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Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

Draft

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This guideline replaces Decision trees for the selection of sterilisation methods (CPMP/QWP/054/98), the Annex to the note for guidance on development pharmaceutics (CPMP/QWP/155/96); and

The Annex "Decision trees for the selection of sterilisation methods" (EMEA/CVMP/065/99) to the note for guidance: Development pharmaceutics for veterinary medicinal products (EMEA/CVMP/315/98).

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Active substance, Aseptic processing, Container, Decision trees, Excipients, Filtration, Finished Dosage form, Sterilisation, Sterilisation assurance level, Terminal sterilisation

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Executive summary

This guideline provides guidance on the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a variation application for a medicinal product, (called quality dossier throughout the guideline), and the selection of appropriate methods of sterilisation for sterile products. Although, terminal sterilisation using a reference condition of the European Pharmacopoeia (Ph. Eur) is the method of choice whenever possible, this guideline provides information on when other terminal sterilisation processes, sterilising filtration or aseptic processing, (either alone or when combined with an additional terminal microbial reduction process), could be accepted as an alternative to a reference terminal sterilisation process.

This guideline replaces the previous Annexes to Pharmaceutical development *Decision trees for the selection of sterilisation methods,* (human and veterinary). In addition, the information on methods of sterilisation previously described in *Note for Guidance on manufacture of the finished dosage form* (human and veterinary) has been revised and included in this guideline.

1. Introduction (background)

Sterility is a critical quality attribute for all sterile products. Sterility of the medicinal product cannot be assured by testing, it needs to be assured by the use of a suitable and validated manufacturing process. Sterility is dependent on several factors such as the bioburden of the formulation components, the sterilisation procedure, the integrity of the container closure system, (abbreviated as container in this document), and in the case of aseptic processing, the use of satisfactory aseptic technique. Container integrity is discussed in ICH Q8, (formally adopted for human medicinal products only, nevertheless the same principles are also applicable to veterinary medicinal products).

Terminal sterilisation is preferred to sterilisation by filtration and/or aseptic processing because it provides a sterility assurance level (SAL) that is possible to calculate, validate and control, and thus incorporates a safety margin. For aseptic processes, a SAL is not applicable as accidental contamination caused by inadequate technique cannot be reliably eliminated by monitoring, control or validation. Therefore, terminal sterilisation provides the highest assurance of sterility and should be used whenever possible. For highly sensitive products such as biological products where terminal sterilisation of the drug product is not possible, aseptic processing under controlled conditions provides a satisfactory quality of the drug product.

In addition to those products where the formulation itself prohibits the possibility of terminal sterilisation, the use of aseptic processing can be accepted in certain situations even if the formulation itself can be terminally sterilised if other benefits are gained for the patients or users of the product. These situations are specified below in section 4.3.

2. Scope

The guideline applies to chemical and biological medicinal products for human and veterinary use, but is not applicable for immunological veterinary medicinal products.

Guidance is provided on the choice of the method of sterilisation, the development and manufacturing data required to support the manufacture of the finished product. The same principles, (choice of method of sterilisation, development data and manufacturing), apply to sterile active substances, excipients and primary containers. Only the information expected in a quality dossier, including information on the need for Good Manufacturing Practice (GMP) certificates, is described. General GMP requirements are not included.

Terminal sterilisation by heat and ionising irradiation, using the reference conditions of Ph. Eur. 5.1.1 "Methods of preparation of sterile products" or other conditions to achieve a SAL of $\leq 10^{-6}$, sterilisation by filtration and aseptic processing are considered. Terminal sterilisation by gas and its limitations is also addressed.

The concepts in this guideline refer only to absence or removal of bacteria and fungi. The absence, removal or inactivation of viruses, mycoplasma and other adventitious agents, which could contaminate a product, are not considered.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC on the community code relating to medicinal products for human use Directive 2001/82/EC on medicinal products for veterinary use as amended and also the current Ph. Eur.

In addition, this guideline should be read in conjunction with all other relevant directives and regulations, and all relevant Commission, (V)ICH and CXMP guidelines, Q&A documents and other documents as linked to or published on the EMA website (www.ema.europa.eu).

4. General requirements

The guideline concerns only specific requirements relating to sterility and sterile products. For other considerations on the manufacturing of the medicinal product, reference is made to other guidance documents such as Guidelines on Manufacture of the Finished Dosage Form.

4.1. Manufacturing of sterile medicinal products

Documentation regarding sterilisation and aseptic processing to be included in the quality dossier, Module 3, sections 3.2.P.2 Pharmaceutical development and 3.2.P.3 Manufacture for human products or Part 2 A.4 Development pharmaceutics and Part 2 B Description of the manufacturing method for veterinary products is presented below. The documentation should be provided for all sites performing sterilisation or aseptic processing related to the medicinal product, regardless of whether the processes are performed in-house or outsourced.

The choice of method of sterilisation or aseptic processing should be justified, see section 4.3 Selection of sterilisation method.

All sterilisation processes should be carried out according to the instructions of the Ph. Eur. unless justified.

All sterilisation procedures for the active substance, the excipient(s) or the primary containers should be described and the name and address of the site responsible should be stated. Validation data should be provided as described below for each sterilisation process. The required validation data for terminal microbial reduction processes is the same as for the sterilisation processes, except for the demonstration of a SAL of 10^{-6} or better.

When parametric release of sterility is proposed, the Guideline on real time release testing (formerly Guideline on parametric release), EMA/CHMP/QWP/811210/2009-Rev1 (human products only), the Guideline on Parametric release, EMEA/CVMP/QWP/339588/2005 (veterinary products only) and the text of Ph. Eur. Chapter 5.1.1 should be taken into account.

The levels of bioburden and bacterial endotoxins in the components (active substance, excipients and primary package), as well as those introduced during manufacture and sterilisation can have an impact on the level of bacterial endotoxins in the finished drug product. To ensure an acceptable level of bacterial endotoxins in the finished drug product, the microbiological contamination of the components should be minimal. Specification limits for endotoxins and bioburden in components and bulk solution should be provided where relevant.

Validation data should be provided for all the filters used in the manufacturing process of the finished dosage form. All non-sterilising filters should be validated with regards to solution compatibility and leachable filter materials, the solution to be filtered should be used in the validation unless justified. Additional validation requirements for sterilising filters are described below.

High bioburden limits should not be justified by the capacity of the sterilisation process or any bioburden reducing step before sterilisation.

If a secondary container, (e.g. secondary pouch for infusion bags or blisters intended to keep the outside of the primary package sterile), is used to provide a specific protection to the medicinal product, the packaging process should be described. Information should be provided on when the packaging is performed (before or after sterilisation), if the primary package is dry at the time of packaging and any aseptic techniques employed. The proposed routines should be justified from a microbiological perspective. If the use of secondary packaging means additional sterilisation of the drug product is performed, this should be justified with regard to sterility assurance and any potential impact on drug product quality.

Steam sterilisation

$F_0 \geq 8$ minutes is required for all steam sterilisation processes. Method (e.g. saturated steam cycle, air/steam-overpressure cycle, vacuum phase), pressure, time and temperature of the sterilisation cycle and a bioburden limit should always be stated.

The cycle lethality, in terms of F_0, should be stated, if used as an additional control measure. The lowest temperature used to determine F_0 should be stated.

Further information regarding the F_0 concept and microbial reduction is provided in Ph. Eur. 5.1.5 *Application of the F_0 concept to steam sterilisation of aqueous preparations*.

For terminal sterilisation using a reference condition of the Ph. Eur. 5.1.1, (≥121 °C, ≥15 min in all units), validation data for the sterilisation cycle is not required. In all other cases physical and biological validation of the sterilisation cycle should be provided, to demonstrate a SAL of 10^{-6} or better, as described in Ph. Eur. 5.1.1. The SAL of such a sterilisation process should be calculated from the maximum bioburden per container.

If, in exceptional cases, steam sterilisation is performed with drug product temperature below 115 °C during the holding phase, this should be scientifically justified and supported by extended data, for instance, by evaluation of heat resistance for the bioburden per batch, as cycle lethality decreases significantly with decreasing temperature. Heat treatment at a temperature below 110 °C is not acceptable for sterilisation purposes.

Where required, sufficient validation data should be submitted to demonstrate that a SAL of not less than 10^{-6} is obtained for all containers. The data should include at least, but is not limited to:

- Load mapping distribution (cold spots) – summary or confirmation of performance;
- Physical and biological cycle effect confirmation summary of at least three autoclave runs ensuring:

- Sufficient time at or above nominal temperature in the whole autoclave;
- Acceptable temperature differences between thermocouples in the load;
- Acceptable F_0 variability within the load;
- Relationship between physical and biological validation.

- For processes carried out at ≤115 °C the following additional data should be provided:
  - A justification for the start point of the sterilisation phase;
  - Several relevant biological indicators could be included in the validation to demonstrate sensitivity to the process.

For the biological validation, a biological indicator as described in Ph. Eur. chapter 5.1.2 *Biological indicators of sterilisation* should be used.

A limit for bioburden should be established. For aqueous solutions, a maximum bioburden limit of 100 CFU/100 ml (TAMC) is acceptable for active substances, excipients and drug product formulations without further justification. Other testing regimes to control bioburden at the defined level could be accepted.

Dry heat sterilisation

Time and temperature of the sterilisation cycle and a bioburden limit should always be stated.

In the case of terminal sterilisation using a reference condition of the Ph. Eur. 5.1.1, no validation data of the sterilisation cycle is requested.

For terminal sterilisation cycles with time and/or temperature lower than the reference conditions of the Ph. Eur., physical and biological validation of the sterilisation cycle should be provided, to demonstrate a SAL of 10^{-6} or better, as described in Ph. Eur. 5.1.1. The SAL of such a sterilisation process should be calculated from the maximum bioburden per container.

Where required, sufficient validation data should be submitted to demonstrate that a SAL of not less than 10^{-6} is obtained for all containers. The data submitted should include at least, but is not limited to

- Load mapping distribution (cold spots) – summary or confirmation of performance;
- Physical and biological cycle effect confirmation summary of at least three sterilisation runs ensuring:
  - Sufficient time at or above nominal temperature in the whole dry heat sterilisation cabinet;
  - Acceptable temperature differences between thermo couples in the load;
  - Acceptable lethality variability within the load;
  - Relationship between physical and biological validation.

For the biological validation, a biological indicator as described in Ph. Eur. chapter 5.1.2 *Biological indicators of sterilisation* should be used.

A limit for bioburden should be established. A maximum bioburden limit of 100 CFU/100 g or ml (TAMC) is acceptable for active substances, excipients and drug product formulations without further justification. Other testing regimes to control bioburden at the defined level could be accepted.

Dry heat at temperatures of greater than 220 °C for a validated time is frequently used for both sterilisation and depyrogenation of glassware. In this case, demonstration of a 3 log reduction in heat-resistant endotoxins can be used as validation criteria.

Ionization radiation sterilisation

Data as requested in Note for Guidance "The use of Ionization Radiation in the Manufacture for Medicinal Products" should be provided, supplemented as necessary by data requirements given in ISO 11137 and Ph. Eur. chapter 5.1.1.

Where any requirements in ISO 11137 are in contradiction to requirements stated in any Note for Guidance issued by the EMA, the requirements of the Note for guidance apply.

Gas sterilisation

This method provides sterilisation of the surface of the goods only. It is mainly employed for sterilising packaging materials and equipment, and has therefore not been included in the decision tree. To ensure adequate sterility, sufficient penetration by gas and moisture is essential. This should be followed by a purging process to ensure that any residues of gas or related transformation by-products are below concentrations that could give rise to toxic effects during use of the product. The effectiveness of the purging process should be demonstrated.

Gas sterilisation of dry powders is not acceptable unless other methods of sterilisation are not feasible and its use is scientifically justified. The substance should be sterile filtered and crystallised under aseptic conditions in order to minimise bioburden and entrapment of microorganisms within the crystals. Convincing evidence should be provided demonstrating that the product is not susceptible to compression preventing gas and moisture penetration during sterilisation.

A description of the apparatus, quantitative data on the mixture of gases to be used, the bioburden prior to sterilisation, the time of exposure to the gas, the temperature and humidity prior to and during each step of the sterilisation cycle, and, if applicable, the conditions for the removal of any toxic gas residues should be provided. These conditions should be monitored by appropriate in-process controls with justified acceptance limits.

Results of the process validation should demonstrate a SAL of 10^{-6} or better and removal of any toxic gas residues to an acceptable level in line with current guidelines.

The effectiveness of the process should be routinely checked for every product batch using a suitable biological indicator and by product sterility testing.

Ethylene oxide (ETO) is a gas which is highly toxic. ETO sterilisation is only acceptable if no other method of sterilisation is possible. The process should be developed and validated according to ISO 11135. Residual genotoxic impurities (for instance ETO and halogenated ethylenehydrines) should be evaluated in accordance with the requirements of ICH M7, unless the product is outside the scope of that guideline. For products outside the scope of ICH M7 the limits below apply.

Material	Ethylene oxide	Ethylene chlorhydrin (or any other halogenated ethylenehydrine)
Raw materials	1 µg/g	50 µg/g
Finished product (when used on the finished product)	1 µg/g	50 µg/g
Container (based on simulated use)	1 µg/ml	50 µg/ml

For empty containers intended to be filled with aqueous products, (e.g. prefilled syringes), the need to justify the use of ETO in the sterilisation of the container prior to filling can be waived, provided the container itself fulfils the requirements of ICH M7, as the degradation kinetics of ETO in an aqueous medium have been sufficiently demonstrated.

Sterile filtration

The type and number of sterilising filters, filter area, material and nominal pore size should be described together with a description of the filter integrity testing (principle of the test and details when the tests are performed including limits before and after filtration). The integrity of the sterilised filter should be verified before use but after its sterilisation unless specifically justified and validated, and should be confirmed immediately after use. Nominal pore sizes of 0.22 µm or less are acceptable without further justification, in accordance with Ph. Eur.

For routine commercial manufacturing, bioburden testing should be performed on the bulk solution immediately before sterile filtration. If a pre-sterilising filter is additionally installed, the filter closest to the filling point in the final container is generally characterised as the sterilising filter. The sampling for bioburden testing may be performed prior to the pre-filtration, provided that no holding time is scheduled for the solution between the two filtration steps.

In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing. If a pre-filter is added as a precaution only and not because the unfiltered bulk solution has a higher bioburden, this limit is applicable also before the prefilter and is strongly recommended from a GMP point of view. A bioburden limit of higher than 10 CFU/100 ml before pre-filtration may be acceptable if this is due to starting material known to have high microbial contamination. In such cases, it should be demonstrated that the first filter is capable of achieving a bioburden of NMT 10 CFU/100 ml prior to the last filtration. Bioburden should be tested in a product sample of 100 ml in order to ensure the sensitivity of the method. Other testing regimes to control bioburden at the defined level could be accepted if adequately justified.

Filter validation data should be included. The filter should be validated with regards to bacterial retention capacity, solution compatibility and leachable filter materials. The solution to be filtered should be used in the validation unless justified, (for instance when the pre-filtration integrity test is performed using water for injections during routine production).

If a sterilising filter is used for more than one working day or is re-used for additional batches, the total filtration time and the number of batches the filter is used for should be stated and justified. If re-used, the filter should be dedicated to a single product and sterilised before re-use. Its integrity should be tested before and after each use. Suitable evidence of the bacterial-retention capability after

challenging the filter system to simulate exposure during a campaign should be provided. This simulation should include any physical handling of the filter during its use, such as maximum combined sterilisation time and temperature, integrity testing, mechanical handling and maximum filtration volume at maximum pressure.

The maximum holding time between bulk solution preparation and sterile filtration should be stated, minimised and appropriately supported by data.

If a sterile bulk solution is not filled immediately into the final product containers, the sterile filtration should, unless justified, be repeated immediately before filling in containers.

Aseptic processing

Aseptic processing is not considered to be a sterilisation process as it does not reduce any microbiological contamination but only concerns techniques to process sterile components without adding any microbiological contamination.

For aseptic processes, information on the bulk holding time before filling and on the filling time should be stated and appropriately supported by data. The times should be minimised. The grounds for holding times longer than 24 hours should be justified and evidence should be provided demonstrating that microbial contamination is not possible during processing, (e.g. tightness of tanks, plumbing, any transportation of storage tank and storage conditions).

It should be confirmed that the results of the media fills support the proposed holding and filling times. The actual results of media filling fall within the field of GMP and need not be presented routinely, but may be requested by the competent authorities in certain circumstances since such data are important to justify proposed holding and filling times.

Sterile primary packaging materials should be used for aseptically processed products.

Where blow-fill-seal technology is used for aseptically processed products, summary validation data should be provided to confirm that the container produced is sterile. The bioburden of the material(s) used for the manufacture of the blow-fill-seal container should be controlled.

4.2. Good manufacturing practice for sterile active substances and sterile excipients

The basic GMP requirements for active substances used as starting materials (European Union (EU) GMP guide part II) only apply to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances is considered to be a step in the manufacture of the medicinal product and shall be performed in accordance with GMP for medicinal products. This implies that for any active substance manufacturer who performs sterilisation and subsequent aseptic handling of the active substance, a valid manufacturing authorisation or GMP certificate from an EEA authority or from an authority of countries where mutual recognition or other Community arrangements apply has to be submitted.

Similarly, for sterile excipients, any sterilisation and aseptic processing should be performed in accordance with GMP for medicinal products with the same requirements as described above for sterile active substances.

The same GMP and data requirements also apply to sterile active substances and excipients supported by a Certificate of Suitability issued by the EDQM.

4.3. Selection of sterilisation method

Products intended to be sterile should be terminally sterilised in their final container whenever possible, as clearly stated in the Ph. Eur., general chapter 5.1.1. When terminal sterilisation by heat is not possible, the application of an alternative method of terminal sterilisation, sterilising filtration and/or aseptic processing may be considered. It is recognised that terminal sterilisation processes utilising conditions other than the Ph. Eur. reference conditions may be developed to provide satisfactory sterility assurance levels and such alternative processes may be acceptable when properly validated.

If a sterilisation process using principles other than those described in the Ph. Eur. (steam, dry heat, ionising radiation, gas sterilisation and sterilising filtration) is intended to be used for the sterilisation of a product, the applicant may consider seeking scientific advice regarding the acceptability of the method and the documentation required.

During the manufacturer's evaluation of whether a terminal sterilisation cycle is possible, substantial efforts should be made to enable terminal sterilisation. If the active substance or some key component of the formulation is shown to degrade significantly or an impurity limit is exceeded during shelf-life under even the least stressful terminal sterilisation conditions, the efforts made to develop a formulation capable of undergoing terminal sterilisation should be presented in the development section.

In case of medicinal products containing highly sensitive active substances, (e.g. proteins or heat labile biological substance), where it is well known that terminal sterilisation is not possible, a justification based on a scientific rationale is generally acceptable and further justification of the choice of aseptic processing discussed later in section 4.3 may not be needed.

The principles for the choice of sterilisation process are presented in the form of decision trees in section 5 of this guideline.

For products where terminal sterilisation is not possible and aseptic processing is proposed, the decision trees should be considered to be applied to individual components of the formulation. Also, the possibility of applying a terminal microbial reduction process may be evaluated. It is emphasised that this additional microbial reduction process should not compensate for poor aseptic manufacturing practice. The same requirements for the aseptic part of the process apply as for products manufactured without such an additional microbial reduction process. In case of any non-compliance in the course of sterile filtration and/or in the aseptic manufacturing chain, decisions on whether to release batches should not rely on the terminal microbial reduction process.

A change in shelf-life or storage conditions caused by a terminal sterilisation process is not in itself a reason to allow aseptic processing, unless the new storage condition or shelf-life would cause problems in the use of the product.

Aseptic processing cannot be accepted based solely on an increase in impurity levels upon terminal sterilisation without further justification. An increased level of impurities above the ICH Q3B or VICH GL11 identification or qualification limit does not necessarily preclude terminal sterilisation of the medicinal product. The risk induced by the degradation should be balanced with the risk induced with an aseptic manufacturing method also taking in account the posology of the product and the nature of the degradation products. Attempts to find terminal sterilisation conditions adjusted to give acceptable impurity levels based on degradation mechanisms of the active substance and the actual bioburden should be described in the quality dossier.

In certain cases, as described in the bullet points below, the use of aseptic processing may be accepted, even if the formulation itself can be terminally sterilised. The aseptic approach should be clearly documented, explained and scientifically justified. Such cases could be justified by:

- User benefit provided by a container that cannot be terminally sterilised such as:
  - Eye drop containers enabling administration of single drops to the eye;
  - Containers enabling non parenteral multi-dose preservative free medicinal product formulation for human use;
  - Enhanced ease of administration, for instance the use of a pre-filled pen compared to a vial;
  - Safer handling of toxic products, for instance plastic vials instead of glass vials for cytotoxic medicinal products.

The choice to use a heat-labile packaging material cannot in itself be the sole reason for not using a terminal sterilisation process and alternative materials could be examined; for instance, polypropylene is not as sensitive to heat as polyethylene and could allow terminal sterilisation. Thus, a discussion regarding the efforts made to develop a container that may be terminally sterilised should be included.

- Enabling as long a shelf-life as possible for radiopharmaceutical medicinal products with a shelf-life of less than one week.

The acceptability of aseptic processing should be based on the application of the decision tree and a risk assessment. The bullet points below are not intended to be used to justify aseptic processing as such, but are only intended to provide guidance on issues that are considered when evaluating the acceptability of a sterilisation or aseptic process. Considerations include (but are not limited to):

- Evidence that the proposed packaging with enhanced user benefits is fit for purpose;
- Stability of the active substance, the degradation mechanism(s) and the toxicity of impurities formed during the sterilisation process;
- The volume to be administered per dose. Large volume parenterals should be terminally sterilised whenever possible.

In conclusion, the justification for the chosen sterilisation or aseptic process should include a thorough benefit risk evaluation and it should be demonstrated that suitable development efforts have been made.

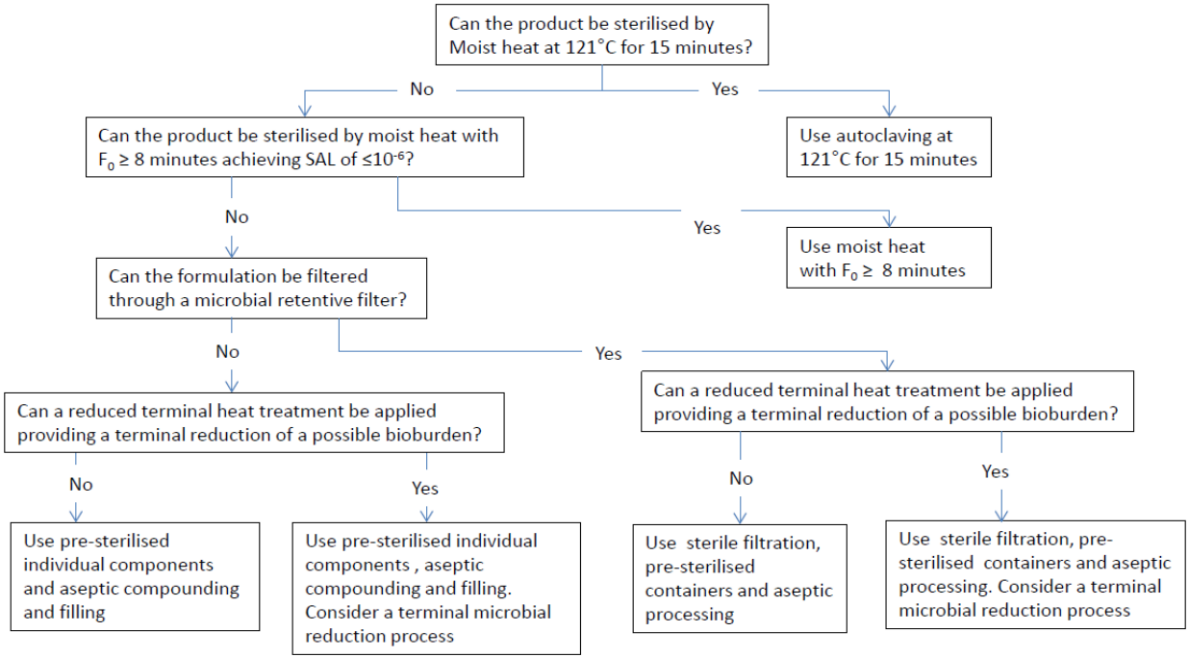
5. Decision trees

The decision trees are intended to assist in the selection of the optimal sterilisation method taking into account the various issues to be considered. When moving down the decision trees, the methods generally show decreasing levels of sterility assurance and therefore the first possible option should normally be chosen. The decision trees have been elaborated primarily for products containing chemical active substances, but may be applicable also to other types of products. In the case of biological products, an alternative approach may be appropriate.

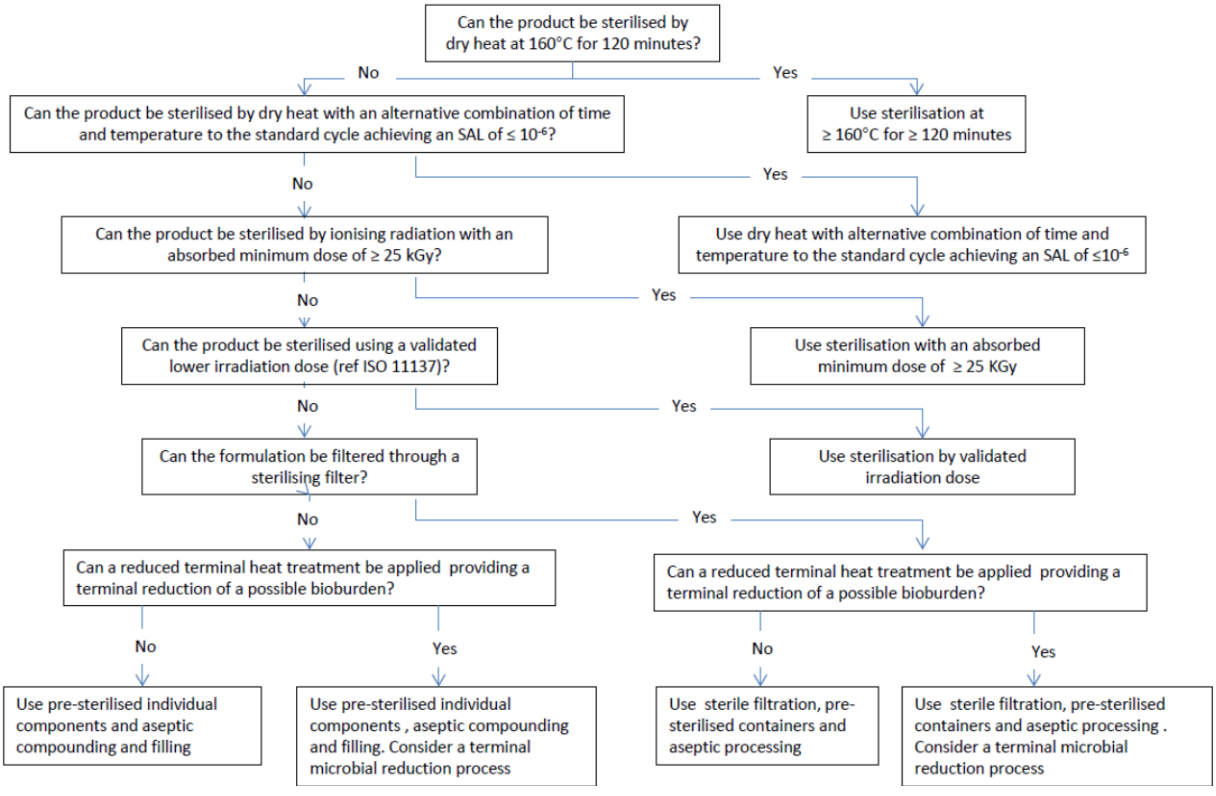
For formulations that cannot withstand a complete terminal sterilisation cycle, a method combining aseptic processing and a terminal microbial reduction process may be considered in order to achieve a higher level of sterility assurance.

For solutions containing an antimicrobial preservative or inherent antimicrobial properties, the bioburden may be more sensitive to a sterilisation process than for a non-preserved solution. Therefore, a terminal microbial reduction process may obtain a SAL of ≤ 10^{-6} and could therefore be considered even though it would not be feasible for a preservative free product. However, the inclusion of a preservative in a product filled in single dose containers is not accepted.

Decision tree for sterilisation choices for aqueous products



Decision tree for sterilisation choices for non-aqueous liquid, semi-solid or dry powder products



394 # 6. Definitions

Aseptic process	A process performed maintaining the sterility of a material* that is assembled from components, each of which has been sterilised by steam, dry heat, ionizing radiation, gas or sterile filtration. This is achieved by using conditions and facilities designed to prevent microbial contamination. * active substance, excipient, container, drug product
Bioburden	A population of viable microorganisms in a product prior to sterilisation
Critical Quality Attribute	A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
D-value (decimal reduction value)	The value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number. It is only of significance under precisely defined experimental conditions. D_{121} is the D-value of the relevant spores at 121 °C.
F_0 value	The F_0 value of a saturated steam sterilisation process is the lethality expressed in terms of the equivalent time in minutes at a temperature of 121 °C delivered by the process to the product in its container with reference to micro-organisms possessing a theoretical Z-value of 10.
Filling time	The time used to fill a bulk product into containers until the container is closed or, in the case of a product which is lyophilized after the filling, until the lyophilisation chamber is closed.
Holding time	The time between two process steps.
Large-volume parenteral	An infusion or injection supplied in a container with a nominal content of more than 100 ml.
Microbial reduction process	Treatment at conditions that provide a lower lethality than sterilisation.
Ph. Eur. sterilisation reference conditions	The reference conditions for sterilisation specified in Ph. Eur. 5.1.1, i.e. terminal steam sterilisation at ≥121 °C for 15 min, terminal dry heat sterilisation at ≥160 °C for ≥2 h or terminal

	ionising radiation of 25 kGy.
SAL	Sterility Assurance Level. The SAL of a sterilising process is the degree of assurance with which the process in question renders a population of items sterile. The SAL for a given process is expressed as the probability of a non-sterile item in that population. An SAL of 10^{-6}, for example, denotes a probability of not more than one viable micro-organism in 1×10^{6} sterilised items of the final product.
Sterilisation	A process that inactivates or removes viable micro-organisms in a product until sterility is obtained.
Sterility	Absence of viable micro-organisms. The inactivation of micro-organisms by physical or chemical means follows an exponential law; thus there is always a finite statistical probability that a micro-organism may survive the sterilising process. For a given process, the probability of survival is determined by the number, types and resistance of the micro-organisms present and by the environment in which the organisms exist during treatment.
TAMC	*Total aerobic microbial count:* The total aerobic microbial count (TAMC) is considered to be equal to the number of CFU found using casein soya bean digest agar.
Terminal microbial reduction process (of product)	Microbial reduction process (of product) in the final container
Terminal sterilisation (of product)	Sterilisation (of a product) in its primary container
Validation	The action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.
Z-value	The Z-value is the change in temperature required to alter the D-value by a factor of 10.

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7. References

Decision trees for the selection of sterilisation methods, CPMP/QWP/054/98;

Note for Guidance: Development Pharmaceutics for veterinary medicinal products: Decision tree for the selection of sterilisation methods, EMEA/CVMP/065/99;

Note for guidance on manufacture of the finished dosage form, CPMP/QWP/486/95;

Note for Guidance: Manufacture of the finished dosage form, EMEA/CVMP/126/95;

ICH guideline Q8 (R2) on pharmaceutical development, EMA/CHMP/ICH/167058/2004;

European Pharmacopoeia general chapter 5.1.1 'Methods of preparation of sterile products';

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use;

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products;

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines;

Guideline on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95 and EMA/CHMP/QWP/245074/2015);

Guideline on real time release testing (formerly Guideline on parametric release), EMA/CHMP/QWP/811210/2009-Rev1;

Guideline on Parametric release, EMEA/CVMP/QWP/339588/2005;

European Pharmacopoeia general chapter 5.1.2 'Biological indicators of sterilisation';

European Pharmacopoeia general chapter 5.1.5 'Application of the F_0 concept to steam sterilisation of aqueous preparations';

NfG on The use of Ionisation Radiation in the Manufacture of Medicinal products 3AQ4A;

EN/ISO 11137, Sterilisation of health care products – Radiation;

ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (EMA/CHMP/ICH/83812/2013);

ISO 11135: Sterilization of health care products – Ethylene oxide;

ICH Topic Q 3 B (R2) Impurities in New Drug Products, CPMP/ICH/2738/99;

VICH Topic GL11 Guideline on impurities in new veterinary medicinal products, EMEA/CVMP/VICH/838/99 Rev.1.