EN/ISO 11737-1 “Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products”

Note on differences between 2006 and 2018 versions

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Introduction

An updated version of document EN/ISO 11737-1 “Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products” was published in 2018, replacing the original version that had been published in 2006.

Although the Scope and overall outline of the two documents are similar, there have been some changes in terms of terminology, more detailed guidance in appendices and a new appendix D.

The purpose of this document is to highlight, in general terms, areas of difference between the two versions of the standard.

Contents of 11737-1:2018

Figure 1 : Content page of ISO11737-1:2018 and ISO 11737-1 :2006 for comparison

ISO 11737-1:2018(E)

Contents

ISO 11737-1:2006(E)

Contents

Figure 1 shows the contents of 11737-1:2018 and 2006. The overall structure is very similar to that of 11737-1:2006, but Sections have been renamed and restructured.

One new informative Annex has been added: Annex D Typical alignment of responsibilities.

In the remainder of this document, differences between the two standards will be given, using the numbering and titles of clauses in 11737-1:2018.

The Foreword lists the following summary of changes:

The main changes compared to the previous edition are as follows:

— the term "bioburden spikes" has been introduced as a normal and consistent part of the bioburden, and examples of data have been provided;

— clarification has been added that package testing is not typically done except when it is an integral part of the product;

— more information has been provided on the most probable number (MPN) technique and its applications;

— details have been provided on ways to improve limit of detection (LOD) and correct use of the data;

— some discussion has been deleted of statistical methods for the evaluation of bioburden data where information was not typical or not required;

— a table has been added with criteria for selection of a bioburden recovery efficiency approach, the use of the correction factor (CF) has been explained, and the bioburden recovery efficiency value of < 50 % mentioned for technique modifications has been eliminated;

— more information has been provided on the application and performance of a bioburden method suitability test;

— a section has been added to detail rules for direct plate counts, estimated counts and counts beyond the ideal range;

— a table has been added to clarify where typical responsibilities reside for the manufacturer or the laboratory;

— the focus on a risk-based approach has been increased, including the purpose for which bioburden data will be used.

Scope (Clause 1)

The Scope introduces the term ‘healthcare product’ to replace the term ‘medical device’ – this continues throughout the document.

Normative References (Clause 2)

Reference added to ISO 15189 Medical laboratories – requirements for quality and competence

Terms and Definitions (Clause 3)

This Clause introduces some new terms: namely batch / bioburden correction factor / bioburden estimate / bioburden method suitability / bioburden spike / facultative microorganism / health care product / obligate anaerobe / requalification / sterile / sterile barrier system.

General requirements (Clause 4)

Title changed from 'quality management system elements'

The main difference is the addition of line 4.4.1 ; 'For the purpose of bioburden test methods and results, measurement uncertainty, precision and bias typically do not apply and therefore this type of data analysis may not be necessary, except in evaluating the overall competency of the laboratory.'

Selection of products (Clause 5)

Section reworded but no change to intent. Reference added to 'product family'.
Reference changed from 'taking samples' to 'manufacturing'.
'When selecting the portion that contains the most severe microbial challenge, the relationship of the bioburden of the SIP tested to the entire product bioburden should be established.'
Added note about adequacy of SIP. Table of SIP calculation moved to Annex A.

Methods of determination and microbial characterisation of bioburden (Clause 6)

New section 6.1.2; 'If the physical or chemical nature of the product is such that substances can be released that adversely affect the detection of the product bioburden, then a system shall be used to neutralize, remove or, if this is not possible, minimize the effect of any such released substance. The effectiveness of such a system shall be demonstrated. NOTE Annex B describes techniques that can be used to assess the release of microbicidal or microbiostatic substances.'

Addition 'for which the data are to be used'.
Addition 'neutralisation of inhibitory substances, if needed'.
Structure change – own paragraph on neutralisation.
Addition 'and the physical or chemical nature of the product to be tested'.
Note addition 'Furthermore, knowledge of the types of microorganisms can be helpful for identifying sources of contamination.'
Addition 'Proteomic methods, eg mass spectrometry'.

Added wording in the note : 'Microbial characterization is necessary to detect a change to the product bioburden that can affect some aspects of the use of bioburden data (e.g. establishing a sterilization process). **Furthermore, knowledge of the types of microorganisms can be helpful for identifying sources of contamination**.'

Validation of the method for determination of bioburden (Clause 7)

No significant changes. Addition: 'assessment of test method suitability to demonstrate lack of inhibition of growth in the test.'

Routine determination of bioburden and interpretation of data (Clause 8)

Section content has been split into numbered sections from 8.1 to 8.7. Content largely unchanged.

New section 8.2 ; The determination of bioburden shall be performed using the method(s) specified for a product or a product family (see 5.1.2). The method selected shall take into account factors that will affect the results, such as the limits of detection and plate counting.

New section 8.5; 'If bioburden data demonstrate a test result that is significantly greater than other values (bioburden spike), these data shall be evaluated for the impact as appropriate depending on the purpose for the data.'

Maintenance of the method for determining bioburden (Clause 9)

No significant changes. Addition: 'with consideration to the purpose for which bioburden data are to be used.'

Annex A

In general more detail added in the guidance sections.

A.4 Quality management system elements

A.4.2	Addition: 'all tests should be conducted in accordance with recognised current/valid best laboratory practices, where applicable, and the data should be evaluated by competent, informed professionals.
A.4.3	Addition: reference to specific pharmacopoeias
A.4.4	Addition of paragraph: statistical analyses
A.4.4.2	Addition: 'deviation to test method (e.g. dilution error, filtration error, aseptic technique error.' Addition: 'and would result in invalid data' Addition: 'to the purpose for which the data will be used.'

A.5 Selection of products

A.5.1.1	Addition: 'Procedures for selecting and handling samples of a product <u>should be documented.</u>' Addition: 'Sampling techniques should be consistent and should allow for <u>event-based</u> and time based comparisons of bioburden.' Addition: 'take an actual product (at random <u>or at a specified frequency.</u>)' Addition: 'manufacture a product specifically for bioburden testing using the routine manufacturing procedures.)' Addition: Paragraph regarding whether bioburden testing of the packaging system is necessary.
A.5.1.2	Significant change and additions to establishing and testing within a product family.
A.5.1.3	Addition: '<u>or maintain</u>'
A.5.2.1	Addition: 'Consideration should be made of the distribution of bioburden across the whole of the product. If the distribution is expected to be uneven across the product, a determination of the area of the product most heavily contaminated should be identified. This area should be included in the SIP selected.'
A.5.2.3	Addition: 'Consideration should be given to aspects of manufacturing that contribute to the distribution of microorganisms on products.'

A.5.2.4	Addition: 'Examples of a SIP that can be selected from the device with a more severe challenge to the sterilization process are tubing sets with connections, stopcocks, etc.'
A.5.2.5	Addition: 'Examples of products for which various bases for SIP calculation are employed are given in Table A.1.' Addition: 'Table A.1 – Examples of SIP calculation'

A.6 Methods of determination and microbial characterization of bioburden

A.6.1.1	Addition: 'This figure can apply to culture and non-culture based methods.' Figure Addition: 'MPN testing.' Addition: 'Addition of two notes relating to figure.' Addition: Passage on bioburden methods for low bioburden products.
A.6.1.2	Addition: 'Section regarding neutralisation of inhibitory substances'.
A.6.1.4	Addition: 'Influence product bioburden'. Addition: 'The recommendations of the laboratory, with the input of the manufacturer, for the use of standard bioburden culture conditions can suffice as the consideration and rationale.' Addition: 'the choice of conditions should minimize the potential to overestimate the average bioburden due to counting the same microorganism on different media.' Addition: 'Health care products manufactured from synthetic material are unlikely to be contaminated with obligate anaerobes. Health care products manufactured from tissue or other natural materials can be at risk of contamination with obligate anaerobes.'
Table A.2	Addition: 'Glucose tryptone agar (plate count agar).' Addition: 'Soybean casein digest agar.' Addition: 'Columbia agar.' Addition: 'Some culture media used for facultative, non-fastidious, aerobic bacteria are able to support the growth of yeasts and moulds.'
A.6.1.5	Addition: 'The laboratory may specify the technique for enumeration, which will suffice as the consideration and rationale.'
A.6.2.1	Addition: 'The degree of characterization necessary is dependent on the nature of the product, diversity of the detected population, and the use of the data (e.g. sterilization qualification).'
A.6.2.2	Addition: Passage on methods used to characterize microorganisms.
Table A.3	Addition: Significant additions to table.

A.7 Validation of the method for determining bioburden

A.7.1	Addition: Two paragraphs concerning validation of bioburden tests.
A.7.2.1	Addition: passage regarding bioburden method suitability.

A.7.2.2	Addition: 'followed by quantitative assessment of the extent of recovery' Addition: 'If this is the case, then the first approach can be preferred based on the product and/or configuration.' Addition: Two paragraphs regarding bioburden recovery of non-traditional products.
A.7.2.3	Addition: 'and the microorganisms expected to be present.' Addition: 'This is of particular concern for health care products where antimicrobials can affect microbial growth.' Addition: 'Risk to the manufactured product considering the mode of sterilization qualification.' Addition: 'previously available data.' Addition: 'the purpose for generating the data' Addition: 'the nature of the manufacturing process (e.g. water involves, manual, automated) and the product.'

A.8 Routine determination of bioburden and interpretation of data

A.8.1	Addition: 'Where bioburden data are used to satisfy the requirements of another International Standard (e.g. the ISO 11137 series), sample size and test frequency can already be predefined by that standard, which would supersede the sample size recommended here.'
A.8.2	Addition: Section on 'Limits of detection and plate counting'.
A.8.3	Addition: Section on 'Microbial characterization'.
A.8.4	Addition: Section on 'Bioburden data for extent of treatment'. NB: 'No additional guidance' for this section.
A.8.5	Addition: Section on 'Bioburden spikes'.
A.8.6	Addition: 'and the purpose for which the data are to be used.' Addition: 'establish temporary levels'. Addition: 'Historical data from similar products, manufacturing processes and/or manufacturing environments may also be used when setting temporary levels for new product lines. For some product sources, significant seasonal variations in bioburden can be expected. Seasonal humidity and/or temperature levels/changes can also alter the types and numbers of microorganisms in the bioburden.' Addition: Passage regarding alert/ action levels and the trending of data.
A.8.7	Addition: 'bioburden averages or bioburden estimates'. Replacement: 'out-of-specification results' to 'deviations'.

A.9 Maintenance of the method for determining bioburden

A.9.1	Addition: Paragraph regarding 'changes to the product and/or manufacturing process'.

Annex B

B.1 General

B.1.1	Addition: 'what extent method development and validation needs to be performed.'
B.1.2	Addition: 'For proper method development and validation it is possible that a combination of different methods might need to be employed initially in order to establish the method(s) most suitable for routine use.'

B.2 Methods where removal of microorganisms by elution is used

B.2.1.3	Addition: 'microorganisms can occur as a biofilm unless appropriate bioburden control measures are taken.' Addition: 'A high level of endotoxin can also be an indication of biofilm.'
B.2.1.6	Addition: 'Certain types of microorganisms or more prone to aggregation/reaggregation than others based primarily on their relative hydrophobicity.'
B.2.2.3.1	Addition: 'for a defined time/number of cycles'.
B.2.2.4.3	Addition: 'in small containers. Variations in removal should be assessed among different individuals operating the vortex mixer.'
B.2.2.7.4	Addition: 'Because of these issues, recovery using this method is generally low.'
B.2.3.2	Addition: 'however, it might not be possible to ascertain this for all potential contaminants.'
Table B.1	Replacement: 'between 0.01% and 0.1%' to 'between 0.1% and 1%'.
B.3.2.1	Addition: 'This method is not commonly used.'
B.3.2.2	Addition: 'Moreover, some microorganisms will not necessarily persist in a viable state following overlay at an unfavourable temperature, which can result in false-negative results or hinder correct evaluation.'

B.4 Transfer to culture medium

B.4.2.1	Addition: 'however, consideration should be given to the use of a smaller pore size if it is expected that the microorganisms present or in the product warrant this.'
B.4.3.4	Addition: 'It is desired to keep the agar temperature as low as possible to avoid damage to microorganisms, because even 45°C can inactivate some environmental microorganisms. Therefore pour plating has limitations in the type of microorganisms that can be detected, though modifications using carboxy methyl cellulose as a setting agent can be possible in specialised cases.'

B.5 Incubation (culture media and incubation conditions)

B.5.1	Addition: 'This list in not all inclusive, and determination of the type(s) of bioburden microorganisms present on products, including by molecular means, can trigger the inclusion or exclusion of these or many other media for microbial culture.'
B.5.2	Addition: 'However, the range of such microorganisms can vary considerably with different culture media and incubation conditions.'

B.6 Enumeration (counting colonies)

B.6.1	Addition: 'obscured colonies'.
B.6.3	Addition: 'This limit is based on the availability of multiple dilutions from which to choose.'
B.6.4	Addition: 'For an example of a reference to acceptable variability between technicians, see Standard Methods 9215 Heterotrophic Plate Count.'
B.6.6	The use of an agar layer poured carefully over the surface of the test plate can provide a test result that is easier to enumerate after incubation, if spreading microorganisms are present.'
B.6.8	Addition: 'If multiple test conditions are used (e.g. aerobic count from one plate and fungal count from another plate), and there are no colonies recovered, the LOD values are cumulative. For example, if the aerobe count is < 2 CFU and the fungal count is < 2 CFU, then the total count is < 4 CFU.

B.7 Other techniques for detecting microorganisms

B.7 Note	Addition: 'Some rapid microbiological methods (e.g. bioluminescence, enzymatic, cytometry) can provide detailed information as to the range and relative numbers of microorganisms present in bioburden and allow assessment of the variability that can occur. They can also provide bioburden information more rapidly than direct culturing.'

B.8 Screening for the release of substances affecting bioburden determinations

B.8.4	Addition: '50 to 100'.
B.8.5	Replacement: 'bacteriostasis test' to 'suitability test'

B.9 Screening for the adverse effects of physical stress

B.9	Addition: 'Used in the absence of the device.'

Annex C

C.1 General

C.1.1	Addition: 'the removal technique should be justified and defined for each product, or parts thereof, or product group. The documented rationale should be included for the product, sample size, choice of recovery technique, etc.'
C.1.2	Addition: paragraph regarding 'Grouping of products for purposes of bioburden recovery efficiency'.
C.1.3.2	Addition: Paragraph regarding common approaches to sample size.
C.1.4	Addition: Passage regarding 'Guidance on selection of bioburden recovery efficiency approach'.
Table C.1	Addition: Table C.1 – General considerations for selecting a bioburden recovery efficiency approach

C.2 Validation using repetitive recovery

C.2.1.1	Replacement: 'no significant increase' to 'a significant decrease'. Addition: 'experience with similar products'.
C.2.1.2	Addition: '(i.e. bioburden recovery efficiency).
C.2.1.3	Addition: Paragraph on aerobe count for repetitive recovery.
C.2.2.1	Addition: 'The data in this example relate to ten replicate health care products and include five treatments in the repetitive recovery tests.'
Table C.2/C.3	Replacement: New example of repetitive recovery data.

C.3 Product inoculation method

C.3.1.1	Addition: 'Microbial inoculation has limitations, such as encrustation, adhesion or non-adhesion of the suspension, and clumping and variation in the level of the inoculum. These limitations should be taken into account when inoculating products.'
C.3.1.3	Addition: 'which will result in a countable range during the plate count step.'
C.3.1.4	Addition: 'Consideration should be given on a case-by-case basis as to whether a sterile product is necessary.' Addition: 'The viable count of the inoculum is determined at the time of inoculation.' Addition: The various material types of the product should also be considered for inoculation.'
C.3.2.4	Replacement: 'Selected portion of the device' to 'Each device'.
C.3.2.5/C.3.2.6	Replacement: New example of validation by inoculated recovery.
C.3.3	Addition: 'Example to illustrate comparisons of two bioburden efficiency methods'.

C.4 Bioburden recovery efficiency for complex product testing

C.4	Addition: Passage and example of bioburden recovery efficiency for complex product testing.

C.5 Data analysis and application of bioburden correction factor

C.5	Addition: passage regarding Data analysis and the application of bioburden correction factor

Example shown - note bioburden correction factor now given to 1 decimal place.

Annex D

In general

Annex D	Addition: New Annex regarding assignment of responsibilities