Draft Gaseous Chlorine Dioxide (CD) Reference File for Medical Device Sterilization

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The purpose of this document is to provide reference material to aid Medical Device manufacturers in their submissions of 510k's to the FDA when utilizing gaseous chlorine dioxide (CD) as the sterilant method. It is formatted based on ANSI/AAMI/ISO 11135:2014 and American National Standard ANSI/AAMI/ISO 14937:2009 so that it is more easily cross-referenced to documents that are commonly referenced and utilized by both Medical Device manufacturers and the FDA. The consistency includes the section numbering with items marked as non-applicable so that the cross-reference integrity can be maintained. The exception is that sections 4 through 12 have been eliminated with the specific information regarding chlorine dioxide being placed in the Annex's C and D.

Sterilization of health care products — Chlorine Dioxide (CD)

— Requirements for the development, validation and routine control of a sterilization process for medical devices

1. Scope

   1.1. Inclusions

   The International Standard that this document is based off of specifies requirements for the development, validation, and routine control of sterilization processes for medical devices in both the industrial and health care facility settings, and it acknowledges the similarities and differences between the two applications.

   NOTE 1 Among the similarities are the common need for quality systems, staff training, and proper safety measures. The major differences relate to the unique physical and organizational conditions in health care facilities, and to the initial condition of reusable medical devices being presented for sterilization.

   NOTE 2 Health care facilities differ from medical device manufacturers in the physical design of processing areas, in the equipment used, and in the availability of personnel with adequate levels of training and experience. The primary function of the health care facility is to provide patient care; medical device reprocessing is just one of a myriad of activities that are performed to support that function.

   NOTE 3 In terms of the initial condition of medical devices, medical device manufacturers generally sterilize large numbers of similar medical devices that have been produced from virgin material. Health care facilities, on the other hand, must handle and process both new medical devices and reusable medical devices of different descriptions and with varying levels of bioburden. They are therefore faced with the additional challenges of cleaning, evaluating, preparing, and packaging a medical device prior to sterilization. In this proposed document, alternative approaches and

specific to health care facilities are identified as such.

NOTE 4 CD gas is an effective sterilant that is primarily used for heat- and/or moisture-sensitive medical devices that cannot be moist heat sterilized, can not see elevated temperatures, contain batteries, as well as devices that are not compatible to gamma radiation.

1.2. Exclusions

1.2.1. The referenced International Standard does not specify requirements for the development, validation, and routine control of a process for inactivating the causative agents of spongiform encephalopathies, such as scrapie, bovine spongiform encephalopathy, and Creutzfeldt-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See ISO 22442-1, ISO 22442-2 and ISO 22442-3.

1.2.2. The referenced International Standard does not detail a specified requirement for designating a medical device as sterile.

NOTE Attention is drawn to national or regional requirements for designating medical devices as “sterile”. See f or example EN 556–1 or ANSI/AAMI ST67.

1.2.3. The referenced International Standard does not specify a quality management system for the control of all stages of production of medical devices.

NOTE The effective implementation of defined and documented procedures is necessary for the development, validation, and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system. It is not a requirement of this document to have a full quality management system during manufacture or reprocessing. The necessary elements are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. National and/or regional regulations for the provision of medical devices might require the implementation of a full quality management system and the assessment of that system by a third party.

1.2.4. The referenced International Standard does not specify requirements for occupational safety associated with the design and operation of CD sterilization facilities.

NOTE 1 For further information on safety, see examples in the Bibliography. National or regional regulations may also exist.

NOTE 2 CD is toxic. Attention is drawn to the possible existence in some countries of regulations giving safety requirements for handling CD and for premises in which it is used.

1.2.5. The referenced International Standard does not cover sterilization by injecting CD directly into packages or a flexible chamber.

1.2.6. The referenced International Standard does not cover analytical methods for determining levels of residual CD and/or its reaction products.

NOTE 2 Attention is drawn to the possible existence of national or regional regulations specifying limits for the level of CD residues present on or in medical devices.

2. Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10012, Measurement management systems — Requirements for measurement processes and measuring equipment

ISO 11138-1:2006, Sterilization of health care products — Biological indicators — Part 1: General requirements

ISO 11140-1, Sterilization of health care products — Chemical indicators — Part 1: General requirements

ISO 11737-1, Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products

ISO 11737-2, Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

ISO 13485:2016, Medical devices — Quality management systems — Requirements for regulatory purposes — Technical Corrigendum 1

3. Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1. aeration

part of the sterilization process during which CD and/or its reaction products desorb from the medical device until predetermined levels are reached

NOTE 1 to entry: This can be performed within the sterilizer and/or in a separate chamber or room.

3.2. aeration area

either a chamber or a room in which aeration occurs

3.3. bioburden

population of viable microorganisms on or in product and/or sterile barrier system

[SOURCE: ISO/TS 11139:2006, definition 2.2]

3.4. biological indicator

test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[SOURCE: ISO/TS 11139:2006, definition 2.3]

3.5. calibration

set of operations that establish, under specified conditions, the relationship between values of a quantity indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[SOURCE: ISO/TS 11139:2006, definition 2.4]

3.6. chemical indicator

test system that reveals a change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

[SOURCE: ISO/TS 11139:2006, definition 2.6]

3.7. CD chlorine dioxide

3.8. conditioning

treatment of product within the sterilization cycle, but prior to chlorine dioxide admission, to attain a predetermined temperature and relative humidity

NOTE 1 to entry: This part of the sterilization cycle can be carried out either at atmospheric pressure or under vacuum. NOTE 2 to entry: See 3.27, preconditioning.

3.9. D value

D10 value

time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[SOURCE: ISO/TS 11139:2006, definition 2.11]

NOTE 1 to entry: For the purposes of the referenced International Standard, the D value is the exposure time required to achieve 90 % inactivation of the population of the test organism.

3.10. development

act of elaborating a specification

[SOURCE: ISO/TS 11139:2006, definition 2.13]

3.11. dew point

The temperature at which the saturation water vapor pressure is equal to the partial pressure of the water vapor in the atmosphere

NOTE 1 to entry: Any cooling of the atmosphere below the dew point would produce water condensation.

3.12. Dosage

The accumulation of sterilant concentration over time or contact time

3.13. establish

determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO/TS 11139:2006, definition 2.17]

3.14. Deleted

3.15. exposure time

period for which the process parameters are maintained within their specified tolerances

[SOURCE: ISO/TS 11139:2006, definition 2.18]

NOTE 1 to entry: For the purpose of calculation of cycle lethality, it is the period of sterilization between the end of CD injection and the beginning of CD removal.

3.16. fault

one or more of the process parameters lying outside of its/their specified tolerance(s)

[SOURCE: ISO/TS 11139:2006, definition 2.19]

3.17. flushing

procedure by which the CD is removed from the load and chamber by either multiple alternate admissions of filtered air, inert gas or steam and evacuations of the chamber or continuous passage of filtered air, inert gas, or steam through the load and chamber

3.18. fractional cycle

a cycle in which the exposure time to CD gas is reduced compared to that specified in the sterilization process

3.19. half cycle

a cycle in which the exposure time to CD gas is reduced by 50 % compared to that specified in the sterilization process

3.20. health care facility

HCF

governmental and private organizations and institutions devoted to the promotion and maintenance of health, and the prevention and treatment of diseases and injuries

EXAMPLE A health care facility can be a hospital, nursing home, extended care facility, free-standing surgical center, clinic, medical office, or dental office.

3.21. health care product

medical device(s), including in vitro diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[SOURCE: ISO/TS 11139:2006, definition 2.20]

3.22. installation qualification

IQ

process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[SOURCE: ISO/TS 11139:2006, definition 2.22]

3.23. medical device

any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

— diagnosis, prevention, monitoring, treatment, or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of, or compensation for an injury,

— investigation, replacement, or modification or support of the anatomy or of a physiological process,

— control of conception,

— disinfection of medical devices,

— providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means

[SOURCE: ISO 13485:2003, definition 3.7]

3.24. microorganism

entity of microscopic size, encompassing bacteria, fungi, protozoa, and viruses

NOTE 1 to entry: A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in the definition above, for validation and/or routine control of the sterilization process.

[SOURCE: ISO/TS 11139:2006, definition 2.26]

3.25. operational qualification

OQ

process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO/TS 11139:2006, definition 2.27]

3.26. overkill approach

approach using sterilization process that delivers a minimum of 12 Spore Log Reduction (SLR) to a biological indicator having a resistance equal to or greater than the product bioburden

3.27. parametric release

declaration that product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[SOURCE: ISO/TS 11139:2006, definition 2.29]

NOTE 1 to entry: This method of process release does not include the use of biological indicators.

3.28. performance qualification

PQ

process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

3.29. preconditioning

treatment of product, prior to the sterilization cycle, in a room or chamber to attain specified conditions for temperature and relative humidity

3.30. process challenge device PCD

item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[SOURCE: ISO/TS 11139:2006, definition 2.33]

NOTE 1 to entry: For the purpose of the referenced International Standard, a PCD can be product, simulated product, or other device that is inoculated directly or indirectly. See 7.1.6 and D.7.1.6.

NOTE 2 to entry: In the referenced International Standard, a distinction is made between an internal PCD and an external PCD. An internal PCD is used to demonstrate that the required product SAL is achieved. A PCD located within the confines of the product or product shipper case is an internal PCD, whereas a PCD located between shipper cases or on the exterior surfaces of the load is an external PCD. An external PCD is an item designed to be used for microbiological monitoring of routine production cycles.

3.31. process parameter

specified value for a process variable

NOTE 1 to entry: The specification for a sterilization process includes the process parameters and their tolerances.

[SOURCE: ISO/TS 11139:2006, definition 2.34]

3.32. process variable

condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLE Time, temperature, pressure, concentration, humidity, wavelength, intensity.

[SOURCE: ISO/TS 11139:2006, definition 2.35]

3.33. processing category

collection of different product or product families that can be sterilized together

NOTE 1 to entry: All products within the category have been determined to present an equal or lesser challenge to the sterilization process than the process challenge device for that group.

3.34. product

result of a process

[ISO 9000:2005, definition 3.4.2]

NOTE 1 to entry: For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub- assembly(ies), and health care products.

3.35. product family

group of products possessing characteristics that allow them to be sterilized using defined process conditions

3.36. product load volume

defined space within the usable chamber volume occupied by product

3.37. recognized culture collection

depository authority under the Budapest Treaty on The International Recognition of the Deposit of Microorganisms for the Purposes of Patent and Regulation

[SOURCE: ISO/TS 11139:2006, definition 2.38]

3.38. reference microorganism

microbial strain obtained from a recognized culture collection

[SOURCE: ISO/TS 11139:2006, definition 2.39]

3.39. requalification

repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO/TS 11139:2006, definition 2.40]

3.40. reusable medical device

medical device designated or intended by the manufacturer as suitable for reprocessing and re-use

NOTE 1 to entry: This is not a medical device that is designated or intended by the manufacturer for single use only.

3.41. safety data sheet (SDS)

Document specifying the properties of a substance, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the substance safely

3.42. services

supplies from an external source, needed for the correct function of equipment

EXAMPLE Electricity, water, compressed air, drainage.

[SOURCE: ISO/TS 11139:2006, definition 2.41]

3.43. single use medical device

medical device designated or intended by the manufacturer for one-time use only

3.44. specify

stipulate in detail within an approved document

[SOURCE: ISO/TS 11139:2006, definition 2.42]

3.45. Spore-log-reduction SLR

log of initial spore population, N0, minus the log of the final population, Nu

[SOURCE: ISO 14161:2009, definition 3.19]

NOTE 1 to entry: Describing the reduction in the number of spores on a biological indicator or inoculated item produced by exposure to specified conditions.

For Direct Enumeration: SLR = log N0 − log Nu

where

N0 is the initial population;

Nu is the final population.

For Fraction Negative:

SLR = log N0 – log [ln (q/n)]

where

N0 is the initial population;

q is the number of replicate samples tested;

n is the number of samples negative for growth.

If there are no survivors, the true SLR cannot be calculated. The SLR can be reported as “greater than” log N0 if one surviving organism is used.

3.46. sterile

free from viable microorganisms

[SOURCE: ISO/TS 11139:2006, definition 2.43]

3.47. sterile barrier system

minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at the point of use

[SOURCE: ISO/TS 11139:2006, definition 2.44]

3.48. sterility

state of being free from viable microorganisms

NOTE 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven. NOTE 2 to entry: See 3.47, sterilization.

[SOURCE: ISO/TS 11139:2006, definition 2.45]

3.49. sterility assurance level

SAL

probability of a single viable microorganism occurring on an item after sterilization

NOTE 1 to entry: The term SAL takes a quantitative value, generally 10-6 or 10-3. When applying this quantitative value to assurance of sterility, a SAL of 10-6 has a lower value but provides a greater assurance of sterility than an SAL of 10-3.

[SOURCE: ISO/TS 11139:2006, definition 2.46]

3.50. sterilization

validated process used to render product free from viable microorganisms

NOTE 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

NOTE 2 to entry: See 3.46, sterility assurance level.

[SOURCE: ISO/TS 11139:2006, definition 2.47]

3.51. sterilization cycle

treatment in a sealed chamber, which includes air removal, conditioning (if used), injection of CD, inert gas (if used), exposure to CD, removal of CD and flushing (if used), and air/inert gas admission

3.52. sterilization load

product to be, or that has been, sterilized together using a given sterilization process

[SOURCE: ISO/TS 11139:2006, definition 2.48]

3.53. sterilization process

series of actions or operations needed to achieve the specified requirements for sterility

[SOURCE: ISO/TS 11139:2006, definition 2.49]

NOTE 1 to entry: This series of actions or operations includes preconditioning (if necessary), exposure to the chlorine dioxide under defined conditions, and any necessary post-treatment required for the removal of chlorine dioxide and its by-products. It does not include any cleaning, disinfection, or packaging operations that precede the sterilization process.

3.54. sterilization specialist

person with technical knowledge of the sterilization technology being utilized and its effects upon materials and microorganisms

3.55. sterilizing agent

physical or chemical entity, or combination of entities having sufficient microbicidal activity to achieve sterility under defined conditions

[SOURCE: ISO/TS 11139:2006, definition 2.50]

3.56. survivor curve

graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[SOURCE: ISO/TS 11139:2006, definition 2.51]

3.57. test for sterility

technical operation defined in a Pharmacopoeia performed on product following exposure to a sterilization process

[SOURCE: ISO/TS 11139:2006, definition 2.53]

3.58. test of sterility

technical operation performed as part of development, validation, or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[SOURCE: ISO/TS 11139:2006, definition 2.54]

3.59. usable chamber volume

defined space within the sterilizer chamber, which is not restricted by fixed or mobile parts and which is available to accept the sterilization load

NOTE 1 to entry: The volume allowed for gas circulation around the load inside the chamber is not included as usable space.

3.60. validation

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

[SOURCE: ISO/TS 11139:2006, definition 2.55]

3.61. virgin material

material that has not been previously used or subjected to processing other than for its original production

Annex A

(normative)

Determination of lethal rate of the sterilization process — Biological indicator/bioburden approach

A1. General

A1.1. This approach combines knowledge of the resistance of a biological indicator to a given sterilization process with knowledge of the bioburden population and resistance to establish the sterilization process parameters (sterilization cycle exposure time).

Use of the method requires that product bioburden levels shall be demonstrated to be relatively consistent over time, and the resistance of the bioburden be shown to be equal to or less resistant than the resistance of the biological indicator.

The resistance of the internal PCD is demonstrated by running the sterilization cycle at graded exposure times or dosages, or by exposing graded BI populations to a single sterilization exposure time, and then determining the lethal rate (rate of inactivation through D-value calculations) when exposed to the sterilization cycle. Knowledge of the BI lethality rate and the population and relative resistance of the bioburden allows one to establish exposure time so that a SAL can be predicted.

Attention shall be given to the impact of packaging and the removal of CD from the PCD. Guidance on this approach can be found in ISO 14161.

A1.2. The conditions used for recovery of biological indicators in qualification studies, including duration of incubation, shall be established and documented. The incubation period shall take into account the possibility of delayed outgrowth of spores that have been exposed to CD. Refer to ISO 14161 for additional information on biological indicator incubation times.

A1.3. After time-graded exposures or dosages to CD or population-graded BIs exposed to CD, with all other parameters remaining the same, the lethality of the process can be determined by using one of the following methods:

a) direct enumeration;

b) the fraction-negative method; or

c) a combination of a) or b) above.

NOTE The fraction-negative method uses growth/no growth data from the recovery test on the reference microorganisms after exposure to fractional gas exposure times or to graded populations of reference microorganisms to a single fractional gas exposure time.

A2. Procedure

For additional guidance on this developmental process, refer to AAMI TIR 16 and ISO 14161, both of which discuss process development in detail.

Annex B

(normative)

Conservative determination of lethal rate of the sterilization process — Overkill approach

B1. General

B1.1. This approach to process definition is based on the inactivation of reference microorganisms and has been widely used (see also ISO 11138-2 or 14937:2009). Sterilization processes qualified in this manner are often conservative and use a treatment that may exceed that required to achieve the specified requirements for sterility.

Guidance on this approach can be found in ISO 14161.

B1.2. Conservative process definition requires use of either of the approaches given in a) and b) below.

a) Half-cycle approach: a total of three consecutive experiments resulting in total inactivation of the biological indicators (with a population of not less than 10^6 and, where appropriate, placed within a PCD) shall be performed in order to confirm the minimum exposure time or dosage. The specified exposure time or dosage for the sterilization process shall be at least double this minimum time. A fractional cycle of short duration from which BI survivors can be recovered shall also be run to demonstrate the adequacy of the recovery technique for BIs exposed to CD gas.

NOTE This short cycle can also be used to demonstrate the relative resistance of Biological Indicator, PCD, and product bioburden.

b) Cycle calculation approach: The routine processing parameters that deliver minimally a 12 SLR of the biological indicator shall be established using one of the methods described in A.1.3. The number of cycles is dictated by the method used.

Note: Testing on *Bacillus atrophaeus* (ATCC9372) spores disbursed in a Microbial challenge room was able to demonstrate greater than 20 log kill[46].

B1.3. The conditions used for recovery of biological indicators in qualification studies shall be established and documented. The incubation period shall take into account the possibility of delayed outgrowth of spores that have been exposed to CD. Further guidance on the biological indicator incubation times can be found in ISO 14161.

B1.4. The resistance of the product bioburden shall be shown to be such that total inactivation time of the product bioburden is less than the total inactivation time of the product BI (internal PCD).

B2. Procedure

B2.1. Create a challenge to the sterilization process, PCD, comprising a known number of microorganisms with known resistance to CD, by placing biological indicators in the product or inoculating product at locations where sterilizing conditions are most difficult to achieve. If

the location(s) of the microbiological challenge is other than the most difficult-to-sterilize within the product, its relationship to the most difficult location(s) shall be established.

B2.2. Use of a PCD that has demonstrated an equivalent or greater microbiological resistance to the sterilization process than the product meets this requirement. Attention must be given to the impact of packaging and the removal of sterilant from the PCD.

B2.3. Place the PCD (in accordance with B.2.1 and B.2.2) within or on the sterilization load as appropriate.

B2.4. Expose the sterilization load to CD under conditions designed to deliver less lethality than the specified sterilization process.

B2.5. For the cycle calculation approach, if the inactivation of a known number of microorganisms has been confirmed according to A.1.3, determine the extent of treatment for the sterilization process by extrapolation to a known predicted probability of a surviving microorganism, taking account of the required SAL.

Annex C

(informative)

Temperature sensors, RH sensors, CD Sensors and biological indicator numbers

C1. Temperature sensors

It is recommended to use one sensor per 2.5 cubic meters during OQ to establish a thermal map of the chamber that captures potential hot or cold locations. Therefore, monitoring should include more than one plane and locations near doors. (Note: In most cases, temperature is not a critical process parameter for CD sterilization)[1]

For PQ, one temperature sensor is required per cubic meter of product volume. The minimum number of temperature sensors is three. For PQ, temperature* sensors should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor within the sterile barrier system or amongst the unit packages.

The result of the calculation should be rounded to the next higher number.

Table C.1 provides guidance for determining the number of temperature sensors.

Table C.1 — Minimum recommended number of temperature sensors

Volume m^3	**Number for OQ** (usable chamber/room volume)			**Number for PQ** (product load volume)		
	Preconditioning	**Conditioning/ sterilization**	**Aeration**	**Preconditioning**	**Conditioning/ sterilization**	**Aeration**
≤ 1	3			3		
10	4			10		
15	6			15		
20	8			20		
25	10			25		
30	12			30		
35	14			35		
40	16			40		
50	20			50		
100	40			100		

EXAMPLE During OQ of a preconditioning room with a usable chamber volume of 70 m : 70/2.5 = 28.

EXAMPLE During PQ with a product load volume of 2 cubic meters: 2/1 = 2. The number of sensors to use is at least three (the minimum number of sensors to use).

C2. Humidity sensors

The recommendation is to use one sensor per 2.5 m3 to establish a humidity map of the area or product that captures potential variability in the humidity levels. The minimum number of sensors is two.

The result of the calculation should be rounded to the next higher number.

For PQ, humidity sensors should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor within the sterile barrier system or amongst the unit packages.

Table C.2 provides guidance for determining the number of humidity sensors.

Table C.2 — Minimum recommended number of humidity sensors

Volume m^3	**Number for OQ** (usable chamber/room volume)			**Number for PQ** (product load volume)		
	Preconditioning	**Conditioning/ sterilization**	**Aeration**	**Preconditioning**	**Conditioning/ sterilization**	**Aeration**
≤ 1	2			2		
10	4			4		
15	6			6		
20	8			8		
25	10		N/A	10		N/A
30	12			12		
35	14			14		
40	16			16		
50	20			20		
100	40			40		

EXAMPLE 1 During OQ for a usable chamber volume of 6 m3: 6/2.5 = 2.4. The number of sensors to use is at least three.

EXAMPLE 2 During PQ for a product volume of 60 m3: 60/2.5 = 24. The number of sensors to use is at least 24.

C3. Chlorine Dioxide sensors/locations

The recommendation is to use one sensor location per 2.5 cubic meters to establish a concentration map of the area or product that captures potential variability in the concentration levels. The minimum number of sensor locations is two. A preferred method is to have one fixed in place sensor measuring the chamber concentration. A second sensor then pulls a sample through a flexible sensing tube. That sensing tube is then moved throughout the chamber to map the chamber concentration in multiple locations comparing it to the concentration measured by the fixed location sensor. Table C.3 designates the minimum number of locations.

For PQ, concentration location sensor should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor near the sterile barrier system or amongst the unit packages.

Table C.3 provides guidance for determining the number of CD sensors.

Table C.3 — Minimum recommended number of CD concentration sensors

Volume m^3	**Number for OQ** (usable chamber/room volume)			**Number for PQ** (product load volume)		
	Charge	**CD Exposure**	**Aeration**	**Charge**	**CD Exposure**	**Aeration**
≤ 1	2			2		
10	4			4		
15	6			6		
20	8			8		
25	10		N/A	10		N/A
30	12			12		
35	14			14		
40	16			16		
50	20			20		
100	40			40		

EXAMPLE 1 During OQ for a usable chamber volume of 6 m3: 6/2.5 = 2.4. The number of sensing locations to use is at least three.

EXAMPLE 2 During PQ for a product volume of 60 m3: 60/2.5 = 24. The number of sensing locations to use is at least 24.

C4. Biological Indicators

The minimum recommended number of BI/PCDs to use is as follows:

a) For MPQ with a product load volume of up to 10 m3, use three BIs per m3 of product volume, with a minimum of five BIs.

b) For MPQ with a product load volume above 10 m3, use one additional BI per additional m3 beyond 10m3. If BIs are used for routine control, use half the number of BIs used during MPQ up to a maximum of 30.

The result of the calculation should be rounded to the next higher number. Table C.3 provides guidance for determining the number of BI/PCDs.

The actual number of BI/PCDs to be used will depend on:

a) microbiological qualification method chosen (see Annex A or Annex B);

b) product volume; and

c) type of chamber (developmental vs. production).

When using the Stumbo-Murphy-Cochran procedure and the Overkill Cycle Calculation approach, the recommended number of BI/PCDs can be based on the product volume to be sterilized. When this approach is being used, a minimum quantity of 10 BI/PCD's are indicated; see Reference [38].

Table C.4 — Examples of minimum recommended number of BI/PCDs

Product load volume m^3	**MPQ**	**Routine control** (if used)
≤ 1	5	3
10	30	15
15	35	18
20	40	20
25	45	23
30	50	25
35	55	28
40	60	30
50	70	30
100	120	30

EXAMPLE 1 For product load volume of 3 m3: 3 × 3 = 9. The number of BIs to use is at least nine for MPQ. For routine control: 9/2 = 4.5. The number of BIs is at least five.

EXAMPLE 2 For a product load volume of 18 m3: 10 × 3 + (18 − 10) × 1 = 38. The number of BIs to use is at least 38 for MPQ. For routine control: 38/2 = 19. The number of BIs is at least 19.

Annex D

(informative)

Guidance on the application of the normative requirements

The guidance given in this annex is not intended as a checklist for assessing compliance with this document. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document by providing explanations and acceptable methods for achieving compliance with specified requirements. Methods other than those given in the guidance can be used, provided their performance achieves compliance with this document

NOTE For ease of reference, the numbering of clauses in this annex corresponds to that in the normative parts of this document.

Scope

No guidance offered.

D.1.Scope

No guidance offered.

D.2.Normative references

The requirements given in documents that are included as normative references are requirements of this document only to the extent that they are cited in normative parts of this document; the citation can be to a whole standard or limited to specific clauses in which case the referenced standard should be dated.

D.3.Terms and definitions

No guidance offered.

D.4.Quality management systems

NOTE As the scope of ISO 13485 focuses on manufacturers of medical devices, health care facilities can use other quality management standards applicable to their organization. ClorDiSys QMS is certified to ISO13485:2016 (Cert No. C2021-03205). ClorDiSys's NJ facility is registered with the US FDA as a Contract Sterilization facility (Registration #3013115071).

D.4.1. Documentation

Refer to ISO 13485.

D.4.2. Management responsibility

D.4.2.1. Requirements for responsibility and authority are specified in ISO 13485:2016, 5.5, and requirements for human resources are specified in ISO 13485:2016, 6.2.

In ISO 13485, the requirements for management responsibility relate to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

Each organization should establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

D.4.2.2. The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. It is important that the respective procedures clearly outline the responsibilities for meeting the requirements of this document. This is especially important where contractors are engaged to carry out specific functions. Contract sterilization activities will require a written processing agreement outling the services to be delivered and the roles and responsibilities of the parties involved.

Even where elements of the sterilization process are contracted out it is important to note that the medical device manufacturer is ultimately responsible for validation, release, and distribution of sterilized product to the market. When a health care facility contracts out the sterilization of reusable medical devices, it is the health care facility's responsibility for validation and release of the sterilized product

Further guidance is available in ISO 14937:2009, E.4.2.2.

D.4.3. Product realization

NOTE In ISO 13485, the requirements for product realization relate to the product lifecycle from the determination of customer requirements, design and development, purchasing, control of production, and calibration of monitoring and measuring devices.

D.4.3.1. Requirements for purchasing are specified in ISO 13485:2016, 7.4. In particular, it should be noted that the requirements in ISO 13485:2016, 7.4 for verification of purchased product apply to product and services that impact on process quality, received from outside the organization.

Purchasing procedures in a health care facility should ensure that reusable medical devices are supplied with validated instructions for cleaning, disinfection, sterilization, and aeration as specified in ISO 17664. It should also be verified that the prescribed procedure for cleaning, disinfection, sterilization, and aeration can be performed in the health care facility.

D.4.3.2. Requirements for identification and traceability are specified in ISO 13485:2016,7.5.8 and 7.5.9

For those facilities that do not fully comply with ISO 13485, such as health care facilities, procedures for identification of product and maintenance of traceability should include the labelling of each item or package prior to sterilization with a lot control identifier that includes the following information:

a) the sterilizer ID or code;

b) the date of sterilization;

c) the cycle number (i.e., the cycle run of the day or sterilizer); and

d) the identity of the person who assembled the pack.

Including the identity of the person who assembled the pack allows for further investigation if a problem should arise. Lot identification information enables personnel to retrieve items sterilized in a specific cycle in the event of a recall and to trace problems to their source.

D.4.3.3. Requirements for calibration of monitoring and measuring instrumentation are specified in ISO 13485:2016, 7.6.

D.4.4. Measurement, analysis and improvement — Control of non-conforming product

Procedures for control of non-conforming product and corrective action are specified in ISO 13485:2016, 8.3 and 8.5.2, respectively.

D.5.Sterilizing agent characterizations

D.5.1. General

The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials, and identify requirements for safety of personnel and protection of the environment. This activity may be undertaken in a test or prototype system. Where this occurs, the final equipment specification (see 6.3) shall be relatable to the results of experimental studies undertaken in the test or prototype equipment. For the purposes of this document, the sterilizing agent is chlorine dioxide..

D.5.2. Sterilizing agent

Chlorine Dioxide (CD) gas is a sterilant gas registered with the US-Environmental Protection Association (EPA label # 80802-1) as a sterilant. The US-EPA label specifies chlorine dioxide can be used to sterilize sealed spaces/enclosures, such as: clean rooms, aseptic manufacturing rooms/suites, isolators, RABS and laboratories. It is used to decontaminate and sterilize equipment and surfaces within spaces including Biological Safety Cabinets, incubators, fume hoods, HEPA housings, implements and components such as: manufacturing vessels, process tanks, piping, filters, portable vessels, beakers, test tubes, medical devices, and laboratory glassware to name some. Medical Devices are typically sterilized in an ambient temperature vacuum sterilizer.

Chlorine dioxide is not sufficiently stable to be stored, it must be generated onsite at the point of use. There are many ways to generate CD gas and one method is using, a low-level chlorine gas (2%) which is passed over solid sodium chlorite CD Generating Cartridges which convert the chlorine to pure chlorine dioxide (>99% yield).[2]

$$2NaClO_2 + Cl_2 \rightarrow 2ClO_2 + 2NaCl$$

The 2% chlorine gas is mixed with nitrogen. This stoichiometrically limits the concentration to 4% which is significantly below the 10% level which is potentially explosive. Purity levels should be 10% =/- %. The CD Generating Cartridges have a 1 year shelf life and generate CD gas for up to 300 minutes before they require replacement. The shelf life of reagent gas tanks are manufacturer specific and must be followed. The sterilizer control systems automatically

prevents the CD Cartridges from being used for more than 310 minutes. This process produces a pure chlorine dioxide gas and is injected into the target chamber for a fixed time or dosage / contact time (CT). The chlorine dioxide flow rate is 20 liters per minute +/- 4 liters per minute. After the exposure is completed the gas is typically exhausted to the outside environment via house exhaust systems. Federal state and local regulations must be verified prior to exhausting CD gas. Scrubber systems are available if exhausting the CD gas is not possible. Target chambers for chlorine dioxide include ambient pressure chambers or vacuum pressure chambers or any chamber where any components are placed within the chamber. The target chamber choice depends upon the product requiring sterilization. If the product is simple in its geometry and has no small openings then the ambient pressure chamber can be used. The product must be wrapped in suitable packaging to maintain the sterility. Tyvek packaging is the suggested packaging, since it allows CD gas to penetrate and does not allow organisms to penetrate. If the product is complex in its geometry and has many lumens or tubing's or small opening then a vacuum process maybe required. This process will remove most of the air particles from both the chamber as well as internal portions of the device itself, then replace the air with CD gas allowing the moisture, as well as the CD, to penetrate into all the small openings.

Chlorine dioxide gas is considered a true ambient temperature process since the ambient temperature is not changed by the process.[3] Since chlorine dioxide has a color its concentration can be monitored and thus it has the ability to utilize product parametric release. Chlorine dioxide gas also has a boiling point between -20 °C and -40°C at use concentrations, thereby making it a true gas at room temperatures (15-25°C).[4] This makes the process simpler since it does not require the condensation or lack of condensation for its effectiveness as with vapor methods. Chlorine dioxide is a true gas so it will not condense at use temperatures and as such it provides a more consistent and reliable process. Chlorine dioxide has a molecular weight of 67.5 but stratification is not an issue with chlorine dioxide. Testing at ambient pressure was performed demonstrating that with minimal circulation, gas concentration is still evenly distributed throughout a chamber.[5]

D.5.3. Microbicidal effectiveness

Chlorine dioxide has been shown to have antimicrobial properties in the 1930s by Schaufler[6] and Kovtunovitch and Chemaya[7] and was found to produce better tasting water when added to the commercial water supplies[8] and has been used ever since in the water treatment industry. It has been proven effective against foodborne illnesses (Escherichia coli O157:H7, Listeria monocytogenes, and Salmonella enterica)[9] along with inactivating viruses (enteroviruses, polioviruses, rotavirus, and human immunodefficiency virus (HIV)). [10] [11] [12] [13] [14] [15] It has also been shown effective again various protozoal, fungal, and algal species (Cryptosporidium parvum oocysts, Streptomyces griseus, and yeasts)[16] [17] [18] [19] and has been demonstrated sporicidal (c*lostridium sporogenes*, b*acillus subtilis*, *bacillus pumilus*, g*eobacillus stearothermophilus)*. [20] [21] [22] [23] [24] Chlorine dioxide gas is also registered as a sterilizing agent by the U.S. EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). ClorDiSys Solutions Registration # 80802-1.

Typical biological indicator organism choice for sterilization tests are *Bacillus atrophaeus* (ATCC9372) and *Geobacillus stearothermophilus* (ATCC7953). Both organisms are resistant to chlorine dioxide gas as both organisms are spore formers. Spores are the hardest organism to kill so the US-EPA considers sporicides and sterilant synonyms. The indicator of choice for chlorine dioxide is *Geobacillus stearothermophilus* since it is a spore and it is one of the more common spores available. Additionally, many facilities currently use G. *stearothermophilus* spore strips and are familiar with using the strips since they are typically used in steam autoclaves. They are currently inhouse in most facilities, they have the media in-house and the incubators are set for the increased temperature compared to *Bacillus atrophaeus* incubators. *Geobacillus stearothermophilus* additionally offers the higher incubation temperature which reduces the risk of cross contaminations since many organisms do not grow at the higher incubation temperatures. *Geobacillus stearothermophilus* is also used as the anthrax surrogate. ClorDiSys has utilized both *Bacillus atrophaeus* and *Geobacillus stearothermophilus* BI's in many formats such as discs, strngs, strips from an assortment of manufacturers. More diference are seen between manufacturers than between those two spore species making either acceptable.

BI Resistance Study Results

Biological Indicator	Run 1 # nonsterile/ total tested	Run 2 # nonsterile/ total tested	Run 3 # nonsterile/ total tested	Total # nonsterile/ total tested
B. subtilis (globigii) A TCC 9372	10/15	13/15	15/15	38/45
B. pumilus ATCC 27142	0/15	2/15	1/15	3/45
B. stearothermophilus A TCC 12980	1/15	2/15	2/15	5/45
B. stearothermophilus VHP	9/15	9/15	8/15	26/45

Cycle parameters: 30 mg/L gas concentration, 90% RH pre-humidification, 6-minute exposure time (1080 ppm-hours)

Chlorine dioxide is effective at various concentrations. To have an effective cycle the contact time or dosage is the more important consideration. Dosage is an accumulation of a concentration over time which is accumulated and displayed as ppm-Hours. The required dosage depends upon the complexity of the product. This also depends upon requiring a vacuum process or ambient process. If the product is simple then a simple ambient pressure process works. If the product contains lumens, tubing and tiny openings then a vacuum process maybe required.

To calculate chlorine dioxide ppm from mg/L, the below calculations can be used:

ppm calculation for 1 mg/L chlorine dioxide concentration

ppm = (mg/m3) (24.45)/molecular weight

= (mg/L) (1000) (24.45)/molecular weight

CD ppm = (1 mg/L) (1000 L/m3) (24.45)/67.5

= 362.2

The number 24.45 in the equations above is the volume (liters) of a mole (gram molecular weight) of a gas at 1 atmosphere and at 25°C.

This leads to the calculations for dosage or ppm-hours. Later section documents various cycles at various dosages.

Exposure contact time = 362 ppm×2 h = 724 ppm-hours

Studies have shown effective dosage of 400 ppm-hours to achieve a 5-log reduction of *bacillus atrophaeus* spores and a 6-log reduction in isolators at 900 ppm-hours. [25] [26] Others have demonstrated 6-log reduction cycles in isolator and processing vessels at dosages of 540ppm-hours to 1800 ppm-hours. [27] [28] [29] Dosages as low at 180 ppm-hours have shown 4-log reductions.[30] Other studies have varied CD gas concentrations (0.3, 0.5, 1, 5, 10, and 20 mg/L) and kept the dosage constant (720ppm-hours) and achieved 6-log reductions for all concentrations.[31]

For the vacuum process, higher concentrations and times are typically utilized to achieve sterilization. The RH requirements are the same, but the CD gas concentrations are increased to a target concentration of 3-30 mg/L compared to the target of 1-5mg/L for ambient pressure chambers. This then equates to a dosage of 3000-5000 PPM-Hours. This is required to allow the gas to penetrate into the small openings. This exposure time must be determined for each product and the exposure times may vary. Studies have demonstrated 6-log reductions at dosages of 5400 ppm-hours to 10,800 ppm-hours [32] [33] [34] [35]

Since ISO 11138 requires BI's to have D-values not less than 2.5 minutes at a 600 mg/liter concentration and 60% RH, testing was performed on BI's to see what corresponding D-Values would be for chlorine dioxide. *Bacillus atrophaeus* BI's were chosen since they can be purchased with known D-Values. For BI's marked with a 2.9 minute D-Value for EtO, the same BI's were calculated out to have a 0.44 minute D-Value for CD at 20 mg/liter concentration, 75% Rh, under atmospheric pressure, Atmospheric pressure was chosen so that square-wave exposures could be performed in a Bier-like chamber.[36]

Testing has been performed for treating BI's in multiple fractional cycles. Utilizing commercially available *Geobacillus stearothermophilus* BI's on a paper substrate, it was demonstrated that three treatments of a 100 ppm-hour dosage gets 6 log sporicidal kill as does one treatment of a 300 ppm-hour dosage indicating the possibility of "topping off" aborted cycles rather than requiring complete repeating of a cycle.[37]

D.5.4. Effects on materials

Chlorine dioxide is an oxidizer and as such it can oxidize materials. It has an oxidation potential of 0.95V which is lower than other common decontaminating/sterilizing agents such as hydrogen peroxide (1.78V), ozone (2.07V), sodium hypochlorite (1.49V) and peracetic acid (1.81V). All grades of stainless steel have good material compatibility with chlorine dioxide gas along with most gasket materials (silicone, EPDM, Buna, Viton, neoprene) and plastics (Teflon, KYNAR (PVDF), PVC, PE, PP) commonly used today in most facilities and chambers. Anodized aluminum also has good material compatibility properties. If un-anodized aluminum is

exposed, aluminum oxide will form. Chlorine dioxide gas will cause corrosion on untreated or uncoated ferrous metals. If the ferrous metal is painted, coated or galvanized then the issues are removed. Studies have shown good electronics compatibility with Girouard (2016)[38] exposing computers to several cycles. Batteries have been tested and CD has been shown to be an effective way to sterilize batteries with no damage.[39] Additionally other lab and production equipment in facilities undergoing whole facility decontamination with chlorine dioxide gas have shown good material compatibility. [40] [41] [42] [43] [44] [45] [46] [47] [48] Stoppers studies have been performed with chlorine dioxide (Datwyler 2019)[49] and results have shown it to be an effective alternative to ethylene oxide. Stoppers made from halobutyl polymer with a saturated aliphatic backbone as well as a styrene-butadiene copolymer underwent an extended exposure. Their properties of fragmentation, piercing force, turbidity, color, alkalinity, absorbance, reducing substrates, heavy metals, zinc, ammonium, residue on evaporation, and volatile sulphides were tested and compared favorably with respect to both EtO and gamma sterilization exposure. The following table shows the general compatibility of chlorine dioxide gas sterilization with various specific materials.[50] [51]

Table .D.1— Material compatibility guidance for chlorine dioxide sterilization— Specific materials

Chlorine dioxide sterilization		
(NL) = not likely **(L) = likely** **(U) = unknown**	**1 = poor** **2 = fair** **3 = good** **4 = excellent**	
Material	**Single use (1 or 2 cycles)**	**Comments**
Thermoplastics		
Acrylonitrile butadiene styrene (ABS)	4	
Fluoropolymers		
Polytetrafluoroethylene (PTFE)	4	
Perfluoro alkoxy (PFA)	4	
Perchlorotrifluoro-ethylene (PCTFE)	4	
Polyvinyl fluoride (PVF)	3	Slight yellowing
Polyvinylidene fluoride (PVDF)	4	
Ethylenetetrafluoro- ethylene (ETFE)	4	
Fluorinated ethylene propylene (FEP)	4	
Polyacetals (e.g., polyoxymethylene)	4	
Polyacrylates (e.g., polymethyl-methacrylate)	3	Slight color change.
Polyamides (e.g., nylon)	4	
Polycarbonate (PC)	3	Discoloration is grade dependent
Polyesters, saturated	4	
Polyethylene (PE), various densities	4	
Polyimides (e.g. polyetherimide)	4	
Polyketones (e.g. polyetheretherketone)	4	
Polypropylene (PP)	4	
Natural	4	

Chlorine dioxide sterilization		
(NL) = not likely **(L) = likely** **(U) = unknown**	**1 = poor** **2 = fair** **3 = good** **4 = excellent**	
Material	**Single use (1 or 2 cycles)**	**Comments**
Stabilized	4	
Polystyrene (PS)	4	
Polysulfones	4	
Polyurethane (PU)	3	Discoloration is grade dependent
Polyvinylacetates (PVA)	4	
Polyvinylchloride (PVC)	4	
PVC, plasticized	4	
Styrene acrylonitrile (SAN)	4	
Polyglycolic acid (PGA)	4	
Polyethylene terephthalate (PET)	4	
Ethylene vinyl acetate (EVA)	4	
Thermosets		
Epoxy	4	Grade-dependent
Phenolics	4	
Silicone	4	Grade-dependent
Polyester, unsaturated	4	
Polyimides	4	
Polyurethanes	3	Discoloration is grade dependent
Aliphatic	U	
Aromatic	U	
Adhesives		
Epoxy	4	Grade-dependent
Fluoroepoxy	4	Grade-dependent
Silicone	4	Grade-dependent
Elastomers		
Butyl	3	Slight color change
Ethylene propylene diene monomer (EPDM)	4	
Natural rubber	3	Slight color change
Nitrile	4	
Polyacrylic	4	
Polychloroprene (neoprene)	4	
Santoprene thermoplastic vulcanizates (TPV)	4	
Silicone	4	
Styrenic block copolymers (e.g., styrene-butadiene- styrene, styrene-ethylene-butylene-styrene)	4	
Urethane	3	Discoloration is grade dependent
Metals		
Aluminum	4	

Chlorine dioxide sterilization		
(NL) = not likely **(L) = likely** **(U) = unknown**	**1 = poor** **2 = fair** **3 = good** **4 = excellent**	
Material	**Single use (1 or 2 cycles)**	**Comments**
Brass	4	
Copper	4	
Gold	4	
Magnesium	3	
Nickel	3	
Nitinol	4	
Silver	3	Slight discoloration
Stainless steel	4	
Titanium	3	Slight discoloration
Ceramics/glasses		
Aluminum oxides	4	
Silica	4	
Zirconium oxides	4	
Other materials		
Bioabsorbables		
Polyglycolides	4	
Polylactides	4	
Poly(lactic-co-glycolic acid) [PLGA] [Class 6 implantable]	4	
Cellulosics		
Cellulose ester	4	
Cellulose acetate propionate	U	
Cellulose acetate butyrate	4	
Cellulose, paper, cardboard	3	Discoloration could occur
Liquid crystal polymer (LCP)	4	
Lubricants		
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	4	Grade dependent
Poly(p-xylylene) polymers (dry)	U	
Liquid or solid lubricants containing PTFE	4	

D.5.5. Safety and the environment

Chlorine dioxide is recognized as a sterilant. As such it is toxic and dangerous since it is used to kill organisms. Any chemical agent that kills organisms is inherently dangerous and any chemical agent providing kill is significantly (>100 times) above the safe levels. One of the safety benefits of chlorine dioxide is the odor threshold. It can be smelled at the low concentration of 0.1 ppm. This is the same concentration as the OSHA 8-hour permissible

exposure level (PEL), 0.1ppm. CD's short-term exposure level (STEL) is 0.3ppm and has a 5ppm immediately dangerous to life and health (IDLH). Chlorine dioxide is typically exhausted to the outside environment after exposure and all local, state and federal codes must be followed when exhausting to the outside environment. The pulp and paper industry is the single largest sector using chlorine dioxide and thereby emit the largest quantities of gas to the outside environment. If this external exhaust if not possible, common activated carbon scrubbers exist which can be used to remove the gas.

When aerating the gas to the outside, exposure of the gas to light leads to decomposition of chlorine dioxide[52] [53] and, in the gas phase, the primary photochemical reaction is the homolytic fission of the chlorine-oxygen bond to form ClO• and O•. The reaction mechanism for the light catalyzed decomposition of gaseous, dry chlorine dioxide is postulated as

$$ClO_2 + h\nu \rightarrow ClO^{\bullet} + O^{\bullet}$$

$$ClO_2 + O^{\bullet} \rightarrow ClO_3$$

$$2ClO^{\bullet} \rightarrow Cl_2 + O_2$$

Another safety feature of chlorine dioxide gas is the short cycle times compared to other agents. This is important such that it reduces the time when a deadly agent is present and shortens the time when things can go wrong as in people creating unsafe conditions.

PHYSICAL AND CHEMICAL PROPERTIES

Form:	Gas
Color:	Greenish-Yellow
Odor:	Similar to chlorine
Boiling Point:	11°C (for 100% CD concentration)
Boiling point at use concentrations:	-40°C (for 1.0 mg/liter CD concentration)[54]
Freezing point:	-59 °C
Solubility (in water):	8 g/L @ 15°C

TOXICOLOGICAL DATA:
Product: Chlorine dioxide

Acute oral	LD50 = 292 mg/kg (males) LD50 = 340 mg/kg (females)
Acute dermal	LD50 > 2000 mg/kg
Acute inhalation	LC50 = 0.29 mg/L

Mutagenicity:	No human data available.
Reproductive Effects:	No human data available.
Teratogenicity and Fetotoxicity:	No evidence

In 2006, Chlorine dioxide and sodium chlorite have gone through a U.S. EPA's Reregistration Eligibility Decision (RED) Case 4023. Sodium chlorite is used as a precursor in the generation of chlorine dioxide, so the U.S. EPA combine the results of both since they have the same toxicological endpoints. The RED compiled data and summed up the safety aspects for chlorine dioxide. One of the changes made for chlorine dioxide was the as the Food Quality Protection Safety Factor (as required by FQPA) was lowered from a 10x safety factor to 1x. The safety factor is intended to provide for infants and children in relation to pesticide residues in food, drinking water, or residential exposures. This was based upon a complete database for developmental and reproductive toxicity. Also, in the RED, the acute toxicity of chlorine dioxide was categorized. The toxicity category for the oral route was found to be moderate (toxicity category II). For skin the toxicity was considered minimal (toxicity category III) and for inhalation there was moderate risk (toxicity category II). For eye irritation it was considered a mild irritant (toxicity category II. Toxicity Category I is considered DANGER, Toxicity Category II is WARNING, Toxicity Category III requires CAUTION and Toxicity Category IV is safe.

Chlorine dioxide is permitted by the FDA as an antimicrobial treatment for a range of food products, including fruits and vegetables and poultry processing (21 CFR §173.300). Chlorine dioxide is used as a bleaching agent in both flour and whole wheat flour (21 CFR §137.105(a) and 137.200(a)). Chlorine dioxide is also used in the sanitation and treatment of water systems and is further allowed by the FDA as a disinfectant in bottled water (21 CFR §165.110(b)).

In organic food production, chlorine dioxide is currently allowed for use in liquid solution in crop production as a pre-harvest algicide, disinfectant, and sanitizer, including in irrigation system cleaning systems (7 CFR §205.601(a)(2)(ii)); in organic livestock production for use in disinfecting and sanitizing facilities and equipment (7 CFR §205.603 (a)(7)(ii)); and in organic handling for disinfecting and sanitizing food contact surfaces (7 CFR §205.605(b)).

For these uses, residual chorine levels in the water cannot exceed the maximum residual disinfectant limit under the Safe Water Drinking Act. As regulated by EPA, the maximum residual disinfectant levels in drinking water for chlorine dioxide and chlorite ion are 0.8 and 1.0 mg/L, respectively.

One other aspect of chlorine dioxide gas is the minimal amounts of residues. Since chlorine dioxide is a true gas at room temperatures and does not condense on surfaces or penetrate into surfaces it does not leave measurable residues. This was confirmed in studies that showed no residuals after gas exposure by rinsing 304 stainless steel coupons with water for injection (WFI) and measured no residual as measured using an HPLC method for detection of chloride.[55]

According to EPA's Toxicological Review of Chlorine dioxide and Chlorite, "Chlorine dioxide and chlorite are rapidly absorbed from the gastrointestinal tract and slowly cleared from the blood. Chlorine dioxide and chlorite, primarily in the form of chloride, are widely distributed throughout the body and predominantly excreted in the urine. Chloride is the major urinary "metabolite" for both chlorine dioxide and chlorite."

Endotoxins: Testing was performed for endotoxins on devices sterilized with CD as well as coupons inoculated with bacterial endotoxins. Endotoxin levels on sterilized devices were below allowable levels of both 20 EU/device and 2.15 EU/device. It was demonstrated with the inoculated coupons that sterilization with CD reduced the endotoxin levels.[56]

Residues: Testing was performed for residues on devices sterilized with CD for both the US and EU markets. [57]CD is known to break down into harmless salts such as chlorites, chlorides, and chlorates.[58] [59]

D.6. Process and equipment characterization

In health care facilities, process and equipment characterization are generally the responsibility of the sterilizer manufacturer. The management of the health care facility should have controls in place to ensure that the equipment it purchases conforms to national, regional, and local regulations and is suitable for use to sterilize products that require CD sterilization. The management of the health care facility should ensure that the facility has the infrastructure necessary to correctly operate the sterilizing equipment and to achieve effective sterilization of medical devices.

D.6.1. General

The process steps for any decontamination/sterilization are typically inject the sterilant, let the sterilant dwell for a certain period of time, then remove the sterilant.

D.6.1.1. Ambient Sterilization Chambers.

For chlorine dioxide gas the typical ambient pressure/temperature chamber sterilization decontamination cycle consists of the following steps (see figure 1 for ambient isolator cycle).

Step 1-Precondition. This step raises the relative humidity to set point (60-95%).

Step 2-Condition. This step holds the relative humidity at set point for typically 5-60 min.

Step 3-Charge. This step raises the chlorine dioxide gas concentration to set point (1-30 mg/L).

Step 4-Exposure. This step holds the chlorine dioxide gas concentration at the desired CD concentration in mg/L until either the dosage or the Exposure time is attained. If the concentration drops for any reason the gas is returned to the target set point. Doubling this exposure time or dosage would then provide the appropriate SAL level.

Step 5-Aeration. This step removes the chlorine dioxide gas from the chamber by using house exhaust to remove the gas. Typically, 12-15 air exchanges are required to remove the gas to safe levels.

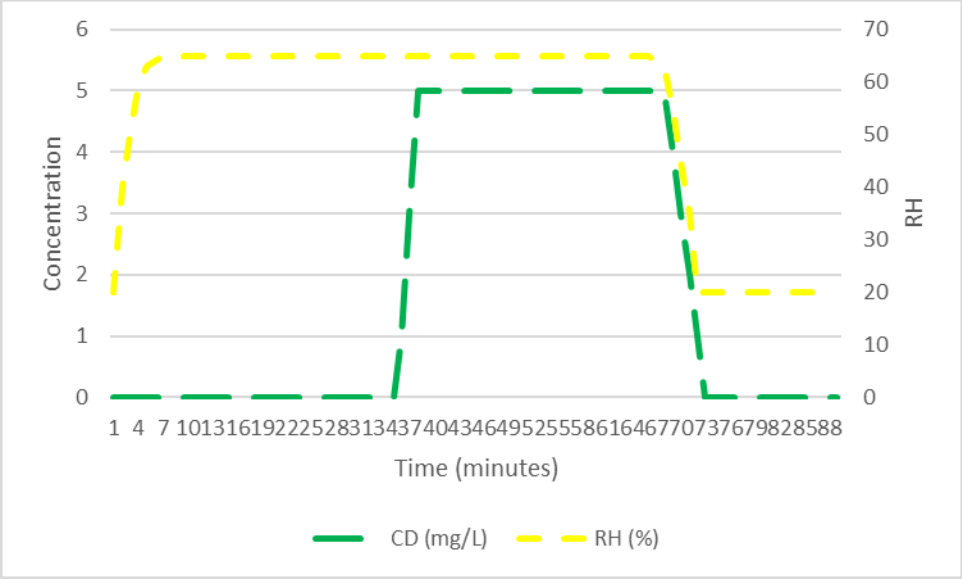


Figure 1: Typical ambient pressure sterilant cycle. Step 1-Precondition. This step raises the relative humidity to set point (65%). 2-Condition. This step holds the relative humidity at set point for typically 30 min. 3-Charge. This step raises the chlorine dioxide gas concentration to set point (5 mg/L). 4-Exposure. This step holds the chlorine dioxide gas concentration at 5 mg/ for 30 min. If the concentration drops for any reason the gas is returned to the target set point. 5-Aeration. This step removes the chlorine dioxide gas from the chamber by using house exhaust to remove the gas. Typically, 12-15 air exchanges are required to remove the gas to safe levels.

D.6.1.2. Vacuum Sterilization Chambers.

If a vacuum chamber process is required for intricate parts, the above steps are the same with the exception of pulling vacuum (typically 5-10KPa) during the Precondition step and returning the chamber to ambient pressure at the completion of aeration (see figure 2 for a vacuum pressure cycle).

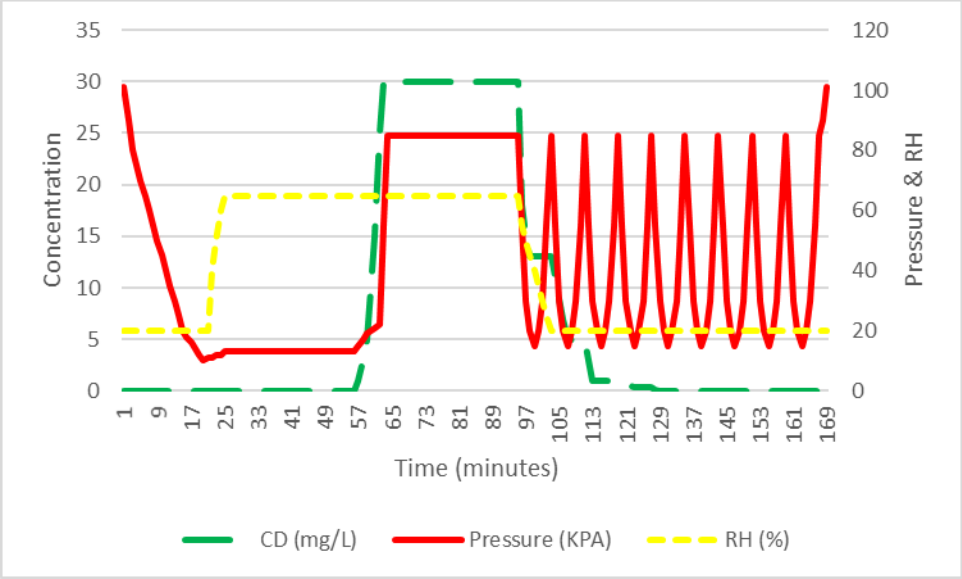


Figure 2: Typical vacuum sterilization cycle. Step 1-Precondition. This step lowers the vacuum to set point (typically 5 to 20 KPa) and adds relative humidity to set point (60-95%%). 2-Condition. This step holds the relative humidity at set point for typically 5 to 90 minutes. 3-Charge. This step raises the chlorine dioxide gas concentration to set point (1 to 30 mg/L) and has the capability to backfill the chamber with filtered air. 4-Exposure. This step holds the chlorine dioxide gas concentration at the select concentration for the selected Exposure time or Dosage. If the concentration drops for any reason the gas is returned to the target set point. 5-Aeration. This step removes the chlorine dioxide gas from the chamber by pulling vacuum and breaking with filtered air. Typically, 8 vacuum/break cycles are required to remove the gas to safe levels.

D.6.2. Process characterization

The steps for chlorine dioxide gas sterilization are listed above in steps 1-5. During these steps certain factors or parameters must be met. There are 2 critical parameters for a successful chlorine dioxide sterilization. One parameter is RH or relative humidity. Humidity or moisture is critical for all spore log reductions, no matter which sterilizing agent is used (formaldehyde, Ethylene Oxide (EO) CD gas, or vapor phase hydrogen peroxide).[60 61 62 63] Moisture conditions the spores and allows the sterilant to enter. The other critical parameter is the gas concentration which is measured with a photometric device. Gas concentration and RH are monitored and controlled in real-time.[64]

D.6.2.1. Specific process parameters must be identified based on the specific load type, the specific load size, and the specific packaging of the load. The cycle parameters to kill spores on a Biological Indicator (BI) sitting on a shelf in the chanber will be different than that same BI in a challenging location in a Medical Device. Those cycle parameters will also be different than if that Medical Device was now located inside of a display box which is inside of a shipper box. Cycle development activities must be undertaken with appropriate BI's placed in the most difficult location of the Device to be sterilized in the specific sterilizer with the load conditions where the ongoing sterilization will take place.

The resistance of microorganisms to deactivation by CD is affected by their moisture content. At low levels of humidity, microbial resistance increases with decreased humidity. Studies performed at varying RH levels (45%, 55% & 65%) showed increasing dosages or exposures are required for lower RH levels. It was found that at a dosage of 720 PPM-Hours is good for 6 SLR at 65% RH, while a 1000 PPM-Hours is good for SLR at 55% RH and 1550 PPM-Hours was necessary for 6 SLR at 45% RH.

For this reason, it is common practice to control and monitor the humidity of the atmosphere to which the product is exposed in order to attempt to equilibrate the moisture content of the microorganisms with the local conditions. Consideration should be given to the packaged product to ensure that excessive relative humidity will not impact the product functionality and package integrity. One of the ways to assist in addressing the humidity in the product is to precondition product at a defined temperature and humidity. Such preconditioning can reduce the duration of the sterilization cycle. For health care facilities, excessive moisture content can also be caused by inadequate drying after cleaning.

Product humidification is used to establish reproducible product moisture content prior to CD exposure. Studies establishing minimum residence time in preconditioning cells/rooms ensure that the required conditions are attained in the sterilization load. Precautions should be taken to prevent excessive water condensation on the sterilization load.

Although it is common practice to perform preconditioning in a separate chamber, room, or cell, sterilization cycles can be designed to attain the required humidity ranges within the load during a conditioning phase in the sterilization chamber. To minimize the risk of excessive condensation, it is recommended that the load temperature should be maintained above the process environmental dewpoint temperature during the preconditioning and conditioning phases of the sterilization process.

The actual temperature and humidity ranges within the sterilization load at the end of preconditioning should be demonstrated during PQ.

Where applicable, a maximum time between removal of the load from preconditioning and the start of the sterilization cycle needs to be established. A transfer time of 60 min or less is common practice.

a) When product enters the sterilization chamber without preconditioning, consideration should be given to the possibility of excessive condensation in product and packaging.

b) It is essential for the manufacturer of the product to be sterilized to be aware of the possible occurrence of residues in the product. Temperature, dwell time, forced heated air circulation, load characteristics, and product and packaging materials all affect the efficiency of aeration, and the set points and tolerances should be taken into account when evaluating residual levels. Aeration can be performed within the sterilizer, in a separate area(s), or in a combination of both.

D.6.2.2 For a chlorine dioxide sterilizer, the process variables to monitor and control are:

- Pressure with two pressure transmitters capable of reading from 5kPa to atmospheric pressure.
- Rh with two Rh probes capable of reading from 20%Rh or lower to 95% Rh or higher.

- CD Concentration with two UV-VIS spectrophotometers capable of reading from 0.1 or lower to 30 mg/liter or higher.

D.6.2.3 Pre-sterilizer treatment sometimes consists of prehumidifying the load in a separate room or chamber prior to it's placement into the vacuum sterilizer. This is used in many EtO processes to save time while in the sterilization chamber. For chlorine dioxide, this would not be detrimental but is not necessarily required either. Prehumidifaction time is typically short enough that performing that as part of the sterilization cycle should not be a hardship timing wise. If items are packed in shipper boxes, placing the load in a prehumidification room might be helpful. This is all to be determined during the cycle development process.

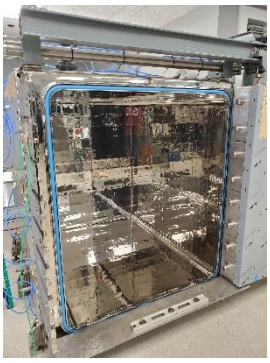
D.6.2.4 Post-sterilizer treatment sometimes consists of aerating the load in a separate room or chamber after it's placement from the vacuum sterilizer. This is used in many EtO processes to save time while in the sterilization chamber. For chlorine dioxide, this would not be detrimental but is not necessarily required either. Aeration time is typically short enough that performing that as part of the sterilization cycle should not be a hardship timing wise. This is all to be determined during the cycle development process. Unlike EtO, Chlorine dioxide is not carcinogenic so offgassing is less of a concern. Offgassing is typically non-existant once aeration inside the chamber as part of the sterilization process is completed.[65]

D.6.3. Equipment characterization

D.6.3.1. The following factors should be considered when characterizing the equipment

Chlorine dioxide gas generators come in a few different forms. There are vacuum chamber sterilizers for the intricate parts/components/medical devices. In each generator the capability to measure the RH and gas concentration is incorporated and provide real time measurement and control.

Steridox-14



Steridox-100

a) Preconditioning area characterization.

Preconditioning can be performed in a separate preconditioning area (chamber, cell, or room). Humidification by steam is preferred because humidifiers that operate by

dispersion of unheated water as an aerosol (e.g., spinning disc humidifiers, ultrasonic humidifiers, and nebulizers) can be a potential source of microbial contamination.

The preconditioning area (if used) should have the following performance and monitoring capabilities:

- adequate air circulation to ensure the uniformity of temperature and humidity in the usable space, and to ensure that uniformity is maintained in a loaded room or chamber;
- airflow detection equipment, alarm systems, or indicators monitoring the circulation system to ensure conformance to predetermined tolerances;
- means of recording time of load entry into and removal from the preconditioning area;
- means of monitoring cell/room temperature and humidity; and
- means of controlling cell/room temperature and humidity.

b) Sterilizer Chamber characterization.

The sterilization chamber should have the following performance and monitoring capabilities:

- means of monitoring time, chamber pressure (if vacuum cycles), CD gas concentration, temperature, and humidity (if humidity additions are controlled by sensor readings);
- means of controlling time, chamber pressure, CD gas concentration, and humidity; and
- if parametric release is used, analytical instrumentation for the direct analysis of humidity during conditioning and CD concentration during CD charge and exposure time (see also, 9.5.5 and D.9.5.5);
- a system controlling the admission of gaseous CD to the chamber;
- means to demonstrate that gaseous CD is injected into the chamber; and
- means to detect and alert deviations to cycle parameters so that remedial action can be taken in a timely fashion; and
- Means for removal of gaseous CD from the chamber.

c) Aeration area characterization.

An aeration area (chamber, cell or room) is not typically needed or utilized but can be used to remove CD residuals from product/packaging. Fresh air make-up, and air re-circulation throughout the area are important to ensure consistent and reproducible results. The aeration area should have the following performance and monitoring capabilities:

- airflow detection equipment, alarm systems or indicators monitoring the air handling system to ensure that it operates within predetermined tolerances and maintains adequate airflow in a loaded room or chamber;
- equipment to re-circulate air;
- means of monitoring low levels of CD gas concentration.

D.6.3.2. The equipment specification should be reviewed to ensure that regulatory and safety requirements are met, technical specifications are appropriate, and services and infrastructure necessary to operate the equipment are available.

The following items should be considered when preparing the equipment specification:

a) Steam is utilized to humidify the load and is not intended to be a sterilant. The consistency of steam supply can be determined by the periodic analysis of the boiler feed water or condensate.

b) A minimum of two probes to measure chamber humidity should be used. Large volume chambers can be fitted with more than two probes so as to ensure that the monitoring/control system captures data that reflects the humidity throughout the chamber during use.

NOTE The purpose of two separate probes is to prevent the failure of one sensor from causing an out-of-specification process from being erroneously accepted. Comparing two separate humidity sensors will detect that one of the sensors has failed.

c) It is important to maintain uniform conditions within the sterilizer chamber during processing. This can be achieved by forced gas circulation. If used, a gas circulation system should be equipped with a monitoring device to indicate when circulation is ineffective, as devices that solely monitor “power on” to the fan or pump are not sufficient. If this is not possible, then redundant circulations systems must be utilized.

d) A minimum of two sensors to measure chamber CD gas concentration should be used. Failure mode for the CD sensor is 0, so non-detection of CD gas will result in cycle failure. The CD concentration monitoring and control system consists of a UV-VIS spectrophotometer that measures the CD concentration via the density of its yellow-green color. A sample pump continuously pulls a sample from the chamber and through the spectrophotometer where absorption of the light is determined. A float switch monitors the functionality of the sample pump ensuring that a real-time concentration of the chamber is occurring.

It might not be possible to calibrate controlling and monitoring instruments under actual processing conditions, e.g., humidity sensors. Calibration results for these instruments should be correlated against qualification studies. Processing conditions can have a detrimental effect on some types of sensors, e.g., humidity sensors. Sensors might require replacement after repeated exposure to processing conditions due to irreversible deterioration of materials currently used as sensing elements. It might be necessary to implement a program of more frequent maintenance for these sensors than that recommended by the sensor manufacturer/supplier.

D.6.3.3. Software used to control and/or monitor shall be prepared and validated in accordance with the elements of a quality system that provides documented evidence that the software meets its design specification.

D.6.3.4. A PLC and HMI are utilized to control and monitor the process parameters as well as provide documentation for the process..

D.6.3.5. If there is an undetected failure of a control or monitoring function, a sterilization load could be released without having met its required processing parameters. To prevent this from happening, it is general practice to have redundant sensors for many critical process parameters. The common options for utilizing these redundant sensors include:

a) use one sensor for control, and another sensor for monitoring and reporting;

b) use two sensors, or their average value, for both monitoring and control; this system needs to generate an automatic fault condition if the difference between the two sensors exceeds a defined value; and

c) use dual element sensors for both monitoring and control; this system needs to generate an automatic fault condition if the difference between the two elements exceeds a defined value.

D) use other sensors to measure parameters. For example, the CD sensor uses a sample pump to bring a continuous air/gas sample to the photometer. A flow switch is employed to ensure proper gas flow. This is adequate to ensure proper measurement. If the CD sensor/photometer fails it will fail with a 0 reading and this will generate system faults. Additionally, the photometer does have lamp fault alarms which alert the control system.

D.7. Product definition

D.7.1. General

D.7.1.1. Product definition involves documentation of essential information about the medical device to be sterilized (i.e., the new or modified product).

Product definition for a medical device includes the medical device itself, the sterile barrier system containing the device, and any accessories, instructions, or other items included in the packaging system. It also includes a description of the intended functionality of the medical device and the available manufacturing and sterilization processes. The product definition process should also consider whether this is a new design or part of an existing product family.

The following should be considered as part of product definition:

a) physical attributes of the medical device (composition and configuration);

b) intended use of the medical device;

c) whether the medical device is intended for single use or for multiple use;

d) design characteristics that would affect the choice of sterilization process (e.g., batteries, fiber-optics, computer chips);

e) raw materials/manufacturing conditions that could affect microbiological quality (e.g., materials of natural origin);

f) required sterility assurance level (SAL);

g) packaging;

h) loading configuration; requirements for a specific load or mixed loading configurations, or range of acceptable loading configurations; and

i) compatibility with CD gas and processing conditions (preconditioning, sterilization, and aeration processes).

D.7.1.2. A technical review should be performed to compare the new or modified product to the validated product and/or PCD that was used to validate the existing CD process. The construction and configuration of the new or modified product should be carefully examined for any features that could present obstacles to the penetration of CD or

humidity. For medical device manufacturers, this comparison should also involve an examination of factors that could affect the initial bioburden on the product, including the location of the manufacturing facilities, the types of raw material used, the sources of these materials, and production methods. For modified reusable products, this comparison should include the evaluation of the cleaning efficacy for the product.

If a new or modified product is demonstrated to be equivalent to an existing medical device or PCD for which sterilization characteristics are already known, the new or modified product might be considered to be part of a product family or a processing category.

NOTE AAMI TIR 28[26] is a useful guide for minimizing the risk of introducing a new or modified product that presents a greater challenge to the sterilization cycle than the product/PCD previously validated.

If the product configuration, density, or load configuration of the candidate product and its packaging could present a greater challenge to the sterilization process than the previously validated product, then CD, and humidity penetration studies and/or cycle lethality studies should be conducted.

As part of the technical review, the following questions should be considered. If the answer to any of the questions is “yes,” then further evaluation of the new or modified product might be necessary to determine if it is more difficult to sterilize than the previously validated product:

a) with respect to the previously validated product, does the new or modified product:

1) have more restricted passageways or inner chambers;
2) have fewer openings;
3) have more internal surfaces;
4) have more mated surface areas and/or occluded spaces;
5) have more closures;
6) have longer or narrower lumens;
7) include changes or differences that could reduce the transfer of humidity, or CD;
8) have a bioburden or bioburden resistance significantly higher than that of the reference product (due to manufacturing conditions, handling, cleaning process, or materials used); or
9) contain materials or structures that could be adversely affected by the proposed processing or sterilization method;

b) with respect to the previously validated product, does the packaging of the new or modified product:

1) have any changes in packaging elements, including instructions or protective barriers;
2) have any additional impermeable protective barriers (e.g., container, case, template, that would restrict or interfere with CD or humidity penetration or removal);

3) have a change in the porosity of the packaging material, (e.g., basis weight, treatment - adhesive or coating);

4) have a decrease in the surface area of the venting material or underlying opening (e.g., application of tape or secondary label, change in size of label);

5) increase the bioburden level of the product; or

6) change the number of barrier layers?

c) with respect to the previously validated product, does the load configuration of the new or modified product:

1) differ significantly from the validated load configuration of the reference load;

2) differ significantly in the amount of absorptive materials;

3) differ significantly in density from that of the reference load; or

4) differ significantly in total load volume.

D.7.1.3. The presence of either occluded spaces or mated surfaces should be evaluated in consideration to the designation of an internal PCD that would be used for subsequent lethality qualification studies.

D.7.1.4. The major function of a sterile barrier system for a sterilized medical device is to ensure that the product remains sterile until used. During sterilization, the sterile barrier system needs to be able to withstand the process conditions and to remain intact to ensure product quality.

When selecting a packaging system for a product that is to be sterilized, certain major design and manufacturing factors are considered with respect to the particular sterilization process. To ensure CD penetration, the permeability of the packaging to the particular sterilizing environment is of utmost importance. As air removal can be part of the CD sterilization process, the packaging system should also allow gases to vent into, and out of, the package during pressure changes, during gas injections and evacuations without damage to, or rupture of, the seal integrity.

The ability of the sterile barrier system (SBS) to protect product during customary handling and distribution should be demonstrated. Evidence should also be generated to show that the SBS can withstand the sterilization process without losing its ability to protect the product. Validation of the SBS should consider the potential stresses that the SBS can be exposed to during an CD sterilization process. Considerations would include vacuum/pressure levels, rate of pressure change, temperature, etc. It is common practice to demonstrate suitability of the SBS by exposure of the SBS to multiple sterilization processes (see, D.7.2.1 and D.7.2.2).

Packaging considerations are addressed in more detail in the ISO 11607-1 and ISO 11607-2.

D.7.1.5. The load configuration in the chamber can influence product humidity, CD gas penetration and CD gas removal. The load configuration is to be defined during the validation to ensure adequate product humidity, and CD penetration and CD removal during processing.

D.7.1.6. A PCD is a device into which a microbiological challenge is located. Examples of ways to develop

PCDs for use in the demonstration of equivalence include, but are not limited to

a) placement of a microbiological challenge between rings, lands, grommets, or ribs of a syringe stopper;

b) placement of a microbiological challenge in the middle of the lumen of a tube that is then reconnected using a solvent bond agent or a connector to restore product integrity;

c) placement of a microbiological challenge in an interface; and

d) placement of a microbiological challenge in a series of envelopes or packages. Several PCD designs have been recommended for use in health care facilities.

NOTE For further information, see ANSI/AAMI ST41.

To prepare the internal PCD, the microbiological challenge can be inoculated on the product either directly or indirectly. Direct inoculation is accomplished by applying a liquid suspension of the spores on the product. Indirect inoculation is accomplished by placing an inoculated carrier either within the package or in/on the product.

Listed below are various ways to prepare a PCD.

a) Inoculated product: the product to be sterilized is used to prepare the PCD and is inoculated directly or indirectly.

b) Inoculated simulated product: a simulated product is used to prepare the PCD and is inoculated directly or indirectly. The simulated product consists of portions of a medical device or a combination of components that are known to represent the greatest challenge to the process while still adequately representing all products within a product family.

c) Inoculated object: such as a package, piece, or tubing, that is used to prepare the PCD and is directly or indirectly inoculated.

NOTE Direct inoculation with a spore suspension can result in variable resistance of the inoculated product because of surface phenomena, other environmental factors, and the occlusion of the spores on or in the product. Therefore, it is important to provide scientific rationale or validation for this practice to ensure that the resistance of the inoculated product is reasonably correlated to the routine product. The inoculum recovery should also be validated if resistance is measured by plate count techniques. See Gillis and Schmidt,[30] West[40], and ISO 11737-1 for additional information.

A means of demonstrating equivalence to a previously qualified product or internal PCD is the comparison of the relative rates of inactivation of BIs placed in a challenge location within the new or modified product and previously qualified product/master product (see D.12.5.2) when both are exposed to a fractional cycle. Equivalence studies should compare the new or modified product to the internal PCD used to validate the process. If a PCD is used for this comparison, this resistance of the PCD should be assessed as part of the annual review.

D.7.2. Product safety, quality and performance

D.7.2.1. It is important to select materials that tolerate the chemical and physical changes caused by CD and/or any diluents over the anticipated range of sterilization conditions. Properties of materials required to satisfy requirements for product performance, such as physical strength, permeability, physical dimensions, and resilience, are evaluated after sterilization to ensure that the materials are still acceptable for use. Degradation effects due to exposure to the sterilization process, such as crazing and embrittlement may need to be considered. Where applicable, the effects of exposure to multiple sterilization processes may also need to be evaluated.

Demonstration that the specified sterilization process does not affect the correct functioning of the product can be accomplished by performing functionality tests, or other appropriate tests, on the medical device and its packaging system. These tests can be performed after exposure in the sterilizer or other environmental chambers that simulate the specified process and can range from a simple visual inspection to a battery of specialized tests.

Elements that could affect safety, quality, or performance include:

a) cycle pressure changes that could affect the sterile barrier system seal integrity;

b) effects of CD exposure time, humidity and, if applicable, any diluent gases present in the intended sterilization mixture;

c) inclusion of new materials known to retain higher CD residuals;

d) packaging characteristics;

e) the presence of lubricants, especially within mated surface areas;

f) whether the medical device requires disassembly or cleaning;

g) number of sterilization cycles.

D.7.2.2. The evaluation of multiple sterilization cycles can be performed utilizing the routine sterilization process for the product/package. The effect of repeated sterilization and any necessary pre-treatment on the materials, functionality, and safety of the product should be evaluated.

For reusable medical devices, the manufacturer’s reprocessing instructions should be available and followed. The instructions should include the recommended sterilization parameters for the process and the limits to the number of sterilization cycles to which the reusable medical device can be exposed. If applicable, testing and inspection should be performed to assess functionality of the reusable medical device following sterilization. The medical device manufacturer’s claims for the number of allowable cycles should be considered to be the maximum. A system should be in place that will provide notification if the maximum number of cycles is reached.

NOTE See ISO 17664 for more information.

D.7.2.3. The biological safety of product following exposure to the sterilization process shall be establishedin accordance with the applicable parts of the ISO 10993 series..

D.7.2.4. Proper aeration is essential to control CD residues in medical devices after CD processing. Consideration should be given to the placement of the residual product test samples within the load, taking into account the most challenging positions for CD

removal. CD breaks down into non-carcinogenic salts such as chloride, chlorite and chlorates.[66] [67]

For health care facilities: If information regarding aeration for a medical device is not available from the manufacturer, the health care facility should establish the aeration process for that device using either data or knowledge of the product and its material and design. The aeration process should be established based upon the most difficult-to-aerate product or product family.

D.7.3. Microbiological quality

D.7.3.1. Guidance on testing for bacterial endotoxins is provided in ANSI/AAMI/ST72 and the applicable pharmacopeia. Testing was performed for endotoxins on devices sterilized with CD as well as coupons inoculated with bacterial endotoxins. Endotoxin levels on sterilized devices were below allowable levels of both 20 EU/device and 2.15 EU/device. It was demonstrated with the inoculated coupons that sterilization with CD reduced the endotoxin levels.[68]

D.7.3.2. In health care facilities, attention to microbiological quality will comprise having strict procedures for collection and handling of used, reusable medical devices, and for validation and control of the cleaning processes for reusable medical devices in accordance with the medical device manufacturer's instructions.

When using the bioburden approach (see Annex A), bioburden testing should be performed at least quarterly. The period of monitoring can be extended following a documented risk analysis that considers the following: the use of product families, historical data, statistical analysis, manufacturing frequency, and product design.

D.7.4. Documentation

Upon completion of the product definition, the following should be documented:

a) A description of the product configuration and how it is to be presented to the CD process (packaging and load configuration). The specification should also include or reference the required SAL, as well as evidence for, or assessment of, the compatibility of the product with the process.

b) The result of the comparison between the new or modified product and the existing validated product(s). This result should clearly demonstrate that product complexity, materials, packaging, and load configuration were assessed.

c) Evidence or assessment of the bioburden of the product and its resistance relative to the internal PCD.

d) The documented conclusion that the new or modified product is suitable for adoption into the product family/processing category specifically referenced in the current validation study to achieve the specified SAL. This conclusion should include or reference any results from additional tests performed to supplement the existing validation study and any further testing performed for confirmation/qualification for routine release of product from the existing validated cycle (i.e., residual testing, functional testing).

This documentation should be approved, retained, and retrievable.

D.8.Process definition

D.8.1 The purpose of this activity is to obtain a process specification which can be applied for the sterilization of the defined product during the validation studies.

D.8.2 The result of the process definition activities is a detailed specification of a sterilization process. The selection of the sterilization process that is to be used for medical devices should include consideration of all factors that can influence the efficacy of the process. The following should be taken into account:

— availability of sterilization equipment;
— range of conditions that can be achieved within the available sterilizing equipment;
— sterilization processes already in use for other products;
— sterilant to be used (chlorine dioxide gas);
— product limitations (i.e. temperature, humidity, pressure sensitivity);
— requirements for levels of residual chlorine dioxide gas and/or its reaction products;
— results of process development experiments.

During process definition, a manufacturer will use microbiological testing and other analytical tools to help establish an appropriate sterilization process for a medical device.
The sterilization process parameters to be established include:

a) temperature range within the preconditioning room (if used);
b) relative humidity range within the preconditioning room (if used);
c) time set point and range within the preconditioning room (if used);
d) vacuum and pressure levels and rates of pressure changes in the sterilization chamber;
e) if used, confirmation that chamber recirculation operational during sterilant dwell;
f) Not applicable
g) humidity control set point (pressure or %RH) and range within the sterilization chamber environment;
h) Chlorine dioxide injection set point;
i) chlorine dioxide dwell time/total dosage;
j) setting for the in-chamber gas flushing prior to the removal of the load from the sterilization chamber (if used);
k) temperature set point and range within the aeration room (if used);
l) time set point and range within the aeration room (if used);
m) air flow/changes parameters.

NOTE For reference in the development of sterilization processes, Annexes A and B provide requirements for determination of cycle lethality.

For health care facilities, for reusable medical devices that will be reprocessed in the health care facility, the manufacturer is expected to provide validated reprocessing instructions, which are based in part on the process definition. It is then the health care facility's responsibility to review this documentation and confirm that it can follow the medical device manufacturer's instructions using its own equipment and sterilization processes. The health care facility's purchasing procedures should require that, prior to the purchase of a chlorine dioxide sterilizer, the reprocessing instructions be evaluated to confirm that the device is compatible with the equipment and sterilization processes that are in use at the facility. See also ISO 17664.

If the medical device or packaging manufacturer supplies instructions for reprocessing that are not specific enough or not appropriate, the facility should either perform a validation or assess the appropriateness of its own reprocessing method, based on materials effect data and reprocessing instructions for other devices. If the health care facility is not able to validate the product or assess the

appropriateness of its own reprocessing method, it should not reprocess the medical device.

D.8.3 A developmental chamber is usually a smaller vessel than the production chamber and can be used to perform studies to support validation. Using a developmental chamber does not preclude confirmation of PQ in a production chamber.

D.8.4 When establishing process definition it is important to consider the impact of the selected processing parameters and their tolerances on the safety and functionality of the product and its packaging. As there are a number of parameters within a sterilization process, (humidity, pressure changes/rates, chlorine dioxide concentration and time), it is impractical to assess the tolerances of all combinations of all variables. A determination should be made as to which variables will have the greatest impact, and those should be assessed. Data supporting this activity can be collected from alternative studies, e.g. product and its packaging validations, product and its package stability test studies, accelerated aging studies, etc. Alternatively, data can be generated from a specific challenge cycle(s) in a developmental or production chamber.

D.8.5 The rate of microbiological inactivation provided by the specified sterilization cycle for a specific microbiological challenge shall be determined, using one of the methods described in Annexes A or B or by an alternative method that demonstrates the product has achieved the required sterility assurance level (SAL).

D.8.6 A number of approaches can be used to show that the BI is appropriate.

Approach 1
This approach is to use the rationale that most of the microorganisms found on product present a lesser challenge than the reference microorganism. This approach is applicable when
a) the BI used in the PCD is in accordance with the applicable sections of ISO 11138-2:2006; and
b) the product bioburden is consistent, and is not likely to contain highly resistant microorganisms.
In this approach, bioburden trending data should be available and should demonstrate the consistency of the bioburden regarding the number and types of microorganisms. Manufacturing processes and product contact materials should also be evaluated to ensure that potential sources of bioburden are identified and controlled.

Approach 2
This approach is to use a test of sterility of the product and PCD, following a fractional cycle. The results of this study should provide a means of lethality comparison using survival data from the tests of sterility for the product and PCD.
Typically in this approach, product tests of sterility samples and BI/PCD are exposed to fractional cycle(s) with the intent of achieving negative growth for all product tests of sterility and survivors of the test microorganism from the BI/PCD.

Approach 3
This approach can be applied in cases where
a) the product bioburden challenge is equal to or greater than the challenge of the BI within the PCD,
b) the product bioburden contains highly resistant microorganisms, or
In this third approach, the lethality challenge of the bioburden and the PCD can be based on direct enumeration methods and/or fraction-negative methods. (See ISO 14161).
If there is an indication that the challenge posed by the product bioburden exceeds that of the PCD (i.e.

if the PCD is not appropriate), one of the following can be used:

a) select a BI to use within the PCD having a higher population and/or resistance;
b) the product can be pre-treated before sterilization to reduce the bioburden numbers;
c) the product, the process or both can be evaluated to determine how to reduce the bioburden number or resistance (e.g. by changing the raw materials or manufacturing process used, by improving the manufacturing environment, or by modifying the product design)
d) develop a new PCD.

If any of the above changes are made, it is important to verify the effectiveness of the changes. Product design might not allow a BI to be positioned in the most difficult-to-sterilize location of the product. In this circumstance it might be appropriate to place the BI in a location to which the relationship with the most difficult-to-sterilize location can be established. Additionally, in many medical devices the most difficult-to sterilize location contains a low number of microorganisms, and therefore the challenge population may be more closely linked to the bioburden of the product.

Different types of PCDs are described in D.7.1.6. Methods similar to those used for determining the appropriateness of the BI can be used for determining the appropriateness of the PCD. A PCD located within the confines of the product, in the product shipper or product shipper case is an internal PCD, whereas a PCD located between shipper cases or on the exterior surfaces of the sterilization load is an external PCD. Internal PCDs can be used for routine product release; however, external PCDs are usually used as they are easier to recover after completion of the sterilization process. Studies conducted in a development chamber can be used to demonstrate the comparative lethality challenge of the internal and external PCDs; however, consideration should be given to the effects of load volume and production sterilizer performance when performing these studies. If the development chamber is not capable of duplicating the production process then the comparative lethality challenge studies should be conducted in the production chamber.

The comparative lethality challenge of the internal versus external PCDs can be assessed using concurrent exposure(s) in a fractional cycle(s). The resulting data can be used for:
a) making decisions about which internal PCD is appropriate to validate the sterilization process;
b) evaluating candidate designs for external PCDs (i.e. for routine monitoring of the process);
c) assessing the equivalence of new or modified products for adoption into a validated sterilization process; or
d) deciding if a new or modified product or internal PCD should become the master product for a product family or processing group.
There can be instances when it is desirable to compare the lethality challenge of one PCD to another without comparing both to the challenge of the product. This is often used when an internal PCD has been proven to be appropriate and an external PCD is being introduced for monitoring routine production cycles for conventional release or when it is desirable to change to another external PCD. In this case, a method of evaluating the appropriateness of the PCD is to demonstrate that the external PCD
presents an equal or greater lethality challenge when compared to the internal PCD. Typically this is done by performing a single fractional cycle that compares the fraction-negative results of the internal and external PCDs. If the lethality challenge of the external PCD is less than the lethality challenge of the internal PCD (not more than 20 %, United States Pharmocopeia Biological indicators for Ethylene Oxide Sterilization), the PCDs may be considered equivalent since this is the confidence level of the biological indicator used within the PCD.
NOTE It is not uncommon to find an external PCD in a less difficult-to-sterilize configuration presenting a

greater lethality challenge than an internal PCD in a more difficult-to-sterilize configuration. It is theorized that this occurs because the EO is removed more rapidly from the external PCD than the internal PCD, resulting in less gas exposure time to the microbiological challenge.

D.8.7 Commercially supplied biological indicators used in the definition of the sterilization process shall comply with the requirements in D.8.6 and all applicable clauses of ISO 11138-1.

D.8.8 If chemical indicators are used as part of the definition of the sterilization process, these shall comply with ISO 11140-1.

D.8.9 If tests of sterility are performed during the definition of the sterilization process, they shall comply with ISO 11737-2.

D.9.Validation

Chlorine dioxide gas is easily validated using standard commercially available biological indicators spore strips. Typically, *geobacillus stearothermophilus* or *Bacillus atrophaeus* is used as this spore is resistance to the gas as all spores are hard to kill. This is why spore strips are used as biological indicators. The thought is if the spores are killed then other organisms that are easier to kill (virus's bacteria & fungi) are also killed. There is installation qualification (IQ) and operation qualifications (OQ) available for all generators and equipment. Performance qualifications (PQ) are also available. Chlorine dioxide gas is easy to validate since cycles are repeatable due to the process parameter measurement. Because of this most cycles are already known. For ambient pressure cycles the concentrations are typically 1-5mg/L and for vacuum pressure applications the concentrations range from 3-30mg/L. This is due to the small openings and intricate parts. These small openings require the vacuum pressure along with increased concentrations.

D.9.1. General

D.9.1.1. The object of validation is to document the evidence required to provide a high degree of assurance that a specific process will consistently produce product meeting the required sterility assurance level (SAL). Product sterilized in the validated process should be shown to meet predetermined specifications and quality characteristics related to product functionality and safety (i.e., through product compatibility studies).

Validation of the sterilization process should be performed according to an approved written document (e.g., protocol) that defines the testing procedures and the acceptance criteria, prior to initiation of testing. This document should be reviewed by a sterilization specialist(s). If protocol deviations occur during validation they will need to be investigated and addressed in accordance with the device manufacturer's quality management system.

The elements of validation, as defined in this clause, are

a) IQ;

b) OQ; and

c) PQ.

In a health care facility, IQ and OQ are typically performed by the sterilizer manufacturer, although they can be performed by any qualified personnel. MPQ data might be available from the sterilizer manufacturer for general loads.

For health care facilities, this means describing and documenting the following:

a) the validation steps that need to be performed;

b) the way in which these validation steps will be performed, along with a listing of responsible individuals, departments, and/or outside contractors; and

c) the criteria for successful validation.

For health care facilities, there is an option of contracting with an outside service to perform this validation; however, the health care facility is still responsible for ensuring that the validation complies with the requirements of this document.

D.9.1.2. IQ is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

D.9.1.3. OQ is undertaken to demonstrate the ability of the equipment to meet the performance requirements of its design specification.

D.9.1.4. PQ is the stage of validation that uses product to demonstrate that the equipment consistently operates in accordance with predetermined acceptance criteria and the process yields product that is sterile and meets the specified requirements. IQ and OQ may be a one-time exercise for the specific equipment being employed for a sterilization process. PQ should be carried out for each new process and/or product to be validated to demonstrate that the process complies with identified acceptance criteria and is capable of delivering the required SAL to the product.

D.9.2. Installation qualification

D.9.2.1. Equipment

D.9.2.1.1. The supporting documentation for IQ should include descriptions of the physical and operational characteristics of the equipment (including ancillary equipment). Examples of relevant documents include design specifications, the original purchase order, user requirements specifications, and functional design specifications.

The following are examples of equipment components that should be qualified to ensure that the equipment was installed according to the applicable specifications and requirements:

a) chamber and door construction;

b) seals and connections on chamber and piping construction (i.e., ability to maintain specified pressure and vacuum extremes);

c) supply systems for gases and liquids (e.g., air, nitrogen, steam, CD, and water), including filters (if used);

d) the electrical supply, which should adequately and consistently supply the power needed for proper equipment and instrumentation operation;

e) gas circulation systems, where used;

f) gas injection systems;

g) vacuum systems, including pumps, pump cooling systems, and piping;

h) exhaust, emission control and abatement systems;

i) other critical systems that could affect process conditions, such as process automation, safety systems, etc.;

j) the calibration of instruments (e.g., sensors, recorders, gauges, and test instruments) that monitor, control, indicate, or record parameters, such as temperature, humidity, pressure, and CD concentration; and

k) the documented procedures for IQ should specify how each element of this qualification is planned, performed, and reviewed.

D.9.2.1.2. Guidance can be found in IEC 61010-2-40.

D.9.2.1.3. Operating procedures for the equipment shall be specified in the Equipment Operations Manual. This is not a comprehensive list, but these operating procedures include step-by-step operating instructions, fault conditions, the manner in which they are indicated, and actions to be taken, instructions for maintenance and calibration, and details of contacts for technical support..

D.9.2.2. Installation qualification

D.9.2.2.1. The location in which the equipment is to be installed should comply with all pertinent national, regional, and local regulations.

D.9.2.2.2. National and local requirements for occupational health and safety should be consulted as to how they apply to potential CD exposure.

To protect the health and the safety of personnel, equipment that detects atmospheric levels of CD gas should be installed near the sterilizer and anywhere else where potential exposure could occur.

CD safety is achieved and maintained through a combination of factors that include:

a) proper design, installation, and maintenance of systems and equipment;

b) compliance with applicable regulations for occupational health and safety and for environmental protection;

c) development and implementation of policies and procedures that support safe work practices;

d) atmospheric monitoring in areas where CD exposure could occur;

e) use of personal monitoring devices as appropriate;

f) personnel training; and

g) periodic audits of equipment, personnel, and processes to ensure on-going compliance with design specifications and with the facility's policies and procedures.

In healthcare facilities, IQ is generally the responsibility of the sterilizer manufacturer; in industrial facilities, it is often performed by site personnel in conjunction with a factory representative. If the IQ is performed by the manufacturer or by a third party, the facility is responsible for retention and management of documents and records relating to the purchase and installation of the equipment.

D.9.2.2.3. The storage conditions for CD consumables should be in accordance with the manufacturer's recommendations and all applicable regulations.

D.9.2.2.4. Prior to IQ, the calibration status of any test instrumentation used during the IQ shall be confirmed.

D.9.2.2.5. Drawings, process and instrumentation diagrams (P&ID), and schematics should be checked against the as-installed configuration and updated where necessary.

Drawings and parts lists for the equipment should include:

a) pipe work and instrumentation schematic drawings (i.e., process and instrumentation diagrams);

b) a list of other pertinent mechanical and electrical drawings and their location;

c) a list of critical instruments and devices, particularly those influencing process control, for which physical characteristics and manufacturer performance claims (e.g., accuracy, repeatability, size and, model) should be kept on file;

d) process control logic or software documentation necessary to support validation, including 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.

D.9.2.2.6. Changes made to the systems during the IQ shall be assessed for their impact on the design and process specifications and documented in the design history file.

D.9.3. Operational qualification

D.9.3.1. The following information should be documented for all instrumentation used for monitoring, controlling, indicating, or recording:

a) equipment identification;

b) calibration schedule;

c) actual completion date for each calibration, as well as who performed it; and

d) the next scheduled calibration date.

D.9.3.2. OQ for CD equipment is carried out either with an empty sterilizer chamber or using appropriate test material to demonstrate the capability of the equipment to deliver the range of operating parameters and operating limits contained in the process specification. This range of parameters and operating limits should include the initial sterilization process that has been defined in process definition (see Clause 8).

The system software (e.g., computerized measurement and control systems) should be tested in all fault conditions during OQ. The user is responsible for assuring the software is validated.

OQ can include the following when using a predefined cycle:

a) Preconditioning Phase

1) The pattern of air circulation throughout the area to be occupied by the sterilization load(s) should be determined. This can be performed by smoke tests in combination with calculation of air change rates and anemometric determinations.

2) Humidity should be monitored throughout the preconditioning area over a period long enough to demonstrate that values are maintained within the desired ranges.

The humidity in a number of locations distributed throughout the preconditioning area should be determined.

NOTE See Table C.1 and Table C.2 for recommendations on the number of temperature and humidity sensors.

b) Sterilization Phase

1) If inert gases are used instead of CD, account should be taken of the differences in the relative heat capacity when assessing the results.

2) Temperature/humidity distribution: Temperature/humidity sensors should be located in those locations that are likely to represent the maximum temperature differential, such as locations near unheated portions of the chamber or door and locations near steam or gas entry ports. The remaining temperature sensors should be distributed evenly throughout the usable chamber volume.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

NOTE See Table C.1 for the recommended number of sensors.

3) In empty chamber OQ exercises, the recorded temperature range, within the usable chamber volume during CD or inert gas exposure, of ± 3 °C of the average recorded chamber temperature at each time point should be obtained after an equilibration period. When the OQ exercise is carried out using a loaded chamber, then the ± 3 °C tolerance might not be achievable. (Note: In most cases, temperature is not a critical process parameter for CD sterilization)

4) chamber leak rate (performed either under vacuum for sub-atmospheric cycles or under vacuum and at pressure for super-atmospheric cycles);

5) pressure rise on injection of steam during the conditioning phase;

7) pressure rise and rate of attainment on admission of CD and correlation of factors with which it is intended to monitor CD concentration;

8) depth and rate of attainment of vacuum used to remove CD (if applicable);

9) pressure rise and rate of attainment of pressure on admission of air (or other gases);

10) number of times these last two stages are repeated and any variations in successive repetitions;

11) the reliability of the supply of filtered air, inert gasses, water, and steam;

12) replicate cycles should be carried out to demonstrate the repeatability of control;

13) a chamber wall temperature study should be completed (if applicable) to verify adequate temperature uniformity provided by the jacket heating system. The study should characterize the temperature profile for comparison on a periodic basis to ensure the system continues to operate effectively. (Note: In most cases, temperature is not a critical process parameter for CD sterilization)

c) Aeration Phase

1) When performing aeration, the temperature profile of the aeration area, although not typically used,should be determined in the same manner as recommended for

preconditioning areas. The airflow rates and airflow patterns through the area should also be determined.

D.9.4. Performance qualification

D.9.4.1. General

PQ consists of rigorous microbiological and physical testing, beyond routine monitoring, to demonstrate the efficacy and reproducibility of the sterilization process. PQ is normally not started until after completion and approval of the IQ and OQ testing. Acceptance criteria should include conformance with the specifications for the sterilization process parameters and microbiological challenge. PQ activities should be clearly defined in a written document (e.g., protocol). Where elements of the PQ are carried out by separate parties, those parties should approve the relevant documentation. See 4.1 and 4.2.

D.9.4.1.1. PQ consists of both microbiological and physical performance qualification and is performed in the equipment used to sterilize the product.

D.9.4.1.2. See AAMI TIR 28:2009[26].

D.9.4.1.3. PQ shall use product, or material representative of that to be sterilized routinely, to demonstrate that the equipment consistently operates in accordance with acceptance criteria and that the process produces product that meets the intended SAL.

D.9.4.1.4. In specifying the presentation of product, both load configuration (the composition of the load) and the placement of items within the load should be considered.

Typical load parameters to be defined might include stacking configuration, overall density, dimensions, material composition, and use and type of pallet wrap. Load configuration should be documented for each sterilizer. If routine sterilization consists of product loads that are less than the full chamber, then the MPQ/PPQ should incorporate the minimum load.

Product placement should also be specified. In a large industrial sterilizer, this would refer to the positioning of cases in a pallet or tote. For smaller sterilizers, as used by health care facilities, this refers to the positioning of baskets, packs, and rigid containers on a sterilization carriage or carrier.

The product and load used during PQ should be at least as difficult to sterilize as the most challenging load expected during normal production. The load can consist of product or materials that have characteristics similar to those of a load to be sterilized routinely. Changes in the load configuration can affect the lethality of a sterilization process. It is important that the acceptable load configurations be specified. If multiple load configurations are allowed, the load configuration used in the PQ studies should represent the most difficult-to-sterilize configuration, or should have a known relationship to the most difficult-to-sterilize configuration. Some variations in the load size might be justified as having no significant impact.

During PQ, two types of load can be chosen:

a) saleable product; and

b) non saleable product or appropriate test material.

D.9.4.1.5. When the load is composed of products, such as surgical kits, lumens of varying size and length, various packaging, and varying physical mass that contain a number of different materials (e.g., plastics, metals, cotton, etc.), it is important to verify the load configuration because these materials might not behave similarly when heated during preconditioning and conditioning.

D.9.4.1.6. In addition to considering maximum/minimum load size (see D.9.4.1.4) and product effects (see D.9.4.1.5), validation load composition should consider any widely varying load material/packaging characteristics routinely sterilized, when developing a representative or most challenging load for validation.

Products or surrogate product materials utilized in validation loads should represent those that typically present the most challenging condition for lethality (i.e., for penetration of heat, humidity, and CD gas diffusion; density). Consideration should be given to include load material with substantially varying characteristics, including absorbent materials and barriers to diffusion, such as rigid materials, sealed liquids, containers, etc.

D.9.4.1.7. If material other than product is used, it shall present at least as great a challenge to the sterilization process as the product.

D.9.4.1.8. If the load is to be re-used during PQ, the loads should be aerated and re-equilibrated to ambient conditions prior to starting the next run. After repeated use, the suitability of the load should be considered. Aeration between exposures will ensure that CD residues in the load do not affect the biological indicator. If equilibration time is insufficient, the load could be warmer than the normal ambient conditions, or the load humidity could be much lower than the normal ambient load conditions. Either of these situations produce data that are not representative of normal production. Too high a starting temperature produces an unrealistically rapid kill rate. Too low a humidity, where test spores become desiccated, produces an unrealistically low kill rate. Also, too high a humidity that results in an environment condition where the environmental dew point is higher than the product and/or load temperature results in condensate formation in the load and product that may result in a low and erratic kill rate.

D.9.4.1.9. If chemical indicators are used as part of PQ, these shall comply with ISO 11140-1, and shall be used in conjunction with microbiological and physical monitoring.

D.9.4.1.10. Biological indicators used in PQ shall comply with the applicable clauses of ISO 11138-1:2006

D.9.4.2. Performance qualification — Microbiological

D.9.4.2.1. Results obtained during process definition and, where applicable, IQ and OQ should be used to set the parameters for MPQ. Exposure time is the key parameter that is varied during microbiological qualification. Other parameters can be adjusted as necessary to provide assurance that the MPQ delivers less lethality than the normal production process. For example, temperature, humidity, and/or CD concentrations could be run at set points that are at the lower extreme of the normal process range. This would provide assurance that any observed values within the specified range will produce acceptable lethality.

MPQ should be conducted using product that is at or below the minimum temperature specified for product to enter the preconditioning area. If it is anticipated that initial product temperature could vary, for example because of transport for sterilization at a remote facility, the design of the qualification testing should reflect this possibility.

For fractional cycles (sub-lethal or half cycle), it might also be necessary to shorten the post-exposure phases of the cycle or to remove BIs prior to the aeration phase or after an abbreviated aeration phase. This is done to minimize "residual kill" of the BIs due to CD that is present in the load during the aeration phases of the cycle. When shortening the post-exposure phases of the cycle, factors such as operator safety should be taken into account. The parameters selected for MPQ, with the exception of exposure time, should remain fixed throughout MPQ. It should be noted that it has been demonstrated utilizing EPA guidance documents, that neutralization of BI's to prevent residual kill is not required.[69] [70]

NOTE Attention is drawn to the existence of statutory regulations existing in some countries on personnel exposure to CD.

D.9.4.2.2. The microbiological challenge defined in MPQ should be designed to ensure the required SAL is attained for all product load combinations. To achieve this objective, it is common to use PCDs or a worst-case product to represent CD product families.

PCDs should be placed within the product case and evenly distributed in the sterilization load, but distribution should include those locations where sterilization conditions are the most difficult to achieve. The locations used should include those selected for temperature monitoring. For loads that are palletized, these locations should also include the top and bottom of the pallets to ensure that all potential stratification within the chamber is assessed.

For guidance on sample numbers, see Table C.3.

D.9.4.2.3. The lethality of the cycle shall be determined using one of the methods described in Annex A or Annex B or by an alternative method that demonstrates achievement of the required product SAL.

D.9.4.2.4. If a developmental chamber was used for process definition, consideration should be given to establishing the relationship between data from the developmental chamber studies and data from the production chamber. The development of the microbial inactivation curves is not always possible in production chambers because of the size of the chamber and the time required to inject and remove CD in the chamber. These long injection and vacuum times limit the ability to obtain the required fractional recovery of indicator organisms. These inactivation curves can be developed in a developmental chamber that can deliver equivalent parameters, especially CD concentration used in the production chamber. Methods for demonstrating a relationship between the data developed in the developmental chamber and a production chamber involve a physical profile comparison and load density comparison. The sterilization conditions delivered in the developmental chamber should be compared with the physical profile obtained in a production chamber. Comparison of the lethality obtained in the development chamber and production chamber should take into account the differences in CD gas injection and evacuation times of the two chambers.

During the development of the sterilization process in a developmental chamber, it is important to place PCDs inside the finished product case or in the routine configuration to provide a relationship of the dynamics of the products within the case against the PCD during process development.

D.9.4.2.5. See AAMI TIR16:2009[25], 4.3.2.

D.9.4.3. Performance qualification — Physical

NOTE Results obtained from OQ can be used to identify features needing evaluation during PPQ.

D.9.4.3.1. If, in any of these runs, sterility or product functionality requirements are not met, an investigation should be conducted to determine if additional qualification runs are necessary. If process parameters cannot be maintained within the defined limits, an investigation should be conducted. If modifications are made, additional runs might be necessary.

D.9.4.3.2. PPQ should be carried out with the loading patterns and pallet separations specified in the documented procedures. For large preconditioning areas where a small load will not have a significant effect on the area dynamics, it is not necessary (and indeed might be impractical) to perform the studies with the preconditioning area in various loading states.

The guidance on PPQ of preconditioning also applies to the performance qualification of conditioning (i.e., during sterilization). See Table C.1 and Table C.2 for the recommended minimum number of sensors.

a) the minimum temperature of product to enter the sterilization process and/or the defined conditions required to achieve it shall be established;

b) It is important to establish and report the product temperature and humidity ranges of the sterilization load after exposure to the specified preconditioning time (if used).

c) During the product transfer from preconditioning (if used) to the sterilization chamber, conditions of product temperature and humidity might be impacted. It is important to ensure that this effect is considered during PQ and is commonly addressed during PQ by ensuring that the time of transfer specified in the PQ reflects the maximum time specification to be used for product transfer during routine sterilization.

d) Temperature and humidity sensors should be located within the sterile barrier system or amongst the unit packages in the sterilization load. When preconditioning is used, the product should be preconditioned within the specified time range. When preconditioning is not used, the temperature and relative humidity within the load should be within defined limits prior to the end of the conditioning phase of the cycle.

The temperature and humidity profile within the sterilization load should be evaluated during the time that is needed for the sterilization load to attain the minimum predetermined temperature and humidity.

For product, consideration should be given to locating humidity sensors in areas of the load that are most likely to experience variation in humidity, e.g., pallet centers, pallet edges and surfaces. For PQ, humidity sensors should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor within the sterile barrier system or amongst the unit packages.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

e) the chamber humidity was recorded if parametric release was to be used.

f) If parametric release is used, the CD concentration profile for the entire gas dwell phase should be assessed to determine how the gas concentration changes over the phase.

g) the concentration of chlorine dioxide in the sterilizer chamber has been established.

h) during the sterilization cycle, the temperature and humidity (if recorded) of the chamber and,where applicable, other process parameters have been established;

i) The temperature sensors within the sterilization load should be placed in the locations that are most likely to experience the greatest temperature variation. These locations should take into account hot or cold spots located during OQ. The locations of hot and cold spots within a load can be significantly different from the locations in an empty chamber. (Note: In most cases, temperature is not a critical process parameter for CD sterilization)

During PQ, it is important to take into account the relationship between the load temperature and the chamber temperature in order to ensure adequate load temperature in the routine process. These sensors should also be functionally compatible with CD and with any diluent gases.

j) The temperature within the sterilization load during the aeration process should be measured over the period of time required for the sterilization load to attain acceptable residual levels or measured over the period of time required for the sterilization load temperature to stabilize.

NOTE This can be established during additional studies after completion of MPQ/PPQ.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

D.9.4.4. Review and approval of validation

D.9.5.

D.9.5.1. The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability against the approved validation procedures/protocol for the sterilization process and to approve the process specification.

D.9.5.2. Any discrepancies observed during the validation process should be documented, and their effect on the results of the validation should be determined and documented.

D.9.5.3. Typically, the validation report is approved by the designated responsible person(s) as defined in the validation protocol.

D.9.5.4. The validation report(s) should also include or reference the following:

- The specifications for the sterilizer and the sterilization process;

a) the IQ/OQ data;

b) the records, physical and microbiological, of all PQ runs;

c) an indication that all gauges, recorders, etc., were calibrated and within their specifications;

d) provision for future review and requalification;

e) the validation protocol(s)/procedure(s);

f) the documented procedures used;

g) the documented operating procedures, including process control limits;

h) if a failure occurred, a description of the issues, the corrective action taken, and the effect of the failure on the intent of the validation; and

i) if a deviation to the protocol occurred, details of this deviation and an assessment of its impact upon the validation and its results.

D.9.5.5. Parametric release is a product release method wherein product is considered to be sterile if the essential physical processing parameters are in conformance with the specifications established during the validation for the specific product(s) in a defined load. Parametric release is based upon a documented review of processing records rather than the testing of biological indicators or PCDs.

The values and tolerances for both RH and CD concentration might need to be generated after review of a predefined number of routine cycles. During this evaluation period, BI's might be used as part of the routine monitoring and control of loads processed. The rationale for the number of runs selected should be justified and recorded. This can be influenced by uniformity of the load, existing data, seasonal variations, or frequency of sterilization.

CD sterilizers used in health care facilities might not be adequately equipped to permit parametric release of product.

D.9.5.6. A process specification including the process parameters and their tolerances shall be established for routine processing based upon the documentation generated during the validation. This process specification shall also include the criteria for designating chlorine dioxide processed product as conforming product and approved for release.

D.10. Routine monitoring and control

The automated equipment uses a sophisticated control system to measure and control all steps of the sequence along with all important process parameters. Each system includes a RH probe to measure and control the RH. If the RH is below the set point, more moisture is injected. When above the set point the RH injection stops. The RH can be controlled for the entire cycle depending upon user specified recipe parameters. The other critical parameter is the chlorine dioxide gas concentration. CD gas has a visible color and because of this it is easily measured

with a spectrophotometer. A spectrophotometer uses light to determine the concentration. Light is passed through a continuous gas sample and a certain amount of light is absorbed by the gas. This absorbance then equates to a certain concentration which is measured and displayed in real time. This device accurately and more importantly repeatably measures the concentration in the chamber. This gives the user the confidence in the process that the cycle performed today will be the same as the previous cycle. This gives the confidence that critical parameters are measured and controlled. It also allows the dosage or contact time (CT) to be measured and accumulated. Dosage is an accumulation of a concentration over time which is accumulated and displayed as ppm-Hours. The required dosage depends upon the complexity of the product. This also depends upon requiring a vacuum process or ambient process. If the product is simple then a simple ambient pressure process works. If the product contains lumens, tubing and tiny openings then a vacuum process maybe required.

To calculate chlorine dioxide ppm from mg/L, the below calculations can be used:

ppm calculation for 1 mg/L chlorine dioxide concentration

ppm = (mg/m3) (24.45)/molecular weight = (mg/L) (1000) (24.45)/molecular weight

Chlorine dioxide ppm = (1 mg/L) (1000 L/m3) (24.45)/67.5 = 362.2

The number 24.45 in the equations above is the volume (liters) of a mole (gram molecular weight) of a gas at 1 atmosphere and at 25°C.

This leads to the calculations for dosage or ppm-hours.

Exposure contact time = 362 ppm×2 h = 724 ppm-hour

So, the overall dosage or contact time starts when gas is being injected and the accumulation starts. This has the effect of combining the exposure time and charge time and shortening the overall cycle time. Studies have shown effective dosage of 400 ppm-hours to achieve a 5-log reduction of *bacillus atrophaeus* spores and a 6-log reduction in isolators at 900 ppm-hours. [71] [72] Others have demonstrated 6-log reduction cycles in isolator and processing vessels at dosages of 540ppm-hours to 1800 ppm-hours. [73] [74] [75] Dosages as low at 180 ppm-hours have shown 4-log reductions.[76] Other studies have varied CD gas concentrations (0.3, 0.5, 1, 5, 10, and 20 mg/L) and kept the dosage constant (720ppm-hours) and achieved 6-log reductions for all concentrations.[77]

For the vacuum process, higher concentrations and times are typically utilized to achieve sterilization. The RH requirements are the same, but the CD gas concentrations are increased to a target concentration of 10-30 mg/L compared to the target of 1-5mg/L for ambient pressure chambers. This then equates to a dosage of 3000-5000 PPM-Hours. This is required to allow the gas to penetrate into the small openings. This exposure time must be determined for each product and the exposure times may vary. Studies have demonstrated 6-log reductions at dosages of 5400 ppm-hours to 10,800 ppm-hours [78] [79] [80] [81]

D.10.1. The purpose of the routine monitoring and control is to demonstrate that the validated and specified sterilization process has been delivered to the product.

D.10.2. Guidance on the bulleted items of 10.2 follows:

a) The temperature of products entering the preconditioning area should be at or above the minimum temperature specified, or the defined conditions of storage should be met. If the product has been exposed to extreme temperatures, for example, during transport, it might be necessary to store the product prior to preconditioning, or extend preconditioning time to allow the internal temperature and humidity to be within acceptable ranges.

NOTE The minimum temperature of products entering preconditioning or the storage conditions are defined during PQ.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

b) The reference position for routine monitoring of temperature and relative humidity during preconditioning should be correlated to the location at which it is most difficult to achieve the desired conditions. Monitoring data for the operation of the preconditioning area should be reviewed in conjunction with other data for the release of product.

c) time of commencement of preconditioning and of removal of load from preconditioning (if used) of each sterilization load;

d) elapsed time between removal of the sterilization load from preconditioning (if used) and the commencement of the sterilization cycle;

e) The humidity in the chamber is measured directly with an Rh probe

f) conditioning time;

g) Forced gas circulation is particularly important in order to ensure uniform conditions are maintained and to avoid stratification of gases that might have an impact on microbial lethality. (See D.6.3.2).

h) pressure in the chamber throughout the sterilization cycle;

i) Since CD has a yellow-green color, accurate direct measurement is available utilizing an integrated UV-VIS spectrophotometer of the mean CD gas concentration in the available space within the sterilizer chamber. As CD concentration is a key variable affecting the efficacy of the sterilization process, it is considered essential that a separate second system be provided for verification of the CD concentration. This can consist of a redundant CD concentration monitor or by monitoring the actual duration that CD gas is entering the chamber.

j) Because CD injection times can vary from cycle to cycle based on load conditions, it is common practice to specify a time range for an acceptable CD injection time based on the specific product and load characteristics.

k) no inert gas will be injected as part of the CD sterilization process

l) exposure time/total dosage

m) The time taken for evacuation immediately after CD exposure can vary from cycle to cycle; it is common practice to specify a range for acceptable evacuation time. This provides guidance on the status and performance of the pumps and blowers utilized for aeration/evacuation.

n) time and pressure changes during aeration.

o) if aeration room is used, time and pressure changes during aeration.

D.10.3. Observations of growth from biological indicators not attributable to failure to meet physical process specifications should be analyzed; this can lead to a need for process or equipment modifications and for the PQ to be repeated.

D.10.4. The following guidance is provided for health care facility applications:

External chemical indicators in health care facilities: Sterilizer indicator tape, an indicating label or an indicating printed legend should be affixed to or printed on each package assembled by the health care facility. The purpose of external chemical indicators is to differentiate between processed and non-processed items. They do not establish whether the parameters for sterilization were achieved. Indicators should be of Class 1 specification in accordance with ISO 11140-1.

Internal chemical indicators in health care facilities:

a) An internal chemical indicator can be used within each package to be sterilized. If used, the chemical indicator should be placed in that area of the package considered to be the least accessible to CD, heat, and humidity penetration; this might or might not be the center of the pack. While internal chemical indicators do not verify sterility, they allow detection of procedural errors and equipment malfunctions. The use of chemical indicators that respond to all the parameters of the CD process is beneficial.

b) The internal chemical indicator is retrieved at point-of-use and interpreted by the user. The user should be adequately trained and knowledgeable about the performance characteristics of the indicator in order to make an informed decision based on the result shown.

c) If the interpretation of the indicator suggests inadequate CD processing, the contents of the package should not be used. The complete unused package, including load identification and the chemical indicator, should be returned to the processing department for appropriate follow up. The results of the physical monitoring, chemical indicators elsewhere in the load, and the biological monitoring, should be reviewed, in order to reach a conclusion as to whether the entire load should be recalled or not. Records of this review should be retained. A single non-responsive or inconclusive indicator should not be considered as evidence that the entire load is non- sterile. Chemical indicators can indicate problems associated with incorrect packaging, incorrect loading of the sterilizer, overloading of the sterilizer chamber, malfunctions of the sterilizer, incomplete delivery of the sterilization parameters, or inadequate preconditioning. The “pass”

result of a chemical indicator does not prove that the item where the indicator is placed is sterile.

d) Indicators should be of Class 3, 4, 5, or 6 in accordance with ISO 11140-1.

D.10.5. Parametric release is a method of releasing product from sterilization as sterile without the use of BIs, relying instead on a demonstration of conformity of the physical processing parameters to all specifications. Therefore, data are gathered for additional processing parameters, such as direct analysis of chamber relative humidity and CD concentration, in order to ensure that the sterilization process has met specification.

a) Temperature measurement.

The requirement to measure temperature within the sterilizer from a minimum of two locations is established in order to ensure that an undetected fault in a temperature sensor does not lead to the inadvertent release of an improperly processed load. If there is a difference in the two temperature data points, the acceptable temperature difference should be defined within the processing specification. If either the controlling or the monitoring sensor do not meet specification and an investigation cannot determine the accuracy of the chamber readings, the load is rejected. For most products, temperature is not a critical parameter for CD so redundancy should not be applicable.

b) Humidity measurement.

Direct analysis of the head space for relative humidity can be performed using electronic sensors, Gas Chromatography (GC), Infrared (IR), or other spectroscopic methods currently available to measure Rh directly or to indicate water vapor concentration and calculation of the relative humidity value. The benefit of these methods is the real-time indication throughout the conditioning phase. Electronic sensors require periodic calibration to offset the effect of exposure to the CD gas and can require replacement after repeated exposures to CD due to irreversible deterioration of materials currently utilized as sensing elements.

c) CD gas concentration measurement.

The frequency of analysis required to demonstrate that the minimum CD concentration is maintained throughout CD exposure should be established during the PQ studies. Monitoring throughout the CD exposure dwell period should also be done as part of the validation, in order to determine how the CD concentration changes over time. The results of this analysis are specific to the product and load configuration being analyzed. The analysis performed during the PQ study will result in documented specifications for how often direct analysis should be performed during the cycle. It is recommended that when direct analysis of CD concentration is performed, at a minimum, direct analysis of CD concentration be performed during the first and last portions of CD exposure.

Particular attention should be given to the measurement and documentation of humidity during conditioning and that of CD concentration during exposure. The CD

sampling device providing direct CD concentration measurement using a UV-VIS spectrophotometer, IR, GC, microwave, and other similar technologies should be positioned in a location to represent the CD gas concentration within the sterilizer chamber. However, it is important to understand that this measurement provides an CD concentration at that position in the chamber throughout the entire exposure phase without any restrictions of reactivity effects or load impact. The reproducibility and accuracy of the results from direct analysis should be determined during PQ. Routine cycle analysis should fall within the determined range for the cycle to be acceptable.

It can be necessary to introduce an equilibration time at the start of the CD dwell phase of the cycle to allow the chamber concentration to stabilize as the CD gas is distributed throughout the chamber and penetrates into the void spaces in the load.

NOTE 1 An electronic sensor measures CD gas concentration at only one sample site, whereas the calculated CD gas concentration represents the mean CD gas concentration within the space (volume) available for CD gas molecules to reside. Due to several factors, such as CD sensor dynamic performance characteristics; placement of the CD sensor within the volume occupied by the CD gas molecules; potential stratification within the chamber, selective absorption and adsorption of CD in the load; and the volume taken up by the load, the values obtained by calculating the mean CD gas concentration can differ from the direct measured value.

NOTE 2 Health care facilities do not routinely use parametric release.

D.11. Product release from sterilization

Chlorine dioxide gas allows for product release from sterilization due to the real time monitoring and control of critical parameters during the sterilization process. The critical parameters are the RH and CD gas concentration. Both of these parameters are measured and more important controlled. Since there are real-time numbers and if these numbers are confirmed with the previously validated cycles, products can be released based upon the RH and concentration/dosage parameters being met. The equipment documents the parameters and ensures these are met thereby allowing parametric release.

D.11.1. This confirmation should include a formal review of the process documentation by a designated individual (or by a validated automated process) to verify and document that the physical cycle variables are within the tolerances defined in the sterilization process specification. If parametric release has been approved and used, product can be released based on compliance with specified process parameters.

Routine release of a product following sterilization can be based on a review of electronic records in lieu of paper records. Likewise, required signatures can be made electronically. Users of electronic signatures and records should be aware of, and should meet, national and/or international requirements for this type of documentation. The review of processing records and the decision to release should be performed by qualified individuals.

D.11.2. If a process does not fulfil all of the conformance criteria above, the cause shall be investigated. If repair or alteration to the equipment is required, the necessary qualification shall be performed before this process can be used again..

D.11.3. Failure to meet the physical specification or the observation of growth of indicator organism from BIs (if used) should lead to the sterilization load being quarantined and the cause of the failure being investigated. This investigation should be documented, and the subsequent handling of product should be in accordance with documented procedures.

If a controlling or monitoring sensor has failed, the run should be rejected, unless

a) there is an assignable cause for the failure, and

b) data from the remaining sensors are within specification.

If the decision is to reprocess the load, the suitability of the product and its packaging system for re-sterilization should be established. The effect of repeated exposure to the sterilization process on product functionality and levels of residual CD, and/or reaction products, should be considered. Records of the original sterilization should be traceable from the re-sterilization records. (See 7.2.2).

If the effect of repeated exposure on the packaging system is not known, product should be repackaged before re-sterilization.

D.11.4. If saleable product is used in validation studies the requirements for release of this product for distribution shall be generated before the start of the validation activities. It is important to assess the effect of repeated exposures to the validation/sterilization processes on product and packaging functionality, and levels of residual EO and/or reaction products prior to release. If saleable product is used in MPQ studies, then procedures shall be established to ensure the product is subjected to a full exposure sterilization process and formal review of its acceptance prior to release to market..

D.12. Maintaining process effectiveness

Periodic process monitoring is important with any process. This is done by periodically placing biological indicators in the chamber during sterilization to re-confirm the process. Additionally, equipment must be maintained by cleaning and calibrating sensors which are critical to the effectiveness of the cycle.

D.12.1. General

D.12.1.1. To ensure that the sterilization process continues to deliver the required product SAL, it is necessary to evaluate any changes to the product and packaging, the processes and equipment. The use of a comprehensive product and process change control system is recommended.

One parameter commonly monitored to ensure the continued ability to sterilize the load is the product bioburden. The bioburden should be monitored per ISO 11737-1. If significant changes are observed in the number and/or types of microorganisms, their possible effect on the ability of the sterilization process to adequately sterilize the load should be evaluated.

In a health care facility, it is recommended that there be a periodic review of the data on the effectiveness of the cleaning/decontamination process to confirm that the process is still effective and provides adequate bioburden reduction in preparation for the subsequent sterilization process. Decontaminated medical devices should be visually examined for cleanliness prior to terminal sterilization. Medical devices that are not clean should not be sterilized. Policies and procedures should be in place to ensure that medical devices are adequately decontaminated prior to sterilization (see ISO 17664 and the ISO 15883 series).

It is essential for health care facilities to obtain from the manufacturers detailed reprocessing instructions specific to the medical device, e.g., disassembly. Policies and procedures should be in place to ensure that medical devices are decontaminated.

D.12.1.2. A documented program for calibration of instrumentation used to control and monitor a sterilization process is necessary to ensure that the process continues to deliver product with the required SAL and performance characteristics.

D.12.2. Maintenance of equipment

D.12.2.1. In order to be effective, preventive maintenance activities should follow a defined schedule based on the manufacturer's recommendations and the performance of the equipment. The procedures should be documented, and maintenance personnel should be trained.

Equipment to be maintained and/or calibrated on a routine basis can include, but is not limited to, the following preconditioning, chamber and aeration equipment:

a) gaskets and seals;

b) monitoring gauges;

c) CD monitoring equipment (i.e., environmental and/or chamber);

d) door safety interlocks;

e) safety pressure relief valves or rupture discs;

f) filters (for periodic replacement);

g) air/gas circulation systems;

h) chamber jacket re-circulation system;

i) chamber jacket system;

j) audible and visual alarms;

k) temperature and humidity sensor equipment;

l) boiler system for steam and heat supply;

m) evacuation equipment (vacuum pumps);

n) weighing scales;

o) valves;

p) pressure transducers;

q) timers;

r) recorders; and

.

D.12.2.2. Sterilization equipment that is not calibrated or is not properly maintained can generate an inaccurate record of the process parameters during the sterilization cycle. If these data are used for product release, it could result in loads being released that have not been adequately sterilized.

D.12.2.3. Records of maintenance shall be maintained.

D.12.2.4. It is necessary to periodically review the maintenance records and to make any adjustments that are indicated by the data.

D.12.3. Requalification

D.12.3.1. IQ, OQ, PQ and subsequent requalification(s) shall be reviewed annually to determine the extent of requalification that is necessary. This shall include an assessment of the need to reconfirm the product SAL through microbiological studies. The outcome of this review, including the rationale for decisions reached, shall be documented. Review of IQ should include confirmation of the acceptable calibration status of control and monitoring equipment. The change control and preventive maintenance programs indicate that no modifications of, or significant changes to, the sterilizing equipment have been made that could affect the process.

D.12.3.2. Review of OQ should include an assessment of the equipment performance and engineering changes that were made during the year to ensure that the results from the original OQ are still valid (see Figure D.1).

In order to do so, it is common practice to perform periodic requalification of equipment and should include:

a) review of IQ status of equipment;

b) assessment of trends in equipment performance;

c) temperature and relative humidity profiles of the preconditioning areas (if used);

d) chamber temperature profile; and

e) temperature profile of the aeration areas (if used).

These requalification exercises should indicate no significant changes in the performance of preconditioning (if used), chamber, or aeration areas since the previous (re)qualification. If equipment changes are necessary as a result of these exercises, requalification of OQ might need to be repeated.

NOTE For large preconditioning or aeration rooms containing multiple sterilization loads, the extent of requalification can be reduced if there have been no significant changes in equipment. The rationale for reduced requalification is documented.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

D.12.3.3. Review of PQ should include assessment that the sterilization process remains valid for the designated product(s).

Factors to be considered include, but are not limited to, the following:

a) review of IQ status of the equipment;

b) review of OQ status of the equipment;

c) confirmation that there have been no significant changes to the product design, manufacturing and packaging materials, PCDs, suppliers, manufacturing area or facility, load configuration, or manufacturing process that could affect product sterility;

d) confirmation that there has not been a significant increase in the product bioburden, and/or a change in the resistance of the product bioburden to the sterilization process, which might adversely affect the ability of the sterilization process to sterilize product to the specified SAL;

e) confirmation that individual sterilization processes have operated within specification since the last qualification;

f) confirmation that there have been no changes to the sterilization process that could affect product sterility; and

g) review of sterility failures of BIs or PCDs that have occurred where process specifications were met to determine whether requalification is warranted.

Based on this review, the sterilization specialist should determine the extent of physical and microbiological requalification required. The review and decision should be documented.

There are three requalification options available as a result of the review:

— Full Qualification – consisting of PPQ and MPQ. This can be required in certain situations, e.g., following a significant change to product/packaging design or configuration (creating a new “worst-case” condition), process design or equipment/service.

— No physical or microbiological qualification required – In circumstances where no changes have been made to product, packaging, equipment/services and process, acceptable chamber performance, and engineering review, and the routine sterilization process has operated reliably in the intervening period, then professional judgment can be used to justify that no physical or microbiological requalification efforts need be performed before the next review.

— Reduced MPQ/PPQ – This can be necessary in certain situations, e.g., to verify continued appropriateness of the resistance of the internal PCD in the product load to the resistance of the product bioburden, or, after a defined interval, to provide evidence

that there has been no inadvertent change since the previous requalification study. This would typically include, minimally, one fractional or half cycle exposure including load temperature and humidity measurements. Fractional cycles in a developmental chamber can also be used to support a requalification program, but requalification of the production chamber should be performed in the production chamber.

It is recommended that a MPQ cycle and load temperature and humidity measurements (MPQ/PPQ) be performed at least every two years to verify that the documented paperwork review has captured any changes in the product or sterilization process.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

Requalification can also include verification that if the sterilization process specification is changed, then requalification of the sterilization process should include confirmation that product meets allowable limits for CD residuals.

In all of the above cases, it is important to document the decisions taken as well as the rationale for those decisions, and to define the plan for future review of requalification.

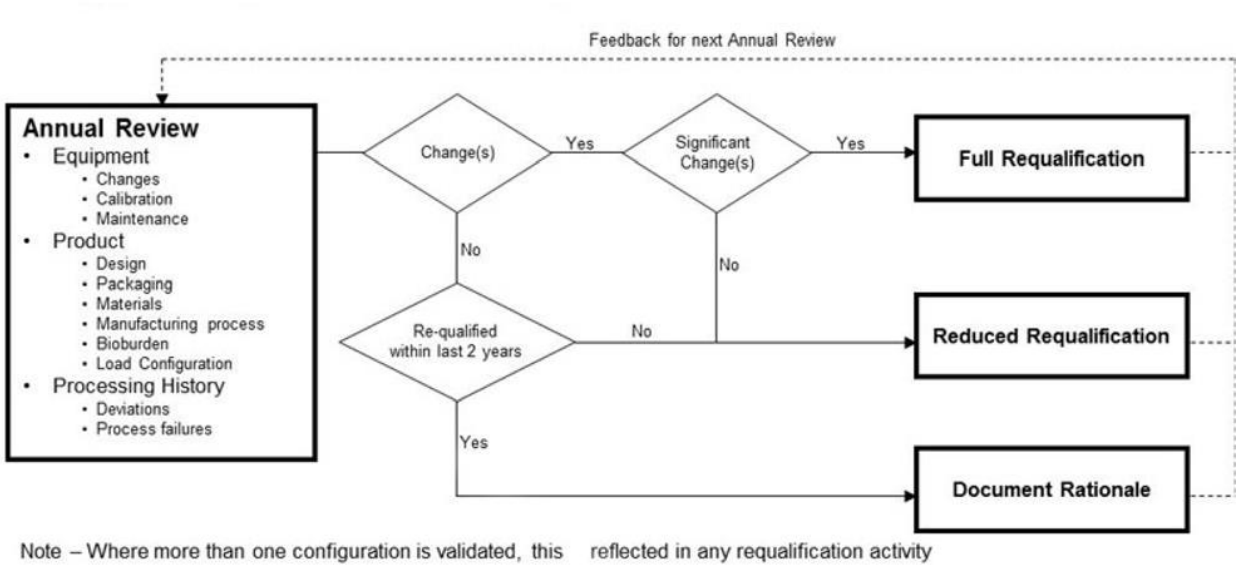


Figure D.1 — Requalification decision tree

D.12.3.4. Requalification is performed to confirm that the cumulative effect of minor changes has not compromised the effectiveness of the sterilization process.

Requalification can include verification that allowable product CD residuals are being met.

It is important to formally assess the need for requalification of the sterilization process at least annually to ensure that inadvertent process changes have not occurred and to demonstrate that the original validation remains valid.

The requalification program should define acceptable ranges and levels of variability in performance that are necessary to maintain the validity of the original validation from year to year.

D.12.3.5. An investigation should be initiated to try to determine the root cause(s) of a non-conformity. The impact of the non-conformity on the validity of the requalification should be assessed and the rationale for the decision(s) reached should be documented. Further activities pertaining to the requalification should proceed with proper quality system oversight.

D.12.4. Assessment of change

D.12.4.1. Events that might require requalification include, but are not limited to:

a) major sterilizer repairs and changes (replacing controls, major rebuilding, or installation of major new components);

b) changes to construction or relocation;

c) unexplained sterility failures in routine sterilization;

d) changes to product;

e) changes to packaging;

f) modification to the sterilizing agent and/or its presentation;

g) changes to presentation of product for sterilization or load configuration; and

h) changes to load density.

It is important to ensure that the reference load used in any requalification takes into account changes that might have been made to ensure that the reference load is representative of the revised product / configuration.

D.12.4.2. A requalification study could be necessary if a change has been made in materials, manufacturing location, or processing method that can impact the product bioburden population or resistance. The study should demonstrate that product bioburden population or resistance has not increased to a level which might potentially invalidate the suitability of the internal PCD, or compromise achievement of the required product SAL.

D.12.4.3. Where re-evaluation of the load and load configuration identifies changes that might impact on the efficacy of the sterilization process, then these changes should be incorporated into the requalification studies.

D.12.4.4. The qualified sterilization process shall be reviewed whenever there has been a change to the sterilization process, the sterilization equipment or product that could alter the efficacy of the process.

D.12.4.5. The magnitude of the change shall be considered in determining the extent to which process definition, IQ, OQ or PQ is undertaken.

D.12.4.6. The outcome of the assessment, including the rationale for decisions reached, shall be documented.

D.12.5. Assessment of equivalence

D.12.5.1. Process equivalence

Process equivalence is a method used to demonstrate that the same validated sterilization process is delivered by two or more pieces or sets of equipment. It does

not require that the equipment be physically identical. Even if the parameters delivered by the equipment are not statistically identical, the processes delivered can still be equivalent if they are all capable of running the process within the defined, validated process limits (see AAMI TIR 28[26]).

Process equivalence among multiple pieces of equipment is intended to minimize the amount of testing required to qualify the process. The sterilization process should be validated in one chamber. The remaining equipment can undergo reduced PQ if the remaining equipment has undergone installation qualification (IQ) and operational qualification (OQ) (see 9.2 and 9.3). Equivalence can also be used to reduce requalification of several pieces of equipment. The equipment used to deliver a sterilization process commonly consists of a chamber or room and ancillary control systems. Sterilization process equipment might be located within a given processing facility or among several facilities. This equipment can be used independently to deliver the same process conditions and could be exactly the same design or might differ in size or in the extent of ancillary equipment.

Process equivalence can be established through analysis of process data in combination with a microbiological evaluation. The process data should demonstrate that the candidate equipment is performing within an acceptable range of control (i.e., validated process parameters can be reliably delivered to the product). The data analysis should confirm that the process operates within the defined tolerances for the validated parameters. The microbiological evaluation will demonstrate that the required SAL is achieved.

D.12.5.2. Criteria for process equivalence

Process equivalence can be established regardless of whether the equipment is located in the same facility or in different facilities. The criteria to be met prior to the establishment of a process equivalence program are:

** The guidance given in subclauses D.1 through D.12.4 align with the clause numbering of the requirements (i.e., 1 through 12.4). Subclauses D.12.5.1 through D.12.5.10, however, provide guidance on subclause 12.5.1, while subclause 12.5.11 gives guidance on subclause 12.5.2. (This footnote appears only in this U.S. adoption and not in the referenced International Standard.

a) full validation of the sterilization process in at least one existing system according to the requirements of Clause 9;

b) performance of the IQ and OQ studies demonstrating and documenting that all equipment has been installed in accordance with engineering specification requirements and operates in accordance with those requirements;

c) definition of the process to include the tolerances allowed and documentation of all phases of the process; and

d) process data analysis associated with the validated tolerances for the candidate equipment and the original equipment.

D.12.5.3. Determination of process equivalence

The equivalence of the sterilization process delivered by one piece of equipment to that delivered by another piece of equipment can be established by comparing the data obtained when running the same validated process in each piece of equipment. This comparison should include an evaluation of the equipment's capability to reproducibly deliver the desired process parameters when running a normal production load. Data obtained during the PQ on the process can also be used. The delivered parameters and tolerances should be those that were previously validated in the PQ of the sterilization process in the original equipment. The evaluation of equivalence involves performing a process analysis and evaluation, as well as a microbiological evaluation.

D.12.5.4. Process analysis and evaluation

An analysis of process data associated with a validated process in the candidate equipment and the original equipment is performed. Process data should be collected from the candidate equipment. These data should be compared with the parameter limits for that specific sterilization process and the results obtained in the PQ of the original equipment. The parameter limits are those established in the initial validation for the sterilization process (including all process requirements identified in this document) in the existing equipment. The specifications, acceptance criteria, and pallet or load configuration should be the same as those defined for the initial PQ. The actual parameters to be evaluated in the equivalence determination are generally a subset of the entire process specification. The parameters selected and the rationale for their selection should be documented. Statistical methods that evaluate both the central tendencies of the test data and the degree of variability of the data can be used in this evaluation. Examples of statistical analysis approaches are presented in AAMI TIR15.[24] The examples are illustrative only, and are intended to provide guidance on statistical calculations, normality requirements, and steps to take if the data fail a normality test. If the process analysis and evaluation do not meet the established acceptance criteria, then it is not possible to demonstrate process equivalence.

D.12.5.5. Evaluation of preconditioning or aeration areas

The criteria for establishing process equivalence are the same for preconditioning or aeration areas, with the exception that humidity usually does not apply to aeration. An evaluation that compares the load temperature and humidity profiles within each environment should be performed. At a minimum, temperature and humidity uniformity within the load and the relationship of this uniformity with the corresponding set points and recorded control variables for the areas should be evaluated. If the pieces of equipment use different set points or have different control limits, it might not be possible to declare that they are equivalent. Process equivalence for the preconditioning or aeration processes can be established if analysis of performance data concludes that conditions within the load meet the parameter limits (e.g., temperature distribution, residual levels, etc.) at the end of preconditioning or the end of aeration. Product CD sterilization residuals levels should be verified in the candidate aeration room/chamber/cell.

D.12.5.6. Evaluation of sterilization chamber performance

An evaluation that compares the delivery of process parameters for the load in the candidate equipment to the data obtained in the PQ or in production runs should be performed. The critical process and load parameters to be compared should be defined for the sterilization process before the evaluation is performed. These parameters are unique for each sterilization process but can include the following:

a) Load parameters:

1) product temperatures — temperatures achieved and their distribution within the load during CD dwell;

2) product humidity — humidity achieved and its distribution within the load at the end of conditioning.

b) Process parameters:

1) chamber humidity at selected times during the cycle (e.g., beginning and/or end of conditioning). This parameter can be measured directly or can be based on pressure rise due to steam injection;

2) chamber process temperature at selected times during the cycle (e.g., end of conditioning or during the CD dwell period);

3) chamber CD gas concentration at selected times during CD dwell period during the cycle (if measured), or CD pressure rise.

(Note: In most cases, temperature is not a critical process parameter for CD sterilization)

c) Other process parameters that might be considered include:

1) vacuum depth and rate of evacuation (ΔP/time) at selected times during the cycle;

2) humidification time and steam injection rate (ΔP/time);

3) CD injection rate (CD Concentration/time) and the amount of CD used (concentration, or charging flow time); and

4) air or nitrogen injection rate (ΔP/time).

An analysis of the process data are used to indicate that the processes are or are not equivalent in their ability to meet the existing process parameter limits and any additional acceptance criteria. The data generated should be analyzed and compiled in a format that will allow for its use in future process equivalence determinations.

D.12.5.7. Microbiological evaluation

In the microbiological evaluation, a fractional or half cycle is performed to demonstrate that the sterilization process is capable of delivering the defined minimum specified product SAL in all the evaluated pieces or sets of equipment.

NOTE If the run used during process analysis was a fractional or half cycle and included microbiological monitoring, then the data can also be used for this evaluation.

In addition to the delivery of the specified product SAL, additional factors that should be evaluated include any changes to the sterilization location or manufacturing location that might have an impact on the bioburden level of the product as presented for sterilization. Increased distances between the manufacturing facility and sterilization site might result in higher bioburden levels, especially if the product will support microbial growth. Differences in manufacturing environments might lead to the manufacture of product with higher or more resistant bioburden levels than previously qualified, even if the product does not support microbiological growth. Another issue to be evaluated when shipping product between sites is the difference in shipping conditions, such as time in transit and seasonal effects (e.g., temperature, humidity, etc.). Holding of product under defined conditions to simulate shipping/transport conditions should be performed if required.

D.12.5.8. Results evaluation

The results of the evaluation will determine whether the different pieces or sets of equipment perform equivalently. If the different pieces or sets of equipment are equivalent, then the requirement for a reduced MPQ has been satisfied through the testing that was already performed and no further qualification would be necessary. If the conclusion of either the process analysis and evaluation or the microbiological evaluation is that the processes are not equivalent, then the process should be declared “not equivalent” and a full PQ should be performed.

D.12.5.9. Maintenance of equivalence

Maintenance of equivalence should include a review of changes to each piece of equipment, the manufacturing process, the product load, and the sterilization process to ensure that these changes do not compromise the overall determination of equivalence. This review should be conducted before changes are made and should be part of the change control process. If any process fails the periodic equivalence review, then it should be removed from the equivalence list and requalified on its own.

D.12.5.10. Documentation

All decisions related to the outcome of the analysis determining whether candidate equipment can be declared equivalent to the existing sterilization process equipment should be documented. At a minimum, this documentation package should include:

a) The complete specification for the candidate equipment, which fully describes the equipment, operating specifications, and tolerances, and that refers to or provides a list of applicable operating procedures, calibration procedures, and maintenance schedules. This specification should include or reference the current IQ per this document.

b) Evidence or assessment of the ability of the equipment to deliver the intended process. The evidence or assessment should include or reference the current OQ.

c) The result of the comparison between the candidate process equipment and the existing validated process equipment. This comparison should

clearly demonstrate that all major systems and critical parameters were assessed, including statistical analysis (if used).

d) Evidence or assessment of the product conditions during processing within the candidate equipment to demonstrate equivalence to the existing process.

e) Results of the evaluation of any additional factors that could affect the lethality of the sterilization process, as appropriate.

f) The documented conclusion that the candidate equipment is equivalent to the equipment specifically referenced in the current validation study to achieve the specified product SAL. This conclusion should include or reference any additional tests performed to supplement the existing validation study and any further testing performed for confirmation or qualification for routine release of product from the existing validated cycle (e.g., residual testing, functional testing on first three lots, etc.).

g) Approval by the sterilization specialist and other individuals as required by the normal change control or process documentation control practices within the organization.

h) A list of applicable sterilizer operating procedures and specifications issued or changed to authorize use of the candidate equipment for routine processing of product.

D.12.5.11. Product

D.12.5.11.1. Product family

A product family is a collection of products determined to be similar or equivalent for validation purposes. Although product families can be used for other reasons (CD residuals, bioburden, or biocompatibility) for CD sterilization, a product family usually refers to products that have been grouped together for the purposes of determining that the required SAL has been delivered to the products during the MPQ.

An CD product family can consist of various combinations of similar products. For example, a product family might contain a series of catheters that differ only in their sizes or a variety of products that are made in the same environment with the same material. When products are grouped into families it is important that they are grouped based on a rationale that is appropriate for the CD sterilization process.

The use of product families makes the validation process simpler as all products in the family would be determined to represent an equivalent or lesser challenge to the sterilization process than the representative product or internal PCD. The product family can be represented by a worst-case product (often called the “master product”); the entire family is considered an equivalent challenge to the sterilization process, or it is represented by a product PCD (internal PCD).

In addition to product families, processing categories can also be used in CD sterilization routinely once the PQ has been completed. A processing category is

a collection of CD product families that can be dissimilar in the details used to establish the product family, such as material of construction or packaging, or manufacturers, but each of the CD product families within a processing category should be qualified in a common sterilization process. For example, a collection of products (intravenous sets) might constitute a product family and might be placed in a processing category that includes a separate collection of products (e.g., a family of syringes). The commonality within the processing category might be the PCD that represents the microbial challenge for those products in that group. All products within this processing category should present an equivalent or lesser challenge to the sterilization process when compared with the worst-case product, representative member, or internal PCD that is placed within the product sterile barrier system.

The review for product equivalence can be conducted within each product family or processing category. Alternatively, a worst-case product or representative member can be selected for the qualification study. In the following paragraphs, several aspects of product evaluation are addressed.

D.12.5.11.2. Determination of adverse effects to product

Before determining whether a candidate product or packaging system can be adopted into a product family or processing category, one should determine whether the candidate product or packaging system will remain functional and effective. A system to evaluate these aspects should be addressed by the design or change control process. Consideration should be given to functionality, integrity, stability, biocompatibility, and residuals, with special consideration given to determining the effect that the sterilization process might have on drugs that could be included in devices or components. For products that contain certain types of finished components (e.g., kits with drugs), the manufacturer should consider regulatory requirements with regard to the safety and efficacy of these components in addition to the impact the sterilization process can have on the expiry date of the products involved.

The sterilization process for which the product will be tested should constitute a representative challenge to the product and its packaging system. Documentation should address how the challenge process differs from the nominal process, and the product qualification should demonstrate that these parameters are acceptable for product acceptance.

The candidate product and its packaging should be evaluated to determine the effect on product CD residual levels, and any changes to either should be evaluated for the impact on product release.

D.12.5.11.3. Determination of product design effects

The design of the candidate product should be carefully reviewed for any changes or differences that could present greater obstacles to CD, heat, or humidity penetration than the existing product or PCD. Examples of possible changes include longer lumens, the addition of closures, or a larger number of mated surfaces or product density.

Review the product design against the original product functionality testing to ensure that the changes do not adversely affect the function of the product.

NOTE This evaluation typically does not include areas of the device that are hermetically sealed and cannot be exposed during intended use. Examples are items such as sealed, hollow, molded parts or sealed lumens.

D.12.5.11.4. Determination of product material and characteristics effects

The characteristics of the candidate product should be carefully examined for any differences that could potentially affect the product bioburden, such as manufacturing production methods, facilities, location, and raw material types and sources. The materials of construction should be reviewed to ensure that the product will not retain higher CD residual levels or levels that will exceed the regulated limits.

D.12.5.11.5. Determination of sterile barrier system effects

The sterile barrier system of the candidate product should be carefully examined for any factors that could present obstacles to CD, or humidity penetration. These factors can include a decrease in porosity of the venting material, a smaller venting surface area, the occlusion of the venting area, or any other feature that would make the candidate product a greater challenge to the sterilization process than the existing product or product internal PCD. In addition, the effects of changes to the sterile barrier system on the bioburden of the product and any effects on CD residual levels should be evaluated.

D.12.5.11.6. Determination of load configuration effects

The load configuration of the candidate product should be carefully examined for any changes that could affect the thermodynamic response to the sterilization process. These changes could include additional layers of stretch wrap, a reconfiguration of the pallet, a change in the load size, a change to the overall density of the load, or any other change that would make the candidate product a greater challenge to the sterilization process.

D.12.5.11.7. Conclusions of product adoption evaluation

If the results of the written technical review show that the candidate product and existing products or internal PCD are similar and the differences between them are determined to be insignificant or to present a lesser challenge than the currently validated product or internal PCD, then the candidate product can be adopted into the product family or processing category without further study. If AAMI TIR28:2009[26], Annex A, was used for the review, this decision would be supported by virtually all “No” answers to the questions. The rationale for this decision should be made by a sterilization specialist and should be documented. If the technical review indicates that the candidate product has the potential to be a greater challenge to the sterilization process than the currently validated product or internal PCD, then further studies are indicated. If the candidate product is determined to represent a greater challenge to the sterilization process, then it does not meet the requirements for adoption into an existing product family or processing category, and a full PQ needs to be performed. This PQ can:

a) establish a new product family or processing category, with the candidate product as the representative product;

b) establish a new internal PCD for the sterilization process;

c) establish that the candidate product is equivalent to the currently validated master product; or

d) establish a new sterilization process for the candidate product.

Annex E

(normative)

Single Lot Release

E1. General

This annex specifies the requirements for the release of product from a sterilization process where there is only sufficient product to comprise a single sterilization load, for example, during research and development of new product or for clinical trial product.

NOTE Attention is drawn to the possible existence of national or regional regulations for clinical product. Where such regulations are in force, the requirements of these regulations should be followed.

E2. Procedure

E2.1. Assess the packaged product to determine if it can be assigned to an existing product family for sterilization purposes. This assessment considers product composition, design, packaging, bioburden, and load density. The outcome of this assessment, including the rationale for decisions reached, is documented.

E2.2. If the packaged product can be assigned to an existing product family refer to 12.5.2 and D.12.5.2.

E2.3. Where there is no existing product family(ies), or where packaged product cannot be assigned to an existing product family:

a) Randomly select samples from the batch and determine the average bioburden of the batch in accordance with ISO 11737-1.

b) Distribute product test of sterility samples and internal PCDs that are located within packaged product throughout the sterilization load, including locations where sterilizing conditions are most difficult to achieve. Place external PCDs (if used) on the load in defined locations. The PCD contains BIs that comply with ISO 11138-2:2006.

NOTE The locations used should include those used for temperature monitoring.

c) Expose the sterilization load to a fractional CD gas exposure cycle at minimum process parameters estimated to deliver an SAL of < 10−1 for product and a 7 to 8 log10 reduction in the PCD.

d) Remove internal PCDs, external PCDs (if used), and product test samples from the load and subject to tests of sterility in accordance with ISO 11737-2.

NOTE If comparative resistance of the internal PCD versus product bioburden has previously been assessed using a fractional cycle of shorter duration than that of the fractional cycle in E.2.3 c), and there have been no positive test results from the product test of sterility samples, then it is not necessary to perform the test of sterility for product test samples exposed to the fractional cycle in E.2.3 c).

e) Aerate and re-equilibrate the load to ambient conditions. The aeration period is sufficient to allow CD residues to dissipate to a level that will not adversely affect new PCDs in the full exposure sterilization cycle (see f) and g) below).

f) Distribute new internal PCDs that are located within packaged product throughout the sterilization load, including locations where sterilizing conditions are most difficult to achieve. Place external PCDs (if used) on the load in defined locations.

NOTE The locations used should include those used for temperature monitoring.

g) Process the same load by exposing it to a second sterilization cycle at nominal process parameters and where the specified exposure time is at least double that of the fractional cycle in c) above (this is a full cycle).

h) Remove external PCDs (if used) and internal PCDs from the reprocessed load and subject to tests of sterility.

E2.4. The sterilization load can be released from sterilization if the following requirements are met:

a) the product bioburden presents less of a challenge to the sterilization process than the biological indicator used in the external PCDs (if used) and internal PCDs;

b) the process parameters for the fractional cycle comply with the process specification;

c) the load has been reprocessed by exposure to a full sterilization cycle at nominal process parameters where the specified exposure time was at least double that of the fractional cycle in E.2.3 c);

d) the process parameters for the full sterilization cycle comply with the process specification;

e) confirmation of no growth of the test microorganisms from external PCDs (if used) and internal PCDs exposed to the fractional sterilization cycle;

f) confirmation of no positive result growth from product test of sterility samples exposed to the fractional sterilization cycle;

NOTE If comparative resistance of the internal PCD versus product bioburden has previously been assessed using a fractional cycle of shorter duration than that of the fractional cycle in E.2.3 c), and there have been no positive test results from the product test of sterility samples, then it is not necessary to perform the test of sterility for product test samples exposed to the fractional cycle in E.2.3 c).

g) confirmation of no growth of the test microorganisms from PCDs exposed to the full sterilization cycle;

h) product functionality, stability and package integrity comply with requirements after exposure to the full sterilization cycle;

i) confirmation that product CD residue levels comply with the requirements after product has been exposed to both the fractional and the full sterilization cycles; and

j) all quality and regulatory requirements have been met.

NOTE Information and data generated from this approach can be used retrospectively to support future validation of the sterilization process.

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