs must be within process control limits and must be under periodic review, at least annually (see 4.4), to reaffirm that the breakpoint-resistance relationship has remained within established control limits.

The level of probability of a survivor of the BIs, when the BIs have been properly used and correlated with the product bioburden, shall be less than 10^{-6}. It is the responsibility of the manufacturer to provide sufficient proof of the safety monitoring factor. An example of the plotting to determine a safety factor (level of probability of a survivor of less than 10^{-6}) is shown in figure 1.

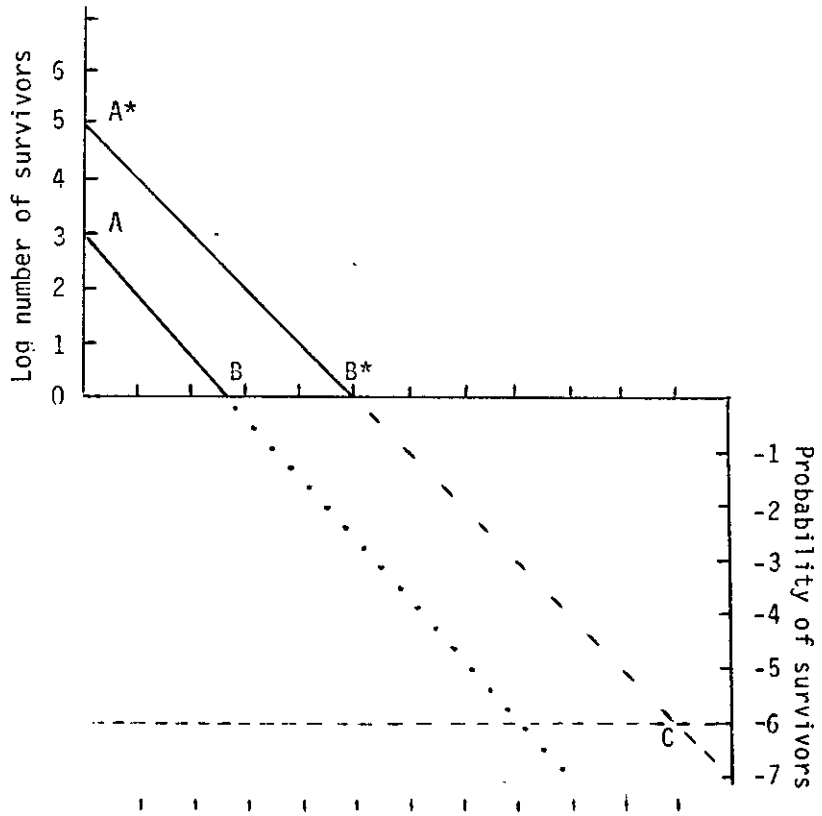

FIGURE 1. Survival-time plot.

(A) Estimated bioburden on product.
(B) Bioburden breakpoint. Intercept log "0" by survival curve projection of the bioburden.
(A*) Population on BI units. (Population exceeds bioburden.)
(B*) Biological indicator breakpoint. Intercept log "0" by survival curve projection of the BI. There must be a reproducible pattern of BI kill. (BI resistance exceeds product bioburden resistance: B*>B).
(C) Defines exposure time to attain a 10^{-6} (1/1,000,000) level of probability of a survivor (on a BI). By inference: probability of sterility of a product.

5.1.4 Used for ionizing radiation only - dosimetry. Approval for use of this method requires dosimetry system to be equivalent to, or a better sterility assurance method than, the biological testing evaluation system specified in 5.1.3. Approved dosimetry ranges cannot be lowered without approval of contracting officials. All sterility certificates by this method shall state the dosimetry readings.

5.2 Suggested organisms. The suggested organisms for use as BIs are as follows:

Type of Sterilization	Organism
Steam	Bacillus stearothermophilus
Dry Heat	Bacillus stearothermophilus, or Bacillus subtilis var. niger (or globigii)
Gas	Bacillus subtilis var. niger (or globigii)
Radiation	Bacillus pumilus

The above list is not all inclusive. If an organism of higher resistance is found on the product, then this organism should be evaluted as the BI, provided its performance can be controlled. Incubation temperature and time on BIs is the responsibility of the user and should follow BI manufacturer's incubation recommendations.

5.3 BI resistance. The BI resistance shall meet those survival/kill conditions specified in MIL-STD-969.

5.4 BI units identification. All packaging units containing a BI shall be distinctly identified. In addition, to differentiate the packaging unit containing BIs from all other products, effective identification must be established so that the opportunity for distribution of product for patient use which contains a BI shall not exist.

5.5 Planting BIs. The BIs shall be planted within the product unit. Products containing BIs shall be distributed throughout the entire sterilization load of the product so that the inoculated units shall be placed in the difficult to sterilize sites of the batch or lot and sterilizer chamber. Individuals who plant and recover the BIs must be under the direction of an individual employed by the supplier who has an overall knowledge of the sterilization program and who is responsible for certifying sterility of the product.

5.6 Sterilization records. Records shall show how many samples of each sterilization lot were planted with BIs and indicate the number recovered after exposure to a sterilization process. Records must indicate by some traceable method, the location of each BI unit and product unit in load, along with the final culture results for each. Records must also indicate use of positive (growth) controls and the results. In addition, sterilization records shall indicate product quarantine dates and final release date or reject date and disposition.

5.7 Personnel. Sterility tests shall be conducted by personnel having training in microbiology and experience with rigid aseptic techniques. These personnel shall be kept informed of any modifications or changes in established manufacturing processes, including sterilization and packaging. They shall reject any BI test units which are not properly planted. The individual conducting the test shall sign the final reports, even though someone else is responsible for final release. The sterilization release records shall contain, as final approval, the signature of a qualified professional person who is actively working in the area and has day-to-day knowledge of the operation and responsibility for the following:

a. The selection of test procedures and controls to be used.

b. The interpretation of test results on each sterilization load.

c. The final decision to accept or reject a lot or batch for reasons pertaining to sterility. "Professional", for this position, refers to a graduate from an accredited college or university with a minimum of a four-year bachelor degree or an equivalent, in one of the biological, chemical, pharmaceutical or allied medical sciences, and sufficient training (not less than one year) in the principles of medical device sterilization processes and sterility testing.

5.8 Contract sterilization responsibility. When contract sterilization is employed, the responsibility for assuring compliance with this standard shall be assigned to a qualified individual who is an employee in the quality department of the supplier.

5.9 Packaging and product changes. The manufacturer is responsible for the final judgment of packaging and product changes and must keep documented evidence of the testing results on file. The procuring agency shall retain the option to disapprove the change after review of test records results.

5.10 Certificate of sterility. A certificate of sterility shall be prepared by the manufacturer of the product, certifying that sterilization was conducted and monitored in accordance with this military standard. The certificate shall be submitted to the procuring activity and shall include:

a. Item identification.

b. National Stock Number (NSN).

c. Contract or purchase order number.

d. Sterility lot or control number.

e. Date of sterilization.

f. Quantity of product in sterilizer lot.

g. Type of sterilization (gas, radiation, heat, steam, etc.).

h. Type of BI (as classified per section 1.2 of MIL-STD-969).

i. The BI trade name (if applicable).

j. The BI organism(s).

k. The BI lot (batch) number.

l. The BIs have met, or exceeded, resistance requirements of MIL-STD-969: Yes _____, No _____.

m. Description of the sample and a description of the inoculation procedure used in the sterility test.

n. Test medium, incubation temperature (taken from calibrated chart recordings), incubation time, and dates of tests.

o. Number of test units: Product _____, BIs _____, Dosimeters _____.

p. Number of positive (growth) BI controls evaluated for survival: _____.

q. Dosimetry readings: Maximum _____, Minimum _____ (as applicable).

r. Statement that test samples pass the sterility tests.

s. Statement that this lot required resterilization due to previous failure. A complete report of the failed lot shall be provided.

t. Those manufacturers sterilizing and/or testing outside their own company must have certified documentation of all operations out of their physical control.

u. Authorized signatures:

(1) Sterility test laboratory.
(2) Supplier.

When inspection is made at destination, the certificate of sterility shall be submitted by the supplier to the procuring agency and a copy forwarded with each shipment to the consignee. When the inspection is made at source, the certificate of sterility shall be furnished to the cognizant Government Quality Assurance Representative for submission to the procuring activity.

5.11 Sterilization lot or batch. A sterilization lot or batch is that quantity of product which, as far as is practicable, consists of units of product of a single type, grade, class, size, and composition manufactured under essentially the same conditions and sterilized at essentially the same time, in the same sterilizer chamber. Each sterilization lot or batch shall be traceable to the pertinent manufacturing lot(s).

5.12 Records. The selection of a satisfactory sterility assurance monitoring system is the complete responsibility of the supplier. Suppliers shall have established a continual updating system of maintaining records. All records shall be available for inspection by contracting officials. All records must be kept for a minimum of three years from date of release. All revalidation records shall be available for inspection upon request by contracting officials.

5.13 Alternate system. Suppliers using a sterilization monitoring system other than that defined herein shall submit proof that the alternate system provides equal assurance concerning the sterility of the product. Requests for approval of any alternate system shall be made to the contracting officer and approval obtained before employment of the alternate system.

STANDARDIZATION DOCUMENT IMPROVEMENT PROPOSAL

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