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Aseptic processing of health care products —

Part 7: Alternative processes for medical devices and combination products

Traitement aseptique des produits de santé —

Partie 7: Procédés alternatifs pour les dispositifs médicaux et les produits de combinaison

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Foreword

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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 13408-7 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

ISO 13408 consists of the following parts, under the general title *Aseptic processing of health care products*:

— *Part 1: General requirements*

— *Part 2: Filtration*

— *Part 3: Lyophilization*

— *Part 4: Clean-in-place technologies*

— *Part 5: Sterilization in place*

— *Part 6: Isolator systems*

— *Part 7: Alternative processes for medical devices and combination products*

Introduction

ISO 13408 is the International Standard, published in a series of parts, for aseptic processing of health care products. Historically, sterile health care products that are aseptically produced have typically been liquids, powders or suspensions that cannot be terminally sterilized. More recently, medical devices and health care products have been developed that are combined with medicinal products, including biological and viable cells, that cannot be terminally sterilized.

The application of ISO 13408-1 to these medical devices and combination products can require the development of alternative approaches to process simulation. This part of ISO 13408 specifies requirements and provides guidance for developing such alternative approaches for the qualification of aseptic processes through process simulation of medical devices and combination products that meet the requirements of ISO 13408-1.

ISO 13408-1:2008, 10.1.2 permits the use of alternative process simulation approaches, based on particular medical devices or combination products, where the substitution in full with sterile liquid media might not be possible.

Medical devices and combination products that typically require aseptic processing might include, for example, the following.

a) Medical devices that cannot be terminally sterilized and where the process simulation approach according to ISO 13408-1 cannot be applied:

   — bioprostheses (e.g. heart valves, vascular implants);

   — biodegradable implants (e.g. hernia meshes);

   — artificial and/or non-viable biologically based matrixes;

   — extracorporeal processing devices (e.g. immuno-adsorbers);

   — implantable osmotic pumps;

   — hermetically sealed electromechanical devices and partially enclosed electronic devices (e.g. invasive and non-invasive diagnostic devices).

b) Combination products (including viable cell-based combination products):

   — implants coated with drug and/or biologically derived substances (e.g. drug-coated stents, carrier materials with protein, bone-graft material with growth factors, biodegradable drug-coated stents);

   — wound dressings (e.g. dressings with haemostatic agents, tissue sealants, or biologics);

   — transdermal or injectable delivery systems (e.g. drug-coated or biologics interstitial patches);

   — kits containing a biological or drug component (e.g. demineralized bone matrices).

For such products, a risk management strategy and method(s) can be used for the identification, evaluation and quantification (estimation) of contamination risks throughout the entire product/process life cycle. Environmental monitoring and microbiological studies can be performed on individual steps of the process to evaluate the effectiveness of contamination controls and risk mitigations. The design of the process simulation can then be driven by the results of the risk analysis. If the results of the process simulation are acceptable, this provides evidence that the aseptic process is in a state of contamination control (i.e. no extrinsic microbiological/microbial contamination has been introduced during the aseptic process).

This part of ISO 13408 should be read in conjunction with ISO 13408-1.

Within this International Standard, text that supplements ISO 13408-1 by providing additional requirements or guidance is identified by the prefix “Addition”.

Aseptic processing of health care products —

Part 7: Alternative processes for medical devices and combination products

1 Scope

This part of ISO 13408 specifies requirements and provides guidance on alternative approaches to process simulations for the qualification of the aseptic processing of medical devices and combination products that cannot be terminally sterilized and where the process simulation approach according to ISO 13408-1 cannot be applied.

This part of ISO 13408 describes how risk assessment can be used during the development of an aseptic process to design a process simulation study for medical devices and combination products in those cases where a straightforward substitution of media for product during aseptic processing is not feasible or would not simulate the actual aseptic process.

2 Normative references

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

ISO 13408-1:2008, *Aseptic processing of health care products — Part 1: General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1 and the following apply.

3.1
extrinsic contamination
ingress of material of external origin during the manufacturing process

NOTE The focus of extrinsic contamination in this part of ISO 13408 is biological agents e.g. bacteria, mould, yeast.

3.2
process simulation
exercise that simulates the manufacturing process or portions of the process in order to demonstrate the capability of the aseptic process to prevent biological contamination

3.3
risk management
systematic application of quality management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[ISO 14971:2007, definition 2.22]

3.4
surrogate product
item designed to represent product in process simulations and which is comparable to the actual product

4 Quality system elements

ISO 13408-1:2008, Clause 4 applies.

5 Aseptic process definition

5.1 General

ISO 13408-1:2008, 5.1 applies.

5.2 Risk management

5.2.1 General

ISO 13408-1:2008, 5.2.1 applies with the following additional requirements.

a) Risk assessment shall consider all steps of the aseptic process and determine whether the aseptic process is to be simulated in one continuous process or divided into sub-processes for the purposes of process simulation.

   Risk assessment shall not be used to justify the simulation of only some but not all of the processes of an aseptic process.

   NOTE 1 Successful process simulation provides evidence of the capability of the specified aseptic process to produce an acceptable overall residual risk of microbiological/microbial contamination.

   NOTE 2 The risk assessment method selected should be appropriate for the given stage of aseptic process development.

b) A comprehensive risk assessment process may not be required for the design of the process simulation in instances where the approach is readily discernable. The rationale for the decisions reached shall be documented.

5.2.2 Identification of microbiological contamination risks

ISO 13408-1:2008, 5.2.2 applies.

5.2.3 Assessment of contamination risks

ISO 13408-1:2008, 5.2.3 applies.

5.2.4 Monitoring and detection of contamination

ISO 13408-1:2008, 5.2.4 applies.

5.2.5 Prevention of contamination

ISO 13408-1:2008, 5.2.5 applies.

The following additional requirements to ISO 13408-1:2008, 5.2, concerning risk management, apply:

5.2.6 Use of risk assessment during the development and initial qualification of the aseptic process prior to commercial production

5.2.6.1 An acceptable level of contamination risk shall be defined. A risk assessment shall be performed during the development of the aseptic process. Risk control measures to prevent microbiological/microbial contamination for each step in the aseptic process shall be identified.

5.2.6.2 The estimation of contamination risk by quantitative methods and the verification of effectiveness of risk mitigation procedures shall be determined. Methods such as microbiological and particulate monitoring of the product, personnel and environment may be used.

NOTE Quantitative risk modelling can also be applied.

5.2.6.3 The outcome of the risk assessment shall be used in the design of the process simulation study.

5.2.6.4 Risk management shall be applied iteratively. The risk assessment shall be updated as necessary as the aseptic process develops and changes during development.

5.2.7 Use of risk assessment for the aseptic process simulation for process validation of commercial production

Risk assessment shall be used to design the process simulation for validation of the commercial aseptic process. Risk assessment shall identify those actions to be included in the process simulation and their appropriateness.

NOTE Annex A provides a practical application of risk management in designing a process simulation for a combination drug/device.

6 Manufacturing environment

ISO 13408-1:2008, Clause 6 applies.

7 Equipment

ISO 13408-1:2008, Clause 7 applies.

8 Personnel

ISO 13408-1:2008, Clause 8 applies.

9 Manufacture of the product

ISO 13408-1:2008, Clause 9 applies.

10 Process simulation

10.1 General

ISO 13408-1:2008, 10.1 applies.

10.2 Media selection and growth support

ISO 13408-1:2008, 10.2 applies.

10.3 Simulation procedures

ISO 13408-1:2008. 10.3.1 applies with the following additional requirements.

a) General considerations

The process simulation approach for a given medical device or combination product is based on a detailed knowledge of the entire aseptic process definition including discrete process steps and interventions as well as

the use of risk assessment tools, as appropriate (see 5.2.6 and 5.2.7). The process simulation approach shall be included in the design/process review for the manufacturing of product.

b) Development of a process simulation strategy

1) A process simulation strategy shall be documented for a process that cannot be validated using a conventional process simulation approach as per ISO 13408-1.

NOTE See Figure 1 for an example of the development of a process simulation study.

2) If the process simulation approach outlined in ISO 13408-1 is not practicable, a rationale shall be documented including evidence that consideration was given during product and process development to:

— use of sterile liquid media as a substitute for product during process simulation, or

— direct media contact at the end of the process, i.e. into the sterile barrier system prior to final closure.

3) The entire aseptic process definition shall be included in the process simulation strategy. If the aseptic process is divided into sub-processes for the purposes of process simulation, the process simulation for each sub-process in total shall include all steps in the aseptic process.

4) Risk assessment shall be part of the life cycle of the aseptic process and shall be used to determine the process simulation strategy throughout the product/process life cycle.

5) The simulation options shall be selected and the process simulation strategy for the entire process shall be documented.

c) Process simulation throughout the product lifecycle

1) The initial process simulation approach shall be established during the development of the aseptic process and the first process simulation shall be performed in advance of the production of the first-in-human clinical products to verify acceptable aseptic processing conditions.

2) As the aseptic process is scaled-up and enhanced for later stages of clinical production, the process simulation approach shall be modified to address the changing aseptic process.

NOTE The aseptic process used for early clinical production is often manual and/or not optimized or scaled up for commercial production.

3) For commercial production, a process simulation study shall be designed and performed as part of the process validation.

4) Any change to the aseptic process which could add risk shall generate additional risk assessment and mitigation and a re-evaluation of the process simulation strategy. This shall include a re-evaluation of the process risk assessment.

d) Selection of sample(s) for testing for microbial contamination

1) Product:

Whenever possible, product shall be tested for microbial contamination. Product testing can take several forms. See Annex B for information.

If the product as designed cannot be tested, then prior to considering use of a surrogate product, the possibility of redesigning the product or process such that the actual product can be tested shall be assessed.

2) Surrogate product:

A surrogate product shall only represent the actual product if it constitutes an equivalent or greater challenge to the maintenance of asepsis than that provided by the actual product. The reason why the

actual product is unsuitable for testing shall be documented and the rationale for the selection of the surrogate product test sample described.

Surrogate product may be used for microbiological testing where product attributes preclude the use of actual product for testing. Examples of product attributes may include those that:

— are too large or irregularly shaped (e.g. osmotic pump);

— have antimicrobial properties (e.g. antibiotic stent);

— are rare and scarce (e.g. autologous chondrocyte);

— cause physical interference with the test method (e.g. product that breaks down in the growth medium generating particles that may be confused with microbial growth).

Selection and design of surrogate product shall reflect as much as possible the design of the actual product. Processing of surrogate product shall include all aseptic processing steps and interventions applied during manufacture of the actual product. See Annex B for guidance.

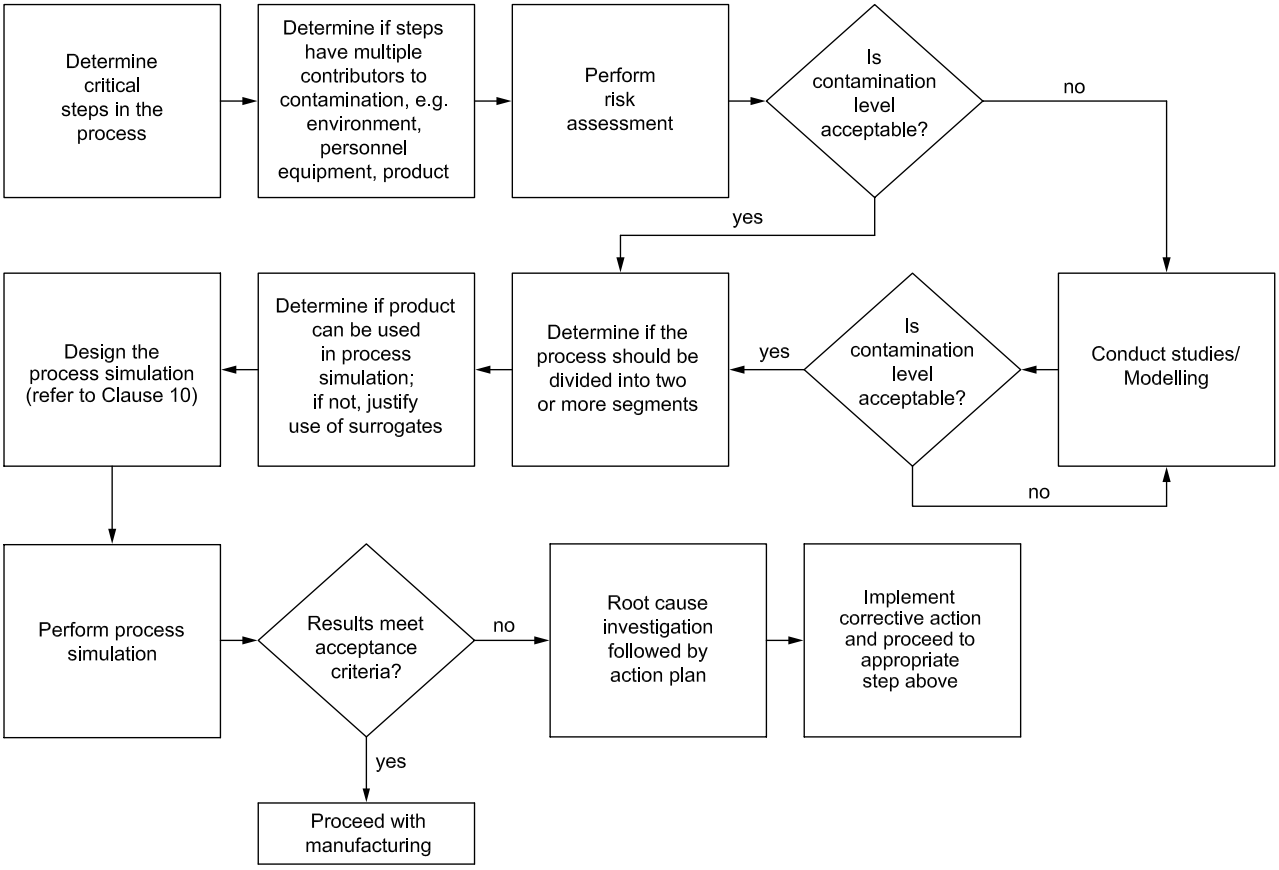


Figure 1 — Flow diagram of risk assessment process

e) Test methods for process simulation

The risk of contamination due to human intervention exists with all tests for microbial contamination. The selection of the test method shall consider both the sensitivity of the test as well as the number of interventions or manipulations. The risk assessment performed in the course of the process simulation study design (5.2.6.3) shall address the risks of introducing contamination during testing and define steps for reducing the likelihood of extrinsic contamination.

The test method shall be designed or selected based on product to be tested (actual or surrogate product). Test method development shall include consideration of suitable test options (see Annex C). The test method shall be validated.

ISO 13408-1:2008, 10.3.2 to 10.3.6 also apply.

10.4 Incubation and inspection of process simulation units

ISO 13408-1:2008, 10.4 applies.

10.5 Initial performance qualification

10.5.1 General

ISO 13408-1:2008, 10.5.1 applies.

10.5.2 Numbers to be filled

ISO 13408-1:2008, 10.5.2.1 applies with the following additional requirements.

a) For operations with production batch sizes of fewer than 5 000 units, the number of process simulation units manufactured shall at least equal the maximum batch size produced.

b) All units manufactured for process simulation shall be tested for the presence of microbial contamination (see also ISO 13408-1:2008, 10.4.2).

c) If the process simulation is divided into subsets, then the number of units tested in each subset shall be justified. At least three consecutive successful simulations shall be performed for each discrete subset of the aseptic process. All of the filled units from each subset shall be tested for the presence of microbial contamination.

ISO 13408-1:2008, 10.5.2.2 also applies.

10.5.3 Acceptance criteria

ISO 13408-1:2008, 10.5.3.1 applies.

ISO 13408-1:2008, 10.5.3.2 applies with the following additional requirement:

When the aseptic process simulation is divided into subsets, all subsets shall have zero contaminated units for the process simulation to be approved. If a single sub-process of the simulation fails, a documented investigation shall be performed to identify the root cause of the failure. If a root cause for the failure can be identified, then that root cause shall be corrected prior to requalification. In the event a definitive root cause cannot be identified, a review of the process and design of the process simulation shall be performed, and modifications made. Following corrective actions, three consecutive simulation tests of that subset shall be performed that have zero contaminated units for the simulation to be approved.

10.6 Periodic performance requalification

10.6.1 Scheduling requirements

ISO 13408-1:2008, 10.6.1 applies.

10.6.2 Numbers to be filled

ISO 13408-1:2008, 10.6.2 applies with the following additional requirement:

For operations with production batch sizes of fewer than 5 000 units, the number of process simulation units manufactured shall at least equal the maximum batch size produced.

10.6.3 Acceptance criteria

ISO 13408-1:2008, 10.6.3 applies.

10.7 Repeat of initial performance qualification

ISO 13408-1:2008, 10.7 applies.

10.8 Documentation of process simulations

ISO 13408-1:2008, 10.8 applies.

10.9 Disposition of filled product

ISO 13408-1:2008, 10.9 applies.

11 Test for sterility

For products where a test for sterility according to the European, US and Japanese Pharmacopoeias cannot be applied, an alternative test regime shall be established and justified. Refer to Annex B for additional guidance.

11.1 General

ISO 13408-1:2008, 11.1 applies with the following additional requirement:

Where a product containing viable cells is shown to interfere with the test for microbial contamination, then a suitable alternative test method for microbiological control of finished product shall be developed. This test method shall be shown to be at least equivalent to the test for microbial contamination in terms of its sensitivity and ability to detect a broader range of microorganisms.

NOTE Alternative test methods can include rapid microbiological methods and non-growth-based test methods. Examples of Pharmacopoeias include Ph.Eur.[10], JP[11] and USP[12].

11.2 Investigation of positive units from tests for sterility

ISO 13408-1:2008,11.2 applies.

Annex A
(informative)

Risk assessment for aseptic processing — Quality risk management method

A.1 General

This annex provides a practical application of the concepts presented in this part of ISO 13408. A Failure Mode and Effects Analysis (FMEA) approach has been selected as the basis for the method because it is one of the methods that works well with the assessment and decision-making needed for aseptic processing.

The following example uses an FMEA method [with risk priority number (RPN) scoring] that contains content chosen to illustrate concepts previously introduced. This is a hypothetical situation. The risk ranking and RPN scoring are presented as examples only. For further details see ISO 14971.

A.2 Background

This case study focuses on the conventional aseptic manufacture of a device coated with an antibiotic which is then primary packaged. In the initial design of the process for product for clinical studies, operations were performed manually, resulting in numerous intrusions into the cleanroom environment (see Figure A.1). The larger the number of interventions, the greater the risk of potential sources of contamination.

With optimization of the aseptic manufacturing process for commercial production, the FMEA process was revisited to verify that mitigations resulted in a reduced risk of contamination to an acceptable level (see Figure A.2 and Table A.1).

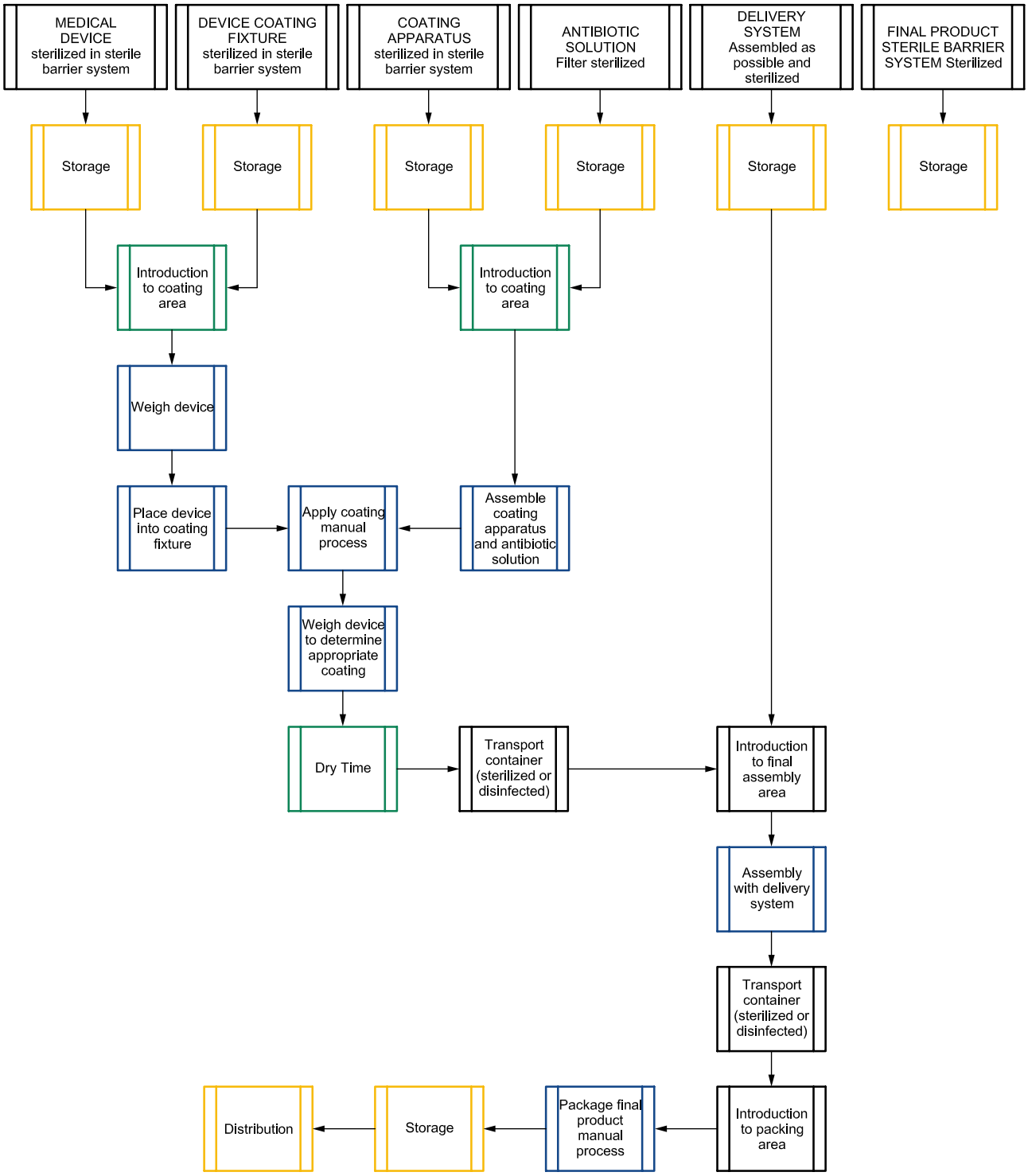
A.3 Risk priority number determination

A semi-quantitative approach was used for assessing the risk of contamination by ranking the severity, occurrence and detection on a numerical scale of 1 to 10. The RPN is calculated by multiplying severity × occurrence × detection. The unwanted event is contamination of the product.

In this example severity has been assigned a value of 10. Occurrence is difficult to quantify for interventions. However, this method requires data to justify the occurrence number (1 being a low likelihood of contamination, and 10 being the highest likelihood of contamination). In this method the inability to detect microbial contamination is high; detection is given a value of 8 to 10 (assumes environmental monitoring and extrinsic microbial contamination testing provide some degree of detection).

A.4 Risk assessment

The initial assessment indicates that the use of a highly manual coating and packaging process requires many human interventions and poses an inherently high risk of contamination (see Figure A.1).



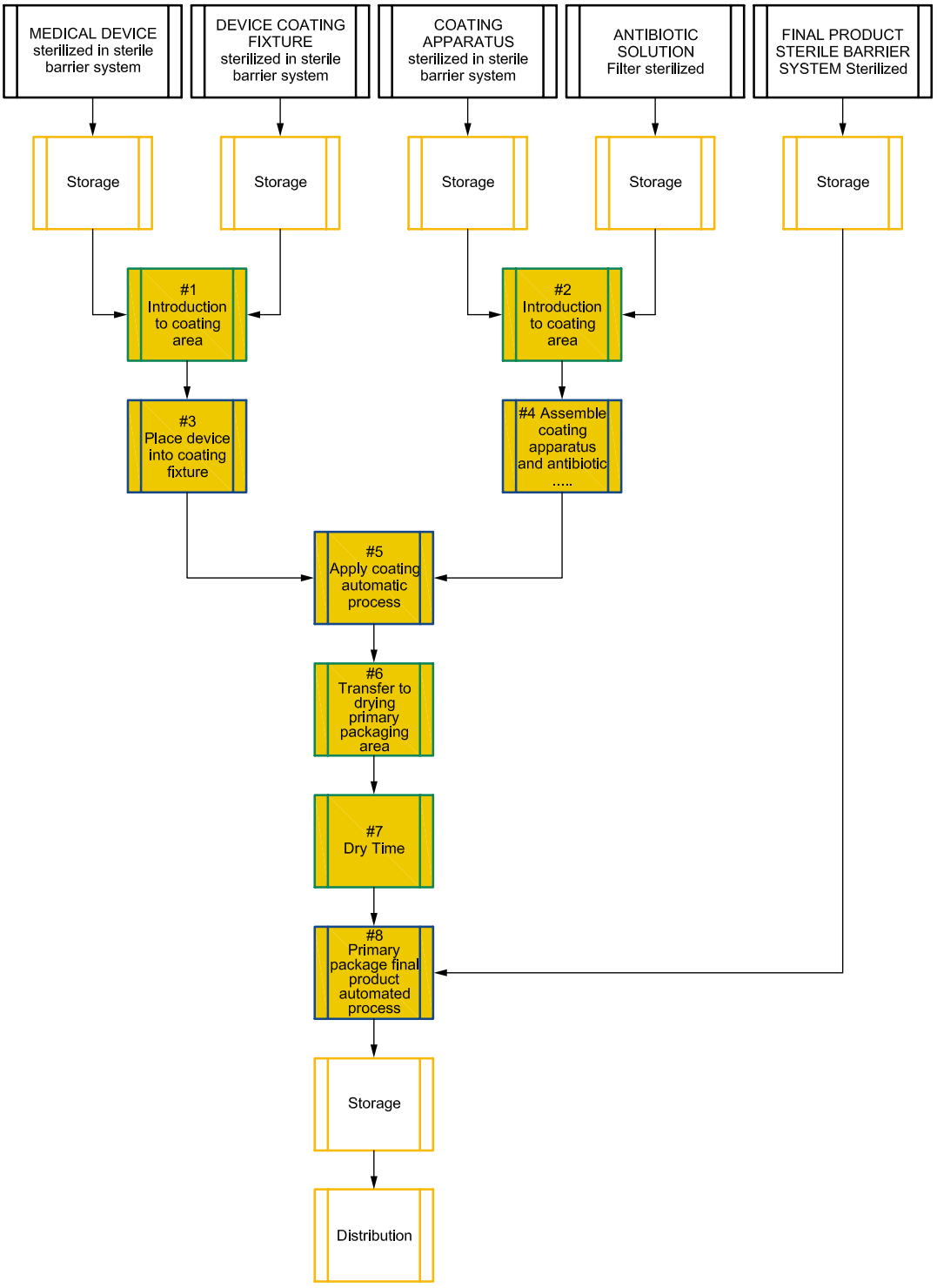
Key

box indicates human and environmental interaction with product/components which can negatively impact product

box indicates only environmental interaction with product/components which can negatively impact product

box indicates steps which have little or no potential negative impact product

Figure A.1 — Initial process flow chart



Key

box indicates steps which are addressed in the FMEA

box indicates human and environmental interaction with product/components which can negatively impact product

box indicates only environmental interaction with product/components which can negatively impact product

box indicates steps which have little or no potential negative impact product

Figure A.2 — Process flow chart following process optimization

A.5 Risk acceptance

For the purposes of this assessment, an initial risk acceptance RPN of 100 was established as the target risk acceptance value. An RPN value greater than 100 would trigger a preventive action (mitigation) to reduce the RPN to 100 or lower. This acceptance value was reassessed periodically to further reduce microbiological/microbial contamination risk in the aseptic process.

A.6 Risk reduction

Possible means of reducing risk (mitigations) were identified. This included automating the coating process, locating the drying and primary packaging processes in a restricted access barrier system (RABS), etc.

NOTE There are many options to address contamination. These options were chosen to illustrate the use of the method for simplicity.

An assessment of the risks associated with the initial aseptic process (Figure A.1) and the optimized process (Figure A.2) is presented in Table A.1. The impact of each mitigation in the optimized process was assessed through microbiological monitoring and studies of contamination, which resulted in an acceptable RPN of 100 or less.

A.7 Verification of acceptability of overall residual risk

A process simulation study protocol was designed that incorporated each of the contamination risk factors (potential causes of failure) described in the FMEA process (Table A.1) and the entire aseptic process to verify that the overall residual risk was acceptable (absence of contaminated product).

A.8 Key process parameters

The following are key process parameters for this example of a combination medical device/drug product.

a) The manufacturing process was designed to aseptically produce a maximum of 300 units of finished product (30 trays of 10 devices and sufficient antibiotic solution to coat 300 units as per specifications). Total processing time is between 3 hours and 4 hours (one shift).

b) The environmental monitoring performed during the process simulation study was based in part on the FMEA, i.e. all high-risk areas were monitored continuously during aseptic operations. Aseptic processing operators perform environmental and personnel monitoring.

c) A maximum of four aseptic processing operators are permitted in the aseptic processing area (APA) at one time (typically, two operators are in the APA). One aseptic processing operator performs aseptic processing steps 1 to 5, and a second aseptic processing operator performs steps 6 to 8 (following Figure A.2). A total of four aseptic processing operators were qualified to perform all aseptic processing steps.

A.9 Process simulation design

A.9.1 Process simulation of the initial aseptic process (manual method)

A.9.1.1 The maximum production size for initial production for clinical studies was 20 units. Therefore the initial process simulation was designed consisting of one run of 20 units of a surrogate product (rejected devices and placebo antibiotic solution). The units were tested for microbial contamination using direct immersion into a microbiological growth medium.

NOTE A placebo antibiotic solution was used as a surrogate product so that a direct immersion microbial contamination test of the final product could be used (see also B.2.3).

Table A.1 — Project worksheet — Failure mode and effect analysis

Process step (initial process)	**Failure mode**	**SEV**	**Potential cause(s)/ mechanism(s) of failure**	**OCC**	**Current process controls (optimized process)**	**DET**	**RPN**	**Recommended action(s)**	**Respons-ibility and completion date**	**Action results and verification of effectiveness**	**SEV**	**OCC**	**DET**	**RPN**
Process steps from the initial (manual) process flow chart (see Figure A.1)	In what ways might the process potentially fail to meet the process require-ments and/ or design intent?	How severe is the effect to the cust-omer?	How can the failure occur? Describe in terms of something that can be corrected or controlled. Be specific. Try to identify the causes that directly impact the failure mode, i.e. root causes.	How often does the cause or failure mode occur?	What are the existing controls and procedures (inspection and test) that either prevent failure mode from occurring or detect the failure should it occur? Should include an SOP number.	How well can you detect cause or FM?	SEV x OCC x DET	What are the actions for reducing the occurrence, or improving detection, or for identifying the root cause if it is unknown? Should have actions only on high RPNs or easy fixes.	Who is responsible for the recomm-ended action?	List the completed actions that are included in the recalculated RPN. Include the implement-ation date for any changes.	What is the new seve-rity?	What is the new proc-ess capab-ility?	Are the dete-ction limits impro-ved?	Recom-pute RPN after actions are com-plete.
Transfer materials into aseptic processing area	Contami-nated product	10	Operator or surface contamination	1		10	100	Grade A, triple wrap, training						
Remove medical device one at a time from tray and place onto individual posts (10)	Contami-nated product	10	Operator contaminates one or more medical devices during removal of tray lid	1		10	100	Grade A environment and use of sterile forceps and tray handle to remove tray; training, EM data shows no contamination of tray surfaces or devices						
Remove medical device one at a time from tray and place onto individual posts (10)	Contami-nated product	10	Operator contaminates one or more medical devices during transfer of 10 devices from tray to post	5	Training and positioning fixtures in laminar flow hood	10	500	Grade A environment and use of sterile forceps to transfer; training		Conduct microbiology simulation study to verify procedure does not result in contamination; qualify all operators	10	1	10	100
Assemble coating apparatus and attach to antibiotic holding tank	Contami-nated product	10	Operator contaminates critical surfaces in coating area	3	Training and positioning fixtures in laminar flow hood	10	300	Grade A environment and use of sterile instruments and gloves; training		Conduct microbiology simulation study to verify procedure does not result in contamination; qualify all operators	10	1	10	100

Table A.1 *(continued)*

Process step (initial process)	Failure mode	SEV	Potential cause(s)/ mechanism(s) of failure	OCC	Current process controls (optimized process)	DET	RPN	Recommended action(s)	Respons-ibility and completion date	Action results and verification of effectiveness	SEV	OCC	DET	RPN
Assemble coating apparatus and attach to antibiotic holding tank	Contami-nated product	10	Operator contaminates critical surfaces on sterilized equipment	7	Training and positioning fixtures in laminar flow hood	10	700	Grade A environment and use of sterile instruments and gloves; training		Conduct microbiology simulation study to verify procedure does not result in contamination; qualify all operators	10	1	10	100
Coat each device on post (automatic process using spray nozzle and rotating post)	Contami-nated product	10	Environmental contamination	1		10	100	Grade A environment; automated process						0
Transfer to adjacent drying/ primary packaging RBS unit using conveyer	Contami-nated product	10	Operator contaminates product	1		10	100	Transfer in Grade A environment, use of conveyor system into RABS unit						0
Allow 30 min air drying (RABS unit)	Contami-nated product	10	Environmental contamination	1		10	100	RABS unit						0
Using mechanical device, remove device from post and place into pre-sterilized pouch and seal (RBS unit)	Contami-nated product	10	Environmental contamination	1		10	100	RABS unit; robotic control						0
							0							0
Total Risk Priority Number =							100-700			”After” Risk Priority Number =				100

A.9.1.2 Each of the processing steps and their interventions were implemented into this simulation. In this example, the process simulation included all process intervention(s) as identified in the FMEA process.

A.9.2 Process simulation for the optimized aseptic process

A.9.2.1 The process simulation was designed consisting of three runs of 300 units of a surrogate product (rejected devices and placebo antibiotic solution). Each of the processing steps and their interventions were implemented into this simulation. In this example the process simulation included the following elements:

a) four aseptic processing operators in the APA;

b) one change of personnel at the midpoint in processing;

c) 4-hour process;

d) all process intervention(s) as identified in the FMEA process.

A.9.2.2 The units were tested for microbial contamination using direct immersion into a microbiological growth medium.

A.10 Acceptance criteria

The process simulation was considered acceptable as there were zero contaminated units from the test for microbial contamination.

Annex B
(informative)

Selection of a sample for testing for microbial contamination

B.1 Actual product

Testing of actual product can take the following forms.

a) Whole product: the entire product is tested for absence of microbiological/microbial contamination.

b) A portion or sub-set of the product (sample item portion): if the product is too large or irregularly shaped, it may be cut into pieces or disassembled for testing purposes.

c) Fluid path: if only the fluid path is intended to be free of microbial contamination, then testing of the fluid path is appropriate.

d) Exterior surface: for hermetically sealed products, such as medical devices where the exposed surface of the device is claimed to be sterile, testing of only the exterior surface is appropriate.

B.2 Surrogate product

B.2.1 A surrogate product can be, for example:

a) one that is representative of the actual product in terms of materials and size;

b) a component or combination of components from the actual product.

B.2.2 For products that are too large or irregularly shaped to be immersed, the product can be broken into parts or disassembled. If the process of breaking or dissembling the product provides an unacceptable risk of contamination, consider using a surrogate product. Alternatively, it may be possible to aseptically process the surrogate product without fully connecting or sealing the parts together so that the unassembled product can be tested without manipulation.

B.2.3 For products with antimicrobial properties, determine whether it is possible to overcome the antimicrobial properties (e.g. neutralization, increased media to product ratio, filtration). If the antimicrobial properties cannot be overcome, consider using a surrogate product that does not contain the antimicrobial agent (e.g. placebo or inert material).

B.2.4 For products that interfere with the microbiological test, determine whether the test method can be designed to overcome the interference. For example, if the product's matrix renders the growth medium turbid, subculturing can be performed (see pharmacopoeias or ISO 11737-2 for guidelines).

B.2.5 For products that contain viable cells which might interfere with the microbiological/microbial contamination test, determine whether the viable cells can grow in the test medium. If the viable cells produce turbidity that mimics microbial contamination, then a suitable surrogate product which does not contain viable cells can be used. Examples of surrogate product include killed cells or tissue, or another entity which is processed in an identical manner to the product that contains viable cells.

Annex C
(informative)

Testing options for process simulation

C.1 Testing option considerations

C.1.1 The risk of contamination due to human intervention exists with all tests for microbial contamination. The selection of the test method should consider both the sensitivity of the test as well as the number of interventions or manipulations required to perform the test. The most sensitive test with the fewest manipulations should be selected, when possible.

C.1.2 Assess the risks of introducing microbial contamination during the test method used to evaluate the process simulation. Since human intervention is a major source of contamination during test manipulations, when possible perform testing in an isolator or restricted access barrier system (RABS). If an isolator or other advanced barrier system is unavailable, testing should be performed in an environment as good as, or better than, that used for manufacturing. Sources of microbiological/microbial contamination during a test may/can include the following:

a) inadequate cleaning and decontamination of the test environment, work surfaces and material placed into the test area;

b) inadequate sterilization of testing equipment, media and transfer instruments;

c) inadequately gowned and gloved personnel;

d) inadequately trained test personnel;

e) contamination occurring during preparation for transport of samples to the test area due to the transportation container or packing;

f) contamination introduced during the opening of the transport packaging or container due to particle generation;

g) contamination on media containers;

h) poor aseptic technique during sample transfer, cutting or sectioning, or surface sampling;

i) poor aseptic technique when completing connections when testing by flushing or *in situ* incubation.

C.1.3 The interval of time between collecting the samples and performing the tests should be as short as practicable.

C.1.4 If the product or surrogate product causes turbidity in the culture media, then a method for differentiating this turbidity from turbidity produced as a result of microbial growth in the medium should be established. See ISO 11737-2 for guidance on verifying microbial growth in a test for microbial contamination.

C.1.5 When the test sample has been defined and the test method has been determined, the test method should be validated to confirm that it is suitable for the recovery of low numbers of microorganisms in the presence of the product to be tested. See ISO 11737-2 and the pharmacopoeias for guidance on verifying the suitability of a test method for recovery of microorganisms in the presence of product.

C.2 Test methods

C.2.1 Direct contact of media with product

C.2.1.1 General considerations

Immersion of the product or surrogate product is the preferred method of testing. This method allows for full media contact with the product surfaces and also addresses contamination risks for all process steps and interventions that are used to make the product.

C.2.1.2 Direct immersion method

If the product or surrogate product can fit into a vessel containing sterile liquid growth medium, then the product should be completely immersed and incubated in this medium. Manipulation of the product or surrogate product may be necessary to ensure that all surfaces are exposed to the growth medium for the duration of the incubation period, e.g. cutting or disassembly of product. If the product size or configuration is such that it cannot be immersed in sterile liquid growth medium, then the product may be broken into pieces or disassembled for testing. If the product is made up of several components, then it may be possible to simulate the aseptic process without actually connecting the component parts. This may reduce the risk of adventitious contamination during testing.

C.2.1.3 *In situ* direct contact of media with patient contact surfaces

If the product claim is “sterile fluid path only”, liquid medium may be added into the fluid path of the product and incubated *in situ*. In this method the product and media are in direct contact, with the product acting as the media container.

An example of an *in situ* test would be the addition of sterile liquid growth medium to a product, e.g. cell culture bag, sealing of the cell culture bag and incubation of the sealed bag. Following incubation the growth medium is examined for evidence of microbial growth. If the container is not transparent it will be necessary to drain the growth medium into a secondary sterile, transparent container for examination.

C.2.2 Elution/removal methods

For those products and parts for which direct immersion or *in situ* testing are not feasible, an elution/removal method may be the only option.

Flush or rinse: if the product can only be flushed or rinsed, the eluate can be either collected in a container for incubation or the eluate can be filtered followed by immersion and incubation of the filter. ISO 11737-2 includes guidance on these approaches. The suitability of this method for removal and recovery of contaminating microorganisms from the product should be determined.

Comparison of methods: the most suitable test method should be selected and the rationale for the choice documented. The benefits and limitations of each of the methods are presented in Table C.1.

Table C.1 — Summary of testing options

Type	Method	Sensitivity	Benefits	Limitations
Direct media contact	Liquid media immersion of actual product or surrogate product	High	Excellent sensitivity Compendial validation method published Regulatory acceptability	Not practical for large items Availability of suitably sized medium container
	In situ media challenge	High	Excellent sensitivity Compendial validation method published Regulatory acceptability	Limited to fluid-path microbial contamination claims May require special connector fabrication and assembly For non-transparent products early detection of positive test samples may not be possible
Elution and removal methods	Flushing or rinsing	Variable	Eliminates media container constraints May be only viable option	Requires validation of recovery efficiency Limited assurance of removing microorganisms from all product surfaces If interior and exterior are claimed sterile, the procedure and validation can be very complex Requires rationale for regulatory acceptance

Bibliography

[1] ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

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

[3] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[4] ISO 14644 (all parts), *Cleanrooms and associated controlled environments*

[5] ISO 14698 (all parts), *Cleanrooms and associated controlled environments — Biocontamination control*

[6] ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

[7] Commission Directive 2004/23/EC, *Standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells*

[8] Commission Directive 2005/17/EC, *Plant passports*

[9] EU Good Manufacturing Practice Directive, Annex 1, *Manufacture of Sterile Medicinal Products*

[10] European Pharmacopoeia

[11] US Pharmacopoeia

[12] JP Pharmacopoeia

[13] EMEA/CHMP/410869/2006, *Guideline on Human Cell-Based Medicinal Products*

[14] Global Harmonization Task Force SG3/N15R8/2005, *Implementation of risk management principles and activities within a Quality Management System*

[15] Global Harmonization Task Force SG3/N99-10, *Quality Management Systems — Process Validation Guidance*

[16] ICH Guidance for Industry — Q9 Quality Risk Management, www.ich.org

[17] PDA Technical Report 22 (TR22), *Process Simulation Testing for Aseptically Filled Products*

[18] PDA Technical Report 44 (TR44), *Quality Risk Management for Aseptic Processes*

[19] PDA Technical Report 34 (TR34), *Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products*

[20] TIDSWELL, EDWARD C. and MCGARVEY, BERNARD, Quantitative risk modelling assists parenteral batch disposition. *European Journal of Parenteral and Pharmaceutical Sciences*, 2007; 12(2):3-7

[21] TIDSWELL, EDWARD C. and MCGARVEY, BERNARD, Quantitative risk modelling in aseptic manufacture. *PDA Journal of Pharmaceutical Science and Technology*, Vol. 60, No.5

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