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Technical Information Report

AAMI TIR13:1997

Principles of industrial moist heat sterilization

AAMI
Association for the Advancement of Medical Instrumentation

AAMI TIR No. 13—1997

Principles of Industrial Moist Heat Sterilization

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Abstract: This Technical Information Report provides tutorial information to industrial users of moist heat sterilization to supplement the requirements of ANSI/AAMI/ISO 11134, *Sterilization of health care products—Requirements for validation and routine control—Industrial moist heat sterilization* (AAMI, 1993). The TIR also provides definitions of terms and a bibliography.

Keywords: bioburden method, commissioning, cycle development, lethality, microbiological challenge, moist heat, overkill method, process control, steam sterilization, sterilization cycles, sterilization validation, validation

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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.

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

FOREWORD

This Technical Information Report (TIR) was developed by the AAMI Industrial Moist Heat Sterilization Working Group, under the auspices of the AAMI Sterilization Standards Committee. Much of the information provided in this TIR was published previously in the American National Standard, *Guideline for industrial moist heat sterilization of medical products* (ANSI/AAMI ST25—1987). Portions of the American National Standard were later incorporated into the International Organization for Standardization (ISO) standard, *Sterilization of health care products—Requirements for validation and routine control—Industrial moist heat sterilization* (ISO 11134—1993). The ISO standard was adopted as an American National Standard, superseding ANSI/AAMI ST25, and published by AAMI in 1993.

The ISO standard establishes minimum requirements for industrial moist heat sterilization and does not include much of the tutorial or explanatory information provided in the original American National Standard. This TIR recapitulates and amplifies that information to provide further guidance to industrial users of moist heat sterilization. Additional information on related subjects may be found in the references listed in the bibliography.

Comments on this Technical Information Report are invited and should be sent to AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

PRINCIPLES OF INDUSTRIAL MOIST HEAT STERILIZATION

1 Introduction and scope

1.1 This Technical Information Report (TIR) is mainly intended to provide tutorial information to industrial users of moist heat sterilization to supplement the requirements of ANSI/AAMI/ISO 11134, *Sterilization of health care products—Requirements for validation and routine control—Industrial moist heat sterilization* (AAMI, 1993). The ANSI/AAMI/ISO standard was developed with a focus on medical devices. However, in its context as a U.S. national standard, ANSI/AAMI/ISO 11134 is applicable to all manufactured health care products sterilized by means of moist heat sterilization. As such, the standard can be considered to be an umbrella document encompassing moist heat sterilization process requirements and guidance applicable to drugs, biologics, and other nondevice solution products as well as to medical devices.

1.2 This TIR covers the following general topics:

a) *Product and process considerations:* Section 3 describes the interrelationship of product and process, the major types of moist heat sterilization cycles, and microbiological and engineering aspects of process development.

b) *Validation:* Section 4 covers the elements of validation (commissioning, verification of process specifications, and performance qualification) and addresses such issues as vessel equivalency, the minimum number of replicate cycles, and decision-making criteria for revalidation.

c) *Routine processing:* Section 5 covers process control, change control and revalidation, preventive maintenance of equipment, and safety issues.

1.3 This TIR also provides definitions of terms, a bibliography, and annexes containing supplementary information.

NOTE—This TIR does not cover moist heat sterilization in health care facilities, nor does it address performance requirements for industrial moist heat sterilizers. Although annex D lists a number of pertinent Food and Drug Administration (FDA) and International Organization for Standardization (ISO) publications, this TIR does not provide substantive guidance on U.S. or international regulatory requirements related to industrial moist heat sterilization processing.

2 Definitions of terms

2.1 air-steam mixture: uniform mixture of air and saturated steam used for sterilization.

NOTE—Air is used to compensate for pressures generated within sealed containers that exceed saturated steam pressures.

2.2 bioburden: population of viable microorganisms on a raw material, component, finished product, and/or package.

2.3 commissioning: obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification and that it functions within predetermined limits when operated in accordance with operational instructions.

2.4 D value: exposure time required under a defined set of conditions to cause a 1-logarithm or 90% reduction in the population of a particular microorganism.

2.5 F value: measure of the microbiological inactivation capability of a heat sterilization process.

2.6 F_0 value: F value calculated at 121.1° C (250° F) with a z value of 10 K and a D value of 1.0 minute.

2.7 moist heat: heat that is derived from water, either as a liquid or as steam under pressure.

2.8 moist heat sterilization: process of using moist heat to produce a sterile product.

2.9 primary packaging: element of the packaging system that maintains the sterility of the product.

2.10 saturated steam: water vapor at a temperature corresponding to the boiling point of the source liquid.

2.11 sterile: state of being free from viable microorganisms.

NOTE—In practice, no such absolute statement regarding the absence of microorganisms can be proven (see **sterilization**).

2.12 sterilization: validated process used to render a product free of all forms of viable microorganisms.

NOTE—In a sterilization process, the nature of microbiological death is described by an exponential function. Therefore, the presence of microorganisms on any individual item can be expressed in terms of probability. While this probability may be reduced to a very low number, it can never be reduced to zero.

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

NOTE—Validation covers three activities: commissioning, verification of process specifications, and performance qualification.

2.14 z value: number of degrees of temperature required for a 1-logarithm change in the D value.

3 Product and process considerations

3.1 General

Moist heat sterilization has many applications throughout the medical industry, ranging from the sterilization of pharmaceutical products to the processing of medical devices and *in vitro* diagnostic products. However, certain sterilization process conditions may adversely affect the product and/or its packaging. This section of the TIR covers elements of product and packaging design that are of major concern and worthy of consideration before the manufacturer uses or recommends moist heat sterilization of the product.

3.2 Product considerations

3.2.1 General

When planning to process a product by moist heat sterilization, it is important to ensure that the product will function safely and effectively and that the package which protects it will remain intact after exposure to the temperatures, pressures, and high humidity of the sterilization process. In the case of a reusable product, it is necessary for safety and effectiveness to be maintained after exposure to the maximum specified number of reprocessings, including decontamination, assembly/packaging, and sterilization, as applicable.

3.2.2 Materials selection

Careful selection of materials during the development of the product design or of subsequent changes will help ensure that permeability, physical properties, dimensions, raw material content, and rate of heat degradation will be appropriate for a product simultaneously exposed to heat, moisture, and pressure changes in the chamber.

3.2.3 Fitments and closures

Fitments and closures that are required to be sterile may be pretreated (presterilized to reduce bioburden) or designed to retain the moisture needed to achieve sterilizing conditions in the moist heat sterilization process. If pretreatment is not used, it is important to ensure that the product or component has been designed to allow adequate moisture into the product through the sterilization process or from the product itself (as in the case of a product with a rubber closure or other component that can be assembled wet). See also "Pretreatment and preconditioning," later in this section.

For products carrying United States Pharmacopoeia (USP) label claims, there are specific requirements for fitments and closures (see the current edition of the USP).

3.3 Package considerations

3.3.1 General

The major purpose of the package of a medical device or diagnostic product is to maintain the sterile barrier until it is used. During sterilization, it is essential that the package be able to tolerate the process parameters with no adverse affect on product quality or package integrity.

3.3.2 Packaging design criteria

The following design criteria are important in the selection of the primary package for a product that will be sterilized or processed using moist heat:

a) *Permeability:* For sterilization to be achieved, the moist heat in the chamber must permeate the package and, if applicable, the product. If air removal is a part of the sterilization process, the package must also permit air evacuation without damage. Before the final sterilization cycle is selected, it is essential to ensure that the package that will be in place during sterilization is adequately permeable.

   In the case of nonpermeable materials, the materials and/or design must allow adequate heat transfer to the product so that internal product moisture will act as the sterilant.

b) *Materials:* Materials selection will be influenced by many factors, including availability, cost, type of package opening, package configuration, and the end use of the product. Early evaluation of materials against the prospective sterilization process parameters will minimize delays due to production and sterilization process failures.

c) *Strength:* The package needs to be strong enough (in its materials, seals, and design) to withstand the sterilization process, as well as shipping and storage conditions, over the specified shelf life of the product. The required strength of the package will be dictated by the size, weight, and shape of the package contents and by the other intended packaging layers.

d) *Sterility maintenance:* If the product itself maintains a sterile barrier, then the primary package need not provide this protection. However, where the package is intended to maintain the sterile integrity of the product, the microbial barrier properties of the package are important and ought to be thoroughly evaluated to ensure that the sterility of the product will be maintained throughout its life. Guidance on this subject is provided in ANSI/AAMI/ISO 11607—1997, *Packaging for terminally sterilized medical devices.*

The secondary and tertiary packages provide additional physical protection during handling, shipping, and distribution of the product and thus facilitate maintenance of the sterile barrier of the product in the primary package. If the product will be sterilized with packaging layers in addition to the primary package, it is important to evaluate the above criteria as well as the impact of moisture and temperature/pressure changes during the sterilization process.

3.3.3 Packaging validation

The effectiveness of the primary packaging is demonstrated during packaging validation, which provides documented evidence of the package's barrier properties and integrity. (See ANSI/AAMI/ISO 11607—1997.)

If the effectiveness of the packaging material as a sterile barrier has not been established (i.e., it is a new type of packaging material), it will be necessary to perform challenge testing to validate the barrier properties of the material. For an established packaging material, it will be sufficient to maintain on file literature from the manufacturer documenting physical and microbial barrier characteristics.

It is also necessary to validate the capability of the packaging and sealing processes to reliably deliver a satisfactory seal while maintaining other attributes of package quality. Important factors to consider when designing a validation program include the following:

a) The packaging materials used during validation studies ought to be representative of those that will be used in routine production.

b) Evidence will be needed to demonstrate that the sealing process does not adversely affect the function of the product or package and that the package can be opened and the product presented according to specifications.

c) The experimental protocol should include qualification runs with the sealing equipment at the appropriate specification limits for temperature, dwell time, and pressure that provide the most severe challenge to the sealing process.

d) It will be necessary to calibrate instruments used to monitor and record sealing process parameters before and after qualification runs.

e) It will be necessary to establish the reproducibility of the packaging process over successive runs under specified operating conditions.

f) The test methods used to measure the quality of the seal need to be validated, and the test instruments need to be calibrated. Among the typical tests are seal strength, seal width, and visual appearance.

g) After package integrity is validated, it is important to demonstrate that it is maintained before, during, and after the sterilization process, during distribution, and for the expected useful life of the sterile product.

3.3.4 Product labeling

Product labeling should provide adequate instructions for shipping, storing, opening, and using the product. The label should also provide a caution that opened or damaged packaging can no longer ensure the sterility of the product. For reusable products, additional information should be provided to assist the user in selecting a process

which will ensure that the device is safe to use after it has been cleaned, decontaminated, repackaged, and resterilized (see AAMI, 1995a).

NOTE—If overlabels are used, it is advisable to evaluate their impact on package performance and on the ability of the process to deliver sterilization.

3.5 Family groupings

For purposes of validating sterilization cycles, families of products and packages can be defined based on similarities in material composition, product design, manufacturing process, intended use (required sterility assurance level [SAL] and biocompatibility), and primary package system design. (See annex A.)

3.6 Sterilization cycles

Many sterilization cycles have been developed for use in a moist heat environment with calibrated equipment that has been properly installed and validated. Among the processes commonly used in industrial moist heat sterilization are the following:

a) *Saturated steam—Vented systems:* This sterilization process is used for products that can tolerate process temperatures at saturated steam pressure and that allow effective air removal from and steam contact with the product.

b) *Saturated steam—Forced air removal:* This process is intended to sterilize products consisting of porous materials and/or items having cavities where air is difficult to remove.

c) *Air pressure systems:* Some product packaging cannot withstand the vapor pressure changes associated with moist heat sterilization. There are a number of available processes in which filtered compressed air is used to ensure that, for part or for the duration of the sterilization cycle, the pressure on the outside of the product equals or exceeds the inside pressure. These processes include cycles using air/steam mixtures, water spray, and water immersion.

See annex B for detailed guidelines on cycle operation.

3.7 Sterilization process development

3.7.1 General

Moist heat sterilization is a process in which the rate of microbial destruction depends on thermal energy, time, moisture content, product bioburden, and the resistance of the bioburden. After the rate of microbial destruction has been described for a process, the time necessary to achieve the appropriate probability of sterility or SAL can be obtained by extrapolation. Different products may require different methods of developing and validating a cycle that will provide the SAL recommended for the product. The number of samples of product or simulated product required for process development and validation also may vary. Typically, 5 to 10 samples will be needed, but the specific number chosen will be dictated by the number required to achieve statistical confidence in the test results. The number chosen should be supported by documented rationale.

Two basic methodologies are used in the development of sterilization processes: the overkill method and the bioburden method.

NOTES

1. European Standard (EN) 556 requires that products labeled sterile have a SAL of 10^{-6}. The information provided in this section is based on AAMI recommendations for industrial steam sterilization process development (AAMI, 1987).

2. Cycle development for closures involves special considerations and is discussed in the next section.

3. If the sterilization process must comply with European or ISO requirements, biological indicators to be used in sterilization process development should comply with the appropriate standards. A biological indicator in compliance with the American National Standard

for biological indicators (AAMI, 1991) does not necessarily comply with the ISO standards for biological indicators (ISO 11138-1: 1994 and ISO 11138-3:1995).

3.7.2 Overkill method

Microbiological challenge populations used in cycle development and routine monitoring are usually not related to the presterilization bioburden. The term "overkill" refers to the fact that the microbiological challenge organism is more numerous and more resistant than the product bioburden.

The overkill methodology is based on the premise that the sterilization process will inactivate the microbiological challenge and provide an additional safety factor. Usually, this safety factor represents the inactivation of 12 logarithms of a microorganism with a $D_{121° C}$ of approximately 1.0 min and a z value of 10° C. For challenge microorganisms having different D values, the population can be adjusted to achieve equivalent lethality; that is, the more resistant the challenge microorganism, the lower the population that can be used. For example, the challenge characteristics of a 10^3 population having a D value of 2.0 min, or a 10^5 population with a D value of 1.2 min, are equivalent to those of a 10^6 population with a D value of 1.0 min.

It is important to remember that the D values and z values of microbiological challenges and product bioburden can vary in different environments (e.g., solutions and different manufacturing sites) and in different containers and closures. Therefore, the selection of the initial microbiological challenge spore count or organism type is based on the resistance of the spore population under the conditions of use. The microbiological challenge is usually 10^3 to 10^6 of heat-resistant spores such as *Bacillus stearothermophilus.*

Because the efficacy of an overkill cycle is dependent upon the challenge organism presenting more resistance then the product bioburden, product samples are typically evaluated for bioburden during cycle development and at periodic intervals after production has begun.

Because the parameters of an overkill cycle are designed to be more severe than are required to achieve sterilization, the process may produce increased particulate levels, a more limited shelf life, and/or accelerated product degradation due to excessive thermal exposure. Consequently, extensive product/package testing during cycle development is necessary to ensure that product quality is not adversely affected by the sterilization process.

3.7.3 Bioburden method

There are two variations of the bioburden method: the absolute bioburden method and the combined bioburden/biological indicator method.

Absolute bioburden: This methodology requires that the product be screened for thermally resistant organisms, with the most resistant isolates selected for the purpose of challenging product sterilization. The initial resistance studies are performed by exposing actual product samples to the proposed cycle conditions at fractional time intervals. The product samples are then tested for microbial survival. From these data, the D values of the resistant isolates can be determined. Alternatively, bioburden organisms can be isolated, cultured, propagated on or into the product or a carrier, and then subjected to various fractional exposures at the proposed cycle conditions and tested for sterility. The D values of the isolates are then calculated. In this approach, it is important to understand that the resistance of the isolates may change during the propagation process.

When the absolute-bioburden method is used for cycle development, it is necessary to perform periodic bioburden resistance studies to ensure that product bioburden resistance has not changed. An extensive bioburden monitoring program is also required in order to establish the normal process control limits and to detect subtle changes in the raw materials, the product, and the manufacturing environment. Because of the impact of

bioburden resistance on the efficacy of the sterilization cycle, it is important that bioburden testing frequency be addressed when modifications to the product or process are made.

Sufficient bioburden data should be obtained to establish a historical record. The frequency of bioburden monitoring depends on the quality and variability of the historical data, the kind of products being sterilized, the manufacturing process, and the type of sterilization process. However, it is common practice to monitor bioburden at least quarterly.

For periodic bioburden monitoring, either actual product samples or appropriate isolates may be evaluated, using one of the fractional exposure times from the initial resistance studies, to verify that the resistance has not shifted.

Combined bioburden and biological indicators: In this method, an organism known to be resistant to moist heat sterilization is used as the microbial challenge; examples include *Clostridium sporogenes, Bacillus coagulans, B. subtilis,* and *B. stearothermophilus.* The relative resistance and mean population of the biological indicator is compared to the resistance and population of bioburden associated with the product (as determined by enumeration and fractional exposure techniques). The objective is to demonstrate that inactivation of a predetermined level of microbial challenge microorganisms ensures a probability of survival no greater than the defined SAL. In other words, if the defined SAL is 10^{-6}, then the challenge must ensure in combination of count and resistance that the probability of a bioburden survival is 10^{-6} or less.

3.8 Pretreatment and preconditioning

3.8.1 Pretreatment processes

The design of some complex products and closure systems prevents effective steam penetration in moist heat sterilization processes, resulting in a dry heat environment rather than a moist heat environment (see "Cycle development for closures and fitments"). At moist heat sterilization temperatures, the dry heat process is not very effective. To assure adequate sterilization, such products or components can be pretreated or presterilized to reduce bioburden.

NOTE—In some cases, presterilization is advisable because pretreatment processing and storage time may allow recovery of the bioburden population or may stress the bioburden in such a way as to alter its resistance.

Pretreatment is also used to reduce the bioburden of individual components for the purpose of reducing the sterilization processing of the final assembled product, or to kill contaminating organisms that are resistant to the desired final sterilization process.

Pretreatment can be performed by means of any method of sterilization or disinfection. A dry heat, moist heat, or radiation process is typically used. Process development is conducted in the accepted manner (see relevant AAMI or ISO standards), but the process need not be as rigorous as a terminal sterilization process because the requirement is for bioburden reduction, not sterility. For example, the microbiological validation of the process typically employs lower inoculation levels of the indicator organism.

3.8.2 Preconditioning process

Preconditioning most commonly involves the addition of moisture to product, components, and/or dry absorbent materials to create a moist heat environment in inaccessible locations or to prevent overheating or superheat conditions. As noted in the previous section, the design of some complex products and closure systems may inhibit effective penetration of moist heat. In addition, dry absorbent materials such as cellulose can absorb and condense excessive steam in the course of reaching equilibrium in water content. The heat from the condensing steam can cause temperatures inside absorbent loads to exceed the sterilization temperature. (See also Block, 1983.)

For these reasons, preconditioning under conditions of controlled humidity may be necessary to allow product to equilibrate in a moisture-rich environment.

3.9 Cycle development for closures and fitments

3.9.1 General

Cycle development and validation for closure systems must be based on microbial inactivation or challenge data. Because of design or process parameters, the environment within closures may vary during the sterilization process, and the heat resistance of the bioburden may change as the cycle progresses. Therefore, the microbial lethality occurring in closures cannot always be readily predicted from the F value because of the difficulty in obtaining physical measurements of the heat delivered. Nevertheless, because closure systems and the sterilization process are subject to defined and reproducible parameters, the level of sterility assurance within closure systems will also be reproducible.

To monitor the microbiological challenge, inoculated products, inoculated carriers, or closure bioburden may be used:

a) The *inoculated product* method involves inoculating the closure with a suspension of spores resistant to moist heat. If moisture is not added to the closure prior to sterilization, the indicator organism should be resistant to dry heat.

b) In the *inoculated carrier* method, heat-resistant spores are placed on an external carrier. It is necessary to establish that the thermal resistance of the carrier is equivalent to direct inoculation of the product site.

c) The *closure bioburden* itself can also be used to establish microbiological death rates and appropriate sterilization cycles.

During development of the sterilization cycle, it is important to ensure that areas of the closure system not in contact with the product have been sterilized or that the product material does not leak to contaminate the product. The most resistant area of the closure is subjected to biological challenges during the validation.

Closures and other initially dry portions of the product may transition from dry heat to moist heat conditions during sterilization as a result of being constructed from materials (e.g., polyvinylchloride plastics) that are highly permeable to moisture at elevated temperatures.

In order to discriminate between dry heat and moist heat conditions, it is necessary to a) use a challenge organism with significantly different dry heat and moist heat D values in initially dry areas, and b) perform a series of fractional exposure cycle trials and generate a survivor curve characterizing the rate of lethality with respect to time. A downward bend in the curve is indicative of a transition to moist heat conditions.

The results should confirm whether the initially dry areas remain under dry heat conditions throughout the cycle. If so, presterilization of closures may be necessary due to the otherwise extremely long sterilization cycle needed. Alternatively, if there is a transition to moist heat conditions during the cycle exposure time, the time delay in achieving effective moist heat sterilization in closure areas can be taken into account during the development of the cycle.

As in the case of the product, there are two recommended methods of developing sterilization cycles for closures: the overkill method and the bioburden method.

3.9.2 Overkill method

The overkill method is generally applied to closures that are sterilized separately from the final production container. As noted previously, this method is based on the concept that the sterilization process will inactivate the microbiological challenge with an additional safety factor. The challenge organisms generally used are not related to the natural product bioburden. If dry heat conditions may exist in the closure, an organism such as *B. subtilis* or *B. subtilus* var. *niger* is recommended.

The overkill method is difficult to use when closures are associated with containers. The microenvironment within many closure systems may not be a true moist heat environment as encountered within the solution. The resulting microbiological inactivation may lag behind the inactivation rate of the solution. Care must be taken to ensure that the cycle developed for the closure does not damage the product.

3.9.3 Bioburden method

The bioburden method requires the determination of the closure bioburden and correlation of the numbers and resistance of the bioburden to a biological indicator, thus enabling a cycle to be developed using a challenge population that exceeds the bioburden counts on the closure.

The minimum effective lethality will be derived from sterilization processes that ensure a SAL defined for the bioburden associated with the solution and the closure system. In closure challenge studies, the type of microbial challenge microorganism that is selected will often depend on the microenvironment present within the closure system (i.e., dry or moist heat).

If only a biological indicator is used for challenge purposes, it is necessary to determine and document the resistance of the biological indicator in relation to the closure bioburden. This is done by performing fractional cycles and then recovering and counting the surviving organisms; alternatively, a positive/negative analysis can be performed on the product. The biological indicator is then selected by multiplying the D value times the log of the product bioburden numbers plus the desired SAL. In this way, the minimum criteria for the resistance and population of the biological indicator can be established.

3.10 Product mapping (temperature profiles)

If the primary unit and package configuration to be sterilized may be nonuniformly heated (e.g., a liquid-filled vial, a complex medical device), appropriate studies are needed to determine the slowest-to-heat zone within the unit as well as the lowest temperature zone during exposure (see “Product temperature profiles” in section 4.3.2).

4 Validation

4.1 General

Sterilization process validation is a documented procedure for obtaining, recording, and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications. Validation provides evidence that the process renders the product sterile to a specified SAL and that the sterilization system (hardware and, if applicable, software) reliably and reproducibly delivers the designed process.

Validation consists of three main activities: commissioning (installation qualification or IQ), performance qualification (PQ), and certification (verification of process specifications). Validation follows a product and process assessment review and the development of the cycle (see section 3.7). After the formal validation program

has been completed, validation is maintained during routine moist heat sterilization through process monitoring, periodic revalidation, and a change control system (see section 5).

4.2 Commissioning

4.2.1 General

After selection of the sterilizer to be used for routine processing, validation begins with the commissioning of the equipment. Commissioning consists of a) documentation of the equipment; b) demonstration of compliance with design performance specification; c) demonstration of conformance of the quality and capacity of utilities; d) calibration of both operating and testing instrumentation; and e) when applicable, demonstration of efficacy of air removal.

4.2.2 Equipment documentation

The documentation needed to support validation includes

a) a basic complete explanation of the physical characteristics and function of the sterilizer and its ancillary equipment;

b) descriptions or definitions of the physical and operational characteristics of the equipment, which may be contained in a design specification, the original purchase order, or a vendor proposal;

c) schematics of pipework and instrumentation (i.e., process and instrumentation diagrams);

d) a list of other pertinent mechanical and electrical drawings and their locations;

e) a list of critical instruments and devices, particularly those used for process control, for which physical characteristics and performance claims of the manufacturers are kept on file (e.g., accuracy, repeatability, size, and model);

f) information about process control logic or software necessary to support validation, including a control system layout, control logic diagrams, and application software (computerized measurement and control systems) such as program listings, flow charts, ladder logic diagrams (where applicable), and strategy diagrams.

4.2.3 Compliance with design performance specifications

The installed equipment is inspected to ensure conformance to the intended design specifications, with any discrepancies documented and resolved. Drawings of or specifications for changes that could affect process conditions are updated to “as built” status at the time of qualification.

Testing is conducted to provide documented evidence that the sterilization system (hardware and, if applicable, software) performs according to the process specification. This testing, which is carried out on an empty chamber or with a representative or simulated load, verifies satisfactory operation before product is risked, establishes baseline data for future system evaluation, and demonstrates system capability under clearly defined conditions. It is important to test all cycles to be used in the sterilizer menu to assure proper control, function, and utility compatibility. In addition, selected alarm, failure-mode, and fail-safe functions should be evaluated. At least three empty-chamber or simulated-load runs should be performed.

Documenting adequate temperature control involves demonstrating that the control point temperature is maintained within specified limits over the longest specified exposure time. Repeatability and reliability are important for both temperature control and distribution. To demonstrate the required temperature uniformity of the intended process, temperature sensors can be placed throughout the chamber, outside the product units or containers. At least five temperature sensors per 100 cubic feet of usable chamber volume should be used.

The sterilizer control system, whether manual, semiautomatic, or automatic, has to be capable of carrying out the intended cycle and responding as specified. Documentation of cycle execution is necessary.

4.2.4 Quality and capacity of utilities

The quality and capacity of the air, steam, power, and water supplies are evaluated to ensure conformance with specifications, taking into account concurrent use of utilities by other process systems.

4.2.5 Calibration of test instrumentation

It is important that test instrumentation related to critical process parameters be calibrated before commissioning or performance qualification tests are initiated, and that calibration be verified at the conclusion of testing. Examples of instrumentation requiring calibration are temperature, time, and pressure controllers and recorders/monitors.

4.2.6 Air removal distribution

It is important to document, where applicable, the efficacy of air removal (e.g., rate, maximum vacuum attained). The adequacy of air removal or air distribution in steam/air sterilizers can be measured in temperature distribution studies where localized concentration of air results in a low temperature reading. This condition is most readily detected in the early phases of the process because the air reaches process temperature or is displaced in later phases.

NOTE—Product heat penetration studies can provide additional information for evaluating the uniformity of the process.

4.3 Performance qualification with product

4.3.1 General

Performance qualification, which is carried out after commissioning, includes

a) demonstration of process reproducibility (through the use of sufficient cycles);

b) demonstration of uniformity within specified limits throughout the chamber and load (through the use of sufficient cycles and sensors);

c) demonstration of the relationship between control and load parameters;

d) demonstration of the correlation of physical parameters with microbiological lethality by data taken from established literature or from original research;

e) demonstration that both maximum and minimum loading (or specified product mix) are compatible;

f) if simulated product loads are used, demonstration that the simulated product loads are representative of actual products;

g) demonstration that qualification loads that will be reused have returned to specified conditions before reuse;

h) demonstration that the product and packaging comply with their specifications after sterilization and, where applicable, resterilization.

NOTE—If physical parameters of the product (e.g., temperature or moisture) cannot be measured or cannot be related to microbial lethality, it is necessary to use a microbial challenge in performance qualification runs. On the other hand, if physical parameters measured in the product can be directly related to microbial lethality, then a microbial challenge may not be required. When sterilizing solutions, for example, data from time and temperature measurements and subsequent determination of F-Physical can be used to adequately describe solution lethality.

For performance qualification, it is customary to include a minimum of three consecutive successful qualification runs in which all acceptance criteria are met. Scheduled qualification runs that are not successfully completed because of an event unrelated to the performance of the equipment or the efficacy of the cycle (e.g., loss of utilities, mechanical failures, or inadvertent error) need not invalidate the series of consecutive runs. If, however, any run shows that sterility assurance or product function requirements cannot be met, or if process parameters cannot be maintained within limits, then additional qualification runs are required after corrections have been made. It is essential to carry out qualification runs with the maximum intended chamber load or with the product mix and loading that are determined to be most difficult to sterilize.

4.3.2 Product temperature profiles

If the primary product unit and package configuration to be sterilized may be nonuniformly heated (e.g., a liquid-filled vial, a complex medical device), appropriate studies are needed to determine the slowest-to-heat zone within the unit as well as the lowest temperature zone during exposure, if these studies were not previously conducted during cycle development. To develop the information necessary to validate the process, temperature sensors and, if applicable, biological indicators are placed so as to define the bottom, center, and top temperature zones. If there is concern about the contents of the container versus the closure area, another temperature sensor should be placed in the area of the closure inside the container. To understand the process, all temperature measurements should be correlated with the temperatures measured by a temperature sensor outside the container and by the chamber controller. If this is not possible, sites can be selected to correlate with the coldest location of the primary unit. It is important to document the relationship between the chamber controller and the slowest-to-heat zone in the product.

For liquid products, fill volume and container orientation are other considerations that must be addressed when defining the product profile.

4.3.3 Load temperature profiles

In loaded chamber studies, the uniformity of temperature throughout the product in the chamber is measured and evaluated. A sufficient number of runs and sensors are needed to determine the slowest-to-heat areas in the product and in the chamber (i.e., the “cold spots”). Sensors should be placed throughout the product load either in the slowest-to-heat zones or in areas within the load that have documented equivalency to these positions. The ultimate objective is to demonstrate that the distribution of temperature in the load is within the limits prescribed by the cycle specifications. It is important to know the relationship between the temperature in the “cold spots” and the temperature indicated by the sensor used to control the exposure temperature and time. It is customary to place this sensor in a location that will allow the temperature distribution within the sterilizing zone to be centered around the control point.

The nature of the load may also affect temperature distribution in the chamber. In nonporous loads, such as liquids in vials or ampules, heat penetration of the product may vary depending on such factors as the size,

loading pattern, and fill volume of the containers. Care must be taken during the product mapping portion of the study to understand the nature of the containers. Containers such as vials become miniature sterilization chambers, and heat transfer to the product is affected by the material and design. For bottles or tubes with rubber closures, cycles should be designed to address the area around and under the closures, because closures do not come to temperature as quickly as the product. If the product contents cannot tolerate the time needed for the closure to become sterilized, "wetting" the closures before they are inserted into the container openings may also create a mini-sterilization chamber and enhance the sterilization process.

For nonporous loads, it is important to use both chamber and product temperature sensors to ensure that all surfaces attain the sterilizing temperature (which depends on heat transfer, not steam penetration).

Loaded chamber studies are usually performed with maximum-sized loads. However, it may be necessary to perform additional tests with minimum loads or loads of various other sizes. Minimum loads may affect certain process conditions (e.g., effectiveness of air removal), so it is important to determine whether process conditions are comparable to larger loads. If the delivered process for the minimum and maximum loads is significantly different, it is important to qualify intermediate load configurations that vary by fraction of chamber volume or product density mix. The qualification testing needed is based on professional judgment and interpolation of data from maximum and minimum load volumes.

During the validation studies, adequate temperature sensors should be used to profile the chamber and product to demonstrate that the recommended temperature data are within the requirements of the process. At least 10 temperature sensors should be used for chambers having 100 cubic feet or more of usable load space, with an additional 5 temperature sensors used per additional 100 cubic feet of volume. For smaller chambers, it is recommended that at least 6 temperature sensors be used to profile the corner, center, and drain positions. If adequate temperature sensors are not available for the profile, one or two center data points can be selected and the other data points rotated to enable the sterilization specialist to analyze the data using common data points and to establish equivalency and the other monitoring points.

NOTE—For nonporous loads, 50% of the temperature sensors should be placed within the load and 50% outside the load.

4.3.4 Range of lethality

Product lethality calculations establish the range of lethality throughout the load. The need to determine a range of lethality depends on the specific product and cycle; for example, an overkill cycle used to sterilize a heat-stable component may require determination of minimum lethality only. If a range of lethality is required, it is necessary to record product temperature over the entire cycle. This information may serve as the basis for lethality calculations (F values) when used in combination with an assumed or experimental z value. For example, using a reference temperature of 121.1° C and a z value of 10° C, the temperature accumulation during the entire process can be converted to the equivalent lethality at 121.1° C. Thus, each min at 114° C has a lethal rate equivalent to 0.2 min at 121.1° C if z = 10° C. Many temperature monitoring devices have the software capability to calculate this information continuously during the cycle to establish the necessary criteria for the release parameters defined during cycle development.

4.3.5 Data analysis

The data analysis for the validation requires an accurate estimation of a process F value that is supported by cycle development data. It is necessary to confirm the process F-Physical value in microbiological studies in the product with the physical process data generated during the performance qualification runs and loaded profile studies. If these data are not available, three additional validation runs using the various product profiles and minimum/maximum load configurations are needed to generate the data.

NOTE—The process F value depends on the time interval of the calculation. F values should be calculated at the same intervals in routine production as in validation.

If the temperature and, when appropriate, relative humidity of the product cannot be measured or cannot be related to microbial lethality with an F-Physical, microbial challenges will be required to provide these data during performance qualification runs. If physical parameters can be measured and are directly related to microbial lethality, a microbial challenge may not be required and product may be released.

4.3.6 Product release

Validation loads may be released if the product release requirements have been met and the sterilization parameters are equivalent to those studied in the cycle development program. If, however, the product must be resterilized, it is important to evaluate the material to ensure that reprocessing has not affected product quality.

4.4 New product validation

If a new product is comparable to an existing product, the new product may be placed into a family grouping and sterilized with an existing qualified cycle. Where process uniformity between sterilizers has been demonstrated and documented, new products may be qualified in one sterilizer. Decisions about equivalency require a formal documented review involving professional judgment regarding sterilization requirements. See also annex A.

4.5 Individual batch release

If sufficient quantities of product are not available for a full qualification program, the product may be released after a thorough review of product and processing data from the sterilization run if the following conditions are met:

a) Cycle development data demonstrate that the product can be sterilized to the desired SAL using the cycle parameters selected.

b) The equipment being used has undergone installation qualification (IQ).

c) Microbiological challenges and process monitoring for each cycle are equivalent to a performance qualification run.

Additional qualification runs are completed when the necessary quantities of product are available.

4.6 Process equivalency

4.6.1 General

The equipment used to deliver a specific sterilization process commonly consists of a chamber and ancillary control systems. Several chambers may be located within a given processing facility or among several facilities. These chambers can be used independently to deliver the same process conditions and may be exactly the same or may differ in size and/or extent of ancillary equipment. Similar design criteria for all processing equipment and a demonstration through commissioning that specifications can be met in a reproducible manner are necessary to establish process equivalency between chambers.

4.6.2 Design criteria for chamber equivalency

The following design characteristics are elements of the sterilization system which are reviewed when comparing systems for process equivalency.

a) *Chamber volume and geometry*

- Volumes to be within ± 5%;
- Correlation between volume and usable space to be within ± 5%;
- Location and dimensions of chamber penetrations;
- Ancillary equipment and effects of utilities.

b) *Vacuum system (if used)*

- Location and size of chamber penetrations;
- Type, length, and size of vacuum line (e.g., valve size and material);
- Specification for vacuum pump (e.g., method of cooling, effects of moisture);
- Method of controlling vacuum rates.

c) *Steam/pressurized water*

- Location and size of steam/water penetrations;
- Type, length, and size of addition line (e.g., valve size and material);
- Specifications for steam generator or heat exchangers (e.g., dedicated, common; if common, effects of more than one chamber);
- Method of controlling pressurization rate.

d) *Air supply/gas inbleed*

- Location and size of chamber penetrations;
- Length and size of vapor line;
- Specifications for gas filter, if applicable (e.g., type, length, size, material);
- Gas supply source (e.g., dedicated, common, bulk).

e) *Chamber/recirculation system*

- Location and size of recirculation penetrations;
- Type, length, and size of recirculation piping (e.g., valve size and material);
- Specifications for recirculation equipment.

f) *Chamber/temperature control system*

- Location of monitoring and control probes;
- Recording and control instrument resolution.

4.6.3 Demonstration of process equivalency

The extent to which a process can be delivered in an equivalent manner, irrespective of equipment, depends upon the degree of variability associated with attaining the process specifications. With respect to the sterilization process, the ability to deliver a set of predetermined process parameters is qualified during commissioning (IQ). The impact of the process on the product is validated during the performance qualification (PQ). Process equivalency can be appropriately assessed during commissioning if process specifications and their respective tolerances are designed to incorporate the ranges (minimum and maximum) used during performance qualification and routine processing.

Establishment of a process equivalency program is consistent with the subparts of the Good Manufacturing Practices/Quality System (GMP/QS) regulations and the International Organization for Standardization (ISO) 9000 series that focus on preproduction quality assurance.

It is important that process equivalency studies be conducted by experienced personnel.

Before any process equivalency study is begun, every sterilizer must undergo a complete commissioning as required by ANSI/AAMI/ISO 11134. A commissioning study includes a minimum of three empty-chamber temperature distribution runs. It should be noted that for some moist heat sterilization processes (e.g., sterilization of solutions), it may be necessary to use a product load when evaluating chamber temperature distribution.

Upon completion of the commissioning study, the following principles can be applied when determining the necessary extent of performance qualification. (A "reduced performance qualification" consists of a portion of the full PQ and could consist of as little as a single one-half-exposure cycle.)

a) *Equivalent chambers in the same facility:* a complete performance qualification of one sterilizer and a reduced performance qualification of all other equivalent sterilizers.

b) *Equivalent chambers in different facilities:* a complete PQ of one sterilizer in each facility and a reduced PQ of all other equivalent sterilizers.

c) *Chambers delivering the same process in the same facility:* a complete PQ of each different chamber and a reduced PQ of remaining sterilizers having equivalent chambers.

d) *Chambers delivering the same process at different facilities:* a complete PQ of each different chamber in each facility and a reduced PQ of remaining sterilizers having equivalent chambers.

See annex C for an example of a statistical determination of equivalency.

4.6.4 Annual revalidation

Each sterilizer should be included in the annual revalidation program. Each sterilizer should be evaluated for performance since the last validation. If this evaluation demonstrates that all equivalent sterilizers are still operating as validated, the following plan can be used with respect to process equivalency:

a) *Equivalent chambers in the same facility:* at least one fractional cycle in one of the equivalent sterilizers. A different sterilizer should be chosen each year.

b) *Equivalent chambers in different facilities:* at least one fractional cycle in one of the equivalent sterilizers in each facility. A different sterilizer should be chosen each year.

c) *Chambers delivering the same process in the same facility:* at least one fractional cycle in each sterilizer configuration. If more than one sterilizer has the same configuration, a different sterilizer should be chosen each year.

d) C*hambers delivering the same process at different facilities:* at least one fractional cycle in each sterilizer configuration at each facility. If more than one sterilizer has the same configuration, a different sterilizer should be chosen each year.

5 Routine processing

5.1 General

Upon completion of cycle development studies and the validation program, it is necessary to specify the sterilization facilities, equipment, and procedures needed to ensure product sterility and efficacy. This section covers utilities, process control, change control, revalidation, preventive maintenance procedures, and safety issues.

5.2 Utilities

5.2.1 Steam

Steam may be supplied from dedicated boilers (including clean steam generation) or from plant-wide steam distribution systems. The steam quality and purity required depend upon the product/packaging configuration, particularly if permeable packaging is used and the steam directly contacts the product.

The attributes of steam used in moist heat sterilization include chemical purity, saturation, temperature (superheating), quality (percent dry steam), presence of noncondensable gases, and microbiological purity.
Chemical purity depends upon the quality of the water used to make the steam and the boiler additives used in the steam system. The common chemical contaminates in water are chlorine and the minerals that cause natural hardness. Boiler additives vary and are used to prevent foaming, corrosion, and scaling. While there is no approval process for boiler water additives intended for use in steam sterilization, the lists in 21 CFR 173.310 and 21 CFR 100.11, developed for food contact, are generally considered applicable. The chemical purity of steam is of primary concern when direct contact with product is involved (i.e., permeable packaging).

Clean steam generators produce USP Water for Injection (WFI) quality steam and are frequently used for sterilization of packaged pharmaceutical products.

The physical attributes of steam (saturation, superheat, and so forth) affect microbiological kill, heat transfer, and wetting of product. In all cases, these are of greater concern if permeable packaging is used.

"Saturation" is the condition in which the steam pressure corresponds to the saturation temperature, e.g., 250° F (121.1° C) at 29.8 pounds per square inch absolute (psia) or 202.6 kiloPascals (kPa). Steam at saturation is the most desirable condition because it maximizes heat transfer, minimizes product water damage, and results in the most effective moist heat microbial kill.

NOTE—For purposes of accuracy and clarity, absolute pressure is used in this document. Absolute pressure, whether expressed as psia or kPa, assumes a reading of zero at absolute vacuum. Most sterilizer monitoring and recording devices indicate gauge pressure (psig). Gauge pressure is based on ambient atmospheric pressure, which decreases with altitude and varies with weather conditions (barometric pressure changes). Thus, gauge pressure is a reliable reference point only if both location and weather are known. In general, psig must be increased 0.05 psi for every 100 feet of elevation above sea level to reach the same psia.

The *presence of noncondensable gases* is evidenced by actual pressures higher than the expected pressures associated with steam at specific saturation temperatures, e.g., 250° F (121.1° C) at 35 psia (240 kPa). Examples of noncondensable gases include air trapped in the system during startup and chlorine from the use of nontreated chlorinated city water for making steam. Noncondensable gases can present a problem if the process is pressure-controlled.

Superheat is evidenced by temperatures higher than that of saturation at the saturation pressure, e.g., 260° F (126.7° C) at 29.8 psia (202.6 kPa). As with noncondensable gases, this situation can result in temperature-control problems if the process is pressure-controlled. Also, in processes where steam is in direct contact with the items to be sterilized, superheat can reduce microbiological effectiveness. This occurs because dry heat sterilization conditions begin to take effect. Superheat occurs in a plant-wide steam system and is the result of significant reductions of line pressure due to heavy steam usage. Superheat less than 5° F (2.8° C) is not usually a significant problem.

Steam of poor *quality* is steam which contains liquid water. This condition cannot be detected from steam temperature and pressure. The presence of water in the steam can damage absorbent packaging and can cause stains on impermeable packages. Steam traps, liquid separators, and coalescing filters can correct this problem.

The *microbiological purity* of steam is generally not a problem except for the rare possibility of high concentrations of pyrogenic material resulting from gram-negative organisms in the system. This would tend to be more of a concern in lower-pressure steam systems which are used intermittently.

5.2.2 Water

In water-spray, submerged-water, and water-cooling processes, water quality is as great a concern as steam quality. By their nature, these types of processes are used only for sterilizing nonpermeable packaging. Water may penetrate some closure systems due to different expansion and contraction values of the closure system versus the container. Also, USP WFI quality water is often used for pharmaceutical containers to avoid the need for a separate final rinse.
Water used in these types of systems is therefore chemically and microbiologically treated to achieve the required quality. This water is then maintained in a closed recirculation system. In-line treatment is also often used to remove contamination washed off in the sterilization load. The use of deionizers, filters, and so forth to treat recirculation water can be a microbiological concern and requires careful monitoring.

5.3 Process control

5.3.1 Control and recording systems

The control system for production sterilizers reproduces the parameters developed and validated for the specific product. All process parameters used for release of the product are continuously recorded. Sufficient redundancy and/or sensor failure detectors are necessary to ensure accurate measurement and recording.

The level of automation used to control moist heat processes varies widely. It is essential that all control systems be validated and that locking-out devices or administrative systems be in place to prevent unauthorized changes to process set points and to ensure selection of the correct cycle. It is also important to establish systems to ensure correct loading of the sterilizer as per validation.

5.3.2 Microbiological testing

Microbiological challenge: If used, the microbiological challenge for routine monitoring should be consistent with the microbiological testing previously conducted during cycle development and validation studies. The number of routine biological indicators used is typically less than that used for validation. A minimum of 10 biological indicators is customary for chambers at least 100 cubic feet in volume; fewer biological indicators may be adequate for smaller chambers. Guidance on biological indicators can be found in AAMI (1991).

NOTE—If appropriate quality systems are in place, parametric release is preferable to the routine use of a microbiological challenge.

Bioburden monitoring: The frequency with which products are sampled for bioburden is determined based on anticipated, historical, seasonal, or manufacturing variations. Monthly or quarterly sampling is typical. Guidance on test methods can be found in ISO 11737-1. Where family categories have been established, one member of each family is selected. Alert and action limits are established based on the number and resistance of bioburden used during cycle development and validation. Two standard deviations above the mean are typically used as the alert level, and three standard deviations are used as the action level.

Bioburden data should be examined as generated, and trends or significant increases should be reviewed. Increased numbers or changes in types of organisms, which could adversely affect the effectiveness of the sterilization process, should trigger an investigation. Significant changes in types of bioburden organisms, particularly increases in spore formers, may require resistance studies.

5.4 Release of sterilized products

Where reliable process measurement and control can be documented for the entire manufacturing process and correlated with sterility assurance, terminally sterilized items can be considered for release in accordance with delivered process parameters. Additionally, the data from all microbial challenges, if used, must be acceptable. Compliance with ANSI/AAMI/ISO 11134 in its entirety allows for parametric release.

5.5 Change control

It is important to establish a change control system to ensure that personnel experienced in sterilization are involved in the review and approval of all changes which could affect sterilization (see ANSI/AAMI/ISO 11134, section A8.2). The extent of revalidation should be determined and documented even if no action is required.
Key components of the sterilization system which could affect process parameters include pressure regulators, control valves, recirculation fans, pumps or blowers, software, and all process monitoring devices. Changes to these critical components require some level of revalidation. To this end, maintenance personnel should be fully involved in change control procedures.

5.6 Product revalidation

Periodic revalidation is typically conducted at 12-month intervals and includes the following:

a) Review of the sterilization records since the last validation/revalidation to determine frequency and resolution of process deviations, cycle failures, and so forth.

b) Review of maintenance records (particularly unscheduled maintenance, repeat problems, and resolutions) and confirmation of preventive maintenance intervals.

c) Review of calibration records, adjustment for trends, and verification of calibration intervals.

d) Review of calibration and preventive maintenance history to determine if intervals can be increased.

The portion of the validation typically repeated during periodic revalidation is one of the microbiological cycles, which allows microbiological lethality and process control to be reaffirmed. Confirmation of bioburden resistance may also be performed within a production or R&D vessel.

5.7 Preventive maintenance

Preventive maintenance procedures and intervals are established before routine sterilization is begun. Preventive maintenance typically includes daily maintenance (often performed by the operator), monthly or quarterly maintenance, and annual maintenance.

Daily maintenance is usually limited to cleaning and safety checks. Other items on preventive maintenance lists include (but are not limited to)

a) steam traps;
b) filters (e.g., steam, air);
c) door gaskets;
d) shaft seals;
e) boiler blow down;

f) water treatment equipment;

g) pumps.

Maintenance intervals are established based upon manufacturers' recommendations and history. It is customary to maintain a log book at each sterilizer to record all maintenance activity. It is important to coordinate maintenance activities with change control to ensure review of all component changes or adjustments to maintain a validated system.

5.8 Safety

Hazards associated with moist heat sterilizers include heat, pressure, electrical shock, moving machinery, and confined space entry. Before routine sterilization operations are begun, all equipment should be inspected for

a) insulation of hot surfaces to protect personnel from burns;

b) presence of guards on all moving or rotating machinery;

c) enclosure of all electrical connections to prevent personnel contact or water/steam contact (per local electrical code);

d) presence of appropriate warning signs.

Lock-out, tag-out, and venting procedures should be developed to ensure that all potential hazards have been rendered safe before repair or maintenance is performed and/or to ensure that all hazards are under the complete control of the personnel performing the repair or maintenance.

In conjunction with the lock-out/tag-out systems, confined entry procedures should be developed to ensure safe entry into confined spaces (e.g., the sterilizer chamber). Hazards associated with confined entry include exposure to steam or hot water and asphyxiation. A "buddy" system is recommended for these entries.

Safe operation during off-shifts or weekends may require a minimum of two personnel.

Safety training should be provided to all personnel involved with the sterilizer, including maintenance, engineering, and quality assurance personnel.

Sterilization of sealed glass containers presents a particular hazard. Unless adequately cooled, such containers, which are under internal pressure, can explode if shocked. The sterilization process should provide adequate cooling of such containers before they are removed from the chamber (see IEC 1010-2-041).

Annex A

Product equivalency

A.1 Introduction

General data previously obtained by product family cycle development and validation can be extrapolated and interpolated for equivalent products in order to validate their routine processing. Manufacturers produce new products in low volumes. These new products may be single-batch custom products, clinical trial samples, new components for custom packs/trays, or products slightly changed from previously validated products or source products from other manufacturers. Such products may be integrated into an existing validated product family through an analysis of product equivalency by personnel experienced in sterilization cycle development and validation.

A.2 Certification of the validated process

It is first necessary to verify that all required documentation is in place to assure that the validation of the sterilization process meets current Good Manufacturing Practice/Quality System (GMP/QS) regulations and internal standard operating procedures (SOPs).

A.3 Product design evaluation

The following sections describe product and package considerations applicable to a modified/new product or component being evaluated for adoption into a validated moist heat sterilization process.

A.3.1 Criteria for establishing product families

The following criteria are used to establish product families:

a) *Material composition*

- Natural fibers vs. synthetic fibers
- Plastics vs. metals
- Variation in bioburden population and type
- Differences in moisture absorption
- Surface reaction to the sterilant
- Effects of the manufacturing process on the resistance of the bioburden population to moist heat sterilization
- Temperature limits
- Sensitivity to resterilization

b) *Product design*

- Simple surface sterilization
- Capillary channels
- Restricted passageways
- Long tubing
- Vented caps
- Mated surfaces
- Long, extensive tubing networks
- Fluid pathway sterility requirements
- Sensitivity to pressure, moisture, and temperature changes

c) *Manufacturing process*

- Wet process
- Dry process
- Clean room manufacturing/assembly
- Plastic molding
- Cleaning process for components
- Manufacturing additives
- Storage conditions
- Change in country of origin

d) *Intended use (sterility assurance level, biocompatibility)*

- Implantable device
- Topical application
- Wound application
- Blood contact/invasive device
- Neural contact device
- Ocular device
- Nonpatient-contact device

e) *Primary package system design*

- Paper/paper pouch
- Paper/plastic pouch
- Plastic pouch
- Header/bag pouch
- Tray system
- Permeable/nonpermeable wrap
- Glass bottle, vial, ampule

NOTE—The above criteria for establishing product families are not all-inclusive.

A.3.2 Product design changes

Product design changes that may affect transfer of moisture and heat include

a) use of nonvented caps/fitments on open ports;

b) changes in thickness, density, or hardness of tubing;

c) use of mated surfaces as contact points;

d) use of impermeable materials placed in regions that affect the entry and removal of steam;

e) changes in restricted passages.

NOTE—The above list is not all-inclusive. It is important that a new product be fully evaluated.

A.3.3 Evaluation of primary package system

Aspects of the primary package system that may affect the moist heat sterilization process include

a) changes in the size, porosity, or other characteristics of the venting material;

b) use of nonpermeable wraps;

c) change to a double primary package;

d) placement of secondary labels;

e) placement of protective, closed-cell foam materials;

f) placement of impermeable protective plastic sheets;

g) arrangement of individual packages in the shipping carton;

h) changes in container wall thickness.

NOTE—The above list is not all-inclusive. It is important that changes in the primary package be fully evaluated.

A.3.4 Evaluation of the secondary/tertiary package system

Aspects of the secondary/tertiary package system that may affect the moist heat sterilization process include

a) the addition of a nonvented case polyliner;

b) change to a double casing;

c) changes to the density, thickness, or type of case material;

d) the addition of thick, moisture-barrier, insulation-type protective materials;

e) rearrangement of product in cases so that breather ports mate with nonbreathable package surfaces.

A.4 Adoption of a product into a validated sterilization process

The following evaluations should be performed to adopt a product into a validated sterilization process:

a) Compare the new product to the old product, a similar approved product, or a master product.

b) Compare the primary package system to the current approved system.

c) Analyze the type, population, and resistance of the bioburden.

d) For new/modified products that are not clearly equivalent to current products, evaluate their sterilizability against the process challenge device:

    1) Equivalency studies may be conducted in a pilot vessel.

    2) Test systems may include inoculated product, product with inoculated carriers, and natural product (natural bioburden) vs. the process challenge device.

    3) If the resistance of the new/modified product to the sterilization process is equal to or less than that of the process challenge device, the products are equivalent.

4) Test for resterilization if a change to a new material has occurred.

A.5 Equivalency studies to be conducted on production loads

A.5.1 It is customary to conduct product load equivalency studies if there are significant differences in the secondary packaging, load configuration, or load density (> 20%) that may have an effect on the temperature distribution or on moisture penetration and desorption. Equivalency studies include

a) load temperature distribution and rate of increase of load temperature;

b) analysis of the delivered lethality to the difficult-to-sterilize zone(s) of the new/modified product vs. the master product;

c) product sterility testing, using fractional exposure cycles, on the new/modified product to assure that the natural bioburden is sterilized to the appropriate SAL. Situations in which product sterility testing is required include

1) qualification of a new/modified product into a bioburden-based process;

2) sourcing of a new/modified device from a new supplier;

3) sourcing of a natural material from a new country;

4) significant differences in bioburden population/type for the new/modified product vs. the original product.

A.5.2 Equivalency analysis of a production load may be limited to a single run for each sterilization process if the study data clearly demonstrate that the changes in primary packaging, secondary packaging, or load geometry do not significantly affect temperature and moisture penetration throughout the load. Factors dictating that more than one equivalency run is needed include

a) differences in temperature penetration in the new load vs. the master load during heat-up and dwell time;

b) lack of equivalency between the various chambers.

A.6 Documentation

It is important to document the rationale for adopting a new/modified product into a validated sterilization process. All equivalency studies should be conducted according to a protocol. A report containing test results, conclusions, and recommendations should be reviewed and approved by individuals experienced in sterilization and product design. The raw data should be maintained on file for the life of the product.

Annex B

Sterilization cycles

B.1 Introduction

As described in section 3, there are two general types of industrial moist heat sterilization processes in common use: saturated steam (vented systems or forced air removal) and air pressurization (air-steam mixtures, water spray, or water immersion). This annex discusses important elements of cycle operation for each of these processes.

B.2 Control and recording systems

B.2.1 Control systems

For all types of moist heat sterilization cycles, one or more of the following process parameters are controlled: pressure, temperature, time, and/or rate of change of temperature and pressure.

Chamber pressure is controlled directly in certain cycles, including those with forced air removal and air overpressure. In saturated steam vented systems, however, the controlled chamber temperature correlates with the indicated chamber pressure.

The chamber temperature must be sensed with an accurate, responsive thermal sensor located in a position with a known relationship to the chamber temperature profile. Resistance temperature detectors (RTDs) or thermocouple sensor signals are generally accepted. The sensor signal is transmitted to a controller, which provides an output signal to the steam control valve. The temperature control system must be capable of maintaining temperature in a specified range appropriate for the particular process.

B.2.2 Recording systems

An automatic measurement and recording system should store analog or digital data on paper or magnetic media. This system may be used with manually recorded data to document the following process parameters and events, where applicable for the particular process:

a) date;

b) sterilizer identification;

c) load identification;

d) operator identification;

e) cycle start time (real time);

f) initiation of steam charging;

g) chamber pressure;

h) chamber temperature;

i) exposure start time;

j) exposure end time;

k) cooling time, final temperature, or both.

B.3 Saturated steam processes

B.3.1 Vented systems

B.3.1.1 Phases of the process

This sterilization process is used for products that can tolerate process temperatures at saturated steam pressure and that allow effective air removal and steam contact with the product. An example of a chamber temperature and pressure profile for a vented, saturated steam cycle is given in figure B.1. The process consists of three major phases:

a) *Heating:* After the chamber is loaded with carriers of product, the door is closed and secured. With the vent open, saturated steam is admitted or generated in the chamber until the desired conditions are met—normally determined by the measurement of temperature. The vent then closes and saturated steam continues to be admitted or generated in the chamber until the exposure temperature and corresponding saturated steam pressure are attained.

b) *Exposure:* The sterilizing temperature is maintained in the chamber by saturated steam for the prescribed exposure time.

c) *Cooling:* This phase may differ for various types of product loads. Filtered, compressed air may be introduced to control chamber pressure and prevent rapid depressurization. Solutions in sealed containers may be cooled at a controlled rate by spraying water directly on the product. This phase is completed when the pressure in the chamber is at atmosphere and, also, in the case of sealed containers, when a safe temperature is reached.

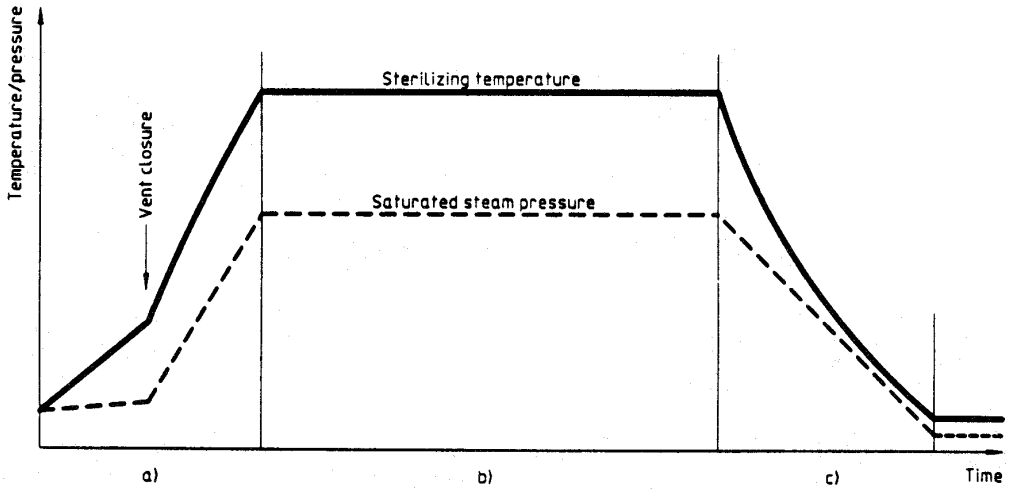

Figure B.1—Example of saturated steam sterilization cycle—vented system

B.3.1.2 Steam introduction

Steam is introduced to the chamber at a location distal to the vent ports and displaces the air entrapped in the chamber and product load. Steam spreaders or multiple ports may be used to ensure that steam is properly distributed for either downward or upward displacement of air. The steam supply pressure is regulated to provide

controlled pressure to the control valve. The design of the steam supply and control system must be appropriate for attaining a saturated steam atmosphere, the process temperature, and the desired chamber temperature uniformity. Steam input is controlled by chamber temperature.

B.3.1.3 Venting of air

The location and size of the vent ports must ensure the desired elimination of air from the chamber. It is important that vents be designed for adequate flow from all locations. Criteria for vent closure are determined experimentally to ensure that the required degree of air removal is achieved. One practice is to close the vent when a particular temperature is attained (the saturation temperature corresponding to the equilibrium vapor pressure occurring during venting). Alternatively, vent closure may be controlled based on elapsed time from the initial introduction of steam, or on a combination of vent line temperature and elapsed time.

B.3.1.4 Condensate control and removal

There must be a means to control or eliminate from the chamber the condensate that is produced as the steam transfers heat to the product load and chamber. The accumulation of condensate in the chamber, to the point where it comes into contact with the product, will significantly affect heating and may compromise product integrity. Condensate may be eliminated through a trap if the sterilizer is not designed to retain water for internal spray cooling. The water level may also be controlled by means of level sensors that operate a drain valve. The sterilizer may have a high-water-level alarm, which will be activated before water reaches the product. Sterilizers designed to retain water must incorporate a means of ensuring that the water level remains within the designated range.

B.3.1.5 Temperature control

See B.2.1.

B.3.1.6 Pressure control during cooling

Sterilizers designed to cool the load by means other than radiation heat loss or evaporative cooling usually provide for chamber pressurization with compressed air upon completion of the exposure phase. Product and package characteristics will dictate the chamber pressure requirements. Pressure regulation is generally used to provide a controlled air supply pressure. A proportional or on/off control valve may be used to control chamber pressure. When a proportional control valve is used, a secondary automatic shut-off valve should be used in conjunction with it to prevent any air leakage before cooling.

B.3.1.7 Cooling system

B.3.1.7.1 General

If product and package permit, the sterilizer may be equipped to provide for rapid product cooling. Chilled air or water may be circulated and sprayed on the product, if appropriate. In general, after the exposure phase, the coolant is introduced while the chamber pressure is maintained. It is important that the system be designed and controlled to prevent a rapid pressure loss due to steam collapse, which could stress the product or its packaging. The cooling system design and capacity must be appropriate for the type and mass of product to be cooled and must maintain the integrity of both process and product.

B.3.1.7.2 Air cooling

Air cooling systems may use air chilled by circulation through a cooling coil. The chamber circulation system continues to operate to circulate the cooling air. Chamber overpressure is maintained for the predetermined cooling time, after which the chamber pressure is reduced to atmospheric pressure.

B.3.1.7.3 Water spray cooling

Two types of water spray systems are commonly used: once-through systems and recirculating water loop systems. A once-through water spray system may consist of a pressurized water source or a water supply with a pump, a water shut-off valve, and an appropriate spray header system. The shut-off valve prevents leakage during the exposure phase of the process.

A recirculating water loop system may consist of a condensate/water level control system, a recirculation pump protected by an appropriate strainer, a means of reducing the recirculating water temperature, and an appropriate spray header system. The control valve prevents leakage during the exposure phase of the process.

Spray headers, pumps, and recirculating piping should be designed to minimize retention of water and microbial growth when the system is not in use.

B.3.1.8 Control and recording system

General considerations are described in B.2.2. In addition, it is necessary to control, measure, and record vent close temperature, pressure, and time, if applicable. The chamber temperature during the exposure phase should be sufficiently controlled to satisfy requirements established during process development. Chamber pressure during exposure will depend on the saturated steam pressure. During cooling, the chamber pressure should be sufficiently controlled to maintain specified process conditions and product integrity.

B.3.2 Forced-air-removal systems

B.3.2.1 Phases of the process

This process is intended to sterilize products consisting of porous materials and/or items having cavities where air is difficult to remove. An example of a chamber temperature and pressure profile is given in figure B.2. The saturated steam process in a forced-air-removal system consists of six major phases:

a) *Air removal/conditioning:* After the chamber is loaded with carriers of product, the door is closed and secured. Air is dynamically removed from the chamber and load by either a deep vacuum, a number of vacuum pulses, or a combination of vacuum and steam pulses.

b) *Charge:* Saturated steam enters the chamber until the sterilization temperature and pressure are attained.

c) *Exposure:* The sterilizing temperature and pressure are maintained in the chamber by saturated steam for the specified exposure time.

d) *Exhaust:* Steam is exhausted from the chamber and a vacuum may be drawn to a predetermined level.

e) *Drying:* For products that are required to be dry, the temperature in the jacket and the vacuum in the chamber are maintained for a predetermined period.

f) *Vacuum relief:* Air is admitted to the chamber through a microbiologically retentive filter until atmospheric pressure is reached.

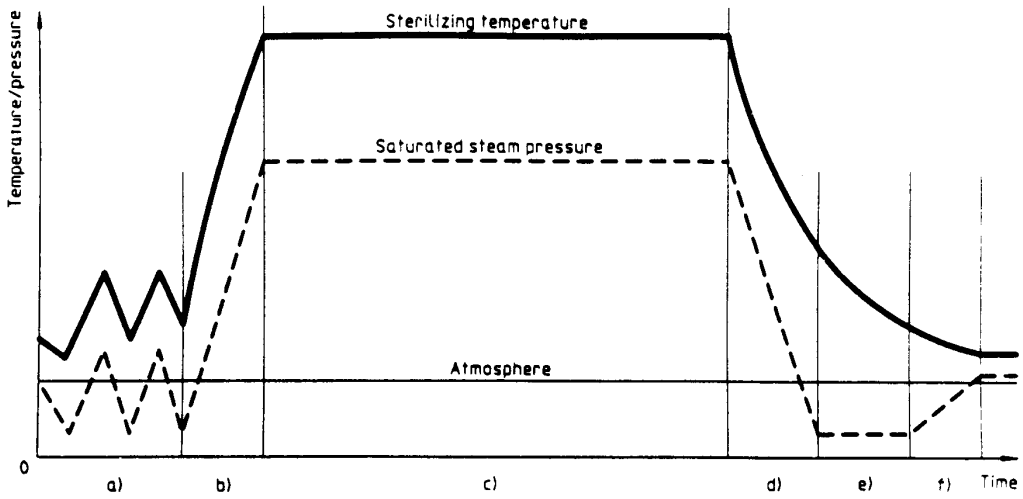

Figure B.2—Example of saturated steam sterilization cycle—with forced-air-removal system

B.3.2.2 Air removal

Air is extracted from the chamber and product load by a combination of dilution with steam and evacuation. The pressure and vacuum levels and the number of pulses depend on the product and load: therefore, their values must be determined experimentally. The chamber may be evacuated by equipment such as a mechanical water ring vacuum pump; a steam-, air-, or water-powered ejector; or a combination of a pump and an ejector. The rate of evacuation efficiency may be increased by installing a condenser upstream from the vacuum pump, ejector, or combination. The combination of an ejector and mechanical pump is often used for deep vacuum systems to create an ultimate vacuum greater (deeper) than 50 millimeters mercury (mmHg) absolute (also expressed as 2 inches Hg absolute, 6.77 kPa absolute, or 28 inches Hg vacuum).

B.3.2.3 Charge (steam introduction)

Steam is introduced to the chamber to facilitate air removal from the chamber through the vacuum system. Steam spreaders or multiple ports may be used to ensure that steam is properly distributed for either downward or upward displacement of air. The steam supply pressure should be regulated to provide a controlled pressure to the control valve. The design of the steam supply and control system needs to be appropriate to enable attainment of a saturated steam atmosphere, the process temperature, and the desired chamber temperature uniformity. Steam input is controlled by chamber temperature.

B.3.2.4 Condensate control and removal

It is important that the chamber design assure that the condensate which contacts the load is that formed by heating the load itself. This is usually accomplished by heating a steam jacket above the dew point of the sterilizing media, which minimizes condensate formation on the chamber walls. Condensate that does form on internal chamber surfaces drains directly to the bottom and is then discharged from the chamber by some appropriate means, such as a steam trap, level control, or constant bleed. Any remaining condensate will vaporize during vacuum pulses, which may limit the effectiveness of the vacuum system in reducing the chamber pressure to the desired depth of vacuum. A valve prevents air from entering the chamber during vacuum pulses.

B.3.2.5 Temperature control

See B.2.1.

B.3.2.6 Product load drying

When product considerations dictate, the load may be dried using vacuum or air by

a) maintaining jacket temperature to provide radiation heating while drawing a vacuum. (The chamber depressurization rate may have to be controlled to avoid product damage. The basic process variables used to control drying are the depth of vacuum and the drying time.)

b) passing dried and/or heated, filtered compressed air through the chamber while maintaining jacket temperature.

c) drawing filtered air through the chamber via the vacuum pump.

B.3.2.7 Control and recording systems

General considerations are described in B.2.2. In addition, it is necessary to control and document the following parameters for this cycle: number of prevacuum pulses, chamber pressure, and vacuum level for conditioning. The chamber temperature during the exposure phase should be sufficiently controlled to satisfy the requirements established during process development. Chamber pressure during exposure will depend on the saturated steam pressure. Evacuation rates and pressures should be sufficiently controlled to maintain the integrity of both process and product.

B.4 Air pressurization processes

B.4.1 Air/steam mixtures

B.4.1.1 Phases of the process

Moist heat sterilization processes using air/steam mixtures consist of three major phases (figure B.3):

a) *Heating:* The first part of this phase is the same as for the vented system except that where product integrity can be affected by rising steam pressure, venting is precluded. Steam continues to enter the chamber until the prescribed sterilizing temperature is attained. When products require overpressure during this phase and when the partial pressure caused by the entrapped air is insufficient, compressed air is introduced. Circulation is normally required to maintain a uniform environment.

b) *Exposure:* The sterilizing temperature is maintained in the chamber by saturated steam and, where overpressure is required, compressed air is also to be used.

c) *Cooling:* Product cooling can be accomplished with cooled, compressed air or with water spray. To maintain product integrity, rapid depressurization is prevented by maintaining the required chamber pressure with compressed air. The pressure is maintained until the product has been sufficiently cooled, and the decompressed air is then vented to atmosphere.

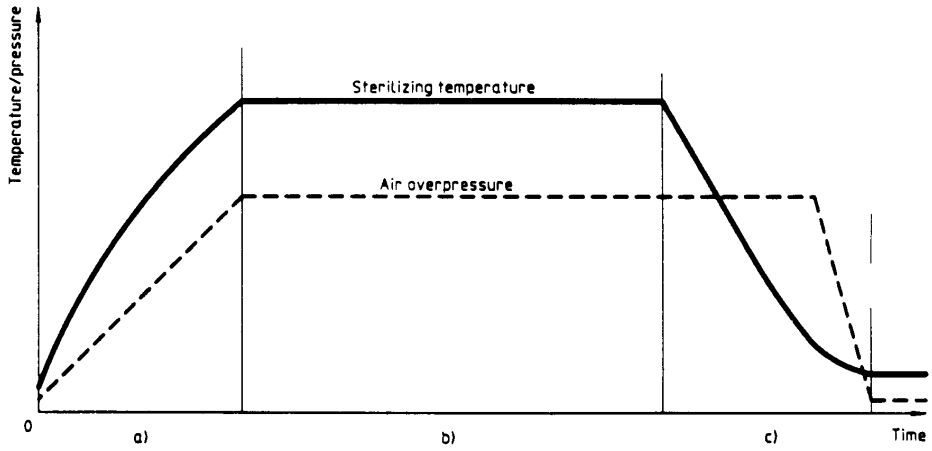

Figure B.3—Example of air-pressurization cycle—air-steam mixture system

B.4.1.2 Steam/air introduction

The means of introducing steam and air are critical to system performance in both the initial overpressure and the delayed overpressure methods.

The chamber circulation must be maintained during air overpressure, and a signal must be provided to alert the operator if circulation stops. The steam/air mixture can be introduced to the chamber through spreaders or multiple ports. It is necessary to regulate the steam and air supplies in order to provide controlled valves. It is
important that the design of the supply and control systems allow for attainment of a uniform process temperature and chamber temperature.

a) *Initial overpressure.* If the product requires the development of overpressure while the chamber temperature is initially rising, the chamber is not vented. As steam is admitted, entrapped air is heated and the chamber pressure increases with the rise in temperature. The steam/air mixing system should operate as soon as steam is introduced at the start of the cycle. Additional overpressure may be provided during heat-up and/or exposure to satisfy product requirements.

   The introduction of filtered, compressed air depends on chamber pressure. The steam and air supply pressures should be regulated to provide controlled pressure to the steam and air control valves. Steam input is based on chamber temperature. Steam and air may be directed into a mixing system or may be distributed using a spreader or multiple ports. It is important that the design of the supply and control systems allow attainment of the process temperature and pressure and the desired chamber temperature and heat transfer uniformity.

b) *Delayed overpressure.* For some products, it may be desirable to initially vent trapped chamber air to accomplish heat transfer until the product approaches the temperature at which additional pressure is necessary to maintain product integrity. In this instance, circulation should be delayed until after the vent is closed and may be delayed until the initiation of overpressure. Steam is introduced at a location distal to the vent ports. Steam spreaders or multiple ports may be used to ensure that steam is properly distributed for either downward or upward displacement of air. The steam supply pressure should be regulated to provide a controlled pressure to the control valve. The design of the steam supply and control system must enable attainment of a saturated steam atmosphere, the process temperature, and the desired uniformity of chamber temperature. Steam input is controlled by chamber temperature.

The vents must be located appropriately and their size must be sufficient to ensure the desired elimination of air from the chamber. Vents must be designed for an adequate flow from all locations. Criteria for vent closure should be determined experimentally and should ensure that the required degree of air removal is achieved. One practice is to close the vent when a particular temperature is attained (the saturation temperature corresponding to the equilibrium vapor pressure occurring during venting); another practice is based on elapsed time from the initial introduction of steam.

At a predetermined temperature or after a predetermined time, the circulation system is started and overpressure is gradually introduced. Chamber pressure controls the addition of filtered, compressed air. The rate of addition maintains the desired chamber temperature uniformity.

B.4.1.3 Equipment to control uniformity of the air-steam mixture

Because of the different densities of steam and air as well as the radically different heat transfer capabilities of condensing steam and air, it is essential to ensure a uniform mixture of steam and air throughout the chamber. Flow and turbulence must also be adequate throughout the product zone to ensure that sufficient thermal energy is transferred to all of the product units. An alarm should alert operating personnel to failures that may affect performance (e.g., out-of-tolerance rotational speed of fans or blowers). Fans, blowers, or other mechanical devices, with or without shrouds or baffles, may be employed. Eductors may also be used to induce circulation.

B.4.1.4 Condensate control and removal

See B.3.1.4.

B.4.1.5 Temperature control

See B.2.1.

B.4.1.6 Pressure control

Pressure control must be independent of temperature control. Product considerations discussed in section 3.2 of the main text will provide guidance in determining the process overpressure requirements. Filtered, compressed air provides chamber overpressure. The compressed air supply pressure is regulated to provide a controlled air supply pressure. A proportional or on/off control valve may be used. Provision must be made for controlling and recording pressure.

B.4.1.7 Cooling system

See B.3.1.7.

B.4.1.8 Control and recording system

General considerations are described in B.2.2. In addition, it is necessary to control and document the following events: vent close pressure, temperature, or time, as applicable; circulation system operation; and overpressure start time. The chamber temperature during the exposure phase should be sufficiently controlled to satisfy requirements established during the process development. Chamber pressure should be sufficiently controlled to maintain process and product integrity.

B.4.2 Water spray

B.4.2.1 Phases of the process

Depending on the design of the process, the sterilizing medium is heated to the sterilization process temperature by steam and/or pressurized water spray. The process consists of four major phases (figure B.4):

1) *Fill:* At the beginning of the cycle, a quantity of water is introduced into the sterilizer system or produced as condensate from the steam. The water is then sprayed over the product.

2) *Heating:* Heating to the required sterilizing temperature is achieved either by introducing air and steam into the circulating system or by heating the water through a heat exchanger and introducing compressed air into the chamber.

3) *Exposure:* The circulating system is operated and the water is maintained at the required sterilizing temperature for the desired time.

4) *Cooling:* The pressure in the chamber is maintained by compressed air and the product is cooled by reducing the temperature of the circulating water at a controlled rate. The chamber is depressurized when the product has cooled to a safe temperature.

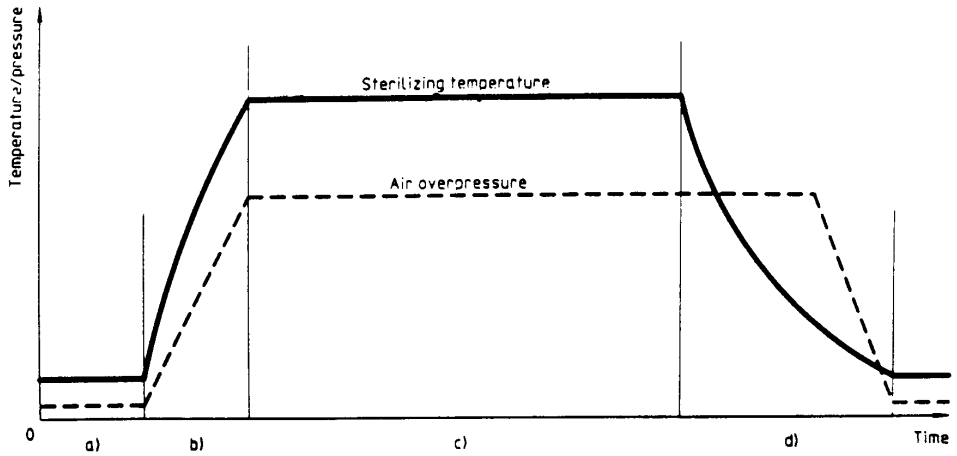

Figure B.4— Example of air-pressurization cycle—water-spray system

B.4.2.2 Steam/air introduction

Steam and air may be introduced to the chamber through spreaders or multiple ports or into the water circulation loop using a mixing device. Indirect heating may also be achieved using a heat exchanger in the water circulation loop. Steam and air should be regulated to provide controlled pressure to the control valves. The design of the steam and air supplies and the control system must enable attainment of the process temperature and the required chamber temperature uniformity.

B.4.2.3 Temperature control

See B.2.1.

B.4.2.4 Pressure control

See B.4.1.6.

B.4.2.5 Cooling system

The product is cooled by reducing the temperature of the water spray. The cooling system design and capacity should be appropriate for the type and mass of product to be cooled. See also B.3.1.7.1 and B.3.1.7.3.

B.4.2.6 Control and recording systems

General considerations are described in B.2.2. In addition, it is necessary to control and document the following events: water fill time; water level; water spray operation; vent close pressure, temperature, or time, as applicable; overpressure start time; chamber pressure during cooling; cooling time or process temperature at the end of cooling. The chamber temperature during the exposure phase should be sufficiently controlled to maintain process and product integrity.

B.4.3 Water immersion

B.4.3.1 Phases of the process

This type of cycle, which is illustrated in figure B.5, is similar to the water spray system except that the product is totally immersed in water. This process is used to maintain product shape.

B.4.3.2 Water level control

All of the product load must be completely submerged during the entire exposure phase. A closed-loop water recirculation system may be employed, providing heat-sterilized cooling water. Control of the water level is critical, and the control system must ensure that a minimum free head space (air/steam mixture) is maintained. High- and low-level alarms are necessary.

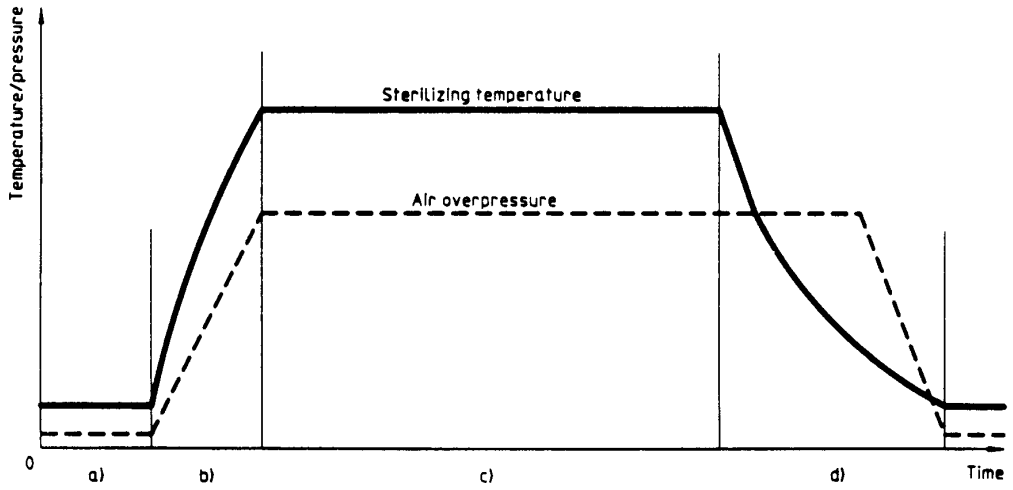

Figure B.5—Example of air-pressurization cycle—water immersion system

B.4.3.3 Steam/air introduction

Steam and air may be introduced into the chamber through spreaders or multiple ports or into the water circulation loop by a mixing device. Indirect heating can also be achieved using a heat exchanger in the water circulation loop. The spreaders are located so that the induced turbulence and convection currents promote circulation of the heated water through the product carriers. The steam and air supplies should be regulated to provide controlled pressure to the control valves. It is necessary that the design of the supply and control system enable attainment of the process temperature and the required chamber temperature uniformity.

B.4.3.4 Internal/external circulation

A water recirculation pump is generally used as an external, closed recirculation loop. Alternatively a continuous flow of compressed air or air and steam rising through the product carriers can be used to promote circulation and mixing.

B.4.3.5 Temperature control

See B.2.1. The water must be kept circulating throughout the cycle to ensure temperature uniformity. A flowmeter or other flow-indicating device should be used. An alarm should be provided to indicate loss of recirculation.

B.4.3.6 Pressure control

See B.4.1.6.

B.4.3.7 Cooling system

The product load is cooled by controlled reduction of the water temperature at a rate appropriate to both product and equipment. Cooling can be achieved by direct introduction of cooling water or by indirect cooling of the recirculation loop with a heat exchanger. After a predetermined cooling time has elapsed and/or the chamber water and product temperature have reached the desired temperature, the cooling phase ends and the chamber is drained and depressurized. The cooling system design and capacity must be appropriate for the type and mass of product to be cooled.

B.4.3.8 Control and recording systems

General considerations are described in B.2.2. In addition, it is necessary to control and document the following events: water fill time; water level; water recirculation; chamber pressure during cooling; cooling time or final temperature. The temperature of the sterilizing medium during the exposure phase should be sufficiently controlled to satisfy requirements established during process development. Chamber overpressure must be sufficiently controlled to maintain process and product integrity.

Annex C

Statistical determination of process equivalency

C.1 Introduction

It is important that the establishment of process equivalency be based on analysis of performance data and that the analysis concludes that equipment is performing within an acceptable range of control, as defined by the ability to reproduce process parameters. The analysis should define the acceptable range and level of variability in performance required to maintain equivalency from year to year. For example, when analyzing the results of temperature data obtained from the annual empty-chamber profiles, a comparison from year to year of the average standard deviation, range, and maximum and minimum temperatures would be appropriate. In addition, the degree to which these profile statistics relate to the validated process specifications should be analyzed. One useful method of establishing this relationship is the calculation of Process Capability Indices.

C.2 Definitions

Process Capability (Cp) is the capability of a process to meet an established (validated) specification range. To calculate Cp, simply divide the specification tolerance by the actual process range. This relationship is defined as:

$$Cp = \frac{USL - LSL}{6 \times O}$$

where: USL = upper specification limit
LSL = lower specification limit
O = sample standard deviation

The Process Capability Centering (CpK) Index is a measurement of the capability of the process to meet specifications when the process average and standard deviation (sigma) are compared to the nearest specification limit. In other words, the CpK Index represents the location of the process in relation to the specification limits:

$$CpK = \frac{CSL - X}{3 \times O}$$

where: CSL = closest specification limit to the process average
X = the process average
O = sample standard deviation

C.3 Evaluation of CpK

The required values of Cp and CpK have been well established in quality engineering references at a minimum of 1.0. This level of process quality produces a 99.73% conformance to specification (2700 defects per million). That is, for a traditional manufacturing process in a state of statistical control:

$Cp \geq 1.0$, and

$CpK \geq 1.0$.

Current quality philosophy, having the goal of zero defects/zero nonconformance, dictates that the desirable process quality reflect a CpK of 1.5 or greater. This level of quality has been termed “Six Sigma” process capability, which is defined as

> Cp $\geq$ 2.0 or greater, with the process average no more than 1.5 standard deviations from the process center; and/or
>
> CpK $\geq$ 1.5.

C.4 Effect of Process Capability Indices on process equivalency programs

The use of Process Capability Indices is only one method of analyzing performance data. The objective is the ability to determine, based on performance data, when a part of a process or an individual piece of equipment has drifted away from the original validated capability of delivering process parameters. It is then necessary to address any identified chamber/room deficiencies through maintenance of the equipment or disqualification from the equivalency program, thereby necessitating independent full validation/revalidation of nonequivalent processes.

Annex D

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* Information on FDA publications is available from FDA's "FACTS-ON-DEMAND." The telephone access numbers at the Center for Devices and Radiological Health are (800) 899-0381 and (301) 827-0111. An automated attendant provides information on how to receive an index of the available materials. From this index, document numbers can be identified, and specific documents can be requested and obtained by FAX. The FDA home page on the Internet is at http://www.fda.gov.com

