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Sterilization of health care products — Chemical indicators — Guidance for selection, use and interpretation of results

Stérilisation des produits de santé — Indicateurs chimiques — Directives pour la sélection, l'utilisation et l'interprétation des résultats

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 15882 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 15882:2003) which has been technically revised.

Introduction

This International Standard provides guidance for users regarding the selection, use and interpretation of results of chemical indicators intended for use with sterilization processes employing steam, dry heat, ethylene oxide, γ or β radiation, low temperature steam and formaldehyde (LTSF), or vapourized hydrogen peroxide as documented in ISO 11140-1 [13]. The ISO 11140 [12], [13], [14], [15], [16] series of standards specifies performance requirements for chemical indicators. These standards are intended primarily for the use of manufacturers of chemical indicators. The guidance in this document is of a general nature; chemical indicators do not, of themselves, constitute a comprehensive monitoring programme with regard to the sterilization of health care products. Users' attention is drawn to the requirements for validation of sterilization processes specified in ISO 14937 [18] for general processes, the ISO 17665 [19], [20] series for moist heat sterilization, the ISO 11135 [5], [6] series for ethylene oxide sterilization, ISO 11137-1 [7] for radiation sterilization and ISO 20857 [22] for dry heat sterilization.

The actual use/frequency of chemical indicators might be regulated by international and or national standards as well as by local regulatory authorities.

The need for convenient and rapid means of detecting sterilization problems occurring during sterilization processes has brought about the development of sterilization process monitors generally referred to as "chemical indicators." In this International Standard, users will find guidance on selection of the correct chemical indicator for their particular sterilization process and critical parameters as well as guidance on its appropriate use. The complexity of modern medical technology and the wide variety of sterilization processing techniques and equipment available have made effective sterility assurance programmes more challenging than ever before.

Sterilization of health care products — Chemical indicators — Guidance for selection, use and interpretation of results

1 Scope

1.1 This International Standard provides guidance for the selection, use and interpretation of results of chemical indicators used in process definition, validation and routine monitoring and overall control of sterilization processes. This International Standard applies to indicators that show exposure to sterilization processes by means of physical and/or chemical change of substances, and which are used to monitor one or more of the variables required of a sterilization process. These chemical indicators are not dependent for their action on the presence or absence of a living organism.

1.2 This International Standard does not consider indicators for use in those processes that rely on physical removal of microorganisms, e.g. filtration.

1.3 This International Standard is not intended to apply to indicators for use in combination processes, for example, washer disinfectors or CIP (cleaning in place) and SIP (sterilization in place).

2 Terms and definitions

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

NOTE A vocabulary of terms used for sterilization of health care products is provided in ISO/TS 11139[11].

2.1
chemical indicator
non-biological indicator
test system that reveals change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

[ISO/TS 11139, definition 2.6]

2.2
endpoint
point of the observed change as defined by the manufacturer occurring after the indicator has been exposed to specified stated values

[ISO 11140-1, definition 3.3]

2.3
indicator
combination of the indicator agent and its substrate in the final form in which it is intended to be used

[ISO 11140-1 definition 3.5]

NOTE 1 An indicator system in combination with a specific test load is also termed an indicator.

NOTE 2 See Annex E.

2.4
indicator agent
indicator reagent
active substance(s) or combination of substances

[ISO 11140-1, definition 3.6]

NOTE See Annex E.

2.5
process challenge device
PCD
item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[ISO/TS 11139, definition 2.33]

2.6
process challenge location
PCL
site which represents “worst case” conditions as they are given for sterilizing agent(s) in the goods to be sterilized

2.7
process parameter
specified value for a process variable

[ISO/TS 11139, definition 2.34]

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

NOTE 2 See Annex B.

2.8
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

[ISO/TS 11139, definition 2.35]

EXAMPLES Time, temperature, pressure, concentration, humidity, wavelength.

NOTE See Annex B.

2.9
resistometer
test equipment designed to create defined combinations of the physical and/or chemical parameters of a sterilization process

2.10
saturated steam
water vapour in a state of equilibrium between condensation and evaporation

[ISO 11140-1 definition 3.11]

2.11
stated value
SV
value or values of a critical variable at which the indicator is designed to reach its endpoint as defined by the manufacturer

[ISO 11140-1, definition 3.12]

2.12
visible change
change defined by the manufacturer, which can be seen in the indicator after exposure to one or more critical variables of the process

NOTE Visible change is used to describe the response of class 1 process indicators.

[ISO 11140-1, definition 3.15]

3 General considerations

3.1 All chemical indicators are intended to provide information about conditions at the location of the indicator within the sterilizer, sterilizer load or PCD. This can alert the user to potential sterilization process failures.

3.2 The value of the information provided by a chemical indicator is dependent upon the class of indicator, number and location of the indicators, being representative of the conditions throughout the sterilizer chamber or load. Representative locations for a load configuration should be identified during process validation studies.

3.3 The basic performance descriptors of any chemical indicator are its visible change, graduated response or "endpoint" response. The endpoint response can, for example, involve either the melting of a chemical substance or a chemical reaction resulting in a specified colour change.

3.4 A number of different classes of chemical indicators have been developed to suit different monitoring needs and to provide information about the sterilization process. Some types are sensitive to certain specific problems, such as a failure to attain a required temperature. Others might not respond only to a single process variable, but might simultaneously respond to several process variables during the sterilization cycle.

Selection of the classes of chemical indicators that are best suited to a particular application should be made only in the context of:

— What characterizes effective sterilization?

— Which problems could prevent sterilization?

— What are the performance characteristics of the indicator(s)?

— What constitutes effective sterility assurance activities during product release?

Once an indicator is selected, it will be of value in sterility assurance only if it is used and interpreted correctly, and if the user takes appropriate action in response to the results.

3.5 Chemical indicators of the same class can differ in response characteristics and their means of detecting exposure conditions. Chemical indicator classification in ISO 11140-1[13] is based on defined performance characteristics (see, e.g., different stated values in that document) rather than on chemical or physical changes as related to specific sterilization processes. For example, in a steam process, some indicator types must be exposed to steam for a minimum length of time to achieve the endpoint, some must be exposed to a minimum temperature, some are affected by a combination of temperature and time of exposure, and still others are affected by time, temperature and saturated steam. In all cases, the user compares the response of the chemical indicator to an endpoint described by the manufacturer.

If a chemical indicator fails to reach its endpoint, the facility should follow a documented protocol to investigate the cause of the problem which could include, but not be limited to, the following items.

a) Was there a sterilizer malfunction that could account for the failure to achieve the endpoint?

b) Has there been a change(s) in the product and/or sterile barrier system?

c) Has the loading density increased or decreased within the sterile barrier system?

d) Has the sterilization processing container/configuration changed (e.g. number of cartons has increased or decreased, or the configuration was not the same as that used during validation)?

e) Was sterilizer calibration and/or routine maintenance conducted appropriately?

f) Was the correct sterilizer process chosen for the product sterilized?

g) Was the chemical indicator handled under manufacturer's recommended practices?

h) Have there been changes in the utilities supplied to the sterilizer that could materially affect cycle execution (pressure, flow rate, non-condensable gases in the steam supply, etc.)?

NOTE For more information, the requirements and guidance provided in the specific process standards, ISO/TS 17665-2[20], ISO 20857[22], ISO 11137-1[7], EN 14180[24] and EN 15424[25] is valid.

3.6 Although other factors can influence the efficacy of a sterilization process, ISO 11140-1[13] identifies the variables for each sterilization process in Table 1. A specific chemical indicator can respond to one, some, or all of the variables, as indicated by its class (see Clause 5) and manufacturer's instructions for use.

If the use of the indicator is limited to a specific sterilization cycle, this information is stated or coded on the product. For example, "STEAM 15 min 121 °C" means that the indicator is for use in a 15 min, 121 °C steam sterilization cycle. The box around the word "STEAM" signifies that the indicator can only be used in the steam sterilization process.

Table 1 — Variables for sterilization processes

Process	Symbol[a]	Variables
Steam	STEAM	Time, temperature and water (as delivered by saturated steam)
Dry heat	DRY	Time and temperature
Ethylene oxide	EO	Time, temperature, humidity, and EO concentration
Irradiation	IRRAD	Total absorbed dose
Low temperature steam and formaldehyde (LTSF)	FORM	Time, temperature, water (as delivered by saturated steam) and formaldehyde concentration
Vapourized hydrogen peroxide	VH2O2	Time, temperature, hydrogen peroxide concentration, and, if applicable, plasma

[a] These are symbols and are not intended to be translated.

3.7 Class 3, 4, 5 and 6 indicators will have one or more stated value (SV) identified by the manufacturer. These stated values identify the parameters that the indicator is designed to react to, and the level of exposure required to achieve the stated visible change, graduated response or endpoint. Details of the SV will be provided on the indicator, on the indicator packaging, or in information provided with the product. Visible change is used to describe the response of class 1 process indicators. Graduated response is the progressive observable change occurring on exposure to one or more process variables allowing assessment of the level achieved.

The SV's are based on the outcome of tests carried out in a resistometer by a manufacturer.

The resistometer (ISO 18472[21] gives further information) is a test vessel that is designed for very rapid attainment of the particular critical parameters of the sterilization process. These parameters are very closely controlled during the exposure phase. Because sterilizers typically do not have the same response

characteristics or accuracy of exposure conditions as found in resistometers, it is very difficult for a user to replicate manufacturer label claims using a sterilizer. Third party independent laboratories with resistometers may be used to verify manufacturers' label claims. Since chemical indicators are tested at specific conditions, inadvertent or intentional exposure to parameters (for example longer time, lower temperature and/or lower sterilant concentration) outside of those specified by the manufacturer can lead to misleading results.

All chemical indicators in classes 3, 4, 5 and 6 have SV(s) at which they will reach their endpoints. A sterilization process is defined by a minimum value with an upper limit, e.g. for a moist heat process a minimum temperature is specified with an upper limit of $+3$ °C. The SV(s) of the chemical indicator will normally be linked to the minimum sterilization parameters for the process employed to process health care products.

The response of the chemical indicator to a fail condition is verified by exposing the chemical indicators to conditions lower than the SVs as specified in the accompanying tables.

4 Classes of chemical indicator

4.1 General

Chemical indicators are classified by their intended use. The chemical indicators described in ISO 11140-1[13] are classified into six groups. The chemical indicators within each of these classifications are further subdivided by the sterilization process for which they are designed to be used. The classification structure is used solely to denote the characteristics and intended use of each type of indicator when used as defined by the manufacturer. This classification has no hierarchical significance.

Chemical indicators are used to detect whether or not certain critical process variables have reached a predetermined level in a given sterilization process. The classification denotes the performance characteristics and intended use of the indicator only.

The performance characteristics of each class enable the respective chemical indicators to convey different types of information and therefore perform different functions.

All chemical indicators are based on either a chemical and/or physical change that results in a colour change or in the migration of a chemical.

The following descriptions for each class of chemical indicator will start with an italicized quote taken directly from ISO 11140-1[13], which has been used to define that specific class of chemical indicator.

4.2 Class 1: Process indicators

Process indicators are intended for use with individual units (e.g. packs, containers) to indicate that the unit has been directly exposed to the sterilization process, and to distinguish between processed and unprocessed units. They shall be designed to react to one or more of the critical process variables (ISO 11140-1:2005, 4.2).

This class of indicator is used to identify packs yet to be processed, i.e., identifying packs yet to be processed versus those processed and ready for distribution if the sterilization cycle ran correctly and if indicators of a higher class show that the conditions required for sterilization were met. A “pass” response of a class 1 process indicator is not intended to indicate attainment of the conditions required for sterilization.

Process indicators are typically applied to, or visible from, the outside of packages. Examples of process indicators include indicator tape and packaging material with a chemical indicator printed on it. These chemical indicators are typically external and exposed directly to the sterilizating agent without the interference imposed by packaging, and will typically “fail” only when there is gross malfunction. Process indicators are intended to exhibit a visual change after exposure to what could be a sub-optimal sterilization cycle.

For the irradiation process ISO 11140-1[13] only describes process indicators for use in γ and β irradiation. For example, Table 1 from ISO 11140-1:2005, Clause 8 contains the tolerances (upper and lower limits of performance acceptability for the steam process indicator, when tested by the manufacturer) that need to be met for each critical parameter. That table is reproduced below.

Table 2 — Test and performance requirements for class 1 process indicators for STEAM

Test environment	Test time	Test temperature	No change or a change that is markedly different from the visible change as specified by the manufacturer	Visible change as specified by the manufacturer
Saturated steam	3,0 min ± 5 s	121 °C (+3/0 °C)	Acceptable result	Unacceptable result
Saturated steam	10,0 min ± 5 s	121 °C (+3/0 °C)	Unacceptable result	Acceptable result
Saturated steam	0,5 min ± 5 s	134 °C (+3/0 °C)	Acceptable result	Unacceptable result
Saturated steam	2 min ± 5 s	134 °C (+3/0 °C)	Unacceptable result	Acceptable result
Dry heat	30 min ± 1 min	140 °C (+2/0 °C)	Acceptable result	Unacceptable result
NOTE The dry heat test is designed to ensure that process indicators for steam require the presence of steam in order to respond.				

4.3 Class 2: Indicators for use in specific tests

Class 2 indicators are intended for use in specific test procedures as defined in relevant sterilizer/sterilization standards (ISO 11140-1:2005, 4.3).

Chemical indicators widely recognised in class 2 are used to perform the Bowie and Dick-type test. This can be carried out using test sheets specified in ISO 11140-3[14] in combination with the standard textile pack specified in EN 285[23]. Chemical indicators for conducting the alternative Bowie and Dick-type steam penetration test are specified in ISO 11140-4[15]. Chemical indicators for conducting the Bowie and Dick-type air removal test are specified in ISO 11140-5[16] and either used in combination with a standard textile test pack or alternatively as a ready-to-use pack. Also see Annex A.

The presence of moisture is critical to the effectiveness of the steam sterilization process. The presence of residual air will impede steam penetration and therefore the presence of moisture on the surfaces to be sterilized. Class 2 Bowie and Dick-type indicators are intended to demonstrate the rapid and even penetration of steam and by implication the adequacy of air removal. This condition is generally demonstrated by a uniform colour change on the indicator sheet. Causes of failure could include the presence of non-condensable gases in the steam (for example fabric conditioning agents used in the laundering of the textile pack) or inadequate air removal or air leaks.

Because Bowie and Dick-type indicators are designed to react to a specified exposure that could be different from those required to achieve effective sterilization, they are not appropriate for use as routine sterilization cycle indicators. Extending the exposure time for the Bowie and Dick-type test, or disregarding the manufacturer's recommendations for how to conduct the Bowie and Dick-type test will entirely defeat the purpose of the test by causing misleading results.

For background information on the Bowie and Dick test, see Annex A.

4.4 Class 3: Single variable indicators

A single variable indicator shall be designed to react to one of the critical variables and is intended to indicate exposure to a sterilization process at a stated value (SV) of the chosen variable (ISO 11140-1:2005, 4.4).

A single variable indicator is intended to respond to only one critical process variable of the sterilization process. The variable and its stated value will be provided by the indicator manufacturer and that indicator can only be used to monitor that process variable.

For example, a single variable indicator for temperature can only indicate the attainment of a stated value for temperature, and will not provide reliable information for other process variables such as exposure time or the presence of steam. The indicator can reveal whether a specific minimum temperature was attained at a particular location within the sterilizer chamber or the load. The indicator must be correctly selected for the minimum temperature of the process.

Single variable indicators should be supplemented by other means of monitoring the sterilization process.

Care should be taken when interpreting the results obtained from single variable indicators. Process parameters (and their tolerances) for chemical indicators share no relationship with process parameters (and their tolerances) for sterilization processes. Most sterilization processes have more than one process parameter which must be attained if sterilization is to occur. Table 3 (adopted from Table 7 from ISO 11140-1:2005) contains tolerances (upper and lower limits of performance acceptability for the chemical indicator, when tested by the indicator manufacturer) that need to be met for each critical parameter.

The stated values are the predetermined conditions that the manufacturer shall maintain during testing.

Table 3 — Test and performance requirements for class 3 and class 4 indicators

Sterilization process	**Test point** [a]	**Test time**	**Test temperature**	**Sterilizing agent concentration** mg/l	**RH** %
Steam	1	SV* + 0 %	SV + 0 °C	Not applicable	Not applicable
	2	SV – 25 %	SV – 2 °C		
Dry heat	1	SV + 0 %	SV + 0 °C	Not applicable	Not applicable
	2	SV – 25 %	SV – 5 °C		
Ethylene oxide	1	SV + 0 %	SV + 0 °C	SV + 0 %	> 30
	2	SV – 25 %	SV – 5 °C	SV – 25 %	> 30
Low temperature steam and formaldehyde (LTSF)	1	SV + 0 %	SV + 0 °C	SV + 0 %	Not applicable
	2	SV – 25 %	SV – 3 °C	SV – 20 %	
NOTE For examples of testing multi-variable (class 4) indicators, see 11140-1[13].					
*SV = Stated value.					
[a] Test point 1: the indicator, when tested at the SV, shall reach its endpoint. Test point 2: the indicator, when tested at all SVs minus the combined tolerances, shall not reach its endpoint.					

Example

Steam sterilization indicator (class 3: Single variable indicator).

Stated value: 121 °C.

Table 3 provides the test points at which the class 3 indicator must show a “pass” response (test point 1) and a “fail” response (test point 2) when tested by the manufacturer using the equipment specified in ISO 18472[21].

Test point 1 for this indicator is 121 °C, i.e., the stated value.

Test point 2 for this indicator is (121 °C minus 2 °C), i.e., 119 °C.

Therefore the indicator tested at 121 °C shall give a “pass” response (test point 1) and when tested at 119 °C shall give a “fail” response (test point 2).

4.5 Class 4: Multi-variable indicators

A multi-variable indicator shall be designed to react to two or more of the critical variables and is intended to indicate exposure to a sterilization cycle at stated values (SVs) of the chosen variables (ISO 11140-1:2005, 4.5).

The manufacturer states the conditions under which multi-variable chemical indicators reach their endpoint. These indicators typically provide more information than either process (class 1) or single variable (class 3) indicators. Chemical indicators are designed to reach their endpoint when the stated values of the critical variables have been achieved.

ISO 11140-1[13] contains tolerances (upper and lower limits of performance acceptability for the chemical indicator, when tested by the manufacturer) that need to be met for each critical variable. See Table 3.

An example of multi-variable indicator performance is given below. Although all parameters have been altered simultaneously in the example, in practice when manufacturers test the indicators, they may vary one or more parameters while holding the remaining parameters at the stated value.

EXAMPLE Ethylene oxide sterilization indicator (class 4: multi-variable indicator).

Stated values: 60 min at 900 mg/l.

Table 3 provides the tolerances and limiting values (upper and lower limits of performance) for this class 4 indicator. The tolerances from this table are 60 +0/−25 % min and 900 +0/−25 % mg/l when tested at a relative humidity greater than 30 %. Therefore, the indicator will not reach its endpoint if the time is less than 45 min [i.e., $60 - (60 \times 0{,}25)$], the gas concentration is less than 675 mg/l [i.e., $900 - (900 \times 0{,}25)$] and the relative humidity is greater than 30 %. If the time is 60 min or longer, and the EO concentration is 900 mg/l or higher, and the relative humidity is greater than 30 %, the indicator must reach its endpoint.

An indicator with the above stated values will respond as follows when exposed to the conditions below:

Exposed to the following conditions	Based on Table 2 an acceptable indicator
$\leqslant$ 44 min at $\leqslant$ 650 mg/l	must show fail
$\geqslant$ 60 min at $\geqslant$ 900 mg/l	must show pass

In this example, the indicator might not respond to temperature or relative humidity. If temperature and/or relative humidity have an influence on the indicator performance, the indicator manufacturer should provide this information.

4.6 Class 5: Integrating indicators

Integrating indicators shall be designed to react to all critical variables. The stated values (SVs) are generated to be equivalent to, or exceed the performance requirements given in the ISO 11138[8][9][10] series for BIs (ISO 11140-1:2005, 4.6). *The stated values for steam class 5 integrating indicators are required over the typical temperature ranges of the steam sterilization process.*

Viable microorganisms are affected by all the complex interrelationships of the critical sterilization process variables. Chemical indicators might not be affected in the same way, but they do provide information about the specified process variables. This does not necessarily allow accurate assessment of microbial inactivation.

A steam class 5 integrating indicator shall have stated values for time at 135 °C, 121 °C, and at one temperature between these; the 121 °C stated value for time must be greater than 16,5 min.

A dry heat class 5 integrating indicator shall have stated values for time at 160 °C and 180 °C and an additional time at either 140 °C or 170 °C.

An ethylene oxide class 5 integrating indicator shall have stated values for time at 54 °C and 37 °C with 600 mg/l of EO and 60 % RH; the 54 °C stated value shall be greater than 30 min and the 37 °C stated value shall be greater than 90 min.

An integrating indicator, by definition, will be affected simultaneously by a number of critical process variables. Because the effects of the critical variables on the integrating indicator are simultaneous, a failure to reach the "endpoint" might or might not be assignable to a specific variable.

The performance requirements for a class 5 Integrating indicator are given in ISO 11140-1[11].

To understand the rationale for the requirements for class 5 integrating indicators and the link to the requirements for biological indicators specified in the ISO 11138 series[8][9][10] and microbial inactivation, see Annex C.

4.7 Class 6: Emulating indicators

Emulating indicators are cycle verification indicators which shall be designed to react to all critical variables for specified sterilization cycles. The stated values (SVs) are generated from the critical variables of the specified sterilization process (ISO 11140-1:2005, 4.7).

Table 4 — Test and performance requirements for class 6 indicators

Sterilization process	Test point [a]	Test time min	Test temperature	Gas concentration mg/l	RH %
Steam	1	SV* + 0 %	SV + 0 °C	Not applicable	Not applicable
	2	SV – 6 %	SV – 1 °C		
Dry heat	1	SV + 0 %	SV + 0 °C	Not applicable	Not applicable
	2	SV – 20 %	SV – 1 °C		
Ethylene oxide	1	SV + 0 %	SV + 0 °C	SV + 0 %	> 30
	2	SV – 10 %	SV – 2 °C	SV – 15 %	> 30

NOTE For an example of testing emulating (class 6) indicators, see ISO 11140-1:2005, Annex B.

*SV = Stated value.

[a] Test point 1: The indicator, when tested at the SV, shall reach its endpoint (pass condition).

Test point 2: The indicator, when tested at all SVs minus the combined tolerances, shall not reach its endpoint (fail condition).

The tolerances defined in Table 4 are the most stringent of the different classes of chemical indicators. These test conditions can only be achieved in a resistometer and would be virtually impossible to reproduce in a hospital sterilizer. Emulating indicators can therefore offer a high level of assurance in demonstrating that critical parameters of a specified cycle have been met. Unless the cycle parameters tested match exactly the SV stated for an emulating indicator, the results can be seriously erroneous and misleading.

An emulating indicator, by definition, will be affected simultaneously by a number of critical process variables. Because the effects of the critical variables on the emulating indicator are simultaneous, a failure to reach the "endpoint" might or might not be assignable to a specific variable.

An example of an emulating indicator performance is given below. Although all parameters have been altered simultaneously in the example, in practice when the manufacturers test the indicators, they may vary one or more parameters while holding the remaining parameters at the stated value.

EXAMPLE

Steam sterilization indicator (class 6: Emulating indicator).

Stated values: 3,5 min, 134 °C.

Table 4 provides the test points at which the class 6 indicator must show a “pass” response (test point 1) and a “fail” response (test point 2) when tested by the manufacturer using the equipment specified in ISO 18472[21].

Test point 1 for this indicator is 134 °C and 3,5 min, i.e., the stated values.

Test point 2 for this indicator is (134 °C minus 1 °C), i.e., 133 °C and (3,5 min minus 6 %), i.e., 3,29 min.

Therefore the indicator tested at 134 °C for 3,5 min shall give a “pass” response (test point 1) and when tested at 133 °C for 3,29 min shall give a “fail” response (test point 2).

5 Selection of chemical indicators

5.1 There are wide variations in sterilization processes and therefore chemical indicator manufacturers label chemical indicators according to their intended use. Chemical indicators are not intended for use in any process other than that specified by the manufacturer. It is the responsibility of the user to select a chemical indicator as described by the manufacturer as being appropriate for the particular process, and use and interpret the results according to the manufacturer's instructions. The stated value provided by the indicator manufacturer will assist the user in determining which indicator is appropriate for his or her application. These stated values can be found on the product or in the literature supplied.

5.2 Chemical indicators are used to demonstrate the attainment of one or more parameters of a sterilization process and are not in themselves sufficient to demonstrate the efficacy of a sterilization process. This demonstration of sterilization efficacy is a combination of validation, equipment maintenance and calibration, appropriate use and physical monitoring and, where appropriate, the use of chemical and/or biological indicators. When any variable of a sterilization process is outside its specified limits, the sterilizer should be removed from service and the cause investigated. The sterilizer should not be returned to use until the defect has been corrected.

5.3 Systems and/or procedures should be established to evaluate any deviations from the cycle process limits, and reasons for accepting any deviation should be fully documented.

5.4 Various types of chemical indicators are available, each with different response characteristics. They could have different stated values for each measured parameter and so different chemical indicators could provide differing challenges to a process.

5.5 Manufacturers should provide information on the reliability, safety, and performance characteristics of their products. In addition, manufacturers of chemical indicators should provide written information on how to interpret indicator results, the reliability of the indicator in maintaining endpoint stability (if applicable) during storage of sterilized items, the process parameters to which the indicator has been designed and tested to react, and the storage requirements for, and shelf life of, the indicator itself. It is the user's responsibility to ensure that they have read and understood this information. Use of an indicator outside its stated values can give misleading results, but this does not mean that the chemical indicator is working inappropriately.

6 Use of chemical indicators

6.1 Class 1 process indicators

The purpose of a class 1 process indicator is to differentiate between processed and unprocessed products, and not whether the parameters for adequate sterilization have been met.

Indicator tape (e.g. autoclave tape), indicator labels, or packaging incorporating a chemical indicator should be on all packages assembled and intended for sterilization in the facility. The chemical indicator needs to be examined after sterilization to confirm that the required visible change has taken place and hence that the item has been exposed to a sterilization process.

6.2 Class 2 indicators

The steam penetration or air removal test is run in an otherwise empty sterilizer. The manufacturer's instructions should be followed for use of the indicator.

6.3 Class 3, 4, 5 and 6 indicators

When a class 3, 4, 5 or 6 chemical indicator is used, it provides information concerning the level of critical variables at that specific location. Many factors can affect the attainment of these critical variables, such as load contents, loading configurations, location within chamber, packaging materials and technique, steam quality and sterilizer malfunction.

For wrapped loads, a chemical indicator should be placed in that area of the package, tray or container considered least accessible to sterilizing agent penetration. This area might or might not be at the centre of the package, tray or container or at the centre of the given sterilizer chamber. Multiple indicators can be used to evaluate each layer of multilayered container or tray. It is advantageous to place chemical indicators in multiple packs within the load in order to monitor different locations within the sterilizer chamber. During process validation, information about the locations within the sterilizer chamber and/or load, which are least accessible for the sterilizing agent, can be obtained. Representative information can only be obtained from an indicator if the indicator is placed in a location that represents those conditions.

For unwrapped loads, a chemical indicator shall be placed in or on the tray with the items to be sterilized.

6.4 Indicators for use with process challenge devices

Process challenge devices (PCDs) have been developed to represent penetration challenge to the sterilization process. The performance of PCDs should be correlated to specific sterilization methods, types of sterilizers and load contents. There is no universal PCD that can be used for all sterilizer types and sterilization procedures. The performance and challenge of the PCD is a result of the combined effect of the chemical indicator and the PCD components; any modification, e.g. use of another indicator, could compromise the performance of the PCD.

Some PCDs could represent a defined product or a specific combination of product and sterile barrier system. They can be used to develop and define a sterilization process. Most commercially available PCDs are designed to assess the penetration of a reference load. Attention is drawn to the fact that these PCDs challenge the process and do not represent the sterilization load.

PCDs can be used to confirm specific process performance(s) for routine monitoring of a sterilization process if performance and use of the PCDs is validated. See, for example, ISO 17665-1:2006, 10.5.

To obtain reliable results when using commercially available chemical indicator PCDs, the placement in the sterilizer and within the load should be validated to represent the most difficult-to-sterilize location, called the process challenge location (PCL). Since in most cases the PCL can be an assumption only, the use of more than one PCD could be reasonable as outlined already.

The performance of PCDs should be correlated to specific sterilization methods, types of sterilizer, and load contents. There is no universal PCD that can be used for all sterilization types and methods. Different products, e.g. hollow loads (beakers, basins, tubing), porous loads (linens, dressings, textiles) and non-porous loads (solid and surgical instruments) can be represented by different PCDs.

Some issues which might be considered when selecting a PCD are:

a) the device should be designed to allow the chemical indicator to be placed in the position that is most difficult for the sterilant to reach;

b) the design of the device should relate to the type of goods to be sterilized and the sterilization procedure;

c) the chemical indicator should not interfere with the function of the device;

d) the potential effect of the PCD and the load.

7 Interpretation of results from chemical indicators

7.1 General

A comprehensive sterility assurance programme incorporates every aspect of processing including cleaning, decontamination, preparation and packaging, loading the sterilizer, sterilization, handling the item after sterilization, storage under appropriate conditions in the packaging system, distribution, and handling to the point of use. Routine monitoring and control of the sterilization process is an important aspect of a comprehensive sterility assurance programme. Chemical indicators complying with the requirements of ISO 11140-1[13], which are used in accordance with the manufacturer's recommendations for use, can provide useful information about the sterilization process. The frequency of use and number of chemical indicators per load or cycle depends on national regulations and recommendations, and/or policies of the institution where the sterilizer is located. Appropriate information can be found, e.g. in ISO 14937:2000, E.7

Chemical indicators should clearly differentiate between the locations where the stated values have been achieved and those where not. For this reason the endpoint should be appropriate and unambiguous. Examples of pass and fail response indicators should be available from the manufacturer and clearly understood by the user.

7.2 Chemical indicator responses

Indicators only signal when certain parameters are met in their particular location. Care should be taken to place all indicators in locations that are representative of the load or, better still, in the most difficult to sterilize locations. Chemical indicators should be viewed as an element of an overall sterility assurance programme.

7.3 Chemical indicators showing “fail” response

If a chemical indicator fails to reach its endpoint, the facility should follow a documented protocol. When an indicator shows a ‘fail' response, it should not be assumed that the indicator has malfunctioned; it should always be interpreted as a fault with the process. An investigation into the cause of the failure should be undertaken.

8 Chemical indicators in sterility assurance procedures

8.1 General

Chemical indicators, whether applied internally or externally to packages, are used to monitor sterilization processes to provide evidence that certain critical parameters have been achieved.

A planned programme for the placement and evaluation of chemical indicators can:

— be part of the sterilizer installation, operating and performance qualification (IQ, OQ and PQ), i.e., validation;

— be part of routine process monitoring;

— assist in the diagnosis of process malfunctions;

— assist in the detection of packaging problems (e.g. excessively large or dense packs);

— assist in the detection of loading problems (e.g. tipped basins that can trap air if not properly oriented);

— reveal unprocessed loads;

— assist in the detection of sterilizer malfunctions relating to air removal and steam penetration or temperature/dwell attainment; and assist in the detection of problems with the sterilizing agent supply.

The processing department should have written procedures for all processes. Because the reprocessing of medical devices is comprised of multiple steps which can include cleaning, decontamination, disassembly, inspection, re-assembly, packaging, terminal sterilization, storage and handling, it is imperative that means be established to differentiate the status of all items during each phase of the process. For example, class 1 indicators differentiate product exposed to the sterilization process from non-exposed product.

The overall sterility assurance programme should include product identification and traceability; sterilizer calibration, maintenance and efficacy testing; mechanical, chemical and biological monitoring of sterilization cycles. No single element of a sterility assurance programme, including the various sterilization monitors, can be relied upon, by itself, to assure sterility. Sterility assurance requires continuous attention to all aspects of sterilizer performance, the sterilization process and continuous compliance with established policies and procedures.

Proper use of mechanical, biological, and chemical sterilization monitors requires an understanding of what each type of monitor is designed to do and what each reveals about the sterilization cycle or process. Mechanical or physical sterilization monitors, which include time, temperature, and pressure recording devices and gauges, provide real-time assessment of the sterilization cycle variables and allow many sterilizer malfunctions to be detected as soon as possible. However, mechanical indicators cannot determine if appropriate variables were achieved throughout the sterilizer and cannot detect problems related to improper load configuration or package composition. Chemical indicators are designed to respond with a characteristic chemical or physical change to one or more of the process variables (e.g. time, temperature, presence of saturated steam, humidity, ethylene oxide gas concentration, radiation dose) within the sterilizer chamber. An endpoint of a chemical indicator does not prove that the item accompanied by the indicator is sterile; it demonstrates that the item has been subjected to certain conditions. Chemical indicators provide a rapid means to detect certain problems within the sterilizer before a potentially non-sterile product is released or used.

Chemical indicators can be helpful in diagnosing certain problems associated with the attainment of critical parameters associated with sterilization conditions. Effective use of chemical indicators requires a thorough understanding of the types of chemical indicator and what they can and cannot indicate about a sterilization process. Consequently any result given by a chemical indicator should be followed by appropriate action to be taken. Individual chemical indicators are usually specific to one type of sterilization process. However, different indicators of the same class and type, when exposed to a sterilization cycle, can show a different response.

8.2 Record keeping

Chemical indicators or a description of their results may be kept as part of the sterilization records. If these results are part of a quality system (e.g. ISO 9000 series) they should be traceable to a specific sterilization cycle and preferably to the patient. The test results should be evaluated by a responsible trained person and should include date, sterilizer identification, load number and recorded process variables. Depending on national and/or local requirements, indicator results may be kept for varying periods of time. All chemical indicator results may be kept manually or electronically.

9 Personnel training

There should be written procedures for the handling and use of chemical indicators. Personnel responsible for the placement and retrieval of chemical indicators should be trained in the reprocessing procedure and the selection, use and interpretation of chemical indicators. This training should include all personnel in the reprocessing procedure areas and anyone who will be using sterile supplies and thus interpreting chemical indicators. The correct interpretation of the chemical indicator endpoint is vital.

Training should be conducted and reviewed periodically, and documented.

10 Storage and handling

The manufacturer or supplier of the chemical indicator is responsible for providing information on the proper storage and handling of the indicator before and after exposure.

The performance of a chemical indicator can be affected by the conditions encountered during shipping or storage prior to its use, the method of use, the techniques employed after exposure to the sterilization process, and the stability of the chemical indicator following its exposure to the sterilization process. For these reasons, the specifications of the chemical indicator manufacturer for storage and use should be followed. Failure to follow these specifications could affect the integrity and performance of the chemical indicator and lead to incorrect assumptions regarding the efficacy of the sterilization process.

Chemical indicators should not be used beyond their expiration date.

11 Labelling

11.1 General

Labelling of chemical indicators should include all of the information outlined in ISO 11140-1[13]. This information is reproduced in 11.2, 11.3 and 11.4.

11.2 Indicator marking

Each indicator shall be clearly marked with the type of process for which it is intended to be used, with the class of indicator, and for class 3, 4, 5 and 6 indicators, with the stated values. Where the size or format of the indicator does not permit this information to be stated in a font of six characters per centimetre or larger, the information shall be provided on the label and/or instructions for use.

11.3 Process marking

If the indicator is designed for use in specific sterilization cycles, this information shall be stated or coded on the indicator, e.g.:

STEAM 121 °C 15 min

11.4 Package marking

Each package of indicators or the technical information leaflet supplied with the package shall provide the following information:

a) the change that is intended to occur; for colour change indicators where the colour change cannot be adequately described, samples of the expected colour range for both changed and unchanged indicators;

b) the critical variable(s) to which the indicator will respond, and where applicable, their stated values;

c) the class, process and intended use for which the indicator is designed;

d) the storage conditions, before and after use;

e) the expiry date, or the manufacturing date plus shelf life, under the specified storage conditions, expressed in accordance with ISO 8601[3] (i.e. YYYY-MM);

f) a unique code (e.g. lot number) to provide traceability;

g) instructions for use essential to ensure proper functioning of the indicator;

h) any interfering substances that are likely to be encountered, or conditions that are likely to occur, during the intended use of the indicator and which are known to adversely affect the performance of the indicator;

i) any safety precautions required during and/or after use;

j) the manufacturer's or supplier's name and address;

k) the nature of any change that can occur when completely/incompletely changed indicators are stored according to the manufacturer's instructions.

NOTE National or regional regulations could contain additional or different requirements.

Annex A
(informative)

Background on the Bowie and Dick test

In 1963 a publication by J. H. Bowie and his co-workers[26] described a simple test suitable to determine if the vacuum system of a pre-vacuum sterilizer was functioning correctly. Pre-vacuum sterilizers present a problem if there is a leak into the chamber or other malfunction(s) of the vacuum pumping system, such that air leaks or inadequate air removal occur. The presence of critical amounts of air in the chamber can result in the formation of air pocket(s) which prevent full steam penetration of all the packs to be sterilized. At the end of come-up time, the temperature within such an air pocket is almost always lower than that of the surrounding steam. Initially, measurements of vacuum system adequacy were made by placing thermocouples within a specified test pack, and in the chamber drain. In the publication by Bowie, a test sheet consisted of a piece of paper onto which a St. Andrew's cross was made with autoclave indicator tape. The test pack Bowie described was composed of huckaback towels having a minimum size of 36 in × 24 in (approximately 91,5 cm × 60 cm) before laundering. These towels were folded into four along their length and then doubled across to give eight thicknesses of cloth. The number of towels will vary depending upon their thickness, but the stack should measure 10 in to 11 in (approximately 25,5 cm to 28 cm) high. When tested in a correctly functioning sterilizer with a holding time of 3,5 min at 134 °C with only the test pack in the chamber, the lines on the autoclave tape will change to a uniform dark colour. A satisfactory test will indicate rapid steam penetration, adequate air removal and freedom from significant air leaks. If operated properly, the sterilizer is capable of producing sterile goods. It is intended that this test be performed each day after the sterilizer is heated to operating temperature.

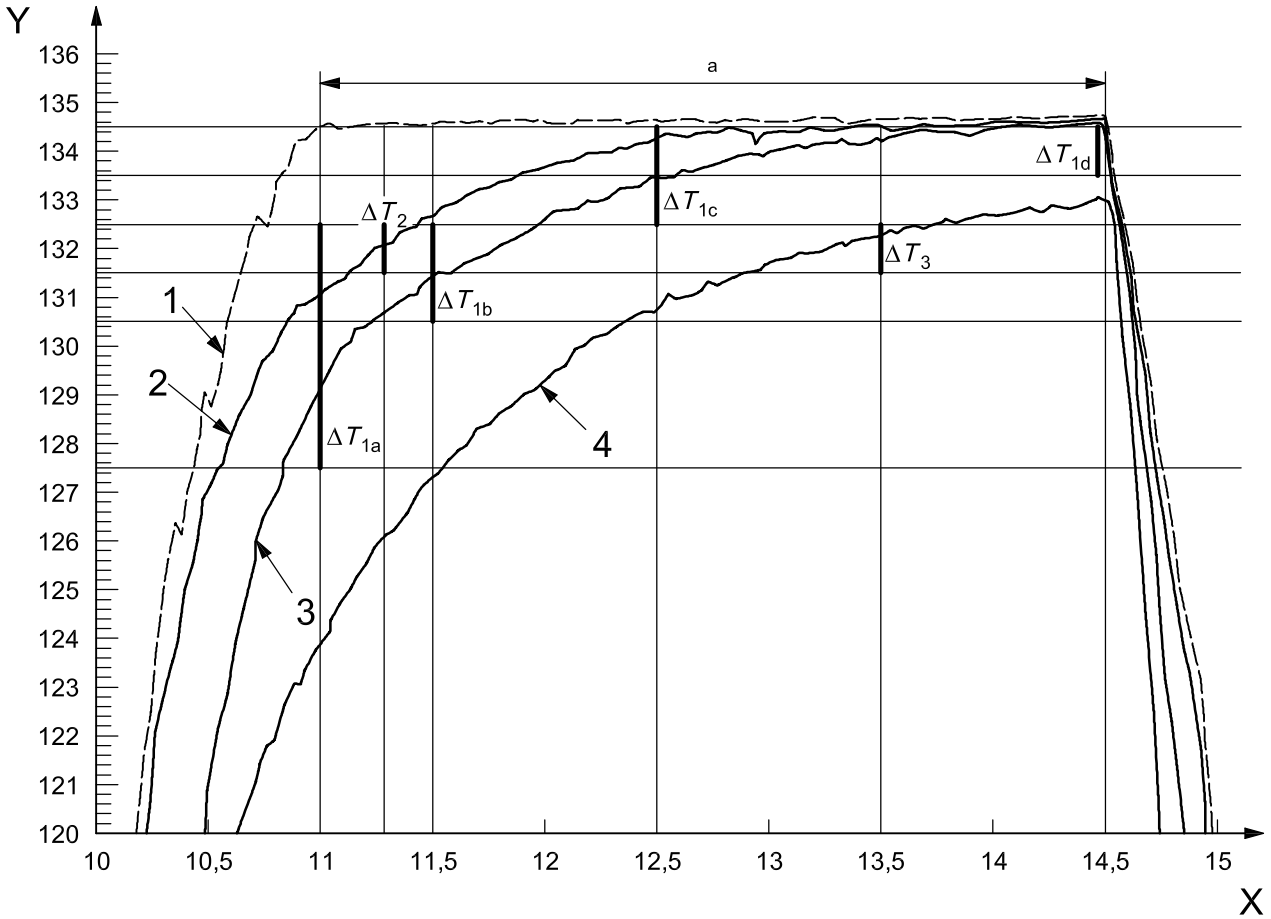
Pre-printed test sheets were created because it was recognized that the autoclave tape did not cover the entire test area and if the air pocket collected in a spot where there was no indicator tape, it would not be detected.

As stated previously, there are three standards for the Bowie and Dick-type test, these are ISO 11140-3[14], ISO 11140-4[15] and ISO 11140-5[16].

These documents were developed because different parts of the world interpreted the original work by Dr. Bowie in different ways. Some countries refer to the test as an air removal test and follow specific criteria for a pass response, while others consider it a steam penetration test with specific acceptance criteria. In reality both are needed. A sterilizer cannot achieve acceptable steam penetration without air removal. In all instances, the disposable/alternative test pack is compared to the cotton sheet or cotton towel pack. The list in Table A.1 describes the significant differences in reference materials and minimum values for pass and fail conditions. For the definitive criteria, see the reference documents.

Table A.1 — Comparison of ISO 11140-3, ISO 11140-4 and ISO 11140-5

Test pack	ISO 11140-3[14]	ISO 11140-4[15]	ISO 11140-5[16]
Test pack reference	EN 285[23]	EN 285[23]	ANSI/AAMI ST46[28]
Test pack weight	(7 ± 0,2) kg	(7 ± 0,2) kg	(4 ± 0,5) kg
Test pack density	0,42 kg/dm^3	0,42 kg/dm^3	0,20 kg/dm^3
Test pack size	220 mm × 300 mm × 250 mm	220 mm × 300 mm × 250 mm	250 mm × 300 mm × (250 mm to 280 mm)
Criteria for pass condition	Temperature in pack not more than 0,5 °C lower than drain throughout holding stage.	Temperature in pack not more than 1 °C lower than set operating temperature measured in drain.	Temperature in pack not more than 0,5 °C lower than drain throughout holding stage.
Criteria for fail condition	Temperature in pack 2 °C to 3 °C lower than drain temperature at the beginning of holding stage.	Temperature in pack 2 °C to 7 °C lower than the drain at the start of the holding stage and 2 °C to 4 °C at the start of, and not more than 1 °C at the end of, the holding stage.	2 °C difference between drain and centre of pack 1 min before end of 3,5 min, 134 °C holding stage.



Key

X time in minutes

Y temperature in degrees centigrade

a Holding stage.

Figure A.1 — Examples of fail conditions

Figure A.1 represents examples of fail conditions described in Table A.1, including:

a) the reference point temperature (curve 1) in the drain (during holding stage);

b) when the range in temperature depression (ΔT_2) (curve 2) exists in the geometric centre of the reference textile pack (7 kg as in ISO 11140-3[14]), the indicator sheet shall show a fail result;

c) when the range in temperature depression (ΔT_1) (curve 3) exists in the geometric centre of the reference textile pack (7 kg as in ISO 11140-4[15]), the alternative test pack shall show a fail result;

d) when the range in temperature depression (ΔT_3) (curve 4) exists in the geometric centre of the reference textile pack (4 kg as in ISO 11140-5[16]), the indicator sheet or the indicator in the pre-assembled test pack shall show a fail result.

Annex B
(informative)

Explanation of the terms “parameter” and “variable”

Concerning changes that alter microbicidal effectiveness, ISO 11140-1[13] defines “parameter” as a specified value for a process variable, and “variable” as a condition within a sterilization process. These terms are modified slightly in ISO/TS 11139[11] by the use of the prefix ‘process' before each term.

By way of an example, if considering a dry heat sterilization process, there are two “variables” or “process variables,” namely time and temperature. The “parameters” or “process parameters” associated with these variables could be the values 160 °C and 120 min.

Annex C
(informative)

Rationale for the requirements for integrating indicators and the link to the requirements for biological indicators (BIs) specified in the ISO 11138 series and microbial inactivation (derived from ISO 11140-1)

C.1 Steam

C.1.1 Introduction

Integrating indicators are designed to respond in a similar manner to that of a biological indicator (BI) when exposed to the critical variables of a sterilization process. For the purposes of this International Standard, the performance of integrating indicators is linked to the minimum requirements for a BI for moist heat sterilization as defined in ISO 11138-3[9]. Subclause C.1.2 provides background information and a detailed rationale for the requirements for the class 5 integrating indicators specified in 4.6.

C.1.2 Background information

ISO 11138-3[9] specifies that a BI for moist heat sterilization processes shall have a D_{121} of not less than 1,5 min, a minimum population of 1×10^5 and a z value > 6. The z value for many species of *Geobacillus stearothermophilus* is often nearer to 10 (ISO 14161). Theoretical calculations relating to validation of moist heat processes, e.g. F_o, normally use a z of 10 (Pflug[27]).

The performance of a BI can also be defined by the survivor kill window (SKW) which, at 121 °C and based on the minimum values specified above, would typically be: survives 4,5 min and is killed in 13,5 min. The SKW is calculated from:

$$\text{Survival time} = (\log P - 2) \times D_{121}; \quad \text{(C.1)}$$

$$\text{Kill time} = (\log P + 4) \times D_{121}; \quad \text{(C.2)}$$

where

log is the log to the base ten of the number;

P is the nominal population;

D_{121} is the decimal reduction time at 121 °C in minutes.

C.2 The link between the integrator stated value (SV) and biological indicator (BI) inactivation

In order to achieve an inactivation of at least 1×10^{-6} in populations of microorganisms, it would be necessary to expose a BI with a D_{121} = 1,5 min and a population of 1×10^5 to a temperature of 121 °C for 16,5 min.

Thus

$$(\log 10^5 - \log 10^{-6}) \times 1{,}5 = 16{,}5 \text{ min} \quad \text{(C.3)}$$

Thus for a class 5 integrator the minimum stated value (SV), i.e., the time at which the endpoint is reached at 121 °C, is required to be not less than 16,5 min. By requiring a minimum SV of 16,5 min, a direct relationship is established between the integrator endpoint and a satisfactory inactivation level in an equivalent BI and therefore the objective of a terminal sterilization process.

In the case where the manufacturer specifies an SV at 121 °C greater than 16,5 min, a greater inactivation level will have been achieved (and therefore a greater safety factor) by the time the indicator reaches its endpoint. Nevertheless, when tested, the integrator should reach or exceed its endpoint when exposed for a time equal to the SV.

The above represents the pass or accept condition for the integrator.

Regarding the fail condition, theoretically a single BI will show no growth when the exposure time is sufficient to reduce the population to less than one surviving organism. However, when actual BIs are in use, the exposure time has to be greater than that specified above because of the natural variation associated with biological systems. Typically, if 50 or more BIs are tested, then an exposure time that reduces the population to a theoretical level of less than 10^{-2} would be required to eliminate any positives for growth (ISO 14161[17]). The determination of the SKW provides an indication of how much more exposure time is required. Thus an exposure period of $(\log P + 4) \times D$ is used to define the kill time, i.e., a further 4 log reduction past the point of one surviving organism per unit, i.e., 1×10^{-4}. Thus, it can be anticipated that some BIs would show positive for growth at a 10^{-2} exposure level but none at a 10^{-4} exposure level.

Adopting these criteria for the definition of the fail response in an integrating indicator at 121 °C with a population of 10^5 and a D value of 1,5, a 7 log reduction is required to reach the 10^{-2} level. The exposure time required for this is:

$$(\log P + 2) \times D = 10{,}5 \text{ min} \tag{C.4}$$

Thus, the integrating indicator should not reach its endpoint when exposed to dry saturated steam at 121 °C for 10,5 min. However, the manufacturer's SV at 121 °C could be greater than 16,5 min, in which case the exposure conditions required to create a failure or reject response in the integrator must be linked to the manufacturer's SV and be at least 10,5 min. Using 10,5 min as a baseline for failure and 16,5 min as a baseline for a pass:

$$\frac{10{,}5}{16{,}5} = 0{,}636 \tag{C.5}$$

Thus, for an indicator with an SV greater than 16,5 min, the fail condition at which it is tested should be an exposure time which is 63,6 % of its SV. Thus, the indicator must show a fail or reject response when exposed to dry saturated steam at 121 °C for 63,6 % of the SV.

In comparison to a BI, the SV of the integrator is related to the time required to achieve an 11 log reduction in population. 63,6 % of the SV is related to the time required to achieve a 7 log reduction in population. Thus the D value of a BI complying with ISO 11138-3[9] is related to the SV of the integrator through the following:

$$(\log P + 6) \times D = \text{SV} \tag{C.6}$$

$$(5 + 6) \times 1{,}5 = 16{,}5 \tag{C.7}$$

i.e., an 11 log reduction in population to an inactivation level of 1×10^{-6}.

Therefore

$$D = \frac{\text{SV}}{(\log P + 6)} = \frac{\text{SV}}{11} \tag{C.8}$$

In a BI, survivors will be observed when the exposure time (survivor time, ST) is

$$(\log P + 2) \times D = \text{ST} \tag{C.9}$$

substituting for D:

$$(\log P + 2) \times \frac{\text{SV}}{11} = \text{ST} \tag{C.10}$$

Now

$$\log P + 2 = 7 \tag{C.11}$$

Therefore

$$7 \times \frac{\text{SV}}{11} = \text{ST} \tag{C.12}$$

Therefore

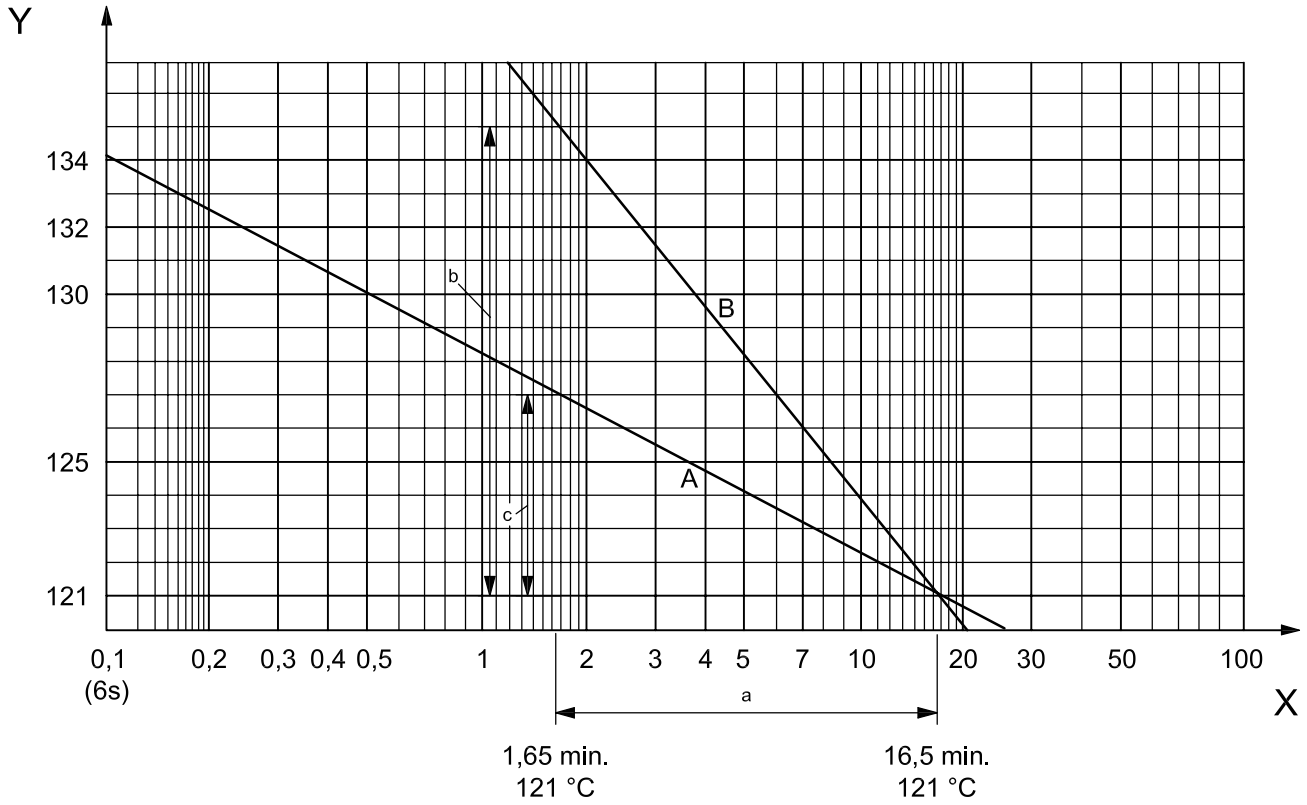
$$\text{SV} \times \frac{7}{11} = \text{SV} \times 0{,}636 = \text{ST} \tag{C.13}$$

Thus, for the integrator the survivor time, i.e., the fail response in the integrator, and hence the time when the endpoint must not be reached, is 63,6 % of the SV.

The class 5 indicator definition can best be understood by initially focusing on performance in steam sterilizers. One factor in the definition is that it be quite similar to BIs in performance. In an attempt to correlate CI performance with BI performance the term “temperature coefficient” is used to somewhat simulate the z value. BIs can have z values of between 6 and 14. If, a temperature coefficient range of 6 °C to 14 °C is established then, plotting the two temperature coefficients at various temperatures can create a graph on semi-log paper. If it is established that the SV at 121 °C is 16,5 min, the two temperature coefficient plots intersect at 16,5 min, 121 °C.

The slope of a line created from a plot of data representing the SV of a CI at various temperatures must fall between the slopes of the lines created from temperature coefficients 6 °C and 14 °C and be linear. In addition, a clear fail result must be obtained if the exposure time for any given stated value is 63,6 % of that time. In other words, if a CI has a stated value PASS of 1,80 min at 134 °C, it must indicate FAIL at 1,14 min at 134 °C. (1,80 min × 0,636 = 1,14 min) or (1 min, 48 s PASS × 0,636 = 1 min, 9 s FAIL).

For an illustration, see Figure C.1. After plotting stated values at four temperature points, the slope of the line connecting the points shall be between lines A and B.



Key

X time in minutes

Y temperature in degrees centigrade

a One log cycle.

b 14° Temp. coefficient.

c 6° Temp. coefficient.

Figure C.1 — Temperature coefficient for steam Class 5 Integrating indicators

C.3 Comparison with the requirements for integrating indicators in ISO 11140-1[12]

ISO 11140-1[12] required that an integrator show a fail response when exposed to its stated value (SV) minus 1 °C on temperature and minus 15 % on time. For an integrator with a SV of 16,5 min at 121 °C, a fail condition should be observed when the indicator is exposed to 120 °C for 14,025 min. Relating this to a biological indicator (BI) response, if the BI has a D_{121} of 1,5 and a z of 10 °C, then the D at 120 °C will be:

$$D_{120} = D_{121} \times 10^{-\left[(T_1 - T_{\text{ref}})/10\right]} \tag{C.14}$$

where

D_{120} is the D value at 120 °C;

D_{121} is the D value at 121 °C;

T_1 is the working temperature (in this case 120 °C);

T_{ref} is the reference temperature (in this case 121 °C);

$D_{120} = 1,5 \times 10^{-[(120-121)/10]} = 1,88$ min.

Assuming the BI has a population of 1×10^5, then the log reduction achieved by exposing the BI at 120 °C for 14,025 min would be:

$$\frac{14,025}{1,88} = 7,427 \tag{C.15}$$

i.e., a 7,4 log reduction.

Thus, the log survivor level in the BI would be

$$5 - 7,427 = -2,427 \tag{C.16}$$

Therefore, the surviving population will be

$$1 \times 10^{-2,427} = 3,7 \times 10^{-3} \tag{C.17}$$

This is very close to the requirements specified in ISO 11140-1[13], i.e., that an integrator should show a fail when the exposure time creates a 7 log reduction in population, i.e., down to 1×10^{-2}.

Thus, the proposed requirements listed above are broadly similar to the previous requirements for the example cited above.

Considering a BI with a z of 6, the D value at 120 °C will be given by:

$$D_{120} = 1,5 \times 10^{-[(120-121)/6]} = 2,2 \text{ min} \tag{C.18}$$

Assuming the BI has a population of 1×10^5, then log reduction by exposing the BI at 120 °C for 14,025 min would be:

$$\frac{14,025}{2,2} = 6,375 \tag{C.19}$$

Thus, the survivor level in the BI would be

$$5 - 6,375 = -1,375 = \log (4,6 \times 10^{-2}) \tag{C.20}$$

Considering a BI with a z of 14:

$$D_{120} = 1,5 \times 10^{-[(120-121)/14]} = 1,768\ 1 \tag{C.21}$$

Assuming the BI has a population of 1×10^5, then log reduction by exposing the BI at 120 °C for 14,025 min would be

$$\frac{14,025}{1,7681} = 7,93 \tag{C.22}$$

Thus, the survivor level in the BI would be

$$5 - 7,93 = -2,9 = \log (1,25 \times 10^{-3}) \tag{C.23}$$

For a summary of the above, see Table C.1.

Table C.1 — BI survivor level

	z = 6	z = 10	z = 14
BI survivor level	$4{,}6 \times 10^{-2}$	$3{,}7 \times 10^{-3}$	$1{,}25 \times 10^{-3}$

Examining the same data at the maximum temperature:

The integrator has an SV at 135 °C of 0,66 min, a BI with a D_{121} of 1,5, population of 1×10^5 and z = 10 °C

$$D_{135} = 1{,}5 \times 10^{-[(135-121)/10]} = 0{,}06 \text{ min} \quad \text{(C.24)}$$

For the pass or accept condition, an 11 log reduction is achieved in

$$11 \times 0{,}06 \text{ min} = 0{,}66 \text{ min} \quad \text{(C.25)}$$

For the fail or reject condition, a 7 log reduction is achieved in

$$7 \times 0{,}06 = 0{,}42 \text{ min} \quad \text{(C.26)}$$

According to our requirements, the integrator should show a fail at SV × 63,6 %;

$$0{,}66 \times 0{,}636 = 0{,}42 \text{ min} \quad \text{(C.27)}$$

Using the previously defined criteria for a fail condition:

SV temperature − 1 °C and SV time − 15 % would mean a fail at 134 °C and 0,56 min

For the BI,

$$D_{134} = 1{,}5 \times 10^{-[(134-121)/10]} = 0{,}075 \text{ min} \quad \text{(C.28)}$$

Thus, exposure for 0,56 min would bring about a log reduction of

$$\frac{0{,}56}{0{,}075} = 7{,}45 \text{ log reduction} \quad \text{(C.29)}$$

Therefore, the survivor level would be

$$5 - 7{,}47 = -2{,}47 = \log (3{,}3 \times 10^{-3}) \quad \text{(C.30)}$$

Which is again close to the acceptance level for fail stated above, i.e., 1×10^{-2}.

C.4 Ethylene oxide

ISO 11138-2[8] specifies that an ethylene oxide (EO) biological indicator (BI) shall have a D Value of not less than 2,5 min at 54 °C, 60 % RH, and 600 mg EO/l with a maximum population of 1×10^6. The performance of the BI may be defined by the survivor kill window which would typically be: survives at least 10 min, killed in no more than 25 min at 54 °C based on the minimum values specified above. The SKW can be calculated from:

$$\text{Survival time} = (\log P - 2) \times D; \quad \text{(C.31)}$$

$$\text{Kill time} = (\log P + 4) \times D. \quad \text{(C.32)}$$

It is common to aim for a final probability of survival in a population of microorganisms of 10^{-6} before a product can be labelled sterile.

Based on the above information, it would be necessary to expose a BI with a D = 2,5 and a population of 1×10^6 to a temperature of 54 °C, 600 mg EO/l, and 60 % RH for 30 min in order to achieve an inactivation level of 10^{-6}.

Thus

$$(\log 10^6 - \log 10^{-6}) \times 2{,}5 = 30{,}0 \text{ min} \tag{C.33}$$

Thus, for a class 5 integrator, the minimum SV, i.e., the time at which the endpoint is reached, should not be less than 30,0 min in order to ensure an adequate inactivation factor has been achieved in an equivalent BI.

In the case when the SV at 54 °C, 600 mg EO/l, and 60 % RH is greater than 30,0 min, then clearly a greater inactivation level will have been achieved by the time the indicator reaches its endpoint. Nevertheless, the integrator should reach or exceed its endpoint when exposed for a time equal to the SV.

The above represents the pass condition. Below represents the fail condition.

Theoretically a single BI will show no growth when the exposure time is sufficient to reduce the population to less than one surviving organism. However, when actual BIs are in use, the exposure time has to be greater than that specified above because of the natural variation associated with biological systems. Typically, if 50 or more BIs were tested, then an exposure time which reduces the population to a theoretical level of less than 10^{-0} would be required to eliminate most positives for growth. This is reflected in the determination of the survival/kill characteristics where an exposure period of $(\log P + 4) \times D$ is used to define the kill time, i.e., a further 4 log reduction past the point of one surviving organism per unit, i.e., 1×10^{-4}. Thus, we might expect to see some BIs showing positive for growth at a 10^{-0} exposure level but none at a 10^{-4} exposure level. Adopting these criteria for the definition of the fail response in an integrating indicator at 54 °C, 600 mg EO/l, and 60 % RH with a population of 1×10^6 and a D value of 2,5, an 8 log reduction is required to reach the 10^{-2} level. The exposure time required for this is:

$$(\log P + 2) \times D = 20 \text{ min} \tag{C.34}$$

Thus, the integrating indicator should not reach its endpoint when exposed to 600 mg EO/l and 60 % RH at 54 °C for 20 min or less. However, the manufacturer's SV at 54 °C could be greater than 30,0 min, therefore the fail condition must be linked to this value and be at least 20 min. Using 20 min as a baseline for failure and 30,0 min as a baseline for a pass:

$$\frac{20}{30} = 0{,}667 \tag{C.35}$$

Thus, for an indicator with an SV greater than 30,0 min, the fail condition at which it is tested should be an exposure time which is 66,7 % of its SV. Thus the indicator must show a fail response when exposed to 600 mg EO/l and 60 % RH at 54 °C for 66,7 % of the SV.

In biological terms, the SV is related to the time required to achieve a 12 log reduction in population; 66,7 % of the SV is related to the time required to achieve an 8 log reduction.

Annex D
(informative)

Specifications for porosity

D.1 General

ISO 11140-3[14] and ISO 11140-5[16] require the porosity of indicator systems to be determined according to ISO 5636-3[1] (Bendtsen method). An alternative method is described in ISO 5636-5[2] (Gurley method). Presented in Clause D.2 is a comparison of five paper samples, showing equivalence between the two methods.

D.2 Comparison of five paper samples

D.2.1 Test materials

The test materials consisted of five samples of paper materials identified as: Sample A, Sample B, Sample C, Sample D and Sample E.

D.2.2 Conditions

The conditions in Table D.1 apply.

Table D.1 — Conditions

Pre-conditioning	Conditioning	Test conditions
None	23 ± 2 °C, 50 ± 5 % RH, for a minimum of 16 h	23 ± 2 °C, 50 ± 5 % RH

D.2.3 Test methods

D.2.3.1 Air permeance in accordance with ISO 5636-3

Using the Bendtsen instrument 150 mm water gauge pressure, 10 replicate tests were performed on samples A, B and E but due to limited quantity of material supplied, 6 replicate tests were performed on samples C and D; alternate sides were tested.

D.2.3.2 Air permeance in accordance with ISO 5636-5[2]

Using the Gurley instrument with a standard 567 g cylinder, 10 replicate tests were performed on samples A, B and E but due to limited quantity of material supplied, 6 replicate tests were performed on samples C and D; alternate sides were tested.

D.2.4 Test results

See Table D.2.

Table D.2 — Bendtsen air permeability (ml/min)

Sample	Mean	Range
A	298	250 – 350
B	3240	3 100 – 3 400
C	328	300 – 360
D	2167	2 100 – 2 250
E	118	100 – 140

NOTE Due to the high permeability of sample B, it was tested using 75 mm water gauge pressure with results corrected for 150 water gauge pressure.

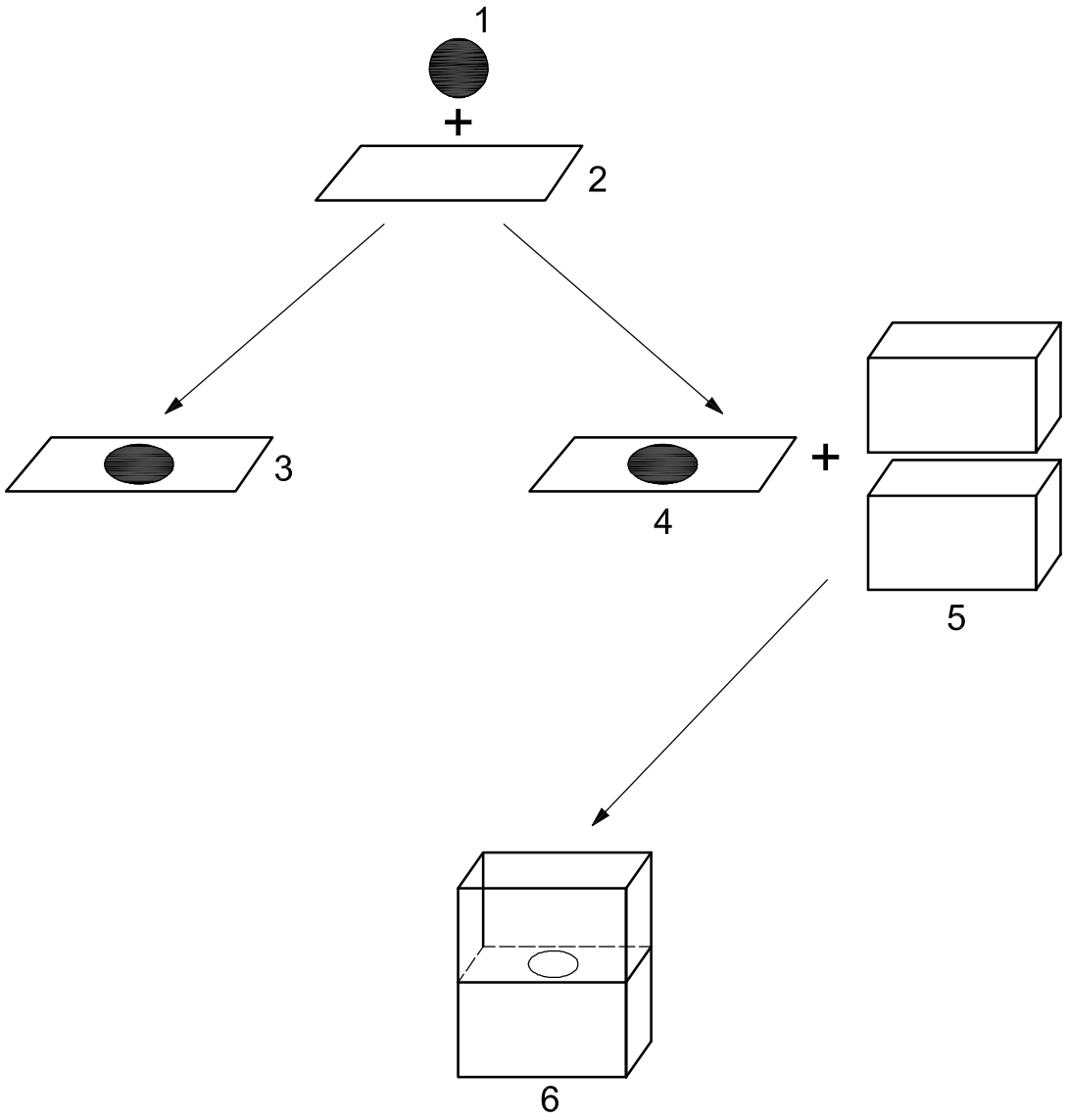
Table D.3 — Gurley air permeability (sec/100 ml)

Sample	Mean	Range
A	57,7	46,4 – 71,1
B	2,56	2,23 – 2,95
C	56,3	53,1 – 60,3
D	5,20	4,74 – 5,97
E	154	126 – 172

NOTE Due to the high permeability of samples B and D, they were tested over 200 ml with results corrected for 100 ml.

Annex E
(informative)

Figure showing relationship of indicator components



Key

1 indicator (re)agent
2 substrate
3 indicator (class 1, 3, 4, 5, 6)
4 indicator system
5 specific test load
6 indicator (class 2)

Figure E.1 — Relationship of indicator components

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