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Sterilization of health care products — Radiation sterilization — Selection of sterilization dose for a single production batch

Stérilisation des produits médicaux — Stérilisation par irradiation — Sélection d'une dose stérilisante pour un lot unique de fabrication

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Contents

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

— type 1, when the required support cannot be obtained for the publication of an International Standard, despite repeated efforts;

— type 2, when the subject is still under technical development or where for any reason there is the future but not immediate possibility of an agreement on an International Standard;

— type 3, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example).

Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until data they provide are considered to be no longer valid or useful.

ISO/TR 15844, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This document is being issued in the type 2 Technical Report series of publications (according to subclause G.3.2.2 of part 1 of the ISO/IEC Directives, 1992) as a "prospective standard for provisional application" in the field of radiation sterilization because there is an urgent need for guidance on how procedures in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard." It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this type 2 Technical Report will be carried out not later than three years after its publication with the options of: extension for another three years; conversion into an International Standard; or withdrawal.

Introduction

This Technical Report is intended to be used in conjunction with ISO 11137, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*. One of the activities encompassed within this Technical Report is the selection of the sterilization dose to be applied to health care products. ISO 11137 specifies that one of two approaches is to be used to select the sterilization dose; either i) the selection of a product-specific sterilization dose, or ii) the application of a minimum dose of 25 kGy following substantiation of the appropriateness of this dose.

An informative annex to ISO 11137:1995 (annex B) describes two methods for selecting a sterilization dose. These methods are designated Method 1 and Method 2. The basis for these methods owes much to the ideas first propounded by Tallentire [4], [5] and [6]. Subsequently, standardized methods were developed [2], [3] and [7] which formed the basis of the dose selection procedures put forward in the AAMI recommended practice for sterilization by gamma irradiation, *Guideline for gamma radiation sterilization* (AAMI, 1984 [1]).

These methods of selection of sterilization dose use data derived from the inactivation of the microbial population in its natural state, and are based on a probability model for the inactivation of microbial populations. The probability model, as applied to bioburden made up of a mixture of various microbial species, assumes that each species has its own unique `D_{10}' value. In the model, the probability that a particular item will be sterile after exposure to a given dose of radiation is defined in terms of the initial number of organisms on the item prior to irradiation and their D_{10} values.

The application of Methods 1 and 2 as described in annex B of ISO 11137:1995 requires that a relatively large number of product items, drawn from a number of separate production batches, are used to establish the sterilization dose. This is not always practicable. Manufacturers of health care products regularly produce new products and they are also on occasion required to manufacture a single batch of a product for a special order, field trial or clinical investigation. In addition, batches of many health care products are small and might be produced infrequently (that is, less than once every three months). For products manufactured in all these situations, selection and maintenance of a validated sterilization dose is as important as for large production batches. The method described in ISO/TR 13409 [8] provides guidance on how to carry out substantiation subject to the following limitations:

a) products with an average bioburden of less than 1 000 colony-forming units (cfu), and

b) products manufactured in small quantities (less than 1 000 product units).

The method described in this report provides guidance on how to select a sterilization dose for a single production batch of health care products. The method is based upon Method 1, described in ISO 11137:1995, B.3.4.1.1 to B.3.4.1.3. Method 1 depends upon experimental verification that the response to radiation of bioburden is greater than that of a microbial population having a standard distribution of resistances. In practice, ten product units from three batches are selected and an estimate is made of the average bioburden prior to irradiation. For this bioburden, the dose that gives an SAL of 10^{-2} for the standard distribution of resistances is obtained. This dose is designated the verification dose, and it represents the dose that will reduce a microbial population with a standard distribution of resistances to a level that gives on average of one in 100 probability of a non-sterile product unit. A sample of 100 product units or portions thereof (SIP) is then exposed to the verification dose and each product unit is tested individually for sterility. If there are no more than two positive tests out of the 100 tests, the sterilization dose is selected for the desired SAL from the response of microorganisms having the standard distribution of resistances at the estimated level of bioburden.

With the present method, only one production batch is manufactured and therefore the estimate of the average bioburden is made on that batch. The verification experiment and selection of the sterilization dose remain consistent with Method 1 in ISO 11137.

It was decided to publish the present method as a Technical Report (type 2) because, unlike Methods 1 and 2 which had been used extensively since 1984, there was little practical experience in the application of this method. Users of this method are urged to submit any comments on the application and content of this document so that this experience can be taken into account when ISO 11137 is next revised.

Manufacturers of health care products who intend to use the protocols contained in this Technical Report are reminded that the requirements contained in ISO 11137 for all users of radiation sterilization equally apply to the manufacture and control of a single production batch for which the selection of a sterilization dose is to be substantiated by this method. In particular, there is a requirement that products be manufactured in circumstances such that the bioburden is controlled. Compliance with the requirements for proper control of the quality of raw materials, for the manufacturing environment, and for the establishment of the basic properties of the packaging material are all essential.

Sterilization of health care products — Radiation sterilization — Selection of sterilization dose for a single production batch

1 Scope

This Technical Report describes a method of selecting a sterilization dose to be used for radiation sterilization of a single production batch of health care products. The sterilization dose established through the use of this method for a particular batch cannot be used for other batches.

NOTE 1 Application of the method of dose selection described in this Technical Report may be used to meet the requirements specified under 6.2.2 relating to product qualification in ISO 11137:1995.

NOTE 2 This Technical Report is considered informative, and use of the terms "shall," "should," etc. should be considered within the context of this Technical Report only. That is, if the decision is made to use this method of dose selection, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this Technical Report.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this Technical Report. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this Technical Report are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization.*

ISO 11737-1:1995, *Sterilization of medical devices — Microbiological methods — Part 1: Estimation of population of microorganisms on product.*

ISO 11737-2:1998, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process.*

3 Terms and definitions

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

3.1
batch
defined quantity of bulk, intermediate, or finished product that is intended or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture

3.2
bioburden
population of viable microorganisms on a product

NOTE In the context of radiation sterilization, bioburden is determined immediately prior to sterilization.

3.3
bioburden estimate
value established for the number of microorganisms comprising the bioburden by applying to a viable count or presterilization count a factor compensating for the recovery efficiency

3.4
D_{10}
radiation dose required to kill 90 % of a homogeneous microbial population where it is assumed that the death of microbes follows first-order kinetics

NOTE In this context, D_{10} is expressed in kilogray (kGy).

3.5
false positive
result of a test of sterility in which a true negative is interpreted as a positive

3.6
positive test of sterility
test of sterility which exhibits detectable microbial growth after incubation

3.7
presterilization count
viable count obtained prior to sterilization

3.8
product unit
health care product, collection of products or components within a primary package

3.9
sample item portion
SIP
defined portion of a health care product unit that is tested

3.10
sterility assurance level
SAL
probability of a viable microorganism being present on a product unit after sterilization

NOTE 1 SAL is normally expressed as 10^{-n}.

NOTE 2 In the context of validation, the SAL may take levels other than that achieved by sterilization.

3.11
sterilization dose
minimum absorbed dose required to achieve the specified sterility assurance level

3.12
test of sterility
test performed to establish the presence or absence of viable microorganisms on product units, or portions thereof, when subjected to defined culture conditions

3.13
verification dose
dose of radiation estimated to produce an SAL of 10^{-2} for a product unit or portion thereof, and used in dose-setting methods to establish or confirm the sterilization dose

3.14
viable count
number of microorganisms estimated by growth of discrete colonies under the stated culture conditions.

NOTE A discrete colony may not necessarily originate from a single viable microorganism.

4 Selection and testing of product

4.1 Selection

4.1.1 Method

The method of selecting product units for subsequent testing can influence the test result observed. Selected product units shall be representative of the batch and be selected at random. Product units for testing may be selected from items rejected during the manufacturing process, provided that they have been subjected to the same processing and conditions as the remainder of the batch.

4.1.2 Sample item portion (SIP)

An entire product unit should be used for testing, but it is recognized that this is not always practicable. In such situations, a selected portion of a product unit (sample item portion, SIP), which is convenient to handle during testing, may be substituted. The SIP should be as large a portion of the product unit as is possible to manipulate readily in the laboratory. SIP can be calculated on the basis of length, mass, volume, or surface area of the product unit to be tested.

The SIP shall represent validly the microbial challenge presented to the sterilization process and the diverse elements of complex product units. The distribution of viable microorganisms on the product unit shall be considered and, if it can be demonstrated that these microorganisms are evenly distributed, the SIP may be selected from any single location of the product unit. In the absence of such a demonstration, the SIP shall be constituted from several portions of a product unit selected at random.

Twenty SIPs should be prepared and a test of sterility on each performed in accordance with ISO 11737-2. There shall be at least 17 positive tests of sterility. If this criterion is not achieved, a larger SIP is required.

NOTE 1 The occurrence of 17 positives out of 20 tests of sterility indicates that there is an average of 2 cfu/SIP.

If the entire product unit is tested, the tests of sterility on non-irradiated products are not required.

If a product unit or SIP cannot be tested in available laboratory glassware, it may be divided into two or more containers and these containers scored together as one unit. If in the performance of a test of sterility one container yields a positive result, the entire unit is considered positive.

If the product unit has a label claim of sterility of the fluid path only, testing the fluid path should be considered as testing the entire product unit (i.e. SIP = 1,0).

The preparation and packaging of an SIP shall be conducted under conditions chosen to minimize alterations in the bioburden.

NOTE 2 Environmentally controlled conditions should be used for preparation of SIPs.

Packaging materials should be equivalent to those used for the finished product. Packaging shall be capable of withstanding the radiation doses to be delivered. Packaging for products, or portions thereof, for irradiation shall be chosen in order to minimize contamination during post-irradiation handling.

4.1.3 Sample item portion for kits

A kit is considered to be a product unit containing more than one health care product; these may be:

a) kits containing multiples of the same health care product;

The SIP for such kits shall be based upon a single health care product and not the summation of all the products in the kit. For example, for a kit containing five syringes, one syringe tested in its entirety would equal an SIP of 1,0.

b) kits containing procedure-related different health care products.

The SIP for such kits shall be based upon each type of health care product and a separate SIP established for each product in the kit. For example, for a kit containing two gowns, two towels, two pairs of gloves and a drape, an individual SIP shall be determined for each type of health care product, independent of the other products in the kit.

4.2 Microbiological testing

Bioburden determinations and tests of sterility conducted as part of this method shall be conducted using acceptable laboratory practices and in accordance with ISO 11737-1 and ISO 11737-2 respectively.

The method described hereafter uses a single culture medium for the performance of the test of sterility. The use of a single medium assumes that the medium will be optimal for the culture of aerobic and facultative organisms which may survive.

When this assumption is not valid, this method shall be conducted using other appropriate media and incubation conditions.

NOTE Soybean-casein digest broth, with an incubation temperature of (30 ± 2) °C and an incubation period of 14 days, is generally recommended when a single growth medium is used.

4.3 Product irradiation

The irradiation of product, or SIPs, shall be in accordance with ISO 11137:1995, C.1.5.4.

It is preferred that the product is irradiated in its original form and package. However, to minimize and/or simplify the manipulations during testing and reduce the possibility of false positives in the performance of tests of sterility, it may be decided to disassemble the product and repackage prior to exposure to the verification dose.

NOTE Manipulations prior to radiation may not always be acceptable. In certain instances, such manipulations may change the response of the microorganisms to radiation. For example, manipulations may alter the chemical environment in the vicinity of the microorganisms, typically oxygen tension.

Materials used for repackaging products or SIPs for irradiation shall be capable of withstanding the radiation doses to be delivered. Packaging for products, or portions thereof, for irradiation shall be chosen in order to minimize contamination during post-irradiation handling.

5 Method of dose selection

5.1 Rationale

This method is an adaptation of Method 1 described in ISO 11137:1995 and is intended to be used for the selection of a sterilization dose for a single production batch only. It is a method of selecting a sterilization dose depending upon experimental verification that the response to radiation of the product microflora is greater than that of a microbial population having a standard distribution of resistances.

A rationalized choice has been made for the standard distribution of resistances (D_{10} values) (see Table 1) and, using computational methods, the individual doses required to achieve values of SAL of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} have been calculated for levels of bioburden on product prior to irradiation (average bioburden). The calculated values of dose for given average bioburdens are tabulated in Table 2.

Table 1 — Reference microbial resistance distribution used in Method 1 [7]

D_{10} kGy	1,0	1,5	2,0	2,5	2,8	3,1	3,4	3,7	4,0	4,2
Frequency	0,654 87	0,224 93	0,063 02	0,031 79	0,012 13	0,007 86	0,003 50	0,001 11	0,000 72	0,000 07

In practice, an estimate is made of the average bioburden. The dose that gives an SAL of 10^{-2} for products units having this bioburden is read from Table 2. This dose is designated the verification dose, and it represents the dose that will reduce the microbial population of standard resistances to a level that gives a one in 100 chance of occurrence of a non-sterile product unit. A sample of 100 product units or SIPs is then exposed to the selected verification dose and each product unit is subjected to a test of sterility. If there are no more than two positive tests out of the 100 tests, Table 2 is again entered at the estimated level of bioburden to provide the sterilization dose for any desired SAL.

5.2 Technical requirement

5.2.1 This method is only used for the selection of a sterilization dose for a single production batch. The basic technical requirements for selection of sterilization dose are:

a) access to competent microbiological laboratory services;

b) microbiological testing performed in accordance with ISO 11737-1 and ISO 11737-2;

c) access to a radiation source capable of delivering accurate and precise doses ranging from 1 kGy upward with either:

   1) a ^{60}Co or ^{137}Cs radiation source; or

   2) an electron beam or X-ray irradiator operated at an energy level and dose rate similar to those used in processing.

5.2.2 In conducting dose selection in accordance with this Technical Report, the requirements of ISO 11137 concerning the manufacture and control of products intended for radiation sterilization shall apply.

5.3 Procedure

The following five procedural stages shall be carried out:

NOTE Worked examples appear in clause 6.

5.3.1 Stage 1: Select SAL and obtain a sample of product units

Record the sterility assurance level (SAL) to be used. Then take a random sample of at least 10 product units from the batch. The number of product units shall be sufficient to represent validly the bioburden on the product to be sterilized.

NOTE With this method, it is necessary to hold product units for the verification dose experiment until determination of the average bioburden is completed. The ability of the product to support microbial growth should be taken into account in selecting storage conditions for the product units while bioburden is being determined.

5.3.2 Stage 2: Determine average bioburden

Determine the bioburden of each product unit or SIP and the average bioburden for SIPs (where appropriate) and product units comprising the sample.

5.3.3 Stage 3: Establish the verification dose

Using Table 2, determine the verification dose based on the average bioburden. If the average bioburden is not listed in Table 2, use the closest number for the bioburden in the table greater than the average bioburden.

NOTE 1 Table 2 is designed to test the resistance of the product microbial population through the use of a verification dose experiment at a SAL of 10^{-2}. The whole product unit or portion thereof may be taken. If an SIP is tested, the bioburden for the SIP (SIP bioburden) should be used to determine the verification dose.

NOTE 2 In this context, the average bioburden can be based upon values of the presterilization count which are potentially underestimates of bioburden. Use of such an average bioburden to enter Table 2 will therefore provide a minimal value of verification dose and thereby an enhanced challenge of the verification dose experiment.

5.3.4 Stage 4: Perform verification dose experiment

Select at random 100 product units from the entire batch.

Irradiate the product units, or portions thereof, at the verification dose obtained from Table 2 in stage 3 above.

The actual dose may vary from the calculated verification dose by not more than +10 %. If the delivered dose is less than 90 % of the verification dose derived from Table 2, the verification dose experiment may be repeated. Use of the verification dose experiment without bioburden estimation is not valid.

NOTE 1 In this context, the "actual dose" refers to the maximum dose received by the group of product units.

NOTE 2 In this context, the "delivered dose" refers to the arithmetic mean of the maximum and minimum doses.

Subject each of the irradiated product units or SIPs to a test of sterility. The test of sterility should be performed using soybean-casein digest broth, incubated at (30 ± 2) °C for 14 days (in accordance with ISO 11737-2). Record the number of positive tests of sterility.

NOTE 3 Other media and incubation conditions may be employed as appropriate (see 4.2).

Statistical verification is accepted if there are no more than two positive tests of sterility from the 100 tests performed.

NOTE 4 The rationale for allowing up to two positives is based on the statistical probability that, when the average bioburden is used to predict the dose at which one of 100 samples is expected to be non-sterile, there is a 0,92 probability that zero, one or two positives may occur (Table 3).

If there are more than two positive tests of sterility, this method of dose-setting is not valid and an alternative dose selection method should be used, unless the result can be ascribed to one or more of the following:

a) the estimation of bioburden (e.g. the average bioburden used to obtain the verification dose was based on values of the presterilization counts and not values of bioburden estimates);

b) the performance of tests of sterility;

c) the delivery of the verification dose (e.g. the delivered dose was less than 90 % of the verification dose obtained from Table 2).

5.3.5 Stage 5: Establish sterilization dose

If the verification dose experiment is passed (that is, statistical verification is accepted), Table 2 is used to obtain the sterilization dose for the batch using the closest value for the bioburden given in the table that is equal to or greater than the average bioburden for the product unit, and then reading off the dose necessary to achieve the desired SAL.

NOTE If a portion of the product was tested (in stage 2) to determine the bioburden (SIP bioburden), the SIP bioburden should be divided by the SIP to determine the bioburden for the entire product unit. The average bioburden for the entire product is used to obtain the sterilization dose.

6 Worked examples

The first example (Table 4) is for a product that is too large to be tested in its entirety, so a portion of the product (SIP<1) is used. The second example (Table 5) is for a product that can be tested using the whole unit (SIP=1).

Table 2 — Radiation dose (kGy) required to achieve a given SAL for different bioburdens having standard distribution of resistances

Average bioburden	Sterility Assurance Level					Average bioburden	Sterility Assurance Level				
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}		10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
0,063	1,0	2,6	4,8	7,4	10,4	28,00	6,4	9,3	12,4	15,8	19,3
0,075	1,1	2,7	5,0	7,6	10,6	30,48	6,5	9,4	12,6	15,9	19,4
0,088	1,2	2,8	5,1	7,8	10,8	33,16	6,6	9,5	12,7	16,0	19,5
0,10	1,3	3,0	5,3	8,0	11,0	36,06	6,7	9,7	12,8	16,1	19,6
0,12	1,4	3,1	5,5	8,2	11,3	39,20	6,8	9,8	12,9	16,2	19,8
0,14	1,5	3,3	5,7	8,4	11,5	42,60	6,9	9,9	13,0	16,4	19,9
0,17	1,6	3,5	5,9	8,6	11,7	46,28	7,0	10,0	13,2	16,5	20,0
0,19	1,7	3,6	6,0	8,8	11,9	50,25	7,1	10,1	13,3	16,6	20,2
0,22	1,8	3,7	6,2	9,0	12,1	54,55	7,2	10,2	13,4	16,8	20,3
0,26	1,9	3,9	6,4	9,2	12,3	59,20	7,3	10,3	13,5	16,9	20,4
0,29	2,0	4,0	6,5	9,4	12,5	64,22	7,4	10,4	13,6	17,0	20,5
0,34	2,1	4,1	6,7	9,6	12,7	69,65	7,5	10,5	13,7	17,1	20,7
0,39	2,2	4,3	6,8	9,8	12,9	75,51	7,6	10,6	13,9	17,3	20,8
0,44	2,3	4,4	7,0	9,9	13,1	81,83	7,7	10,7	14,0	17,4	20,9
0,50	2,4	4,5	7,1	10,1	13,3	88,67	7,8	10,9	14,1	17,5	21,0
0,57	2,5	4,7	7,3	10,3	13,5	96,04	7,9	11,0	14,2	17,6	21,2
0,65	2,6	4,8	7,5	10,4	13,6	104,0	8,0	11,1	14,3	17,7	21,3
0,73	2,7	4,9	7,6	10,6	13,8	112,6	8,1	11,2	14,4	17,9	21,4
0,83	2,8	5,1	7,8	10,8	14,0	121,9	8,2	11,3	14,5	18,0	21,5
0,93	2,9	5,2	8,0	10,9	14,2	131,9	8,3	11,4	14,7	18,1	21,7
1,05	3,0	5,3	8,1	11,1	14,3	142,6	8,4	11,5	14,8	18,2	21,8
1,17	3,1	5,4	8,2	11,2	14,5	154,3	8,5	11,6	14,9	18,3	21,9
1,32	3,2	5,6	8,3	11,4	14,7	166,8	8,6	11,7	15,0	18,5	22,0
1,47	3,3	5,7	8,5	11,5	14,8	180,3	8,7	11,8	15,1	18,6	22,2
1,64	3,4	5,8	8,6	11,7	15,0	194,8	8,8	11,9	15,2	18,7	22,3
1,83	3,5	6,0	8,8	11,9	15,1	210,5	8,9	12,0	15,3	18,8	22,4
2,04	3,6	6,1	8,9	12,0	15,3	227,4	9,0	12,2	15,5	18,9	22,5
2,27	3,7	6,2	9,0	12,2	15,5	245,6	9,1	12,3	15,6	19,0	22,7
2,51	3,8	6,3	9,2	12,3	15,6	265,2	9,2	12,4	15,7	19,2	22,8
2,79	3,9	6,4	9,3	12,4	15,8	286,3	9,3	12,5	15,8	19,3	22,9
3,09	4,0	6,6	9,4	12,6	15,9	309,0	9,4	12,6	15,9	19,4	23,0
3,42	4,1	6,7	9,6	12,7	16,1	333,4	9,5	12,7	16,0	19,5	23,1
3,77	4,2	6,8	9,7	12,9	16,2	359,7	9,6	12,8	16,1	19,6	23,3
4,17	4,3	6,9	9,9	13,0	16,4	388,0	9,7	12,9	16,2	19,8	23,4
4,60	4,4	7,0	10,0	13,1	16,5	418,4	9,8	13,0	16,4	19,9	23,5
5,06	4,5	7,1	10,1	13,3	16,6	451,1	9,9	13,1	16,5	20,0	23,6
5,57	4,6	7,3	10,2	13,4	16,8	486,3	10,0	13,2	16,6	20,1	23,7
6,13	4,7	7,4	10,4	13,6	16,9	524,2	10,1	13,3	16,7	20,2	23,9
6,74	4,8	7,5	10,5	13,7	17,1	564,9	10,2	13,4	16,8	20,3	24,0
7,40	4,9	7,6	10,6	13,8	17,2	606,6	10,3	13,5	16,9	20,5	24,1
8,12	5,0	7,7	10,7	14,0	17,4	655,6	10,4	13,7	17,0	20,6	24,2
8,91	5,1	7,9	10,9	14,1	17,5	706,2	10,5	13,8	17,1	20,7	24,3
9,76	5,2	8,0	11,0	14,2	17,6	760,5	10,6	13,9	17,3	20,8	24,5
10,69	5,3	8,1	11,1	14,4	17,8	818,8	10,7	14,0	17,4	20,9	24,6
11,70	5,4	8,2	11,2	14,5	17,9	881,4	10,8	14,1	17,5	21,0	24,7
12,80	5,5	8,3	11,4	14,6	18,1	948,7	10,9	14,2	17,6	21,1	24,8
13,99	5,6	8,4	11,5	14,7	18,2	1 021	11,0	14,3	17,7	21,3	24,9
15,28	5,7	8,5	11,6	14,9	18,3	1 099	11,1	14,4	17,8	21,4	25,1
16,69	5,8	8,6	11,7	15,0	18,5	1 182	11,2	14,5	17,9	21,5	25,2
18,21	5,9	8,8	11,8	15,1	18,6	1 271	11,3	14,6	18,0	21,6	25,3
19,87	6,0	8,9	12,0	15,3	18,7	1 387	11,4	14,7	18,2	21,8	25,4
21,66	6,1	9,0	12,1	15,4	18,8	1 470	11,5	14,8	18,3	21,9	25,5
23,61	6,2	9,1	12,2	15,5	19,0	1 581	11,6	14,9	18,4	22,0	25,7
25,72	6,3	9,2	12,3	15,6	19,1	1 699	11,7	15,0	18,5	22,1	25,8

Table 2 — (*Continued*)

Average bioburden	Sterility Assurance Level					Average bioburden	Sterility Assurance Level				
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}		10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
1 827	11,8	15,1	18,6	22,2	25,9	75 463	17,2	20,8	24,5	28,2	32,0
1 963	11,9	15,2	18,7	22,3	26,0	80 629	17,3	20,9	24,6	28,3	32,1
2 109	12,0	15,3	18,8	22,4	26,1	86 142	17,4	21,0	24,7	28,4	32,3
2 266	12,1	15,5	18,9	22,6	26,2	92 025	17,5	21,1	24,8	28,5	32,4
2 435	12,2	15,6	19,0	22,7	26,4	98 302	17,6	21,2	24,9	28,6	32,5
2 615	12,3	15,7	19,1	22,8	26,5	105 000	17,7	21,3	25,0	28,8	32,6
2 808	12,4	15,8	19,3	22,9	26,6	112 140	17,8	21,4	25,1	28,9	32,7
3 016	12,5	15,9	19,4	23,0	26,7	119 760	17,9	21,5	25,2	29,0	32,8
3 238	12,6	16,0	19,5	23,1	26,8	127 890	18,0	21,6	25,3	29,1	32,9
3 476	12,7	16,1	19,6	23,2	26,9	136 560	18,1	21,7	25,4	29,2	33,0
3 731	12,8	16,2	19,7	23,3	27,1	145 810	18,2	21,8	25,5	29,3	33,1
4 004	12,9	16,3	19,8	23,4	27,2	155 670	18,3	21,9	25,6	29,4	33,3
4 297	13,0	16,4	19,9	23,6	27,3	166 190	18,4	22,0	25,7	29,5	33,4
4 611	13,1	16,5	20,0	23,7	27,4	177 410	18,5	22,1	25,8	29,6	33,5
4 946	13,2	16,6	20,1	23,8	27,5	189 360	18,6	22,2	25,9	29,7	33,6
5 306	13,3	16,7	20,2	23,9	27,6	202 110	18,7	22,3	26,1	29,8	33,7
5 691	13,4	16,8	20,4	24,0	27,7	215 710	18,8	22,5	26,2	29,9	33,8
6 104	13,5	16,9	20,5	24,1	27,9	230 200	18,9	22,6	26,3	30,1	33,9
6 545	13,6	17,0	20,6	24,2	28,0	245 650	19,0	22,7	26,4	30,2	34,0
7 018	13,7	17,1	20,7	24,3	28,1	262 110	19,1	22,8	26,5	30,3	34,1
7 524	13,8	17,2	20,8	24,5	28,2	279 660	19,2	22,9	26,6	30,4	34,2
8 065	13,9	17,4	20,9	24,6	28,3	298 370	19,3	23,0	26,7	30,5	34,3
8 645	14,0	17,5	21,0	24,7	28,4	318 310	19,4	23,1	26,8	30,6	34,5
9 265	14,1	17,6	21,1	24,8	28,6	339 560	19,5	23,2	26,9	30,7	34,6
9 928	14,2	17,7	21,2	24,9	28,7	362 200	19,6	23,3	27,0	30,8	34,7
10 638	14,3	17,8	21,3	25,1	28,8	386 320	19,7	23,4	27,1	30,9	34,8
11 397	14,4	17,9	21,4	25,2	28,9	412 030	19,8	23,5	27,2	31,0	34,9
12 209	14,5	18,0	21,6	25,3	29,0	439 420	19,9	23,6	27,3	31,1	35,0
13 078	14,6	18,1	21,7	25,4	29,1	468 600	20,0	23,7	27,4	31,2	35,1
14 006	14,7	18,2	21,8	25,5	29,2	499 690	20,1	23,8	27,5	31,3	35,2
15 000	14,8	18,3	21,9	25,6	29,3	532 810	20,2	23,9	27,6	31,5	35,3
16 062	14,9	18,4	22,0	25,7	29,5	568 080	20,3	24,0	27,7	31,6	35,4
17 197	15,0	18,5	22,1	25,8	29,6	605 660	20,4	24,1	27,8	31,7	35,5
18 411	15,1	18,6	22,2	25,9	29,7	645 680	20,5	24,2	28,0	31,8	35,7
19 709	15,2	18,7	22,3	26,0	29,8	688 310	20,6	24,3	28,1	31,9	35,8
21 096	15,3	18,8	22,4	26,1	29,9	733 710	20,7	24,4	28,2	32,0	35,9
22 578	15,4	18,9	22,5	26,2	30,0	782 060	20,8	24,5	28,3	32,1	36,0
24 162	15,5	19,0	22,6	26,3	30,1	833 540	20,9	24,6	28,4	32,2	36,1
25 885	15,6	19,1	22,7	26,4	30,3	888 370	21,0	24,7	28,5	32,3	36,2
27 664	15,7	19,2	22,8	26,6	30,4	946 746	21,1	24,8	28,6	32,4	36,3
29 596	15,8	19,3	23,0	26,7	30,5	1 008 900	21,2	24,9	28,7	32,5	36,4
31 661	15,9	19,4	23,1	26,8	30,6						
33 867	16,0	19,5	23,2	26,9	30,7						
36 222	16,1	19,7	23,3	27,0	30,8						
39 739	16,2	19,8	23,4	27,1	31,0						
41 426	16,3	19,9	23,5	27,2	31,1						
44 296	16,4	20,0	23,6	27,3	31,2						
47 360	16,5	20,1	23,7	27,4	31,3						
50 632	16,6	20,2	23,8	27,6	31,4						
54 126	16,7	20,3	23,9	27,7	31,5						
57 855	16,8	20,4	24,0	27,8	31,6						
61 836	16,9	20,5	24,1	27,9	31,7						
66 086	17,0	20,6	24,2	28,0	31,8						
70 622	17,1	20,7	24,3	28,1	31,9						

NOTE The presence in Table 2 of high bioburden levels is not intended to imply that such levels are the norm.