6 March 2019
EMA/CHMP/CVMP/QWP/366428/2018
Committee for medicinal products for human use (CHMP)
Committee for medicinal products for veterinary use (CVMP)

Overview of comments received on the 'Draft guideline on the sterilisation of the medicinal product, active substance, excipients and primary container' (EMA/CHMP/CVMP/QWP/BWP/850374/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	APIC
2	Medicines Evaluation Board (MEB)
3	Parenteral Drug Association (PDA)
4	A3P
5	AstraZeneca
6	B. Braun Melsungen AG
7	Baxter Healthcare Corporation
8	Brij Patel
9	Cenexi
10	Commission on Human Medicines, Chemistry, Pharmacy and Standards Expert Advisory Group
11	Cook Pharmica LLC
12	Dada Consultancy BV
13	EBE, EFPIA and Vaccines Europe
14	ECI-EEIG
15	Therapeutic Goods Administration (TGA)
16	German Pharmaceutical Industry Association
17	Helm AG
18	IFAH-Europe
19	Japan Electron Beam Irradiation Service

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Stakeholder no.	Name of organisation or individual
20	Magnus Stering / Sartorius Stedim Biotech
21	Medicines for Europe
22	Morven McAlister (Pall Corporation)
23	PHARMIG – Association of the Austrian Pharmaceutical Industry
24	AESGP
25	B. Braun Medical AG
26	BVL

1. General comments – overview

Stakeholder no.	General comment	Outcome
1	Clear differentiation between drug products and drug substances / excipients and packaging materials is required. The word 'product' is used ambiguously throughout the entire document	Further clarifications on specific requirements with regards to the different components have been provided.
1	Clear differentiation between sterile filtration and aseptic processing is required. Sterile filtration is an accepted method for sterilisation according Ph.Eur. 5.1.1 In contrast: Aseptic processing refers to maintaining the sterility of a product (covers API, drug product, excipient, packaging) which has been sterilised by one of the accepted sterilisation methods (Ph.Eur. 5.1.1).	Agreed. A clarification is added to the guideline.
1	The quality dossier and the documentation there in should be in-line with CHMP/QWP/227/02 Rev 3/Corr * and EMEA/CVMP/134/02 Rev 3/Corr *	Agreed. A clarification is provided that the documentation on different components may be provided under a relevant section in relation to the item that is sterilised or in connection with the development or manufacture of the drug product.
1	Differentiation regarding requirements and acceptance criteria for legacy products vs. new products should be made where applicable	Agreed. A clarification that the guideline is prospective has been added.
1	Sections 4.1 and 4.2 should consider and refer to the significant differences in manufacturing processes applied for manufacturing of sterile drug substances vs. sterile drug products from non sterile or from sterile API	Not agreed. Section 4.1 describes the documentation required in the dossier in relation to the development and sterilisation or aseptic processing, whereas section 4.2 describes the documentation required in relation to GMP.
1	A separate section covering requirements and aspects related to packaging materials would be useful. Also here packaging materials and size for APIs / excipients are very different from what is used for drug products.	Specific requirements for packaging materials have been further elaborated and specified where required. Even though the package size may differ, the same principles generally apply.
1	Section 4.3. needs complete revision since sterilisation filtration as method of choice and accepted sterilisation method (Ph. Eur. 5.1.1)	Sterile filtration is discussed in the section. Sterile filtration and aseptic treatment are closely related and difficult to

Stakeholder no.	General comment	Outcome
	is not considered throughout the entire section. Differentiation to aseptic processing is not clear.	handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related.
1	Following should be considered: A sterile filtration process performed in line with GMP Annex 1 can also be validated and controlled. Regarding an 'assurance level on sterility' from sterile filtration: **Log Reduction** shows the potential of the sterilization method using 0.2 µm sterilizing grade filters. Bacterial challenge test is based on a reduction of bacteria and should therefore also allow a rationale or statistic on CFU being removed. Hence there should be a possibility for define a suitable factor and sterilization by filtration should be valorized. Please note that the defined Validation requirements simulate conditions which are far away from realistic conditions in manufacturing. And also well controlled and validated sterile filtration performed under in line with GMP requirements is successfully applied for decades for a variety of products	Sterile filtration is an acceptable sterilisation method which can be controlled and validated. However, it is always followed by aseptic processing which introduces a risk of contamination due to accidental contamination which is not present for terminally sterilised products. Therefore, terminal sterilisation is required when possible.
2	The development of a guideline on the sterilisation of the medicinal product, active substance, excipient and primary container is highly appreciated. Overall, the scientific content of the document is supported as it is consistent with the most CHMP decisions. Please find enclosed some suggestions for further improvement below.	The comment is noted.

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3	PDA supports both aseptic and terminal sterilisation approaches being included in the guidance. Based on the documented, successful, safe application of aseptic processing for many years, there is a lack of scientific and risk-based evidence to support the need for application of terminal sterilization or other lethal treatment processes in well designed, properly controlled and operated aseptic processes. Accordingly, PDA believes that aseptic manufacture in these cases can provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated 'terminal sterilisation' or other lethal treatment conditions. However, where there is interest in reducing the ongoing testing requirements (i.e., bioburden testing, environmental monitoring or media fills), post-aseptic processing lethal treatment options up to and including traditional terminal sterilization using moist heat or an alternate technology should be considered.	The comment is noted. The current view is that terminal lethal processes should be used whenever possible.
3	**Comments on $F_0 \geq 8$ Minutes Mandate for Terminal Moist Heat Sterilization Processes** An inconsistent position is presented in this document regarding the preference of terminal sterilization processes over aseptic processing. The document states that "terminal sterilization is preferred to sterilization by filtration and/or aseptic processing because it provides a sterility assurance level (SAL) that is possible to calculate, validate and control…" (Lines 53-55). However, there are sections (Lines 133 and 388) in this document where $F_0 \geq 8$ minutes is mandated for terminal moist heat sterilization processes. If the heat history associated with this minimum physical lethality ($F_0 \geq 8$ minutes) cannot be tolerated by the product, then aseptic	In Ph. Eur. monograph 5.1.1 F0≥ 8 minutes is required for steam sterilisation. The requirements in the guideline are in line with this, but the guideline has also been further elaborated to describe the requirements for processes where aseptic processing is combined with a terminal heat treatment of lower physical lethality. The D-value needs to be justified if lower than those specified in Ph. Eur. 5.1.2.

Stakeholder no.	General comment	Outcome
	processing is the required approach and this fails to recognize the scientific validity and associated historical and successful use of moist heat sterilization processes which operate at F_0 < 8 minutes with capability to provide a product SAL ≤ 10^{-6}. From a patient risk perspective, terminal moist heat sterilization processes that operate at F_0 < 8 minutes and deliver an SAL of ≤ 10^{-6} represent a risk level that is significantly lower than filter sterilization and/or aseptic processing. In support of these lower process F_0 values and their associated ability to provide a ≤ 10^{-6} SAL, the following example of an application of the Product Specific Approach (i.e., Combined Bioburden/BI Approach) taken from PDA Technical Report No. 1 (2007 Revision – Page 27) must be considered: Example 1 a) Bioburden testing of product N_0< 10^1 resistant microorganisms per unit of product. $D_{121° C}$ < 0.25 minutes b) values used for process design N_0 = 10^2 microorganisms N_F = 10^{-6} (PNSU) $D_{121° C}$ = 0.4 minutes	

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	c) calculated minimum lethality to achieve a PNSU of less than 10^{-6} $F_{121° C} = (Log N_o - Log N_F) \times D_T$ (Log 10^2 - Log 10^{-6}) x 0.4 minute = **3.2 minutes** **An SAL or PNSU of 10^{-6} is achieved in this example with a physical lethality of 3.2 minutes for a product bioburden of 10^2 spores with a $D_{121° C}$ value of 0.4 minutes.** It should be noted that ongoing bioburden monitoring (i.e. population and resistance) should be performed for sterilization processes developed with this approach. The estimate of bioburden population and resistance used in this example is considered extremely conservative when compared to the much lower population and heat resistance for the bioburden in products manufactured under typical pharmaceutical GMP controls used for terminally sterilized products. Additionally, it is possible that even lower physical lethality requirements may also be scientifically supported with proper control over bioburden. Examples of the use of F_0 < 8 minutes for terminal moist heat sterilization processes can be further confirmed in the literature and based on commentary from Regulators in the public forum. For example, Pflug and Evans (2000) *(Carrying Out Biological Qualification, the Control Operation of Moist-Heat (Steam Sterilization) Processes for Producing Sterile Pharmaceutical and Medical Devices, PDA J Pharm Sci and Tech 2000, 54 117-135.)*	

<table>
<tr><th>Stakeholder no.</th><th>General comment</th><th>Outcome</th></tr>
<tr><td></td><td>determined that a sterilization process with an F_0 of 1.75 minutes was capable of achieving a 10^{-6} SAL for a liquid pharmaceutical product that contained 10 spores with a D_{121C}value of 0.25 minutes. Additionally, moist heat sterilization processes with F_0 values of less than 8 minutes are in widespread use in Japan-see Table 1.

Table 1 taken from Roundtable on Parametric Release published in Pharmaceutical and Medical Device Regulatory Science Society of Japan, Vol. 46, No. 9, pp 572-588, 2015.
<table><tr><td>F_0 value range (Minutes)</td><td>Accumulated number of manufactured units</td><td>%</td></tr><tr><td>≥ 8</td><td>7,090,000</td><td>0.2</td></tr><tr><td>4 to < 8</td><td>15,189,750</td><td>0.5</td></tr><tr><td>2 to <4</td><td>569,348,566</td><td>19.9</td></tr><tr><td>< 2</td><td>2,272,129,587</td><td>79.3</td></tr></table>From the survey by The Intravenous Solution Society</td><td></td></tr>
<tr><td>4</td><td>As the text is for medicinal product (Chapter 4.1), active substance, excipient (Chapter 4.2) AND primary container, it might be considered necessary to add a chapter for primary container sterilisation.</td><td>Chapter 4.1 concerns the documentation requirements for all types of sterilisation processes covered by the guideline, whereas Chapter 4.2 concerns GMP requirements. The headings have been amended for clarification.</td></tr>
<tr><td>4</td><td>Throughout the text, the term "container" is regularly used but it seems too restrictive. We propose to replace the term "items".</td><td>Not accepted. “Items” is considered too vague.</td></tr>
<tr><td>4</td><td>Autoclave is defined as pressure vessel, inside which reactions are produced. We propose to replace "autoclave" by "sterilizer" and autoclaving" by "sterilizing"</td><td>Accepted.</td></tr>
</table>

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4	In "the chapter 4.3. Selection of sterilisation method", it is possible to add some others processes (e.g. pasteurization is an interesting method for protein)	Not agreed, pasteurisation is not a sterilisation method since the lethality provided is not high enough. However, the guideline has been further elaborated with regards to the requirements for manufacturing methods combining aseptic processing with terminal steam lethal treatment.
4	"Cycle lethality": this expression is written several times and not appropriate. The lethality is not from the operating cycle, which is defined as a complete set of stages of a process, carried out in a specific sequence. The lethality resulting from the application of a sterilizing agent against organisms during an operating cycle. We propose to replace **"Process lethality".**	Agreed.
5	AstraZeneca generally supports and welcomes the draft guideline and clarification regarding the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a variation application for a medicinal product.	The comment is noted.
7	Baxter International Inc. (“Baxter”) is pleased to have this opportunity to submit comments to this draft guideline on the sterilisation of the medicinal product, active substance, excipient and primary container.	The comment is noted.
8	It should be made clear at the start of the guideline whether the concepts are expected to be applied for new applications only (which is what I am expecting) or whether the guideline applies retrospectively too ... and if so, whether a period of grace is permitted for older products that might need to reconsider their sterilisation strategy.	Agreed. It is now stated that the guideline is prospective.
10	At its April 2016 meeting, the Chemistry, Pharmacy and Standards Expert Advisory Group of the Commission on Human Medicines reviewed the draft guideline.	Accepted. Further clarification has been provided with regards to the requirements for reduced terminal heat treatment (now called terminal lethal treatment) in the

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	The revision is welcome and supported. We have the following comments 1 The guideline should be reviewed to ensure that it is complementary and consistent with the revised Ph Eur 5.1.1 METHODS OF PREPARATION OF STERILE PRODUCTS and 5.1.2. BIOLOGICAL INDICATORS OF STERILISATION. 2 The Decision Trees, crucial to the guideline, should be made clearer. The text boxes relating to "reduced terminal heat treatment" are particularly unclear as to what is being recommended and why. 3 There is a concern the guideline implies aseptic manufacture of biological drug products is acceptable by default. The choice of the method of sterilisation is always, by necessity, to be taken on case-by-case, guided by the Decision Trees, and this should also apply to biological products.	text in Sections 4.1. and 5. The reference to "reduced terminal heat treatment" has been deleted from the decision trees.
12	According to EMA *Quality of medicines questions and answers: Part 1* of July 2010, GMP basic requirements for active substances used as starting materials (EU GMP guide part II) only applies to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. Sterilisation and aseptic processing of sterile active substances are not covered by this guideline and shall be performed in accordance with GMP for medicinal products (directive 2003/94/EC as interpreted in the basic requirements for medicinal products including annex 1 of EU GMP Guide part I).	Even though sterilisation is part of finished product manufacture; degradation impurities resulting from sterilisation should comply with the relevant Ph. Eur. monograph, ICH Q3A or VICH GL10, and, if applicable, ICH M7. *(Note: outcome edited for clarity 12.12.2019)*

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	Moreover, according to the EDQM guideline on *Certificates of suitability for sterile active substances* (PA/PH/Exp. CEP/T (06) 13, 1R), it should be noted that sterilisation of the active ingredient is generally regarded by the licensing authorities as part of finished product manufacture. Now, the question is whether a sterile active substance should be regarded as a drug substance or intermediate of the drug product. This question is important, since it determines whether a sterile active substance needs to comply with the Ph. Eur. monograph (or, if non-existent, the monograph from the pharmacopoeia of another EU member state or the USP) and ICH guideline Q3A (or, where applicable, VICH guideline GL10), or, whether it needs to comply with ICH guideline Q3B (or, where applicable, VICH guideline GL11). Applying the correct limits for impurities in the sterile active substance is considered critical. Since degradation may occur during the sterilization process, the impurity limits are expected to play a major role in answering the questions in the decision trees for sterilization choices. Impurity limits for drug products and their intermediates are generally wider than for drug substances. Therefore, regarding a sterile active substance as an intermediate of the drug product will likely enable the use of more effective sterilization methods. It is recommended that the EMA takes a clear stand on the nature of sterile active substances in order to ensure that the decision trees for sterilization choices are used correctly and that the best sterilization methods are used.	

Stakeholder no.	General comment	Outcome
13	EFPIA, EBE and Vaccines Europe appreciate the opportunity to comment on this new and very well prepared draft guideline. The content of the guideline and the clarification it supports are highly appreciated. We also appreciate that the guideline focuses on data for the critical quality attributes and is omitting all GMP issues in dossiers. To avoid any misunderstandings, specifically in the countries outside EU that use EU requirements, please state this fact in Executive Summary after line 44: *"This guideline only focus on submission of information on the critical quality attributes, any details on the production area, e.g. classification of rooms (A, B, C, D), sterilisation of equipment etc. fall within the field of GMP and are subject for inspection".*	Not accepted. The proposed additional text is not required. The guideline scope includes appropriate text.

13	Clarification regarding applicability is needed to ensure that required sterilisation methods will be validated and when required appropriately described in the dossier, e.g.:
	
	• What methods should be validated for their intended purpose?
	  ○ All sterilisation methods with impact on the medicinal product should be validated
	  ▪ Reference to Eudralex Vol. 4, Annex 15: Qualification and Validation
	  ○ All analytical methods used in the control strategy should be validated
	  ▪ Reference to Eudralex Vol. 4. Part I, Chapter 6: Quality Control
	• What methods fall within the field of GMP and are subject for inspections?
	  ○ All manufacturing processes
	• What methods need method descriptions included in the dossier?
	  ○ Mentioned by topic and/or in new proposed Annex I of this EMA guideline – see below
	• What methods should include validation data in the dossier?
		Clarification has been provided that the guideline only concerns the sterilisation of the drug product and product components.
		Clarification has also been provided on the validation data requested to be included in the dossier.
		The proposed annex 1 has not been adopted.

Stakeholder no.	General comment	Outcome
	○ Methods not detailed described in Ph.Eur 5.1.1. (non-standard methods) or other recognised standard referred to in this guideline • What kind of data should be included? ○ Clarified by topic and mentioned in new proposed Annex I of this EMA guideline – see below We recommend preparing examples on how it could be distributed e.g. by structuring each part of information by topic together with the narrative description or in a new proposed Annex I of this EMA guideline – see below suggestion for an Annex I.  Annex I.doc	
13	We recommend use of a risk-based approach with respect to the test conditions; specifically for sterile filtration and the testing limits for bioburden prior to sterile filtration	Bioburden limits prior to sterilisation should be comply with those specified in the guideline, as these are well-established, practical and achievable, unless otherwise justified. Risk based approaches are not prohibited by this guideline, and may be appropriate, on a case by case basis.
13	We recommend that the wording in the new proposed Annex I is used when corrections are made to the narrative guideline text; preferably reference should be made instead of having redundant text in the narrative description and the Annex I.  Annex I.doc	The proposed Annex 1 is not necessary.
13	It is EFPIA's, EBE's and Vaccines Europe's understanding that the guidance applies to new marketing authorisation applications and variation applications where there are changes in the methods	The guideline is prospective and will not affect existing products unless a variation application is submitted concerning any issue related to the guideline.

Stakeholder no.	General comment	Outcome
	described. Retrospective application of the guideline (renewals) will not be recommended.	
17	For generic developments and to reflect the state of the art it would be helpful if EMA generate a list of products where for example • terminal sterilisation is mandatory • aseptic processing may be acceptable	Not accepted. Each product should be developed based on their own properties.
18	IFAH-Europe welcomes the opportunity to comment on this guideline. However we would like to highlight some points of high concern. This draft guideline seems to have deviated from the aim described in the EMA/CHMP/CVMP/QWP/128000/2014 concept paper. There it was stated that the human guideline on development pharmaceutics should be withdrawn and a new one to be developed combining the decision trees for human and veterinary products. The basis for that was that for the human pharmaceutical products the ICH Q8 covers all the requirements on development pharmaceutics. However, ICH Q8 does not detail in depth sterilisation. This new draft guideline now combines human and veterinary pharmaceutical requirements on sterilisation specifically although it is not stated that the EMEA/CVMP/315/98 will be withdrawn. This seems confusing and contradictory.	In the Concept paper it is stated that the human Note for Guidance (NfG) on development pharmaceutics is deleted since its information has been revised in other guidelines. The main reason for keeping the guideline active this long is that its Annex has been relevant. The veterinary main NfG on development pharmaceutics will remain since ICH Q8 is not applicable for veterinary products. It is also stated that the human and veterinary annexes to the NfG on development pharmaceutics are combined in a new guideline and the text on sterilisation provided in the human NfG on the manufacture of the dosage form is revised and transferred into this new guideline. This is reflected in the proposed new guideline.
18	Biological products have been introduced in the scope of this document whereas it is recognised in section 1 – Introduction - that biological products are very sensitive to terminal sterilisation and therefore this method of sterilisation is not possible for this category of products. This is creating much ambiguity. IFAH-Europe would recommend adopting the same approach as for the immunologicals and clarifying this document by removing the biological products	Terminal sterilisation may rarely be applicable for biological products. Also, the guideline provides information on sterile filtration and aseptic processes which is relevant for biological products.

Stakeholder no.	General comment	Outcome
	from the scope of this document. Please also refer to specific comments section below.	
18	This draft guidance really gives the impression to discredit the practice of sterilising filtration/aseptic filling. Even if it is admitted that terminal sterilisation methods in the final packaging are generally preferable as they offer more guarantees on sterility, suitable sterility assurance levels are obtained with sterilisation by filtration. It is wondered why so high risk is associated with this sterilisation method in this guideline whereas the industry has gained expertise in this technique years after years. The vast majority (ratio is about 80 %!) of the methods of sterilisation used by the veterinary industry are non-terminal sterilisation methods. When evaluated during more and more demanding GMP inspections, they are approved and pass the inspection successfully. The veterinary practice specificity (large packaging/volume, specific veterinary excipients...) and the need to develop adapted products need to be better taken into account in establishing the benefit/risk approach used to draft this common human/vet guidance. As it is written and presented, the section 4.3, questions the aim of developing a drug product: indeed, up to now, the aim is to develop a stable formulation adapted to the treatment of a given pathology, focused on species, adapted to users; now this guideline asks to develop a formulation to be terminal-sterilised by sacrificing stability, shelf-life, storage conditions, packaging innovation and specificity to veterinary use. As an additional consequence, applying this guideline to existing products would have a dramatic impact on the industry activity. The additional requirements brought by this guideline will dramatically impact the development of medicinal products; put a brake on innovation and thus veterinary medicine availability.	The request to include considerations on the sterilisation method during the development of the drug product is not new (the veterinary guideline on Manufacture of the finished dosage form states According to the text of the Ph. Eur.: "Methods of preparation of sterile products", terminal sterilisation in the final container is to be preferred. Refraining from terminal sterilisation in the final container should be justified in the application file). This guideline is primarily providing more detailed information on the justification requested. Also, during the inspections it is not scrutinised whether a specific product should be terminally sterilised or if it may be produced using aseptic processes. The guideline is intended for new products and for variation applications related to the sterilisation method for existing products.

Stakeholder no.	General comment	Outcome
21	Medicines for Europe welcomes the draft EMA guideline on the sterilisation of the medicinal product, active substance and primary container and the guidance that it gives on the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a variation application and the selection of appropriate methods. Understanding that the scope of the draft guideline extends to both originator and off-patent medicines, it is important to discuss the impact of the guideline implementation. Medicines for Europe members support the advances in technology and science and as such, the continuous update of guidelines and the implementation of new and improved processes with a view to enhance public health. Taking the example of a medicine including a chemical active substance, it often occurs that the originator medicine is manufactured using aseptic filtration and that in a majority of cases, so will the generic medicines. There are practical reasons to this: the final choice of a formulation in the generic medicine's development can be linked to an important manufacturing step such as the sterilisation step. In turn, formulation plays an important role in the post-authorisation phase and particularly on the substitutability of the generic medicines in some markets and the shelf life which then translates, or not, into an opportunity in terms of access to treatment. This obviously concerns sterile medicines for which there is already a generic medicine available but also for which a generic medicine is or will shortly be under development.	Each product should be developed based on their own properties and those requirements in place at the time of submission. Reduced terminal treatment (now called terminal heat treatment) is not a new concept, it has been described in Ph. Eur. 5.1.1 for an extensive period of time.

Stakeholder no.	General comment	Outcome
	Consequently, and with a view to foster a pragmatic and effective use of resources to maximise public health benefits, Medicines for Europe recommends that the guideline should not mandate the use of terminal sterilisation (including the new concept of "reduced terminal heat treatment") for generic medicinal products where the originator is not manufactured using such process. This prospective approach will allow, overtime, the implementation of new approaches to sterilisation for all medicines.	
21	This guideline does not include other sterilisation methods used in the aseptic process such as Vapour Hydrogen Peroxide (VHP) used for sanitation of the filling isolators leading to aseptic processing. Proposed change: Please consider including other sterilisation methods used in the aseptic process.	Sanitation of equipment is not included in the scope of this guideline. Other principles of sterilisation are not excluded even if not described.
22	Needs further proof read to allow for consistency throughout (e.g. With the word "Section", either keep as uppercase or lowercase but be consistent. Same comment for micro-organism vs microorganism for example)	Agreed.
22	Need reviewed to remove unnecessary comments etc. (e.g. Line 49, page 3 "...the integrity of the container closure system, (abbreviated as..."). Comma needs removed.	Agreed

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
7	4	Comment: Aseptic processing is not a sterilization method thus the title shall be modified Proposed change: Guideline on the sterilization **and microbial reduction process** of the medicinal product, active substance, excipient and primary container	Not accepted. The title is high level and sufficiently describes the content of the guideline.
13	18	**Comment:** It is understood that the Annex "decision trees for the selection of sterilisation methods" (EMEA/CVMP/065/99) will no longer exist. However, for the IVMPs no guidance will be available then, except the Ph. Eur. relevant monographs. Furthermore, IVMPs are not really in the scope of the EMEA/CVMP/315/98. Please see also comment below (line 67). Without proper guidance excessive data could be required by the NCAs, both for new product applications and for variations. This could hinder the development of new IVMPs.	Partly accepted. The CVMP and IWP considered that the existing quality and GMP regulatory requirements are adequate at the current time to ensure the sterility of such products. However, the immunological products are not prohibited to apply relevant aspects of this guideline.
33-36	1	Comment: This guideline should be applicable to both, drug products, and drug substances. Reference to API should be included here. Regarding the term Quality Dossier – this needs further clarification i.e. regarding the drug substance since this can be presented in the application by a CEP, ASMF. Also sterile information of packaging material can be related to sterile drug substance	Not accepted. Sterilisation of active substances is in the scope of the guideline and is part of finished product manufacture. The term Quality Dossier is sufficiently descriptive.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
33-36	14	Comment: There is no need for re-assessment of already assessed and accepted sterilisation processes for existing MAs. Therefore, the guideline should apply to new or fundamentally revised processes. Proposed change: This guideline provides guidance on the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a relevant variation application for a medicinal product, (called quality dossier throughout the guideline), and the selection of appropriate methods of sterilisation for sterile products when the relevant production process is new or when the production process is fundamentally revised.	Partly Accepted Guideline now states that it is for new applications and variations. It will not affect existing products unless a variation application is submitted concerning any issue related to the guideline.
33-40	16	Comment: All previous sterilisation processes for existing marketing authorisations and processes have been validated, risk-based assessed and accepted by the authorities. A reassessment of all sterilisation processes of all drug substances, excipients, drug products and primary containers will not increase the microbiological safety nor is it possible for both, industry and authorities, to reevaluate the sterilisation processes. Please rework paragraph	Partly Accepted Guideline now states that it is for new applications and variations. It will not affect existing products unless a variation application is submitted concerning any issue related to the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: This guideline provides guidance on the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a relevant variation application for a medicinal product, (called quality dossier throughout the guideline), and the selection of appropriate methods of sterilisation for sterile products when the relevant production process is new or when the production process is revised fundamentally. 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.	
34	18	**Comment:** The GL should not impact existing registered products, whatever their sterilisation process. Only changes of the sterilisation method for existing product would be into the scope of this guidance. **Proposed change:** The sentence should be changed to read"…or variation application **to change the sterilisation method** for a medicinal product…"	Partly Accepted Guideline now states that it is for new applications and variations. It will not affect existing products unless a variation application is submitted concerning any issue related to the guideline.
34	18	**Comment:** Based on the spirit of the proposed GL, it should not be applied to products which were not	Partly Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		developed with the first aim to pass a terminal sterilisation. This is also a question in case of generic. **Proposed change:** please refer to the scope, line 67.	Guideline now states that it is for new applications and variations. It will not affect existing products unless a variation application is submitted concerning any issue related to the guideline. Each product should be developed based on their own properties and those requirements in place at the time of submission.
36	4	Comment: Different terms in this guideline will need to refer to their definition in §6, and e.g. reference condition of the European Pharmacopoeia Proposed change: ...using reference condition **(see 6. Definitions)** of the European Pharmacopoeia...	Partly accepted. Additional definitions have been added, and the guideline has been scrutinised for consistence. A general reference to the table of definitions is included in the text.
39, 106, 328 – 333, 381, 385, glossary,	3	Comment: This introduces the use of an undefined "terminal microbial reduction' process. It would be preferable to expand the use of terminal sterilization to conditions where the bioburden can be reproducibly destroyed. A terminal sterilization process is understood as one that inactivates the bioburden present to a SAL of≤ 10^{-6}. Cycles that follow aseptic processing may not require the same time-temperature conditions as those performed without preceding aseptic fill to achieve the required SAL. In PDA's experience, these are still effective and safe sterilization processes. Proposed change: Replace 'terminal microbial reduction' with 'post aseptic processing lethal	Partly accepted. A redefinition of steam sterilisation is not possible as an F0 of not less than 8 minutes for Stem sterilisation is required in Ph. Eur. However, the concept of "terminal microbial reduction" has been rephrased to post-aseptic processing terminal heat treatment and further clarified and defined allowing lower temperature and F0 in combination with previous aseptic filling.

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		treatment' throughout the document. Add to glossary with the following definition: the application of a terminal treatment (e.g., heat or other technology) capable of inactivating specified microorganisms. For example, this treatment could range from the application of a mild treatment that is capable of inactivating only vegetative organisms through application of classical sterilization treatment which is capable inactivating all heat resistant spores while supporting a 10^{-6} SAL	
45-47	1	Comment: '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.' Proposed change (if any): 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.	Partly accepted. The test is revised and does not mention "medicinal product"
46-47	15	Comment: The current text states, *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*. We agree with this statement; however, further clarification is required – the manufacturing process should be 'suitably designed, validated and controlled', rather than just 'validated'.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: Sterility of the medicinal product cannot be assured by testing, it needs to be assured by the use of a suitably designed, validated and controlled manufacturing process.	
46-48	16	Comment: Please rework this paragraph Proposed change: Sterility is a critical quality attribute for all sterile products. Sterility of the medicinal product cannot be assured by testing alone, it needs to be assured by the use of a suitable and validated manufacturing process.	Partly accepted. See comment on lines 46-47 by stakeholder 15.
48	1	Comment: 'Formulation components' refers predominantly to drug products. Proposed change (if any): components used for manufacturing	Partly accepted. The text has been revised to more suitably describe also the sterilisation of substances and containers.
48	4	Comment: "bioburden" could be more detailed. Proposed change (if any): Sterility is dependent on several factors **such as the bioburden of the raw and starting material**, the formulation components, the sterilisation procedure, the integrity of the container closure system,	Partly accepted. A definition of bioburden has been added to Chapter 6. See also comment on lines 46-47 by stakeholder 15.
48	10	Comment: "Sterility is dependent on several factors……" Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Sterility is achieved by controlling several factors ……"	
48-50	4	Comment: All the factors are not listed. Then it could be specified "for example" Proposed change: ...several factors such **as e.g.** the bioburden of the formulation...	Not accepted. The phrase "such as" is considered equivalent to e.g.
48-51	15	Comment: The current text states, *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*. Assurance of sterility for aseptically processed product extends beyond satisfactory aseptic technique. It also requires suitable design and control of the aseptic processing environment, process simulation, the application of suitable in-process controls during manufacture, and testing to demonstrate achievement of aseptic processing conditions. Proposed change - change existing text to: 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	Not accepted. It is agreed that only parts of the aseptic concept is described in the text. The text is however provided to clarify the difference in sterility assurance between terminally sterilised products and aseptically sterilised product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		document), and in the case of aseptic processing, the use of a suitably designed and controlled aseptic processing environment, process simulation, the application of suitable in-process controls during manufacture, and testing to demonstrate achievement of aseptic processing conditions.	
51	1	Comment: ICH Q8 refers to 1. containers only in context of drug products, please clarify 2. to new drug products only. What about legacy products/APIs? Please clarify.	Partly accepted. A clarification is provided. The guideline is intended to be used prospectively.
53	13	Comment: Sterile filtration, which according Ph.Eur. 5.1.1 is an accepted method for sterilisation, is missing here. Please include. Aseptic processing refers to maintaining the sterility of a product (covers API, drug product, excipient, and packaging) which has been sterilised by one of the accepted sterilisation methods (Ph.Eur. 5.1.1). A sterile filtration process performed in line with Eudralex Vol. 4, Annex 1: Manufacture of Sterile Medicinal Product, can also be validated and controlled. Proposed change: Terminal sterilisation is preferred to sterilisation by filtration **followed by aseptic**	Not accepted. Aseptic processing may be performed without sterile filtration, hence "and/or". The focus of the text is the additional risk with aseptic processing, thus the text proposed to be deleted is considered important.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		processing due to the lower risk for contamination that will be applied to the product e.g. accidental contamination caused by inadequate technique. ~~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, **filtration and** aseptic processing under controlled conditions provides a satisfactory quality of the drug product.	
53	15	Comment: The current text states, *Terminal sterilization is preferred to sterilization by filtration and/or aseptic processing because it …..* Sterilised, single-use, integral closed systems are available where formulated bulk, e.g. cell-based health care product, is sterile filtered directly into a collection bag that is then sealed closed prior to detachment from the system. This collection bag could be the container in which a finished product might be supplied. The current definition of terminal sterilisation is *sterilisation of a product in its primary container*. Would the scenario described above constitute terminal sterilization, given that the current definition does not delineate between microbicidal and	Not accepted. The description is sterile filtration and filling via a closed system which is preferred to an open system, but it is not terminal sterilisation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		non-microbicidal sterilisation processes? If so, then the current text, *Terminal sterilization is preferred to sterilization by filtration* …. might need to be reworded. Proposed change: Consider if the scenario described above constitutes terminal sterilization. If so, then consider rewording the current text along the lines of: Terminal sterilisation of product by a microbicidal process is preferred to sterilization by filtration and/or aseptic processing because it …..	
53-54	18	**Comment:** SAL notion is understandable when referring to the standard Ph. Eur conditions (autoclave 120°C/15 min; ionising radiation ≥ 25kGy). The evidence of superiority of non-standard Ph. Eur conditions (for ex: ionising radiation below 25 kGy based on an ISO norm (adapted for medical device only) or heat below 160°C/120min in comparison of a long-term experience of sterilising filtration seems to be more questionable for the sterilisation of a finished product. Same question in term of risk assessment and risk management.	Not accepted. For non-standard processes the validation demonstrating a suitable SAL should be described in the dossier allowing the assessment of the suitability of the process. For aseptic processes, there is always the risk of inadequate technique present.
53 – 55	6	Comment: Sterility assurance level of a terminal sterilisation cycle is defined by the bioburden and the heat resistance of a bioindicator in the product matrix. Safety margin is calculated comparing the resistance of the bioindicator used for validation purpose	Not accepted. For terminal sterilisation the SAL can be calculated, validated and controlled, whereas there is no possibility to validate and control inadequate technique in relation to aseptic processes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		compared to the actual bioburden and the actual resistance of bioburden found in the product. Proposed change (if any): Safety margin can be designed in the terminal sterility process, and draft guideline should explain the concept of safety margin and the relation to SAL.	The safety margin is in the SAL definition of sterilisation: the probability of not more than 1 non-sterile item in 1×10^6 sterilised items of the final product.
53 - 60	10	Comment: Terminal sterilisation is lethal to all microbiological organisms and this is another important reason for preference over sterilisation by filtration. Proposed change: 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. Additional TEXT to be included: In addition, terminal sterilisation is lethal to all microorganisms, whereas sterilisation by filtration removes bacteria only. Therefore, terminal sterilisation provides the highest assurance of sterility and should be used whenever possible.	Partly accepted. Slightly rephrased.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
53-60	15	Comment: The current text states, *Terminal sterilization is preferred to sterilization 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*. SAL is the probability of *a single* microorganism surviving on an item after exposure to a microbicidal sterilization process. It is a mathematical extrapolation and the survival of a single microorganism on an item cannot be demonstrated in practice. As the current text points out, SAL is not applicable to aseptic processing; however, the reason given in the current text, i.e. *as accidental contamination caused by inadequate technique cannot be reliably eliminated by monitoring, control or validation*, is not entirely correct. A non-sterile item can have one or more than one viable microorganism present. Microbial inactivation kinetics enable the reduction in the number of surviving microorganisms after exposure to a terminal sterilization process treatment to be extrapolated to determine the level of treatment required to achieve the probability of survival of a single microorganism. Aseptic processing is not based on known or	Partly accepted. The text in the final guideline has been updated and is considered to be sufficient and clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		predictable microbial inactivation kinetics but relies on a series of independent factors that are validated and controlled to prevent contamination of previously sterilised materials, components, formulated bulk etc. during filling of product into a final container. An aseptic manufacturing process is qualified by process simulation with the number of units contaminated used to estimate the contamination rate. A unit contaminated during aseptic processing might be contaminated with more than a single microbial cell. Proposed change - change existing text to: A non-sterile item can have one or more than one viable microorganisms present. SAL is defined as the probability of a single microorganism surviving on an item after exposure to a microbicidal sterilization process. Microbial inactivation kinetics enable the reduction in the number of surviving microorganisms after exposure to a terminal sterilization process to be extrapolated to determine the level of treatment required to achieve the probability of survival of a single microorganism. Aseptic processing is not based on known or predictable microbial inactivation kinetics but relies on a series of independent factors that are validated and controlled to prevent contamination of previously sterilised materials, components, formulated bulk etc. during filling of product into a final container. An aseptic manufacturing process is qualified by process simulation with the number of units contaminated used to estimate the contamination rate. A unit contaminated during aseptic processing might be contaminated with more than one microbial cell. Terminal sterilization is preferred to sterilization by filtration and/or aseptic processing because it provides a sterility assurance	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level (SAL) that is possible to calculate, validate and control, and thus incorporates a safety margin.	
54	4	Comment: SAL could be calculate by deduction through a mathematical extrapolation of the kinetic of SLR (spore log reduction) but is neither controllable nor validatable. Only demonstration of the calculation is validatable. Proposed change: ...provides a sterility assurance level (SAL) **for which only the demonstration of the mathematical extrapolation calculation is validatable** and thus...	Not accepted. The text in the revised guideline is considered to be sufficient and clearer.
55ff	1	Comment: Sterile filtration, which according Ph.Eur. 5.1.1 is an accepted method for sterilisation, is missing here'. Please include. Aseptic processing refers to maintaining the sterility of a product (covers API, drug product, excipient, packaging) which has been sterilised by one of the accepted sterilisation methods (Ph.Eur. 5.1.1). A sterile filtration process performed in line with GMP Annex 1 can also be validated and controlled. Regarding an 'assurance level on sterility' from sterile filtration: **Log Reduction** shows the potential of the sterilization method using 0.2 µm sterilizing grade filters. Bacterial challenge test is based on a reduction of bacteria and should therefore also allow a rationale or statistic on CFUs being removed.	Not accepted. It is agreed that the log reduction in a sterile filtration process may be established, however, sterile filtration is followed by an aseptic process. Thus the current text and decision trees are satisfactory in this regard.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Hence there should be a possibility for define a suitable factor and sterilization by filtration should be valorized. Please note that the defined Validation requirements simulate conditions which are far away from realistic conditions in manufacturing. And also well controlled and validated sterile filtration performed under in line with GMP requirements is successfully applied for decades for a variety of products	
55	4	Comment: The expression "incorporates a safety margin" looks like inappropriate because without comments, this sentence leaves to believe that a SAL 10^{-6} has a safety margin regarding sterility assurance. The idea is understandable but in term of definition and legally, there is no sterility if 10^{-6} is not achieved or with SAL greater than 10^{-6} (e.g. 10^{-5}). A safety margin would achieve 10^{-7} or 10^{-9} at the end of the sterilization cycle even if it formally declares a Probability of Survival of a Single Microorganism (PSSM) of 10^{-6}. Proposed change: …and thus **offer possibility to determine a Probability of Survival of a Single Microorganism (PSSM) and to incorporate a safety a margin with SAL less than 10^{-6} (e.g. 10^{-7} or 10^{-9}).**	Partly accepted. The text has been further elaborated to increase readability.
55-56	4	Comment: SAL cannot be calculated for the product aseptically manufactured. SAL is applicable for	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterilization processes (autoclave sterilization of filling parts, for example) used in aseptic manufacturing. For aseptic process only a Probability (to find) of a Non Sterile Unit (PNSU) after a simulation test could be determined. Proposed change: Please to replace SAL by **PNSU**	The text intended to clarify the risk for accidental contamination using aseptic process compared to terminal sterilisation. The revised guideline clearly distinguishes between terminal sterilisation processes and aseptic manufacturing processes.
57	4	Comment: ...validation. The results of the aseptic process are expressed as a PNSU found among a determined quantity of items. Both the different nature of the 2 probabilities PSSM and PNSU represent different concepts and are not comparable. Proposed change: ...validation. **The results of the aseptic process are expressed as a PNSU deduced after finding a determined quantity of non-compliant items. Both the 2 terms of different nature, called "probabilities" PSSM and PNSU represent different concepts and cannot be compared.**	Not accepted. The text intended to clarify the risk for accidental contamination using aseptic process compared to terminal sterilisation.
57	4	Comment: Strictly the Assurance of the sterility is a qualitative concept, so not high or low, but only best or worst with superlative form. Proposed change: ... provides the **best** assurance of sterility and ...	Not accepted. Highest assurance is acceptable English language.
58-60	1	Comment:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1. Clarification regarding 'products' is required (API, excipient drug product, ..). 2. Sterile filtration is not equal to aseptic processing. Aseptic processing is not a sterilisation method. Proposed change (if any): 'For highly sensitive products such as biological 1products where terminal sterilisation of the ~~drug~~ product is not possible, ~~aseptic processing~~ sterile filtration under controlled conditions provides a satisfactory quality of the ~~drug~~ product.'	The text in the body of the guideline is clear. 1. Clarification has been provided. 2. A clarification regarding the choice to describe either or both "sterile filtration" and "aseptic processing" in different sections in the dossier has been clarified. In this context aseptic processing is described since this step provides the higher risk.
58- 60 and 377 – 379	10	Comment: There is a concern the guideline implies that aseptic manufacture of biological drug products is accepted by default. The case by case approach and use of the Decision Trees are also appropriate for biologics. Proposed change: Change 58-60 to: For all drug products, the sterilisation method should be chosen on a case-by-case basis, guided by the Decision Trees in Section 5. For highly heat-sensitive products, where terminal sterilisation of the drug product is generally not possible, e.g. some biological products, aseptic processing under controlled conditions would be accepted as providing satisfactory quality of the drug product.	Not accepted. Clear guidance is provided where aseptic processing can and cannot be accepted is provided. The text describes that where necessary (sterile filtration and) aseptic processing provides sterile products of satisfactory quality also without terminal sterilisation. The text in the guideline is sufficiently clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Change Lines 377 – 379 to: The decision trees have been elaborated for all products, but alternative approaches may be appropriate e.g. for biological products.	
58-60	15	Comment: The current text states, *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*. This section of the document is referring specifically to assurance of sterility rather than to 'quality' in general. 'Quality' of a sterile product is wider than assurance of sterility. Replace 'quality' with the specific term, 'assurance of sterility'. Proposed change - change existing text to: For highly sensitive products such as biological products where terminal sterilisation of the drug product is not possible, assurance of sterility is achieved via aseptic processing under validated and controlled conditions.	Partly accepted. The sentence has been rephrased,
66-67	1	Comment: Besides the drug products (human of veterinary) additionally API, excipient and packaging material need to be included in the scope – see also title	Accepted. In the Scope it is already stated that the GL applies also for sterile APIs, sterile excipients and sterile primary containers.
66-67	2	This information seems not correct and the sentence should be reconsidered. It would be expected that the guideline is in general applicable to immunological veterinary medicinal products but not applicable to	Not accepted. The GL is not applicable for immunological veterinary medicinal products. Furthermore the guideline only refers to sterile products. Non-sterile products are not covered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		some immunological veterinary medicinal products (e.g. administered orally or as an aerosol). (Experts regarding immunological veterinary medicinal products should be consulted).	
66 - 67	6	Comment: Exclusion of immunological veterinary medicinal products should be explained.	Partly accepted. The CVMP and IWP considered that the existing quality and GMP regulatory requirements are adequate at the current time to ensure the sterility of such products. However, the immunological products are not prohibited to apply relevant aspects of this guideline.
66-67	13	Comments: Current text that describes the applicability of the guideline needs clarification to ensure that all required sterilisation methods will be appropriately described in the dossier. Proposed change: The guideline applies to chemical and biological medicinal products for human and veterinary use. **This includes the methods used for sterilising the components and/or the final medicinal products.** The guideline is not applicable for immunological veterinary medicinal products.	Not accepted. The clarification is already included in the scope.
69-70	1	Comment: Please clarify what is expected for legacy/ existing sterile APIs. (i.e. development data are limited,	Accepted. It is described under "Executive summary" that the GL applies to new marketing authorisation applications or variation applications for a medicinal product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		applied sterilisation method is established and working for years),	It is not retrospectively applicable to existing medicinal products.
66-67	18	**Comment:** Comments done for line 34 should also be repeated into the section 2 "scope" **Proposed change:** Please change the lines 66-67 to read: "The guideline applies to **new** chemical and biological medicinal products for human and veterinary use, but is not applicable for immunological veterinary medicinal products. **It also applies in case of change of the sterilisation method of existing medicinal products. This guideline is not applicable for existing products and or in development at the date of publication of the GL."** Please also add the definition of "immunological veterinary products"	Partly accepted. The GL applies to new marketing authorisation applications or variation applications for a medicinal product. It is sufficient that this aspect is mentioned under "Executive summary".
67	18	**Comment:** It is unclear why human and Vet biological products, equally highly sensitive to terminal sterilisation (specifically mentioned at line 58), are not excluded from the scope whereas immunological veterinary products are out of the scope of this guideline. Recent experiences during procedures show that much more details are now asked, e.g. about sterilisation of the primary packaging of IVMPs, and it seems this is based on this draft guideline. It is also unclear whether so-called borderline products are or not in the scope of this guideline.	Partly accepted. The CVMP and IWP considered that the existing quality and GMP regulatory requirements are adequate at the current time to ensure the sterility of such products. However, the immunological products are not prohibited to apply relevant aspects of this guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
69 – 71 103	6	Proposed change: Sterile bulk manufacturing should be included in the scope of the guideline.	Not accepted. Sterile bulk manufacture is already included in the scope, since the bulk sterilisation process is considered to be part of the manufacture of the medicinal product.
72	3	Comment: The GMP certificate for API is not mandatory in Europe. See also comments to line 286-301. Proposed Change: 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.	Not accepted. A GMP certificate is mandatory for the sterilisation process in the manufacture of sterile active substances, regardless by whom the sterilisation process is performed, since the sterilisation process is considered to be a part of the manufacture of the medicinal product.
72-73	1	Comment: This approach is greatly appreciated: Please clarify/specify what is considered as General GMP; i.e.: Media fill and environmental monitoring are covered by GMP but are often demanded by Authorities. Please confirm that the expected information for sterile APIs, the API, is in line with CHMP/QWP/227/02 Rev 3/Corr * and EMEA/CVMP/134/02 Rev 3/Corr *	The comment is noted. It is agreed to include examples for general GMP requirements (e.g. environmental monitoring, sterilisation of manufacturing equipment). Request for media fill results is not meant here. As already stated under section 4.1.6 "Aseptic treatment" it may be possible to request for media fill results in special cases. Under section 4.1 it is mentioned in which part of the Module 3 the sterilisation of the API should be described.
74-75	1	Comment: Conditions for sterile filtration are also referenced in Ph. Eur. 5.1.1. – please include	Not accepted. The addition of a reference to Ph. Eur. 5.1.1 in relation to sterile filtration would add very limited information.
74-76	3	Comment: Restricting terminal sterilization to the conditions listed in Ph. Eur 5.1.1 is overly restrictive and actually precludes the expanded use of terminal	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterilization which is the clear preference of EMA (see Lines 57 and 58). A simplification of the sentence maintains the intent of expanding the use of terminal sterilization by removing the artificial constraints that are imposed. Proposed change: Terminal sterilisation by heat and ionising irradiation to achieve an SAL of $\leq 10^{-6}$, sterilisation by filtration and aseptic processing are considered.	The guideline decision trees clearly lay out the expectations for selection of sterilisation methods, which are fully in line with Ph. Eur. 5.1.1.
74-76	16	Comment: Please rework this paragraph Proposed change: Terminal sterilisation by heat and/ or 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.	Not accepted. The scope covers both heat sterilisation and ionisation radiation, the word "or" is not relevant. However, the term "heat sterilisation" has been reworded in "steam and dry heat sterilisation" to clarify what is meant here with "heat sterilisation".
74 - 76	22	Comment: Terminal sterilisation by heat and ionising irradiation, using the reference conditions of Ph. Eur. 5.1.1 74 "Methods of preparation of sterile products" or other conditions to achieve a SAL of $\leq 10^{-6}$, sterilisation 75 by filtration and aseptic processing are considered. Proposed change: The scope of this document covers terminal sterilisation by heat and ionising irradiation, using the reference conditions of Ph. Eur. 5.1.1 74 "Methods of preparation of sterile products" or other	Comment noted. The paragraph has been restructured.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		conditions to achieve a SAL of ≤10^{-6}. Sterilisation by filtration and aseptic processing are also considered. This change is proposed to simplify the sentence which is too long and difficult to understand.	
78-80	4	Comment: There is no mention of endotoxin removal or depyrogenation requirements in the scope. Should this be mentioned in these lines? This is especially relevant for primary product contact surfaces and container / closure. Moreover, endotoxins can affect the stability of biological products. Proposed change: …are not considered. **Endotoxin level should be considered.**	Accepted. The phrasing has been changed as follows: "The concepts in this guideline refer only to absence or removal of bacteria, fungi and bacterial endotoxins."
78-80	4	Comment: There is an important problem of consistency between these lines and the adequate terminology for sterilization health care products. Everywhere in the document the key words are microorganism sterilization and sterility. We needed long time to harmonize the language with international definitions. It would be a pity and a sanitary risk to introduce confusion with other definitions. Microorganism encompass all small organisms, living like microbes, or not, like viruses. This definition, may be not perfect, for more than 15 years helps to build a consistent terminology in the sterilization activities worldwide. What would become a definition like sterile: exempt of viable	Not accepted. The terminology has been chosen based on terminology of Ph. Eur. and Annex I of GMP guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		microorganism ? Sterile excludes yet viruses, mycoplasma and others !! Proposed change: The concepts in the guideline refer **to sterilization methods verified only by the absence of microorganism, either entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses.** Other adventitious or non-conventional agents, which could contaminate a product, are not considered.	
78-80	10	Comment: This statement is not supported. Proposed change: Include relevant text and / or appropriate cross-references to other guidance addressing the removal of viruses, mycoplasma and other adventitious agents.	Accepted. Reference to Note for Guidance on virus validation studies (CPMP/BWP/268/95) has been included.
79	13	Comment: Unclear why mycoplasma is excluded from the guideline. Mycoplasma is bacteria sensitive to steam sterilisation. Proposed change: The absence, removal or inactivation of viruses~~, mycoplasma~~ and other adventitious agents, which could contaminate a product, are not considered.	Not accepted. The guideline allows sterilisation methods where sterilisation with regards to mycoplasma may not have been satisfactorily demonstrated.
83	26	A comma should be added before "Directive 2001/82/EC …": "This guideline should be read in conjunction with Directive 2001/83/EC on the community code relating	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to medicinal products for human use, Directive 2001/82/EC on medicinal products for veterinary use as amended and also the current Ph. Eur.	
85 – 87	6	Comment: The reference to EMA website is very general and should include more specific EMA documents linked to sterilisation and container closure system.	Not accepted. Reference to specific documents is not feasible since this would need to unnecessary revisions of the guideline.
89	4	Comment: According to line 42-44, it could be consistent to add sterilization methods. Proposed change: … relating to sterility, **sterilization process** and methods and sterile products	Accepted.
89-91	1	Comment: paragraph refers only to drug products. APIs, excipients and if applicable Packaging materials should also be included in this introductory sentence.	Accepted. The Section 4.1. is renamed as "Requirements for the manufacture of sterile medicinal products and sterile components"
93-96	5	Comment: There is no corresponding section concerning the location of sterilisation and aseptic processing information for active substances & excipients. This could result in applicants & assessors incorrectly assuming that all information concerning sterilisation should be included in 3.2.P.2 & 3.2.P.3.3 Proposed change: Rename section 4.2 as 'Manufacturing of sterile active substances and sterile excipients'. This section can then be updated to	Accepted. The Section 4.1 is renamed as "Requirements for the manufacture of sterile medicinal products and sterile components".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		include guidance concerning both GMP & where to include info in Module 3.	
93-98	1	Comment: In this paragraph it is only referred to the medicinal product sterilisation and aseptic processing – please confirm	Please see the comment above
96 - 98	7	Comment: Gamma irradiation is typically subcontracted. Gamma processing facilities are not considered pharmaceutical companies in the country where they are located. They are not controlled by the Ministry of Health, but by other regulated authorities. Gamma processing facilities therefore do not have a Qualified Professional in residence. This may cause difficulty demonstrating "Pharmaceutical Manufacturing" site for 3.2.P.3 with some health authorities. When subcontracted, the finished drug product manufacturer may remain responsible for all quality aspects including validation of the gamma irradiation process (i.e., the drug product manufacturer validates the process for the subcontractor) and that the subcontractor's responsibility is to execute the validated process. Proposed change: Current: "The documentation should be provided for all sites performing sterilization or aseptic processing related to the medicinal product,	Not accepted. It is not in scope of the guideline to explain the responsibility in case of outsourced activities. Information on sterilisation site, sterilisation method, in-process controls and validation is expected for all sterile substances, containers and drug products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		regardless of whether the processes are performed in-house or outsourced". Proposed: "The documentation should be provided for all sites performing sterilization or aseptic processing related to the medicinal product, regardless of whether the processes are performed in-house or outsourced. When sterilisation is outsourced the finished drug product manufacturer may remain responsible for all quality aspects including validation of the process (i.e. that the drug product manufacturer validate the process for the subcontractor) and that the subcontractor's responsibility is to execute the validated process. In this case the subcontractor should not be considered as a pharmaceutical company."	
99-100	1	Comment: Please specify to what extent justification for legacy product is required and what would be acceptable.	Accepted. Further clarification that the guideline is relevant for a **new** marketing authorisation application or a variation application for a medicinal product has been added.
103-104	2	Comment: At this moment information regarding sterilisation procedures of excipients and primary containers is not systematically included in Module 3. Proposed change: This inclusion is agreed but should be flagged to all stakeholders (including assessors).	Not accepted. The issue is ensured by publication of this guideline.
103-104	15	Comment: The current text states, *All sterilisation procedures for the active substance, the excipient(s)*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		or the primary containers should be described and the name and address of the site responsible should be stated. The sterilisation process for the finished product should also be described and the sites responsible for sterilisation identified. Proposed change - change existing text to: All sterilisation procedures for the active substance, the excipient(s), the primary containers and the finished drug product should be described and the name and address of the site responsible should be stated.	
103-105	1	Comment: Contradictory to lines 93-98 and as well to CHMP/QWP/227/02 Rev 3/Corr * and EMEA/CVMP/134/02 Rev 3/Corr * Documentation on the manufacturing and packaging of sterile API is to be part of 3.2.S (see also line 72-73). For use of sterile API in drug product manufacturing according to lines 93-98 aspect processing need to be described. Please note demanded suitable control of the quality is possible by GMP-certificates and the prerequisite audit of the manufacturer allows allowing the (MA) Applicant to take full responsibility for the quality and quality control of the active substance.	Partly accepted. The guideline has been revised to state the site performing the sterilisation. Further clarification is provided on where in the CTD structure the documentation should be provided. The requested documentation is considered essential for the assessment of the application.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
103 - 123	6	Comment: Bioburden is influenced significantly by the nature and / or origin, isolation or manufacturing of the starting material. Proposed change: High bioburden limits should not **only** be justified by the capacity of the sterilization process or any bioburden reducing step before sterilisation.	Not accepted. Higher bioburden of the components could be accepted where justified as described in lines 112 – 117. Lines 122-123 states that the filter capacity is not accepted (as the only justification) for high bioburden limits.
104-105 140-141 170-171	21	Comment: Lines 104-105 describe "Validation date should be provided as described below for each sterilization process" but lines 140 and 141 describe "For terminal sterilization using the reference condition of the Ph. Eur. 5.1.1 (≥121 ° C, ≥15 min in all units), validation date for the sterilization cycle is not required" and lines 170 and 171 describe that "In the case of terminal sterilization using the reference condition of the Ph. Eur. 5.1.1, no validation date of the sterilization cycle is requested." Proposed change: Please clarify in lines 104-105 that exceptions may apply when the reference condition of the Ph. Eur. is used as described below.	Partly accepted. A statement to inform that further details on the validation data requested are presented later in the document has been added. The guideline has been revised to further clarify the documentation required for post-aseptic processing terminal heat treatment processes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
105	26	Comment: The wording "an additional" should be amended before "terminal microbial reduction process…": Proposed change: "The required validation data for an additional terminal microbial reduction process is the same as for the sterilisation processes, except for the demonstration of a SAL of 10-6 or better."	Not accepted. The terminal microbial reduction processes would usually be the only terminal process when applied. The guideline has been revised to further clarify the documentation required for post-aseptic processing terminal heat treatment processes.
105-107	4	Comment: Clarify wording to make it clear what terminal microbial reduction refers to. Clarify wording pertaining to not requiring same SAL as for sterilization process. Consistency requested with requirements in line 150 and the followings. Proposed change: The required validation data for terminal microbial reduction processes **(e.g. an additional step following aseptic filling)** is the same as for the sterilisation processes, except to **not require** the demonstration of a SAL of 10^{-6} or less.	Accepted. The wording is revised as "A description of the sterilisation method and aseptic processing, including in-process controls and validation data should be provided"
105-107	13	Comment: Please clarify wording to make it clear what terminal microbial reduction refers to. Please also clarify wording pertaining to not requiring same SAL as for sterilization process. Proposed change: The required validation data for terminal microbial reduction processes **(ie. an additional step following aseptic filling)** is the same as for the sterilisation processes, except for ~~the~~	Accepted. Please see comment to Line 105-107 by Stakeholder 4 above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not requiring demonstration of a SAL of 10^{-6} or better.	
105-107	15	Comment: The current text states, *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.* Assurance of sterility is a qualitative concept, i.e. there can be a greater or lesser assurance of sterility. An SAL however, has a quantitative value where mathematically a 10^{-6} SAL takes a lesser value than a 10^{-4} SAL. Numerically an SAL of 10^{-6} is less than an SAL of 10^{-4}, but an SAL of 10^{-6} provides a greater assurance of sterility. The use of the word *better* in relation to SAL implies a difference in quality that might cause confusion. This can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: The required validation data for terminal microbial reduction processes is the same as for the sterilisation processes, except for the demonstration of an SAL that is less than or equal to 10^{-6}.	Accepted. Please see comment to Line 105-107 by Stakeholder 4 above.
105-107	18	**Comment:** Without definition of performance objectives, the application of a "terminal microbial	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reduction process" has no scientific rationale. (see also comments for definition, line 394) **Proposed change:** Please remove any reference to this microbial reduction process in the guidance or clarify the performance objectives.	Please see comment to Line 105-107 by Stakeholder 4 above.
105-107	18	**Comment:** What does "*or better*" at the end of the sentence mean? **Proposed change:** Please clarify.	Accepted. Please see comment to Line 105-107 by Stakeholder 4 above.
107	3	Comment: The statement regarding SAL is mathematically imprecise and must be improved with the use of "≤". This comment applies to this entire document in all cases where "SAL of 10^{-6} or better" is used. Proposed change: "…demonstration of a SAL ~~of~~ **≤** 10^{-6} ~~or better"~~	Accepted. Please see comment to Line 105-107 by Stakeholder 4 above.
107	7	Comment: The statement regarding SAL is mathematically incorrect. Proposed change: Change "SAL of 10^{-6} or better" to "SAL ≤ 10^{-6}"	Accepted. Please see comment to Line 105-107 by Stakeholder 4 above.
108	15	Comment: The current text states, *When parametric release of sterility is proposed, the …* Improve clarity of the text by relating parametric release to sterilised product rather than to sterility.	Not accepted. Parametric release is a substitute for sterility release requirement and therefore the statement sterility is applicable

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: *When parametric release of sterilised product is proposed, the …*	
112	4	Comment: "Bacterial" endotoxins looks like restrictive in this general context. Proposed change: The level of bioburden and endotoxins in the...	Not accepted. Endotoxin is bacterial lipopolysaccharide components of the gram negative bacteria cell wall. Hence it is correct to state bacterial endotoxin.
112-117	16	Comment: It should be considered that the test on bacterial endotoxins is not a requirement for all sterile finished products e.g. this test is not foreseen for eye preparations, see also the relevant Ph.Eur. monograph. Contrary to this, the general Ph.Eur. monograph parenteralia is listing the test on bacterial endotoxins as obligatory for finished products for parenteral use. Please rework the paragraph Proposed change: 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, if concerned by this	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		requirement, 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.	
112-117	18	**Comment:** For veterinary industry it is really challenging to impose bioburden specifications to the raw material suppliers. Indeed, regarding specific ingredients of veterinary products (e.g. some solvents for parenteral preparation are rarely used in human medicine, but could be widely used in other chemical industries...) it would be very difficult to impose such specifications to our suppliers as obviously the veterinary industry has not the same influence as others industries. Moreover, if applicable, these new requirements will inevitably raise production and control costs of these ingredients: that may put a brake on innovation and thus could impact the medicine availability for a parameter not appearing as essential for finished product quality. Indeed, in place of setting bioburden specifications for control of each ingredient batches, a bioburden of the bulk before sterilisation is generally preferred. In addition, the final bioburden load in the bulk product is the result of the relative proportion of each ingredient. Setting microbial limits for each individual ingredient is not relevant because it does not presume at all the final bioburden load in a final product. Then, whenever possible, a pre-filtration is generally applied before bioburden checking to	Partly accepted. There is no method for reduction of endotoxin in the components of the product. Therefore it should be in the interest of manufacturer that the components are of good quality to fulfil the endotoxin requirement of the bulk solution.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		guarantee acceptable bioburden level prior to sterilisation. In addition, endotoxins testing requirements are different in human and veterinary medicines *(Ph.Eur 0520: Preparations for veterinary use. When the volume to be injected in a single dose is 15 mL or more and is equivalent to a dose of 0.2 mL or more per kilogram of body mass, the preparation complies with a test for bacterial endotoxins),* meaning that endotoxins are not systematically required for veterinary products. Endotoxin levels and bioburden values for active substance, excipients, primary package (container, closure) and bulk solution can be replaced by an endotoxin test on the finished product with maximum limits proven to be safe in the target species. **Proposed change:** Please modify the sentence to read: "Specification limits for endotoxins and bioburden in ~~**components and**~~ bulk solution should be provided where relevant.	
114-117	14	Comment: The bacterial endotoxin test is not a requirement for all sterile medicinal products. In particular, there is no requirement to test eye drops and other topically applied ophthalmic products for endotoxins. Proposed change: To ensure an acceptable level of bacterial endotoxins in the finished drug product, which is subject to endotoxin testing, the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		microbiological contamination of the components should be minimal.	
115	4	Comment: The microbiological contamination of usual expression is not appropriate. Contamination or bio-contamination is an operation, series of actions to (bio)contaminate. The results are presence or level of biocontaminant(s). Contamination cannot be minimal or max (line 116) Proposed change: ... drug product, the **level of microbiological contaminant** of the components...	Accepted.
116-117	1	Comment: Please confirm or clarify: sterile API is considered a component. Hence a specification limit for endotoxins and bioburden (i.e. sterile) is sufficient for control at drug product manufacturer. (described in 3.2.S.4.1 – Applicants Part)	Partly accepted. Sterile API is a component and should be controlled with regards to sterility and, if applicable bacterial endotoxins. However, the documentation requested in the guideline with regards to sterilisation process development, process description, process validation, GMP etc. should also be provided in the application dossier or the Applicant's part of an ASMF.
116-117	17	Comment: *"…….. where relevant".*is not clear Proposed change: Specification limits for bioburden in components and bulk solution should be provided and for endotoxins where relevant.	Accepted.
116-117	18	**Comment:** "*Specifications limits for endotoxins and bioburden in components and bulk solution should be provided where relevant*". Distinction should be made	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		between endotoxins and bioburden, as well as between components and bulk solution. Regarding bioburden, its control is always required on the bulk before terminal sterilisation to support the Sterility Assurance Level, whereas not always suitable on components considering their quantity and their potential for microbial growth. Regarding endotoxins, it is unclear as to what should be applied for veterinary products falling under the conditions of the exemption for endotoxins testing allowed by Ph. Eur. (based on posology and injected volume). **Proposed change:** Please clarify this sentence and clarify expectations for veterinary products exempted from endotoxins testing.	
118	1	Comment: 1. Please confirm: only for filters used in manufacturing process of the finished dosage form. 2. please confirm: applicable just for product contact filters Proposed change (if any): Validation data should be provided for all sterile filters in contact with the product used in the manufacturing process of the finished dosage form.	Partly accepted. A clarification that filters in contact with the drug product or its components are concerned is added. The text has been rephrased accordingly.
118-120	1	Comment: Requirement to be limited to "sterilising" filters only, in agreement with the scope of this guidance. Contamination risk due to compatibility/leachables from all product contact materials (other types of	Partly accepted. The pre-filters are part of the sterile-filtration process although the comment is right regarding the other product contact materials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		filters, tubes, bags, vessels, etc.) is a more general GMP requirement, outside the scope of this guidance. (Text alignment with "responsibilities" section of USP <1229.4> is also suggested) Proposed change (if any): All sterilising filters should be validated with regards to product solution compatibility and leachable filter materials. The filter manufacturer may conduct these studies to ensure that the filter does not release objectionable levels of these materials into the solvent systems typically employed in pharmaceutical manufacturing.	The comment regarding the compatibility and leachables in sterilising filters are well taken.
118-121	14	Comment: This paragraph is redundant, since the requirement is covered in GMP guidelines. Propose change: ~~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.~~	Not accepted. All manufacturing can be regarded as GMP issue. Justification is not precise enough.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
118-121	16	Comment: The proposed requirement on product safety of non-sterilisation filters is redundant since it is a matter of GMP and sufficiently regulated in the respective Guidelines. Please delete this paragraph: ~~Validation data should be provided for all the filters used in the manufacturing process of the finished 118 dosage form. All non-sterilising filters should be validated with regards to solution compatibility and 119 leachable filter materials, the solution to be filtered should be used in the validation unless justified. 120 Additional validation requirements for sterilising filters are described below.~~	Please see the comment to the same lines by stakeholder 14.
119	1	Comment: Please clarify kind of data what is expected for legacy products	Accepted Comment noted. Legacy products are not within the scope.
119	18	**Comment:** It is unclear why non-sterilising filters are mentioned in this guideline since they do not aim at achieving sterility. Validation of non-sterilising filters not intended to sterilize should not be included here. To our opinion, it would be more relevant to include this in the process validation guideline.	Please see the comment to the same line by stakeholder 1.
119	22	Comment: Change proposed to line 119 re filter compatibility. Specifically, "All non-sterilising filters should be validated with regards to solution compatibility…"	Accepted Line 119 has been deleted from the guideline but the requested data is now included in Table 2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "All non-sterilising filters should be validated with regards to compatibility of the filter with the process fluid and parameters (e.g. maximum temperature, contact time)". This is required to appropriately assess the impact of temperature and time on filter compatibility.	
119	22	Comment: Propose adding that any adsorption of the process fluid to the filter should also be validated. Proposed change (if any): "All non-sterilising filters should be validated with regards to solution compatibility, potential adsorption and…." Important to have data to demonstrate that the filter will not impact the final product specifications.	Accepted.
119-120	4	Comment: Leachable studies are generally performed by filter supplier with solvent model not with product. Some inhibition linked to product could impact the analytical methods. Propose change: All non-sterilising filters should be validated with regards to solution compatibility and leachable filter materials, the product **(or at least an appropriate model of the solution)** to be filtered should be used in the validation unless justified.	Accepted. The text has been reworded for clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
119 - 120	7	Comment: The operating conditions used in the actual process are critical attributes to the filter validation. Proposed change: Modify the sentence as follows (insert underlined): "All non-sterilising filters should be validated with regards to solution compatibility and leachable filter materials, the solution to be filtered <u>and process conditions</u> should be used in the validation unless justified."	Accepted. The text has been reworded for clarity.
119 - 120	13	Comment: The term 'validated' is misleading for the attributes 'solution compatibility' and 'filter material leachables'. Instead, application of Quality by Design principles should allow characterisation of these attributes in process design studies without necessity of pre-defined acceptance criteria. Proposed change: All non-sterilising filters should be ~~validated~~ **characterized** with regards to solution compatibility and leachable filter materials, the solution to be filtered should be used in the ~~validation~~ **characterization studies** unless justified.	Not accepted. The term validation is well established and understood in the context of filter validation and what is needed to be presented.
119-121	21	Comment: Lines 119 – 121 describe that "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". Medicines for Europe	Not accepted. The GL text includes already a possibility for justification. If the manufacturer concludes that some solutions intended to be filtered are similar to the one already validated/characterised by the filter manufacturer it would be accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would like clarification on whether WFI could be accepted as a "general validation" for aqueous solutions such as NaCl 0,9%, KCl 2M, Glucose 5%. Proposed change: Please clarify	
120	3	Comment: The operating conditions used in the actual process are also of importance to the validation. Proposed Change: "the solution to be filtered **and process conditions** should be used in the validation unless justified."	Accepted.
120	22	Comment: "leachable filter materials" Proposed change (if any): Change to "extractable filter materials". We believe it is appropriate to add the term "extractable" in this context as the proposed method (by BPSA and BPOG) is to determine extractables first and use leachables if necessary.	Partly accepted. The both terms are included in the text.
122	4	Comment: In "High" bioburden limit, high is qualitative and is not a problem of height. Proposed change: Bioburden **greater** limits should...	Not accepted. High bioburden is an established statement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
122	18	**Comment:** The scientific reasoning for saying that high bioburden limits should not be justified by the capacity of the sterilisation process or any bioburden reducing step before sterilisation is unclear. For antigens such as influenza produced in SPF eggs a high bioburden may exist. When the downstream processing ensures sufficient reduction of the bioburden levels this should be sufficient. **Proposed change:** Please modify line 122 to read: "High bioburden limits ~~**should not**~~ **could** be justified by the capacity of the sterilisation process or any bioburden reducing step before sterilisation **where relevant**."	Not accepted. High bioburden is not only risk for endotoxins but also other toxin metabolites produced by the microbes. Therefore the requirement of low bioburden during the whole manufacturing steps is justified.
122-123 See also 164- 167, 187-189	1	Comment: Please clarify in more detail and put in context. Also alignment with other sections may be required.	Not accepted. The sentence is clear and additional information is elaborated in other parts of the guideline.
122-123	18	**Comment:** "*High bioburden should not be justified by the capacity of the sterilisation process or any bioburden reducing step before sterilisation*". This sentence is ambiguous and it is not clear what bioburden is addressed. The bioburden is defined in the definition section as "*a population of viable microorganisms in a product prior to sterilisation*". A bioburden reducing operation before (terminal) sterilisation, such as filtration (that will not increase the level of endotoxins), should be possible, resulting in an acceptable bioburden before sterilisation. **Proposed change:** Please clarify.	Not accepted. High bioburden is not only risk for endotoxins but also other toxin metabolites produced by the microbes. Therefore the requirement of low bioburden during the whole manufacturing steps is justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
124-125	1	Proposed change: is used to provide a specific protection to the medicinal product to maintain sterility,	Not accepted. The intended meaning of the text was that when an additional container is added the manufacturing steps should be described to enable evaluation that it does not add any risks. The secondary container may be added for other purposes than the maintenance of sterility (e.g. protection from light).
124 - 126	7	Comment: Secondary containers can provide other forms of protection not relevant to sterilisation, for example protection from water loss or light exposure. Addition of "microbial" keeps focus on the subject of the guidance. Proposed change: Modify the sentence as follows (insert underlined): "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 microbial barrier protection to the medicinal product, the packaging system should be described.	*Not accepted.* *See comment above.*
127	1	Please clarify: dry primary package material is considered the standard, please clarify how 'dry' is expected to be proven or to what extent standard processes i.e. washed vials passing a sterilisation/depyrogenisation tunnel (defined conditions) are acceptable resulting in dry vials. Moist primary packaging would also have an impact on	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product quality, composition not only on sterility and should be the exception and therefore be explained.	
132	7	Comment: The term "steam" implies saturated steam and there are methods in use (air overpressure water spray) that are not true saturated steam processes. Proposed change: Replace the Title of this Section "Steam Sterilisation" with "Moist Heat Sterilisation". In addition the term "steam sterilisation" should be replaced with "moist heat sterilisation" throughout this entire guidance (e.g., lines, 133, 145 and Glossary F_0).	Partly accepted. Steam sterilisation is the terminology of Ph. Eur. 5.1.1. A definition has been added.
132 - 135	6	Comment: Phrase "Steam Sterilisation" is used for sterilisation with moist heat. Same phrase is used in Ph. Eur. 5.1.1., followed by "Heating in an autoclave". Actual industry practice for the terminal sterilisation of medicinal products in closed container system is the use of saturated steam, steam air and hot water cascade or water spray sterilisation agent. The phrase "moist heat" is used in ISO standards on sterilisation of health care products (ISO 17665) as well as in USP <1211> describing under "Methods of Sterilization" "... forms of moist heat other than saturated steam....". Proposed change: At least as explanatory note the phrase "moist heat" should be mentioned to widen the	Partly accepted. Steam sterilisation is the terminology of Ph. Eur. 5.1.1. A definition has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterilisation methods to other moist heat sterilisation processes than saturated steam.	
132-167	15	Comment: This section refers to 'steam' as the sterilising agent; however, the decision tree in line 388 for aqueous products refers to the sterilising agent as 'moist heat'. The preferred term 'moist heat' encompasses steam, steam-air mixtures and superheated water used as sterilising agents. Consider adopting a standard term for use in the document, i.e. 'moist heat', or alternatively 'steam', and then use this term consistently throughout the document. Proposed change: Consider adopting a standard term for use in the document, i.e. 'moist heat', or alternatively 'steam', and then use this term consistently throughout the document.	Partly accepted. Steam sterilisation is the terminology of Ph. Eur. 5.1.1. A definition has been added.
133	1	Comment: A value of $F_o \geq 8$ is not in line with Ph. Eur. 5.1.1: reference requirement for steam sterilisation is ≥121 °C, ≥15 min (SAL 10^{-6}). Please clarify. Please also clarify why a reduction of $F_o \geq 8$ is considered suitable to ensure sterility, while validated sterile filtration processes (in line with Ph.Eur. 5.1.1)	Not accepted. The revised guideline is fully in line with Ph. Eur. 5.1.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		which are employed successfully in routine use for decades are still considered not acceptable.	
133	4	Comment: This sentence, not introduced with operating conditions and strict limits of use is dangerous and open doors to sanitary risk. Fo steam sterilizing value varies in particular according to the bioburden, and D and z values (see formula). The "length of the road" does not assure to achieve the destination. In link with our "decisions tree" proposal, please delete the first sentence. Proposed change**: Delete** "$F_0 \geq 8$ minutes is required for all steam sterilization processes"	Partly accepted. The text has been revised for clarification.
133; also 150-151	3	Comment: This statement contradicts the following statement from Line 57: "Therefore, terminal sterilisation provides the highest assurance of sterility and should be used whenever possible." This statement precludes the use of terminal sterilization processes where F_0 is less than 8 minutes even though these processes are capable of providing and $\leq 10^{-6}$ SAL and have been successfully utilized for many years. Also, the term "moist heat" should be used in place of "steam" (implies saturated steam) as there are terminal sterilization processes available and in common use (e.g., air overpressure water spray) that are not true saturated steam processes.	Not Accepted In line with Ph. Eur. 5.1.1, Steam Sterilisation: *The minimum temperature acceptable for a steam sterilisation process is 110 °C. The minimum F_0, calculated in the slowest-to-heat position of the load is not less than 8 min.* The text has been revised for clarification.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "**An SAL ≤ 10^{-6}** ~~$F_0 \geq 8$ minutes~~ is required for all ~~steam~~ **moist heat** sterilisation processes."	
133	7	Comment: Moist heat terminal sterilisation processes are capable of providing a ≤ 10-6 SAL and have been successfully utilized for many years. Proposed change: Replace the sentence "F0 ≥ 8 minutes is required for all steam sterilisation processes." with the sentence "An SAL ≤ 10-6 is required for all moist heat sterilisation processes."	Not Accepted In line with Ph. Eur. 5.1.1, Steam Sterilisation: *The minimum temperature acceptable for a steam sterilisation process is 110 °C. The minimum F_0, calculated in the slowest-to-heat position of the load is not less than 8 min.* The text has been revised for clarification.
133	13	Comment: *"$F_0 \geq 8$ minutes is required for all steam sterilisation processes."* This requirement is too restrictive and not based on a scientific justification or method described in Ph.Eur. Proposed change: **Delete the sentence:** ~~*"$F_0 \geq 8$ minutes is required for all steam sterilisation processes."*~~	Not Accepted In line with Ph. Eur. 5.1.1, Steam Sterilisation: *The minimum temperature acceptable for a steam sterilisation process is 110 °C. The minimum F_0, calculated in the slowest-to-heat position of the load is not less than 8 min.* The text has been revised for clarification.
133-134	4	Comment: If the headline 132 really is Steam sterilisation, examples of method should not include steps of cycle as vacuum phases but if the Headline should be Moist heat examples are Steam sterilisation cycle and air steam mixture and waterflow.	Partly accepted. Steam sterilisation is the terminology of Ph. Eur. 5.1.1. A definition has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: **Delete vacuum phases** and **add…waterflow cycle**)	
133 -149	21	Comment: In line with the industry expectations and guidelines from FDA and the Parenteral Drug Association (PDA), Medicines for Europe would like to propose to discuss the two basic approaches that are employed to develop sterilization cycles for moist heat processes i.e. **Overkill** and **Probability of Survival** in these paragraphs instead of giving an F_0 minimum at 8 minutes. The **Overkill** method is used when the product can withstand excessive heat treatment such as an F_0 > 12 without adverse effects. Bioburden and resistance data are not required to determine the required "F_0" values. Cycle parameters are adjusted to assure that the coldest point within the load receives an "F_0" that will provide at least a 12-log reduction of microorganisms having a "D_{121}" value of at least one minute (i.e.: F_0 > 12). The rationale for the Overkill approach should be documented in dossier.	Partly accepted. The guideline has been revised to further clarify, see the decision tree and tables.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The **Probability of Survival** approach is used primarily for heat labile products. In this approach, the process for the terminal sterilization of a sealed container is validated to achieve the destruction of pre-sterilization bioburden to a level of 10^0, with a **minimum safety factor** of an additional six-log reduction ($1x10^{-6}$). The probability that any one unit is contaminated is therefore **no more** than one in a million; this is considered to be an acceptable level of sterility assurance. Proposed change: Please replace the $F_0 \geq 8$ minutes requirement with a discussion of the **Overkill** and **Probability of Survival approaches** which is in line with with the industry expectations and guidelines from FDA and PDA.	
136-137	12	Comment: It is indicated that 'The lowest temperature used to determine F_0 should be stated.' Does the statement on lines 148-149 that 'Heat treatment at a temperature below 110ºC is not acceptable for sterilisation purposes.' also imply that the lowest temperature used for determination of F_0 should be at least 110ºC or are lower temperatures (e.g. 100ºC) acceptable?	Partly accepted. Further clarification on the required documentation in relation to the lowest temperature used to determine F_0 is provided In line with Ph. Eur. 5.1.1, Steam Sterilisation: *The minimum temperature acceptable for a steam sterilisation process is 110 °C. The minimum F_0, calculated in the slowest-to-heat position of the load is not less than 8 min.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Indicate the lowest acceptable temperature for determination of F_0.	The text has been revised for clarification
137	4	Comment: The "lowest" temperature..., lowest is qualitative and is not a problem of height. Proposed change: The **inferior limit of** temperature used to...	Not accepted. The word lowest is appropriate in the English language in this context.
137	13	Comment line 137: "The lowest temperature used to determine F0 should be stated." - F_0 is calculated based on a reference temperature (121.1°C) and the z-value, integrating the temperature curve measured by thermocouples. Hence, there is no lowest temperature. Please specify whether you mean the setpoint of the sterilizer, or the lowest thermocouple reading used to calculate the F_0. Proposed change: The lowest temperature **defined as the lowest thermocouple reading** used to determine F0 should be stated.	Partly accepted. The text has been further elaborated to provide clarification.
140	24	**Comment:** Also for other conditions than the 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 if the equivalence of both conditions is demonstrated. **Proposed change:** We apply to change sentence one in chapter 4 (line 140) as follows (changes in bold): "For terminal **moist heat** sterilisation using a reference condition of the Ph. Eur. 5.1.1 (≥121 °C, ≥ 15 min in	Not accepted. It is not clear what is meant by "equivalence". However, acceptable data to demonstrate any equivalence would essentially be the same as validation data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		all units) **or an equivalent,** validation data for the sterilisation cycle is not required. **This pertains not only for sterilisation using a reference condition but also for those moist heat sterilisation cycles carried out with other conditions than those in Ph. Eur. 5.1.1, if the equivalence of both conditions is demonstrated."**	
140-141	3	Comment: It is only the heat resistant or spore bioburden that potentially represent a challenge to the moist heat sterilization process. From: As is Proposed change: *"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 sterilization cycle should be provided to demonstrate a SAL of 10^{-6} or better, as described in PH. Er. 5.1.1. The SAL of such sterilization process should be calculated from the maximum number of heat resistant or spore bioburden per container."*	Partly accepted. To avoid the problem of defining "heat resistant or spore" bioburden, the total bioburden should be used to calculate the SAL (assuming that the total bioburden is heat resistant). The text has been revised for clarification.
140-141	4	Comment: To avoid misunderstanding, clarify that the process still needs to be validated, though the resulting data is not required to be submitted. Current wording could be misinterpreted to mean that validation itself is not required.	Not accepted. It is already stated in the guideline that it relates only to the data to be included in the application, not data required by GMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: For terminal sterilisation using a reference **steam sterilization parameters** (≥121 °C, ≥15 min in all units) of the Ph. Eur. 5.1.1**, in determined conditions (mainly bioburden, D and z values), data summary from the completed sterilisation process validation shall be submitted.**	
140-141	15	Comment: The current text states, *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*. The TGA requires supporting physical and microbiological performance qualification data for all terminal sterilisation processes irrespective of whether or not a standard Ph. Eur. cycle has been used. The effectiveness of a sterilisation process is not solely dependent on critical process parameters, but is dependent in part on several product variables that should be considered, e.g. viscosity, container/packaging type, product volume, etc. Proposed change: Consider the inclusion of a Note to the effect that some overseas regulatory agencies might not accept a standard Ph. Eur. cycle without supporting physical and microbiological performance qualification data.	Not accepted. The guideline is an EU guideline and reflects the regulatory standards of the EU.
140- 144	1	Comment:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
170 - 171		Please clarify why for steam and dry heat sterilisation documentation requirements can be loosened to the extent that even validation data are not required anymore and sterile filtration is still not accepted by regulatory bodies although it is in routine use employed successfully for decades.	The guideline only describes the documentation requested to be included in the dossier. It does not provide information on requests raised in GMP (e.g. in Annex 1 with regards to the requirements on validation of sterilisation processes). The validation requirements for sterilisation processes have not been loosened, but are the same as those currently in place.
141-143	15	Comment: The current text states, *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.* As per our previous comment in relation to lines 105-107, the use of the word *better* in relation to SAL implies a difference in quality that might cause confusion. This can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: In all other cases physical and biological validation of the sterilisation cycle should be provided, to demonstrate an SAL of less than or equal to 10^{-6}, as described in Ph. Eur. 5.1.1.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
143 - 144	7	Comment: Heat resistant or spore bioburden potentially represent a challenge to the moist heat sterilisation process. Proposed change: Modify the sentence as follows (insert underlined): "The SAL of such sterilisation process should be calculated from the maximum <u>number of heat resistant or spore</u> bioburden per container."	Partly accepted. To avoid the problem of defining "heat resistant or spore" bioburden, the total bioburden should be used to calculate the SAL (assuming that the total bioburden is heat resistant). The text has been revised for clarification.
144	4	Comment: ...the maximum bioburden container. Proposed change: ... maximum bioburden specification per **item**	Not accepted. It could cause confusion on what "item" refers to (e.g. does item refer to a bag of rubber stoppers or each piece of rubber stopper). Container is considered to be better specified.
145-149, see also comment to lines 158-161	3	Comment: As written with the stated limitation on exposure or hold time temperatures, this text restricts the use of terminal sterilization rather than expanding its use which PDA believes to be the more appropriate intent. A sterilization process must predictably and reproducibly destroy the bioburden present to an acceptable level of probability; and with the use of the F_0 concept and biological indicators, this is scientifically valid at temperatures ≤ 115°C. Also, the requirement for bioburden population and testing should be based whether or not the Overkill Design approach was used as the use of this approach is	Not accepted. The linearity of the F_0 concept is not indefinite, and there is no agreed scientifically justified temperature for when sterilisation is no longer applicable. However, the guideline has been re-written to allow a wider range of temperature for steam heat sterilisation/post-aseptic processing terminal heat treatment together with more detail on the requested documentation to support the proposed process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		possible, although much longer exposure times are required, at temperatures ≤ 115°C. Proposed change: Delete this section.	
145 – 149	6	Comment: The temperatures of 110 and 115 °C are defined as borderline temperatures for moist heat sterilisation. No rationale is provided, why temperatures below 115 °C trigger justification and risk mitigation measures while temperatures above 115 °C do not. Proposed change: To be consistent, any temperature below 121 °C during holding time should be handled equally.	Not accepted. The linearity of the F_0 concept is not indefinite, and there is no agreed scientifically justified temperature for when sterilisation is no longer applicable. Also, the revised Ph. Eur. 5.1.1 defines the lowest temperature for steam sterilisation as 110°C. However, the guideline has been re-written to allow a wider range of temperature for steam heat sterilisation/ post-aseptic processing terminal heat treatment together with more detail on the requested documentation to support the proposed process.
148	24	**Comment:** On the one hand there is no explanation, why a temperature below 110°C is not acceptable for sterilisation purposes and on the other hand for steam sterilisation processes below 115°C (drug product temperature during the holding time), a scientific justification and extended data, for instance, by evaluation of heat resistance for the bioburden per batch, as cycle lethality decreases significantly with decreasing temperature, is still required by the guideline as pointed out in line 145 of the guideline. Therefore, there is no need to set another limit at 110°C.	Not accepted. The linearity of the F_0 concept is not indefinite, and there is no agreed scientifically justified temperature for when sterilisation is no longer applicable. Also, the revised Ph. Eur. 5.1.1 defines the lowest temperature for steam sterilisation as 110°C. However, the guideline has been re-written to allow a wider range of temperature for steam heat sterilisation/post-aseptic processing terminal heat treatment together with more detail on the requested documentation to support the proposed process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We apply **to delete** the last sentence in para 5, chapter 4, ("Heat treatment at a temperature below 110°C is not acceptable for sterilisation purposes").	
148-149	4	Comment: By consistency with International reference temperature of 250°F or 121,11°C in moist heat sterilisation process it could be relevant to propose 111°C (=121°C – 10K). 10K correspond at once the z value. Please replace 110°C by 111°C Proposed change: Heat treatment at a temperature below **111°C** is not recommended for sterilization purpose. *The use of the Fo model should be limited at Tref ± 2 z for estimation, calculation and process. (Some seconds at huge temperatures or months at low temperature does not make sense).*	Not accepted. There is no agreed scientifically justified temperature for when sterilisation is no longer applicable. Also, the revised Ph. Eur. 5.1.1 defines the lowest temperature for steam sterilisation as 110°C. However, the guideline has been re-written to allow a wider range of temperature for steam heat sterilisation/post-aseptic processing terminal heat treatment together with more detail on the requested documentation to support the proposed process.
150	22	Comment: Change sentence "…demonstrate that a SAL of not less than 10^{-6} is obtained for all containers" Proposed change (if any): Change to: "…demonstrate that a SAL of not more than 10^{-6} is obtained for all containers" or reword completely and state "minimum SAL of 10^{-6}"	Accepted. "≤" will be used throughout the document in relation to SAL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
150-151 (see also 120)	3	Comment: Statement is mathematically incorrect; SAL requirements are always expressed as "less than" or "less than or equal to". Proposed change : "…demonstrate that a SAL ~~≤of not less than~~ 10^{-6}"	Accepted. "≤" will be used throughout the document in relation to SAL.
150-151	4	Comment: A SAL of not less than 10^{-6} or sup to 10^{-6} (e.g. 10^{-4}) is not a sterility assurance level. It is a microbial reduction level (MRL 10^{-4}). Proposed change: - In line 132: Steam sterilisation and **microbial reduction process** - In line 145: Replacement of "steam sterilisation" par "**microbial reduction process** - In line 150: ... to demonstrate a **microbial reduction level** of not less than 10^{-6} **(e.g. 10^{-4})** is obtained for all **items.**	Partly accepted. "≤" will be used throughout the document in relation to SAL. The term microbiological reduction process is not accepted to describe a sterilisation process.
150-151	15	Comment: The current text states, *Where required, sufficient validation data should be submitted to demonstrate that a SAL of not less than 10^{-6} is obtained for all containers.* As per our previous comments in relation to lines 105-107 and 141-143, the use of 'not less than 10^{-6}' is potentially confusing as this would incorrectly imply an SAL of 10^{-5}, 10^{-4} etc. The potential for confusion	Partly accepted. "≤" will be used throughout the document in relation to SAL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: Where required, sufficient validation data should be submitted to demonstrate that an SAL that is less than or equal to 10^{-6} is obtained for all containers.	
150 - 157	6	Comment: The lines 150 to 157 reflect the requirements for a non-reference cycle, which may be controlled by time / temperature or via F0 concept. For time / temperature and F0 controlled cycles, the requirements for process control are different. Proposed change: Add in lines 154 and 155 "for time / temperature cycles" and in line 156 add "for F0 controlled cycles".	Partly accepted. The document has been re-written to describe several levels of post-aseptic processing terminal heat treatment.
152	4	Comment: Identify "cold spots" in the load and in the item is important Proposed change: Load mapping distribution (colds **points in the load and in the item)**	Partly accepted. Load mapping of the chamber and the items have been specified. Slowest to heat point has been defined.
152	7	Comment: There are no "cold" spots within a moist heat sterilizer, only possible locations that may heat slower than others. Therefore the descriptor should be replaced with a more technically accurate term.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Replace "cold spots" with "slowest to heat locations".	
154 and 181	7	Comment: The term nominal is somewhat imprecise; the term "minimal" or "range" are more precise terms. Proposed change: Change from: "Sufficient time at or above the nominal temperature in the whole autoclave." Change to: "Sufficient time at or above a minimal temperature or time within a stated temperature range in the sterilization chamber."	Partly accepted. The nominal temperature is the set point temperature for the cycle. The validation data should show that the set cycle parameters are achieved. The guideline has been revised to reflect this.
154	15	Comment: The current text states, *Sufficient time at or above nominal temperature in the whole autoclave;*. It is also important that validation data demonstrate that the sterilisation load itself is held for sufficient time at or above nominal temperature (not just the chamber temperature) – this aspect seems to be missing from the list of dot points. Proposed change - change existing text to:	Partly accepted. See the comment on the same line by stakeholder 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Demonstration that the sterilisation load in the steriliser chamber is held for sufficient time at or above nominal temperature;	
154-155	21	Comment: Medicines for Europe would appreciate a further clarification of the terms "*Sufficient time*" or "*Acceptable temperatures"* etc. Proposed change: Please explain in more detail what is considered to be "*Sufficient time*" or "*Acceptable temperatures".*	Partly accepted. See the comment on the same line by stakeholder 7.
155	4	Comment: Thermocouples are one type of sensors. The expression could be interpreted as design restrictive. Proposed change: ...between **sensors (or thermosensors)** in the load	Accepted. The phrase "temperature sensors" will be used.
155	6	Comment: For temperature measurement and F0 calculation different temperature sensing elements are used. More often than thermocouples resistance thermometers, also boxed in data loggers, were used for temperature measurement and F0 determination. Proposed change: Thermocouple should be replaced by temperature sensing element.	Accepted. The phrase "temperature sensors" will be used.
158 to 161, see	3	Comment: The validity of sterilization processes at 115ºC and below is not enhanced through the use of	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
also comments to line 145-149		incremental requirements for justification of sterilisation start time or through the use of several relevant biological indicators. The use of "several relevant biological indicators" is scientifically unnecessary if using an overkill biological indicator such as *Geobacillus stearothermophilus* or a biological indicator that models product bioburden with the Product Specific Approach. Proposed change: Delete section.	The document has been re-written to describe several levels of steam sterilisation/post-aseptic processing terminal heat treatment and their requested documentation. Lethality kinetic models assumes that pharmacopoeial BIs and less heat resistant BIs would give the same Fo bio for these rare cycles – but data supporting this is not known.
160 - 161	6	Comment: A suitable bioindicator shows sufficient kill at the sterilisation conditions chosen to achieve a SAL of 10E-6 or better by experimental evidence. The usage of several biological indicators is not required. Proposed change: Several relevant biological indicators should be changed to "Suitable biological indicators".	Partly accepted. The document has been re-written to describe several levels of steam sterilisation/post-aseptic processing terminal heat treatment and their requested documentation.
160-161	15	Comment: The current text states, *Several relevant biological indicators could be included in the validation to demonstrate sensitivity to the process*. As written, this text is somewhat vague. What is meant by 'several' (in relation to biological indicators)? Also, the use of 'could' implies the use of biological indicators is optional for a process carried out at ≤115°C (which contradicts text in lines 141-143).	Partly accepted. The document has been re-written to describe several levels of steam sterilisation/post-aseptic processing terminal heat treatment and their requested documentation. Lethality kinetic models assumes that pharmacopoeial BIs and less heat resistant BIs would give the same Fo bio for these rare cycles – but data supporting this is not known.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: Suitable biological indicators should be located within the sterilisation load during the validation to demonstrate achievement of the required SAL.	
162 - 163	6	Comment: Reference to Ph. Eur. 5.1.2 for the bioindicator Geobacillus stearothermophilus is suitable for moist heat sterilisation at reference conditions (121 °C / 15 minutes). The EMA paper should discuss the requirements for bioindicators more suitable for other than reference sterilisation processes. For example Geobacillus stearothermophilus in the given framework of Ph. Eur. 5.1.2 will not necessarily show complete deactivation at sterilisation temperatures of less than 121 °C and / or 8 >= F0 <=15 minutes values at a number of viable spores >= 5 x 10E5 spores per item to be sterilised. Primary endpoint detection by complete inactivation as requested for bioindicator verification according to Ph. Eur. 5.1.2 will not be possible under such alternative sterilisation cycles.	Partly accepted. Ph. Eur. 5.1.2 has been revised and is now considered a suitable reference, but further guidance with regards to the documentation requested partially based on the D-value of the bioindicator used in the validation of the process is provided.
162 – 163 and 185 - 186	7	Comment: Different Biological Indicators should be usable as long as their selection is justified. Proposed change: Modify the sentence (insert underlined) as follows: "For the biological validation, a biological indicator as described in Ph. Eur. chapter	Partly accepted. Ph. Eur. 5.1.2 has been revised and is now considered a suitable reference, but further guidance with regards to the documentation requested partially based on the D-value of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		5.1.2 Biological indicators of sterilisation should be used unless use of an alternate biological indicator is justified."	the bioindicator used in the validation of the process is provided.
163	4	Comment: Title is not exact Proposed change: … a biological indicator as described in Ph.Eur. § 5.1.2. *Biolological indicators of sterilization*, ***and related microbial preparations used in the manufacture of sterile products, and indicators for depyrogenation processes*** should be used.	Partly accepted. Ph. Eur. 5.1.2 has been revised and is now considered a suitable reference, but further guidance with regards to the documentation requested partially based on the D-value of the bioindicator used in the validation of the process is provided. In Ph. Eur. 5.1.2 no bioindicator for depyrogenation processes (by dry heat) is defined.
164	24	**Comment:** The stated value of a maximum bioburden limit of 100 CFU/ 100 ml (TAMC) seems to be very strong. In the EU GMP guideline (Part II) no specific limit for the bioburden is named – only a control of the bioburden is required and a microbiological specification (action limits) is addressed. **Proposed change (if any):** We propose to change the draft maximum bioburden limit of 100 CFU/100 mL (TAMC) to an appropriate bioburden limit. A limit for the bioburden should be established in regard to further process steps.	Not accepted. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
164 - 166 and 187 - 189	7	Comment: Limits for Bioburden should be consistent with the population of moist heat resistant / dry heat resistant spores used in SAL calculations. Proposed change: Delete the maximum bioburden limit of 100 CFU/100 g or mL (TAMC).	Not accepted. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.
164-166	15	Comment: The current text states, *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.* Some terminally sterilised products are subject to pre-filtration through a 0.45 µm filter followed by a 0.2 µm filter, or through two 0.2 µm filters in series. In this situation it would be reasonable to assume that prior to the second filter, a bioburden limit of ≤ 10 CFU/100 mL is achievable even though the product is terminally sterilised. Proposed change: Consider inclusion of an additional sentence to the effect that: Where a manufacturing process utilises bioburden reduction steps prior to product filling, e.g. the use of bioburden reduction or sterilising grade filters, the maximum bioburden limit would be expected to be more stringent than a limit of 100 CFU/100 mL.	Not accepted. The limit is considered suitable from a safety perspective. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
164 – 167 187 – 189 122 - 123	1	Comment: 1. Section 4.1. refers to drug products. Reference to API and excipients is consequently here not applicable (chapter 4.2) 2. Please clarify for what and where a bioburden should be established –in i.e. bulk solution immediately prior to sterile filtration.	Partly accepted. 1. The heading of Chapter 4.1 has been extended to state "Manufacturing of sterile medicinal products and sterile components" and relates to the documentation requested in the dossier. Chapter 4.2 relates to the GMP requested, and has also been amended to include containers. 2. Further clarification has been provided.
164-167	4	Comment: The suggested bioburden limit of 100cfu/100ml is arbitrary. It would be better to state that the limit must be determined based on the sterilization cycle and for potential impact to product quality and patient safety. While other limits may be acceptable with justification, the stated limit of 100cfu/100ml will likely become the de facto expectation. It may also be beneficial to state that the bioburden may be reduced by various means prior to terminal sterilization. Proposed change: A limit for bioburden should be established **commensurate with the sterilization method and ensuring lack of adverse impact to product quality and patient safety. Where required, the bioburden may be reduced by various means (e.g. filtration) prior to the terminal sterilization process.**	Not accepted. However, the text has been amended to state …"other testing regimes **and limits** to control the bioburden at the defined level **should be justified**.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
164-167	14	Comment: As endotoxins are not relevant for non-parenteral products a higher bioburden limit of 100 CFU/g or ml is regarded to be sufficient in these cases. Proposed change: A limit for bioburden should be established. ~~For aqueous solutions~~, ~~a~~ A maximum bioburden limit of 100 CFU/100 ml (TAMC) is acceptable for ~~active substances, excipients and~~ parenteral drug product formulations without further justification. Other testing regimes to control bioburden at the defined level could be accepted. For active substances excipients and drug products that are not used for parenteral administration, a maximum total bioburden limit of 100 CFU/g or ml is acceptable without further risk-based justification.	Not accepted. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.
164-167	18	**Comment:** The meaning of "regime" in "Other testing regimes to control bioburden at the defined level could be accepted" is not clear. For veterinary industry it is really challenging to impose bioburden specifications to the raw material suppliers. In place of setting bioburden specifications for control of each ingredient batches, a bioburden of the bulk before sterilisation is often preferred. In addition, the final bioburden load in the bulk product is the result of the relative proportion of each ingredient. Setting microbial limits for each individual ingredient is not relevant because it does not presume at all the final bioburden load in a final	Not accepted. The word "Regime" is used since other control strategies than 100 CFU/100 ml may be used. An example could be to use a smaller sample volume in combination with a stricter limit. Alternatively a bioburden sample with the same numerical limit with a smaller sample volume in combination with identification of the contaminating organisms to demonstrate their sensitivity to the sterilisation process could be used. All these options are not possible to describe in detail in the guideline, thus the vague phrasing. Additional filters as a substitute for good manufacturing practice is not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product. Then, whenever possible, a pre-filtration is generally applied before bioburden checking to guarantee acceptable bioburden level prior to sterilisation. Also refer to comment 112-117. **Proposed change:** Please modify this sentence to read: "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 **(e.g. applying pre-filtration whenever possible as precaution measure before bioburden checking) or other limit applied if justified**.	If justified adapted microbiological limits may be applied for the different components of the product (active substance, excipients and containers) to compensate for inherent levels of contamination. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.
164-167	13	Comment: The suggested bioburden limit of 100cfu/100ml is arbitrary. It would be better to state that the limit must be determined based on the sterilization cycle and for potential impact to product quality and patient safety. While other limits may be acceptable with justification, the stated limit of 100cfu/100ml will likely become the de facto expectation. It may also be beneficial to state that the bioburden may be reduced by various means prior to terminal sterilization. Proposed change: A limit for bioburden should be established **commensurate with the sterilization method and ensuring lack of adverse impact to product quality and patient safety.** ~~For aqueous~~	Not accepted. Not Accepted The limit is empirical and is achievable for most manufacturing processes. According to GMP Annex 1 it is not acceptable to justify bad manufacturing practices with higher bioburden limits or the sterilisation method effectiveness The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~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.~~ **Where required, the bioburden may be reduced by various means (eg. Filtration) prior to the terminal sterilization process.**	
164-167	16	The wording should be stated in accordance with the terms of the relevant decision tree under lines 388-389: "Decision tree for sterilization choices for aqueous products". A risk based approach should be applied: The bioburden limit should be specified in such a way to guarantee a SAL of 10-6 or better for the chosen sterilization process, as described in Ph.Eur. 5.1.1. Proposed change: Steam sterilisation […] "A limit for bioburden should be established. For aqueous ~~solutions~~ products, 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	Not accepted The limit is empirical and is achievable for most manufacturing processes. According to GMP Annex 1 it is not acceptable to justify bad manufacturing practices with higher bioburden limits or the sterilisation method effectiveness. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group However, the text has been amended to state …"other testing regimes **and limits** to control the bioburden at the defined level **should be justified**.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level could be accepted as long as a SAL of 10^{-6} or better is assured for the chosen sterilization process.	
165 - 167 And 189	3	Comment: What is the scientific justification for the maximum bioburden limit of 100 CFU/100mL? Proposed change: Recommend deletion of this limit or modification to require that the bioburden limit should be consistent with the population of moist heat resistant spores used in SAL calculations.	Not accepted. See the comments to the responses to the comments on the same lines.
165 and 187	26	Comment: A maximum bioburden limit of 100 CFU/100 ml (TAMC) has been stated for steam and dry heat sterilisation processes. Where does this limit come from? The required bioburden limit depends on the efficacy of the sterilisation process. If overkill processes are used, the bioburden limit could theoretically be 106 CFU/g or ml, but a bioburden limit of 103 CFU/g or ml (TAMC) is considered acceptable at present for terminal sterilisation processes with a required SAL of 10-6 or better.	Partly accepted. See the comments to the responses to the comments on the same lines.
166 and 188	26	Comment: What does the sentence "Other testing regimes to control bioburden at the defined level could be accepted if adequately justified." refer to? No test regime is mentioned before in the relevant sections.	The word "Regime" is used since other control strategies than 100 CFU/100 ml may be used. An example could be to use a smaller sample volume in combination with a stricter limit. Alternatively a bioburden sample with the same numerical limit with a smaller sample volume in combination with identification of the contaminating organisms to demonstrate their sensitivity to the sterilisation process could be used. All these options are not possible to describe in detail in the guideline, thus the vague phrasing. Additional

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			filters as a substitute for good manufacturing practice is not accepted. If justified adapted microbiological limits may be applied for the different components of the product (active substance, excipients and containers) to compensate for inherent levels of contamination. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.
167 and 187	2	Comment: The sentence "A limit for bioburden …." should be further specified as it is not clear what is meant. Proposed change: "A pre-sterilisation limit for bioburden should be established ".	Partly accepted. The word bioburden has been defined.
168 187 - 188	6	Comment: Typically APIs, excipients and bulk products are not sterilised by dry heat. Dry heat is used frequently for decontamination of packaging material. The requirement to define bioburden limits expressed as CFU per volume should be reconsidered.	Partly accepted The revised guideline has been updated.
168 -192	18	**Comment:** Dry heat method is only used in the case of glassware sterilisation. The fact that this method is included in the decision tree for non-aqueous, semi-solids and dry powders is confusing because it seems to suggest that this method could be used to sterilise products which is not the case.	Not accepted. In some cases, such as non-aqueous veterinary medicinal products where the active substance is dissolved in glycols or macrogols, the drug product may be sterilised by dry heat.
170-171	4	Comment: To avoid misunderstanding, clarify that the process still needs to be validated, though the	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		resulting data is not required to be submitted. Current wording could be misinterpreted to mean that validation itself is not required. Proposed change: For terminal sterilisation using a reference condition of the Ph. Eur. 5.1.1, (≥121 °C, ≥15 min in all units), **data summary from the completed sterilisation process validation** shall be submitted.	It is already stated in the guideline that it relates only to the data to be included in the application, not data required by GMP.
172-174	15	Comment: The current text states, *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.* As per our previous comments in relation to lines 105-107, 141-143 and 150-151, the use of the word *better* in relation to SAL implies a difference in quality that might cause confusion. This can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: For terminal sterilisation cycles with time and/or temperature lower than the reference conditions of the Ph. Eur., physical and biological validation of the	Partly accepted. "≤" is used

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterilisation cycle should be provided, to demonstrate an SAL that is less than or equal to 10^{-6}, as described in Ph. Eur. 5.1.1.	
174	4	Comment: ...to demonstrate a SAL of 10^{-6} or better, ... As already commented "better" is qualitative. Proposed change: ...10^{-6} or lower (e.g. 10^{-7})...	Partly accepted. "≤" is used
176	22	Comment: Change sentence "…a SAL of not less than 10^{-6} is obtained for all containers" Proposed change (if any): Change to: "…demonstrate that a SAL of not more than 10^{-6} is obtained for all containers" or reword completely and state "minimum SAL of 10^{-6}"	Partly accepted. "≤" is used
176-177	4	Comment: SAL of not less than... looks like inappropriate because : 1. that includes the value 10^{-6} (irrelevant out of scope of these lines) 2. by consistency with comment on lines 150-151 that is not a SAL but a MRL (microbial reduction level). Proposed change: ...to demonstrate a **MRL greater than** 10^{-6} (e.g. 10^{-4})	Partly accepted. "≤" is used. SAL is the preferred terminology.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
176-177	15	Comment: The current text states, *Where required, sufficient validation data should be submitted to demonstrate that a SAL of not less than 10^{-6} is obtained for all containers.* As per our previous comments in relation to lines 150-151, the use of 'not less than 10^{-6}' is potentially confusing as this would incorrectly imply an SAL of 10^{-5}, 10^{-4} etc. The potential for confusion can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: Where required, sufficient validation data should be submitted to demonstrate that an SAL that is less than or equal to 10^{-6} is obtained for all containers.	Accepted. "≤" is used.
181	15	Comment: The current text states, *Sufficient time at or above nominal temperature in the whole dry heat sterilisation cabinet;*. It is also important that validation data demonstrate that the sterilisation load itself is held for sufficient time at or above nominal temperature (not just the dry heat chamber temperature) – this aspect seems to be missing from the list of dot points.	Partly accepted. . As above. The guideline has been updated to state; "Demonstration that the steriliser chamber achieves the specified cycle parameters, including time, temperature, pressure and F0, if applicable"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: Demonstration that the sterilisation load in the steriliser chamber is held for sufficient time at or above nominal temperature;	
182	22	Comment: Change "thermo couples" Proposed change: Change to "thermocouples" (one word)	Accepted. The phrase "temperature sensors" will be used.
187	4	Comment: liquid is not adapted in dry heat sterilization Proposed change: **Remove "or mL"**	Not accepted. Non-aqueous liquids may be dry heat sterilised.
187-188	4	Comment: Same comment as for 164-167, in that the suggested limit is arbitrary and would be better determined using risk assessment, rather than suggesting that higher limits require unique justification Proposed change: A limit for bioburden should be established **commensurate with the sterilization method and ensuring lack of adverse impact to product quality and patient safety…**	Not accepted. However, the text has been amended to state …"other testing regimes **and limits** to control the bioburden at the defined level **should be justified**.
187-189	13	Comment: Same comment as for 164-167, in that the suggested limit is arbitrary and would be better determined using risk assessment, rather than	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		suggesting that higher limits require unique justification Proposed change: A limit for bioburden should be established **commensurate with the sterilization method and ensuring lack of adverse impact to product quality and patient safety.** ~~. 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.~~	However, the text has been amended to state …"other testing regimes **and limits** to control the bioburden at the defined level **should be justified**.
187-189	14	Comment: The general limit specified in the current Draft Guideline (100 CFU/100 g or ml) is only important for formulations used for parenteral administration in order to avoid higher endotoxin levels. As endotoxins are not relevant for all other products a higher bioburden limit of 100 CFU/g or ml is regarded to be sufficient. Testing of non-filterable active substances, excipients and drug product formulations is not practical for a sample size of 100 g or ml. Proposed change: A limit for bioburden should be established. A maximum bioburden limit of 100 CFU/~~100~~ g or ml is acceptable for <u>non-filterable</u> active substances, excipients and drug product formulations without further justification. Other testing regimes to	Not accepted. The proposed limit has been confirmed suitable by the EMA GMP/GDP Inspectors Working Group.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		control bioburden at the defined level could be accepted.	
187-189	18	**Comment:** For veterinary industry it is really challenging to impose bioburden specifications to the raw material suppliers. In place of setting bioburden specifications for control of each ingredient batches, a bioburden of the bulk before sterilisation is often preferred. In addition, the final bioburden load in the bulk product is the result of the relative proportion of each ingredient. Setting microbial limits for each individual ingredient is not relevant because it does not presume at all the final bioburden load in a final product. Then, whenever possible, a pre-filtration is generally applied before bioburden checking to guarantee acceptable bioburden level prior to sterilisation. Also refer to comment 112-117 and 164-167. **Proposed change:** 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 **(e.g. applying pre-filtration whenever possible as precaution measure before bioburden checking) or other limit applied if justified**.	Partly accepted. Where justified, higher acceptance criteria for bioburden can be accepted, and for these cases the excipient specification can be considered extra important.
187-189	16	The wording should be stated in accordance with the terms of the relevant decision tree under lines 390-	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		391: "Decision tree for sterilisation choices for non-aqueous liquid, semi-solid or dry powder products". A risk based approach should be applied: The bioburden limit should be specified in such a way to guarantee a SAL of 10-6 or better for the chosen sterilization process, as described in Ph.Eur. 5.1.1. Proposed change: Dry heat sterilisation […] A limit for bioburden should be established. A maximum bioburden limit of 100 CFU/100 g or ml (TAMC) is acceptable for non-aqueous liquid, semi-solid or dry powder products~~active substances, excipients and drug product formulations~~ without further justification. Other testing regimes to control bioburden at the defined level could be accepted as long as a SAL of 10^{-6} or better is assured for the chosen sterilization process.	The terminology has been harmonised and the text been further elaborated. It is not necessary to repeat the requirement with regards to SAL.
189	16	Currently, the method of dry heat sterilisation is not sufficiently regulated for active substances, excipients and medicinal products in Europe in contrast to the method of steam sterilisation (see line 138-139 [link to Ph.Eur.5.1.5]). Therefore, we suggest an addition of detailed recommendations with regard to the relationship between physical (temperature distribution within the load) and biological (bioindicators, bioburden isolates) validation.	Not accepted. The combined information in the guideline, Ph. Eur. 5.1.1 and 5.1.2 are considered sufficient at this stage. A general reference to ISO 20857 is not considered relevant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Currently, only medical device standards as ISO 20857 [Sterilisation of health care products – dry heat – requirements for the development validation and routine control of a sterilisation process for medical devices]) or scientific data for medicinal products from USP and PDA can alternatively be used. Please add this paragraph. Proposed change: "In addition to Ph. Eur., recommendations made in ISO 20857 are accepted. Where any requirements in ISO 20857 are in contradiction to requirements stated in the Ph. Eur., the requirements of the Ph. Eur. apply. "	
190-191	1	Comment: not just glassware, eg: it is also common for aluminium containers, crimps, etc. more general would be 'heat resistant materials' Would it be possible to define an acceptable reference condition for combination of sterilisation/depyrogenisation at 220°C where 3 log reduction is achieved?	Partly accepted. See the response to the next comment made by stakeholder 15 on lines 190-192.
190-192	15	Comment: The current text states, *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.*	Partly accepted. It is agreed that the 3-log reduction requirement is an empirical limit and there are limitations to the suitability of the limit with regards to e.g. level of bioburden, thus the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The USP has a new general chapter (non-mandatory) in USP 39-NF 43: <1228> Depyrogenation and <1228.1> Dry heat depyrogenation. Chapter 1228 mentions that since 1984, the efficiency of depyrogenation processes has been assessed by a requirement to demonstrate at least a 3 $\log_{10}$ reduction in spiked endotoxin challenge. As endotoxin is inactivated more slowly than spores of *B. atrophaeus*, a process that results in a minimum 3 $\log_{10}$ reduction in endotoxin is considered to also result in a probability of non-sterility significantly less than 10^{-6}. Implementation of risk management and quality by design principles now mean that a single, standard endotoxin reduction criterion (i.e. a minimum 3 $\log_{10}$ reduction) might not be valid for all depyrogenation processes in use today. For example, glass vials are moulded at high temperatures (~900°C) and promptly packaged and shrink-wrapped prior to shipping and so have low endotoxin content per unit volume (<0.003 EU/mL) prior to washing in WFI. A requirement to demonstrate a 3 $\log_{10}$ reduction in endotoxin content could be seen as excessive. Bacterial fermentation broths however, could be expected to have a high endotoxin content and so might require more than a 3 $\log_{10}$ reduction in endotoxin content to ensure the endotoxin content of the finished product is at a safe level. Chapter <1228> mentions that *the appropriate endotoxin log reduction for the process should be determined by the user based on a full understanding of the product and process capability including input sources, levels of endotoxin, efficiency of depyrogenation methods, and output (product- or process-specific) endotoxin requirements. Effective process control requires knowledge of input, in-process (where appropriate) and output endotoxin levels. Under these*	limitation to glassware and other heat resistant container materials. Other approaches, including the use of endotoxin lethality kinetics, are possible, but require justification. It is recommended that applicants explore such alternative approaches via established regulatory procedures, e.g. by requesting scientific advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		circumstances, with appropriate process development, justification for reduced endotoxin challenges or the elimination of endotoxin challenges may be made based on historical data and demonstration of continued control. Proposed change - change existing text to: Consider the inclusion of an additional sentence with words to the effect of: For a process where a reduced endotoxin challenge might be necessary, this should be scientifically justified and supported by suitable validation data.	
191-192	4	Comment: Clarify that a biological indicator strain is not required Proposed change: In this case, demonstration of a 3 log reduction in heat resistant endotoxins can be used as the **sole** validation criteria.	Not accepted. It is well-established that demonstration of 3-log reduction is sufficient for validation. The inclusion of "sole" is unnecessary.
191-192	13	Comment: We recommend that description of sterilisation methods in Ph.Eur. etc. are referred to instead of duplicated in the text and decision tree; this will ease maintenance of the document. Proposed change: **Delete line 191 and 192**	Partly accepted. However, some duplication improve the readability of the document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
193 – 198	6	Comment: The Note for Guidance "The use of Ionization Radiation..." is dated from December 1991. It does not represent the state of art compared to harmonized EN ISO 11137 (first issued in 2006, amended in 2013 and 2015), well established in medical device industry worldwide. Draft EMA Guideline should not rank an outdated Note for Guidance higher than a current EN ISO standard.	Partly accepted. Additional information is provided in the Note for Guidance that is absent both in Ph. Eur. 5.1 and in EN ISO 11137. The text has however been rephrased to clarify the relevance of EN ISO 11137.
193 – 198	16	Proposed change: Ionization radiation sterilisation Data as requested in Ph.Eur. chapter 5.1.1. and in the 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 Ph.Eur. chapter 5.1.1 or any Note for Guidance issued by the EMA, the requirements of the Ph.Eur. and the Note for guidance apply. Rationale for change: In case of terminal sterilisation acc. to reference condition of Ph.Eur. chapter 5.1.1 (25 kGy) no validation data beyond Ph.Eur. should be requested. For terminal sterilisation cycles under other conditions, the requirements of the NfG should be	Accepted. Proposal for revision of the GL: Amend to state Ph. Eur. 5.1.1 in the last disclaimer: Where any requirements in ISO 11137 are in contradiction to requirements stated in any Note for Guidance issued by the EMA, the requirements of Ph. Eur. 5.1.1 and the Note for guidance apply.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered, added by the requirements given in ISO 11137 if necessary. Please rework this paragraph	
194-198	18	**Comment:** The norm ISO 11137 is for medical devices. Referring to this document can potentially lead to misunderstanding on how to properly adapt the requirements to raw material or finished product. It should not be presented as a reference but as a source of inspiration. **Proposed change:** Please modify the line 197 to read: "Where any requirements in ISO 11137 are **not adapted or are** in contradiction …."	Not accepted. ISO standards are not adapted in relation to medicinal manufacture.
197-198	15	Comment: The current text states, *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*. What is the rationale for overriding the requirements of ISO 11137, which is a state-of-the-art standard for radiation sterilisation of health care products (i.e. medicines and medical devices)? It is noted that ISO 11135 is acceptable as the reference standard for Ethylene oxide sterilisation (see line 222). It appears contradictory to accept one ISO standard but not the other. Proposed change:	Not accepted. ISO standards are written in relation to medical devices that are not ruled by the same legal framing as medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Delete the existing text in lines 197-198.	
199-224	26	Comment: (gas sterilisation) Contrary to the other sterilisation processes, no bioburden limit is specified. Is this information not required in gas sterilisation processes?	Partly accepted. A test for bioburden is required with justified limits in relation to gas sterilisation. However, the limit may vary dependent on the issues to be sterilised.
199 - 231	6	Comment: The whole paragraph on gas sterilisation has no link to the respective Ph. Eur. monographs 5.1.1 and 5.1.2 while such references to Ph. Eur. are stated for the chapters on moist heat and ionisation irradiation sterilisation. It lacks consistency to reference EN ISO, if limited information is available in Ph. Eur. or in the Note for Guidance but to ignore EN ISO, if some, but not comprehensive information is available in Ph. Eur. or in the Note for Guidance respectively. Proposed change: As EN ISO standards provide suitable guidance additionally to Ph. Eur. or Note for Guidance, these standards should clearly be valid sources for guidance.	Accepted. The text ("The process should be developed and validated in compliance with Ph. Eur. 5.1.1 and 5.1.2.") is added under general considerations for gas sterilisation.
200	1	Comment Gas sterilisation applicable for packaging materials and equipment-. A separate section for packaging materials and equipment would probably be useful.	Partly accepted. Further references to the materials for which the text applies to.
200	18	**Comment:** Gas sterilisation is not limited to sterilisation of surface of goods but could also be applicable to porous compounds and powders that	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allow penetration of gas. It should remain a possible alternative to such medicinal products when other sterilisation methods cannot be followed. **Proposed change:** Please amend to: "This method provides sterilisation of the surface of the goods ~~only~~."	
202	4	Comment: "...by gas and moisture is essential" is not complete Proposed change: ...by gas **in appropriate conditions of temperature and moisture**, is essential	Accepted. The text has been amended.
206	18	**Comment:** See above comments for line 200. **Proposed change:** Gas sterilisation of ~~**dry powders**~~ **raw materials and finished products** is not acceptable unless other methods of sterilisation are not feasible and its use is scientifically justified **(e.g. porous compounds allowing suitable penetration of gas)**.	Partly accepted. The text has been rephrased.
207	4	Comment: "The substance should be..." is not enough clear Proposed change: **Upstream the active substance or excipient** should be sterilized filtered…	Not accepted. It is obvious that bioburden relates to the material prior to gas sterilisation, thus the proposed text does not add to the text.
207-209	18	**Comment:** The advice to pre-treat the powder by sterile filtration + aseptic crystallisation before gas treatment is scientifically not relevant as the substance would then be sterile and would not need to be further sterilised by gas. Is our understanding correct here?	Not accepted. Data demonstrating the possibility of entrapment of microorganisms within the particulate goods to be sterilised (thus escaping the lethal treatment) is available

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please clarify whether this GL proposes to apply gas sterilisation after sterile filtration and crystallisation. If this is the process that is proposed, please delete this sentence as this is not scientifically sound: ~~**The substance should be sterile filtered and crystallised under aseptic conditions in order to minimise bioburden and entrapment of microorganisms within the crystals.**~~	
211	4	Comment: "..quantitative data on the mixture of gas to be used,..." is not exact, because it is not systematically a mixture of gas. Proposed change: ...**quantitative data on gas(es)** to be used,...	Accepted.
212	4	Comment: the water used to maintain humidity should be able to be vaporised as clean steam. Proposed change: ...the time of exposure to the gas, **the temperature and clean steam** prior to and during each step of the sterilisation cycle…	Accepted.
216	4	Comment: SAL of 10^{-6} By consistency SAL shall be equal or inferior to 10^{-6} Proposed change: SAL of 10^{-6} or lesser…	Accepted. The phrase "an SAL of $\leq 10^{-6}$" is used throughout the document.
216	15	Comment: The current text states, *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.*	Accepted. The phrase "an SAL of $\leq 10^{-6}$" is used throughout the document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		As per our previous comments in relation to lines 105-107, 141-143 and 150-151, the use of the word *better* in relation to SAL implies a difference in quality that might cause confusion. This can be avoided by expressing a specified SAL as a maximum value and by using terms *less than* or *greater than* when comparing different values for SAL. Proposed change - change existing text to: Results of the process validation should demonstrate an SAL that is less than or equal to 10^{-6} and removal of any toxic gas residues to an acceptable level in line with current guidelines.	
216-217	12	Comment: It is indicated that '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.' Considering the high reactivity of ethylene oxide, it is assumed that gas sterilisation of dry powders (e.g. active substance) can lead to chemical changes in those powders (e.g. formation of reaction products of ethylene oxide and active substance) that should more likely be qualified as degradation products than as gas residues.	Partly accepted. The text has been revised to refer to residual toxic impurities in general.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: In case of sterilisation of dry powders, potential reaction products of ethylene oxide and goods being sterilised (e.g. active substance) should be controlled to an acceptable level in line with current guidelines.	
216-219	13	Comment: We recommend that description of sterilisation methods in Ph.Eur. etc. are referred to instead of duplicated in the text and decision tree; this will ease maintenance of the document. Proposed change: **Delete line 216 to 219**	Not accepted. Some duplication improves the readability of the document.
218-219	1	Comment: Once successfully validated, the use of one BI in routine cycle to show effectiveness should not be required (it would be like putting a BI into any routine autoclave cycle): the reliability in routine is given by establishing adequate in process controls, as required in lines 211 to 215. (The use of BIs for routine operations in aseptic processing should be avoided, to prevent the risk of spores spread-out contamination in case of Bi breakage). In certain cases the use of a chemical indicator may be more appropriate (eg: H2O2). Product Sterility test is always needed, for every sterilization method chosen and should not be presented as a specific condition to demonstrate effectiveness of gas sterilization. Instead, periodic re-validation should be required	Not accepted. Ph. Eur. 5.1.2 requires the use of biological indicators in the monitoring of all gaseous sterilisation processes. The guideline wording is updated; "The effectiveness of the process should be routinely checked for every batch confirming that the process parameters and biological indicators are all within their acceptance criteria and by sterility testing."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The effectiveness of the process should be routinely verified.	
218-219	15	Comment: The current text states, *The effectiveness of the process should be routinely checked for every product batch using a suitable biological indicator and by product sterility testing.* Parametric release is often used for release of ethylene oxide sterilised product. Proposed change - change existing text to: The effectiveness of the sterilisation process should be routinely checked for every sterilisation load using suitable biological indicators and a product test for sterility unless parametric release of sterilised product has been approved.	Not accepted. Parametric release in relation to gas sterilisation is not accepted, please refer to Ph. Eur. 5.1.1 and Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) where gas sterilisation is not mentioned in relation to parametric release.
219	3	Comment: Parametric release is not permitted by this statement and product sterility testing is not recognized as a release requirement in ISO11135:2014 Parametric Release Definition 3.2.5 and Section 11.1 for product release criteria Proposed change: ”The effectiveness of the process should be routinely checked for every product batch using a suitable biological indicator ~~and by product~~	Not accepted. Parametric release in relation to gas sterilisation is not accepted, please refer to Ph. Eur. 5.1.1 and Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) where gas sterilisation is not mentioned in relation to parametric release.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~sterility testing~~. **unless parametric release has been approved**."	
220 – 221	13	Comment: In section 4.1 (Manufacturing of sterile medicinal products) of the draft guidance, the EMA clearly states that the choice of sterilisation method or aseptic processing should be justified. The guidance should allow flexibility for manufacturers to utilize ETO sterilisation method provided it's scientifically justified. Proposed change: Ethylene oxide (ETO) is a gas which is highly toxic **and should only be used when other methods of sterilisation are not feasible and its use is scientifically justified**. **Manufacturers must demonstrate that the ETO residuals have been reduced to an acceptable level according to the applicable guidelines and/or harmonised standards.** ~~ETO sterilisation is only acceptable if no other method of sterilisation is possible.~~	Not accepted. Ethylene oxide sterilization processes are not considered sufficiently robust to be used when other sterilization methods are possible. However, evaluation of residual genotoxic impurities have been elaborated.
220 – 224	5	Comment: In respect to Ethylene oxide specific reference is made to ICH M7. ICH M7 is based on the principle of a virtually safe dose based on either the generic principle of the TTC or a compound specific limit derived from safety data pertaining to the compound in question. To illustrate this principle the example of ethylene oxide is actually used, the	Not accepted. The Table 3 included at this section can be used when the medicinal product is outside of the scope of the M7 guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		calculated limit being 21.3 ug/day. It should be stressed that the limit is expressed in terms of a dose not a specific concentration, hence the table included with draft sterilisation guideline is a concern as limits are based on concentration and not dose and take no account of the product concerned, the dose of product administered or other factors such as treatment duration or disease area. It is therefore concluded that this is inconsistent with the principles of ICH M7 it purports to reflect.	
224 - 226	18	**Comment:** According to ICH M7, "a daily life-long intake of 21.3µg ethylene oxide would correspond to a theoretical cancer risk of 10^{-5} and therefore be an acceptable intake when present as an impurity in a drug substance". Veterinary products are out of scope of ICH M7 guidance and a limit of 1µg/g for ethylene oxide residue should apply. This limit is consequently stricter than the limit for humans. E.g. a 100mg daily dose of a substance sterilised by ethylene oxide would allow only 0.1µg residual ethylene oxide for a vet. product when the same dose for human would allow 21.3µg residual ethylene oxide (i.e. 213 times more). The calculation as per ICH M7 should be an option for vet products as well. **Proposed change: Please amend line 224 to read:** "For products outside the scope of ICH M7 **(for instance products for veterinary use), setting limits for ETO and halogenated ethylenehydrines**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		may nevertheless follow the principles of the ICH M7 guideline, otherwise, the limits below apply."	
228 - 231	5	Comment: The comment is made that 'provided the container itself fulfils the requirements of ICH M7'. Containers are not currently included within the scope of ICH M7. The requirement should be removed.	Not accepted. The text has been amended to state that if the relevant product is outside the scope of that guideline, its limits for highly toxic impurities could be applied.
232	20	Comment: Please specify if this chapter concerns both gas and liquid sterilizing grade filtration. Users are commonly treating liquid filters and gas filters differently although both are sterilizing grade. This behaviour is based on the actual version of EU guidelines §113 Proposed change: Sterile filtration of liquids and gases	Partly accepted. It has been clarified that the filters concerned in the guideline are those in contact with the drug product or any of the product components.
232	24	**Comment:** This content of the guideline exceeds the scope/ title of the guideline, which reads "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container". A remark that sterile filtration is used for aseptic processing could be made and the chapters "Sterile filtration" and "Aseptic processing" could be inserted as informative appendices. **Proposed change:** We apply to remove the chapters "Sterile filtration" and Aseptic processing" from chapter 4 and list them separately as appendices.	Not accepted. Sterile filtration is a sterilisation method, and aseptic processing is highly related to sterile products is better suited in this guideline rather than in the guideline on manufacturing of the drug product. This is reflected in the revised scope of the guideline (line 77).
233	18	**Comment:** Details such as number of filters, filter area, filter material are deemed not necessary as they are usually linked to equipment. It would also lead to	Not accepted. The text describes the level of detail expected in the dossier to enable assessment of the suitability of the process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		unnecessary variations every time a change in equipment is accompanied by a change in filter area. **Proposed change: Please modify the sentence to read: "**The type ~~**and number**~~ of sterilising filters ~~**filter area,**~~ material and nominal pore size should be described…"	
l233-235	3	Comment: It is necessary to accurately and completely specify the filtration system and its components. The original text is ambiguous. Proposed change : " ~~The type and number of sterilising filters, filter area, material and nominal pore size should be described~~ "**For each product and batch size thereof, the catalogue number and number of each sterilising filter should be specified**. ~~together with a description of the filter integrity testing.~~ **The filter integrity test procedure(s) should be specified** (principle of the test and details when the tests are performed including the test limits ~~before and after filtration~~).	Partly accepted. The catalogue number for filters may vary over time and is therefore not suitable to be stated in the dossier, therefore the first proposal with regards to description of the filter is not changed.
233-235	18	**Comment:** Details on filter integrity testing are under the scope of GMP and should not need to be presented in the marketing authorisation dossier as this is duplication of efforts and contributes to administrative burden. **Proposed change:** Please amend this sentence to have: "The type ~~**and number**~~ of sterilising filters ~~**filter area, material**~~ and nominal pore size should be described. ~~**together with a description of the filter**~~	Not accepted. The requested information is important for the assessment of the suitability of the process.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~integrity testing (principle of the test and details when the tests are performed including limits before and after filtration)~~"	
233-238	21	Comment: The Guideline describes that "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. in relation to the filter integrity test before use but after its sterilisation, Medicines for Europe would like to ask to take into consideration PDAs "Point to consider for aseptic processes- Part 1" Topic J and the relevant risk to apply preuse post-sterilization integrity testing (PUPSIT). The integrity of the sterilised filter before use is not always advisable due to the possible re-introduction of contamination especially for inline filling lines where steam in place is used as a method of sterilization. The pre-use post sterilization integrity test should be performed following a risk based approach based on	Not accepted. The revised text on integrity testing is in line with the GMP Annex 1 requirements.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the type of filter and sterilization method (Eg.-Gamma irradiated/single use filter of which the sterilization and integrity is certified by the filter manufacturers shall provide enough assurance level to avoid pre-use testing to avoid the risk of re-introduction of contamination) Proposed change (if any): Performing integrity testing of the sterilized filter pre-use should be performed as a risk based approach and properly documented. Origin, type of sterilization method and filter, single/multiple use risk factor have to be taken into account and properly justified. Additional factors to be taken into account are: 1. The validation of the filter integrity by the manufacturer. 2. The existence of a double filtration system i.e. 2 x 0,2 micron filters in parallel 3. A Pre-sterilization bioburden less than 100. 4. The performance of a post-filtration filter integrity test.	
235	4	Comment: Substitute "limit" by "acceptance criteria" to clarify that this refers to physical test data and not bioburden limits. Nothing being legal, it could be a	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level but because several criteria, we propose and recommend "acceptance criteria" Proposed change: ...when the tests are performed including **acceptance criteria** before and after filtration).	
235-236	1	Comment: 1. In certain systems the connections needed to perform the FIT may provide risk of contaminating the line downstream of the filter (i.e. hygroscopic product). This risk can be avoided with testing pre SIP and post-use. The potential risk of having a filter with initial pass test, being damaged during SIP and then getting clogged during use so that post use test is conform, is avoided when prefilters (which are to our definition 0.45 µm, not bacterial retaining) or a second (redundant) bacterial retaining filter are installed, retaining the "potentially filter-clogging" particulates. This scenario can be easily justified through Risk Assessment but is unclear which would be expectations for its "validation" 2. "immediate" is not feasible when working in campaign mode 3. Please clarify the wording, the use of 'but' is not clear Proposed change (if any): The integrity of the sterilised filter should be verified before use <u>but must be</u> after its sterilisation unless	Not accepted. 1. The revised text on integrity testing is in line with the GMP Annex 1 requirements and allows flexibility if specially justified and validated. 2. The sterilisation filter is expected to be exchanged between the batches. 3. The text implies that the filter should be tested for integrity after sterilisation but before the filtration of the solution.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		specifically justified, and should be confirmed after use in a timely manner	
235-236	3	Comment: The choice whether a filter is integrity tested before use and after the sterilization of the filter should be based upon risk assessment and be kept as a decision by the filter user. There is no description of what "specifically justified and validated" means, which will result in confusion and multiple ways of interpretation. Proposed change: ~~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~~. **The necessity of a pre-use post-sterile integrity test of a filter should be determined by a risk assessment process.**	Not accepted. The requirement is in line with GMP Annex 1.
235-236	15	Comment: The existing text states, *The integrity of the sterilised filter should be verified before use but after its sterilisation …..* The use and intent of the word 'verified' has been the source of much confusion over the years in relation to pre-use filter integrity testing. In using 'verify', is the intent to physically test filter integrity, or for example, to prove/confirm filter integrity by presentation of a filter supplier's test certificate? If the intention is that	Partly accepted. Additional clarification is provided, but the same phrasing as in GMP Annex 1 is kept to avoid confusion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		'verify' means 'test', then why not replace 'verify' with 'test'? Proposed change: Consider inclusion of a Note to clarify exactly what is meant by 'verify', i.e. is the intent to physically test filter integrity, or for example, to prove/confirm filter integrity by presentation of a filter supplier's test certificate.	
235 - 237	7	Comment: Whether a filter is integrity tested before use and after the sterilisation of the filter should be based upon risk assessment by the filter user. There is no description of what "specifically justified and validated" means, which may result in confusion and different interpretations. Proposed change: Delete the Sentence: "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." Replace with: "The necessity of a pre-use / post-sterilized integrity test of a filter should be determined by a risk assessment process."	Not accepted. The requirement is in line with GMP Annex 1.
235-237	13	Comment: *"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*".	Not accepted. The requirement is in line with GMP Annex 1. However, the text "unless specifically justified and validated" provides the possibility to justify different approaches (e.g. based on risk assessment).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Should be changed so pre-use sterilisation integrity test should be performed based on a comprehensive risk assessment for conducting or not-conducting the test. E.g. the risk of contaminating the filters, that otherwise are "ready to use" and pre-sterilised, might be high compared to the risk of the filters are delivered with contamination. Please see Points to Consider for Aseptic Processing, Part 1, January 2015, PDA – Page 48 – Topic J: Pre-Use, Post Sterilization Integrity Test of Sterilizing Filters (PUPSIT) for further argumentation. Proposed change: *"The integrity of the sterilising* ***filter should be confirmed immediately after use and the need of verifying*** *the integrity of the sterilisinged filter* ***before use*** *should be* ***based on risk assessment, executed by line and by product where the risk of conducting compared to not-conducting the integrity test should be evaluated. If the outcome is a need of integrity testing before use, then integrity should be*** *verified before use but after its sterilisation* ~~*unless specifically justified and validated, and should be confirmed immediately after use"*~~	
235-238	11	Comment: Cook Pharmica understands this guidance is meant to support dossier submissions and not GMP as stated in lines 71-73, however, the guidance is silent on batch acceptance if a failing post-use integrity result is obtained on the sterilising filter but	Not accepted. The issues are considered GMP related and are not within the scope of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a passing result is obtained on the pre-sterilising filter in a redundant sterile filtration (two 0.22 µm filters) setup. In the described redundant sterile filtration setup situation which would include two 0.22 µm filters inline, the testing and results obtained would be included in an investigation. If upon the completion of the investigation and the determination that the SISPQ of the batch was acceptable, would obtaining a passing result on the post-use integrity test on the pre-sterilising filter deem the batch acceptable, even though a post-use integrity test failing result was obtained on the sterilising filter? Proposed change: Beginning at line 237: "…immediately after use. *In redundant sterile filtration setups that may include one or more pre-sterilising filters immediately before the sterilising filter, the integrity of all filters should be verified before use unless specifically justified and validated. The post-use integrity should be confirmed immediately after use of at least one of the filters in the redundant sterile filtration setup, preferably the filter closest to the filling point in the final container.* Nominal pore sizes…"	
236	4	Comment: "…before and after is required for sterilization…". In these case, integrity test before use should be performed in aseptic conditions	Not accepted. This considered to be fundamental knowledge and is not necessary to state.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ...before use **in aseptic conditions** but after its sterilisation....	
237	4	Comment: 0.22 µm to be replaced by 0.2 µm, as 0.22 µm refers to a Millipore claim, and a pore size difference between 0.2 and 0.22 is not physically measurable. Proposed change: Nominal pore sizes **of 0.2 µm** or less are acceptable without further justification, in accordance with Ph. Eur.	Not accepted. 0.22 µm is in line with Monograph 5.1.1 in Ph. Eur.
237	20	Comment: During my more than 20 years of experience I have come across a lot of operators making mistakes during filter integrity testing resulting in quality deviations, if at all detected by QA. Most operator mistakes could have been avoided by a solid FMEA. The remaining part could certainly have been identified on an early stage by QA if a solid FMEA had been in place. After the words "confirmed immediately after use." on line 237 make a jump and insert the proposed change. The remaining words "Nominal pore sizes of 0.22 µm or less are acceptable without further justification, in accordance with Ph. Eur." should remain at the end. Proposed change:	Not accepted. The proposed changes are considered to be GMP aspects not covered in the scope of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In addition a risk assessment by e.g. Failure Mode Effects Analysis (FMEA) should be done to evaluate risks such as: - False passed integrity test results that could put the patient's life in danger - False failed integrity test results that could result in drug shortage - Cross contamination of the filter being tested from e.g. previous use of the integrity testing device - Impact on performed integrity test results in case of a calibration offset outside the predefined range at the yearly maintenance Tools and trainings should be developed to evaluate and mitigate the risks and quantify the impact in case of occurrence.	
239	18	**Comment:** Bioburden testing may be done at an earlier step in production in the case of biological products. The sentence seems to be written having chemically defined products in mind only. **Proposed change:** Please extend this sentence to also include the bioburden testing in the case of biological products for example: "For routine commercial manufacturing, **when applicable,** bioburden testing should be performed on the bulk solution immediately before sterile filtration."	Not accepted. The proposed wording is too vague. The guideline cannot cover all possible situations. Where the actual manufacturing process does not exactly fit with the guideline, the applicant should describe the differences and justify the proposed manufacturing and control principles.
239 - 243	22	Comment: I would like this document to be more closely harmonized with the FDA Guidance for	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Industry and clearly state that process bioburden should be evaluated and a risk assessment performed to determine whether *B. diminuta* is the most appropriate organism to use when validating the filter for microbial retention. Proposed change: Include additional 1-2 sentences to include that process bioburden should be reviewed in terms of ability to penetrate the sterilizing grade filter.	Information on the recommended test organism for filter retention validation is provided in Ph. Eur. and should not be duplicated in this guideline.
240	18	**Comment:** The sentence "immediately before filtration" is confusing because it is not clear whether it is related to a notion of time (for example: in case of holding time, the bioburden is to be performed just before the filtration) or to the process sequence (for example: between pre-filtration and filtration)? Please clarify.	Not Accepted. The text is in line with the Draft GMP Annex 1.
240 - 243	3	Comment: Pre-sterilising filter or pre-filtration can be misinterpreted. Proposed change: If ~~a pre-sterilising~~ **an additional** filter is installed, the filter closest to the filling …. The sampling for bioburden testing may be performed prior to ~~the pre-filtration~~ **the additional filter**, provided that no hold time is scheduled …"	Partly accepted. The phrasing has been revised to harmonise with that of GMP Annex 1.
242	22	Comment: Change "holding to "hold"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
244	4	Comment: The suggested bioburden limit of 10cfu/100ml is arbitrary and unrelated to filter retention capability. Propose that the bioburden limit is determined based on filter capability and lack of impact to product quality and patient safety. This would then impact lines 250-251 regarding sample volumes. Proposed change: **Pre-filtration bioburden acceptance criteria should be developed based on filter validation studies and no adverse impact** to product quality and patient safety.	Not accepted. Bioburden is not only related to filter retention capacity, it is also related to the endotoxin level of the finished product. The level is considered achievable for most manufacturing processes and the guideline allows for other limits if justified. A different limit should be approved by the competent authority.
244	8	Comment: "In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing". As this guideline is intended for both Small molecules and Biologicals, the statement above would benefit from further elaboration to acknowledge the case for certain products. In the specific case of high potency / low volume products (e.g. biotech proteins), there has been granted an allowance to relax the volume required for sterility sampling in order to balance the need for sterility sampling versus conservation of product. This is the case for a number of (recent and historical) licenced EU products. Proposed change: In order to specifically acknowledge such cases that are licensed already, I would	Partly accepted. The phrasing "Other testing regimes to control bioburden at the defined level" is included to allow other regimes, such as a combination of smaller sampling volume and tighter limit. Such a change in test regime should be justified, e.g. by statistical analysis and be approved by the competent authority.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		recommend QWP/BWP consider an additional sentence, for example: "In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing. **However, it is acknowledged that in exceptional cases (e.g. high potency drugs/biologics produced in small volumes), that a reduced sampling volume for bioburden testing might be justifiable on a case by case basis - to be agreed with the Agency".**	
244	13	Comment: "*In most situations, a limit of 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing*" By setting a limit with an exact number for CFU and the sample volume this gives a direct expectation for this parameter. The limit should be as low as possible taking the actual situation into consideration, e.g. the bioburden level of the incoming materials and the capacity of the filter (even though a high capacity shouldn't justify a high limit), the fact that pre-filter is used or not etc. Proposed change: ~~"*In most situations, a limit of 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing*"~~ ***"The limit for bioburden before filtration should be set as low as possible and justified taken the actual situation into consideration, like use of***	Not accepted. Bioburden is not only related to filter retention capacity, it is also related to the endotoxin level of the finished product. The level is considered achievable for most manufacturing processes and the guideline allows for other limits if justified, e.g. by inherent high bioburden of certain excipients. However, the microbial capacity of the filter(s) is not a justification for a widening of the limits. Also, the phrasing "Other testing regimes to control bioburden at the defined level" is included to allow other regimes, such as a combination of smaller sampling volume and tighter limit. Such a change in test regime should be justified, e.g. by statistical analysis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		double- and/or pre filter, the level of microbial contamination of the materials used, the size and retention capacity of the filters etc."	
244	23	Comment: The wording "In most situations" needs clarification. At this process step "prior to sterile filtration" EMA strongly proposes a limit of NMT 10CFU/100ml. For a lot of biological medicinal products, this represents a significant volume, e.g. the raw material "blood plasma" is ethically very valuable and of limited supply. Therefore a limit of e.g.: NMT 3 CFU/30 ml should be considered acceptable. Proposed change: ~~In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing.~~ A limit of NMT 10 CFU/ 100 ml (TAMC) is acceptable. If this limit cannot be met alternative limits may be applied with appropriate rational and justification based on the overall risk. ...	Partly accepted. See the responses to the same line to stakeholders 4, 8 and 13.
244-248	18	**Comment:** For veterinary industry it is really challenging to impose bioburden specifications to the raw material suppliers and/or to guarantee these specifications during use and storage. Applying bioburden limit of NMT 10 CFU/100 ml before the pre-filtration is very strict and is consequently a very high risk for this industry. On another hand, the pre-filtration is widely used and guarantees acceptable bioburden level (NMT 10 CFU/100 ml) prior to sterilising filtration. As long as the limit of bioburden NMT 10 CFU/100 ml is retained before the sterilising filtration, whether a pre-filtration is used or not, this	Not accepted. See the responses to the same line to stakeholders 4, 8 and 13.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be acceptable without further justification for this industry. **Proposed change:** Please amend these sentences to read: "In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing. ~~**If a**~~ A pre-filter is **often** added as a precaution only and not because the unfiltered bulk solution has a higher bioburden. ~~**this**~~ **Setting suitable limit may be** applicable also before the pre-filter and is strongly recommended from a GMP point of view. A bioburden limit of ~~**higher**~~ **not more than 100 CFU/100** ml before pre-filtration ~~**may be**~~ **is** acceptable; **higher limit may also be acceptable** if this is due to starting material known to have high microbial contamination." Please also clarify "as a precaution"	
244 - 250	3	Comment: In PDA's opinion the limit of 10 CFU/100 ml is not scientifically justified in all cases and recommends instead to require an understanding of bioburden (source, nature, concentration), robustness in the removal process, and impact on quality. Proposed change: Delete this section and replace as indicated. **Sterilising filtration must be validated to demonstrate complete removal of bioburden organisms under process conditions. Bioburden levels in front of the sterilising grade filter shall not exceed the validated limits. If necessary, additional filters can be used in front of the**	Not accepted. See the responses to the same line to stakeholders 4, 8 and 13.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		terminal sterilising grade filter to reduce the bioburden to an acceptable level. This reduction has to be tested and documented.	
245-246 Relates to 122-123	1	Comment: within the context of this guidance a "pre-filter" is not clear. Please confirm that 0.45 µm filters (not bacterial retaining) used to clarify solution or remove particulates is considered a 'pre-filter'. A second bacterial retaining filter (0.2 µm or less) is NOT considered a 'pre filter' but rather a redundant filter	Partly accepted. Reference is made to the definitions in GMP Annex 1.
244 -252	1	Comment: 1. Please provide explanation why for the sterile filtration the bioburden is set to 10 CFU/100 ml were as for steam and dry heat sterilisation the acceptable limit is defined as 100 CFU/100 ml. Although all methods are covered by Ph.Eur. 5.1.1 and the obligatory bacterial retention capacity of a 0.2 µm sterile filter is $10^7/cm^2$, which is significantly higher that what could be achieved even with a bioburden of 100 CFU/100ml 2. In API manufacturing the bioburden of the bulk solution is in general higher than 10 CFU per/100 ml due to micro-organisms that can be present in raw materials, API starting materials, or intermediates. A general limit of 100 CFU/100ml for the bulk solution should be acceptable and in a deviation case, justification should be provided and in case redundant filters (0.2 mm) are used in series it should be	Not accepted. 1.Sterile filtration processes are connected with aseptic processing which is associated with higher risk with regards to sterility. The microbial retention capacity is related not only to retention per area, but also to the filter area and the solution volume to be filtered. 2. The limit 10 CFU/100 ml is considered achievable using normal GMP procedures unless there is a specific source of microbiological contamination, such as a component with inherently high bioburden level. It also provides an assurance with regards to the endotoxin level in the finished substance or product. 3. The information provided in section 4 (including the sub-sections) is relevant for the drug product, substances and containers. The section has been amended to provide higher detail on which sections that are relevant to components and/or finished product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		acceptable to demonstrate that the first filter has the capability to achieve a bioburden prior to the last filtration of NMT 10 CFUs/100 ml. Also the volumina to be filtered, the retentive capacity of the used filter and the filter size should be taken into consideration 3. This suggested requirement on sterile API manufacturing should be covered in section 4.2	
247-247	4	Comment: By consistency with previous comments : 1) A bioburden limit of HIGHER than… 2) ...known to have HIGH microbial contamination. Proposed change: 1) A bioburden limit of **greater** than… 2) ...known to have **great level** of microbial **contaminants.**	Partly accepted. Higher and high is acceptable English language. The text is revised to state contaminants.
250	3	Comment: The 100 ml sample size may be valid for the microbial filtration test method, but other technologies allow smaller sample volumes. Proposed change: "Bioburden should be tested in a product sample of 100 ml in order to ensure the sensitivity of the method. **Smaller volumes may be used when justified.**"	Not accepted. See the comments to line 244 for stakeholders 4, 8 and 13.
250	4	Comment: Sample volume of at least 100 ml	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ...in a product sample of **at least** 100 ml…	See the comments to line 244 for stakeholders 4, 8 and 13.
250	18	**Comment:** In very small productions, the volume produced could be limited. More flexibility for the selection of adequate volume for testing purposes should be possible provided that the sample is representative. **Proposed change:** Please modify the sentence to read: **"**Bioburden should be tested in a product sample of 100 ml in order to ensure the sensitivity of the method **except for small productions, where other sample sizes could be considered**".	Not accepted. See the comments to line 244 for stakeholders 4, 8 and 13.
250-251	13	Comments: "*Bioburden should be tested in product sample of 100 ml in order to ensure the sensitivity of the method. Other testing regimes to control the bioburden at the defined level could be accepted if adequately justified*." Setting an exact limit for the test volume gives an unreflective expectation. It must be a matter of having enough sample material to perform the test in accordance with the analytical method and ensuring that the sample represents the bulk solution. The variation in bulk sizes varies a lot from less than one litre to more than 1000 litres why one common sample size seems inadequate. Based on this it is proposed to change the wording to the following:	Not accepted. See the comments to line 244 for stakeholders 4, 8 and 13.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ~~"*Bioburden should be tested in product sample of 100 ml in order to ensure the sensitivity of the method. Other testing regimes to control the bioburden at the defined level could be accepted if adequately justified.*"~~ ***"The volume of the product sample to test for bioburden should be sufficient to perform the bioburden test and appropriate to control the filtration risk considering the probability of any contamination higher than the limit for bioburden will be detected."***	
251	4	Comment: incubation regime for bioburden recovery Proposed change: ...sensitivity of the **validated** method **with a justified incubation regime**.	Not accepted. The text is not necessary. A control method should always be validated and justified.
253	5	Comment: Sentence could be open to misinterpretation – do we need to validate and show solution compatibility testing and leachable testing as part of validation. These tests are normally carried out in the filter selection phase where the data is generated to support selection. Proposed change: clarification required	Partly accepted. The data requested in the dossier with regards to the filter is now summarised in a table. If not stated otherwise in the guideline, the data may be presented in section 3.2.P.2 as part of the pharmaceutical development or in section 3.2.P.3 as part of the manufacturing (or in relevant section for an active substance or an excipient).
253	18	**Comment:** Concerning "Filter validation data should be included". This type of data pertains to GMP domain, is already available elsewhere and should not be primarily part of the product registration dossier. Duplication of data is resource demanding and could be seen as administrative burden.	Not accepted. The data requested is considered necessary to enable assessment of the dossier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Delete this sentence: **"~~Filter validation data should be included.~~"**	
253-256	1	Comment: Please clarify exactly which filter must be validated (sterilizing grade – NOT 0.45 µm pre filters)	Accepted.
253-256	3	Comment: Text revised for clarification. Proposed change: Change to read: "**In addition to microbial retention, filter validation data should include** bacterial retention capacity, solution compatibility and leachable filter materials. The solution to be filtered should be used in the validation unless justified, **for example when the solution is hostile to the challenge organism**. ~~(for instance when the pre-filtration integrity test is performed using water for injections during routine production)~~.	Partly accepted. Further clarification is provided.
254	22	Comment: Change proposed to line 254 re filter compatibility. Specifically, "The filter should be validated with regards to bacterial retention capacity, solution compatibility …" Proposed change (if any): The filter should be validated with regards to bacterial retention capacity, compatibility of the filter with the process fluid and parameters (e.g. maximum temperature, contact time)…"	Partly accepted. The data requested in the dossier with regards to the filter is now summarised in a table.
254	22	Comment: Change "leachable" to "extractable"	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Change "leachable" to "extractable"	Further clarification is provided when extractable data is sufficient and when leachable data is also required.
254-256	4	Comment: Clarify that product solution may be replaced by appropriate models of solution. Proposed change: The solution **(or at least the appropriate model of the solution to be filtered)** should be used in the validation unless justified ...	Partly accepted. Further clarification is provided.
254-256	15	Comment: The existing text states, *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)*. The text in brackets seems to be confusing the solution used for pre-use integrity testing and the product solution used during filter validation studies to demonstrate bacterial retention capability of the filter and product solution-filter compatibility. Proposed change - change existing text to: The solution to be filtered should be used in the validation unless justified, (for instance a surrogate solution might be considered for the bacterial retention capability studies where the product solution	Partly accepted. Further clarification is provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		has an antimicrobial effect on the challenge organism).	
257	1	Comment: As a criterion for use of a filter, 'time or duration' (one working day) seems not a suitable parameter, rather the volumina to be filtered, the retentive capacity, the exclusion size, the size and the related flow rates of the used filter should rather be taken into consideration.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since a filter is expected only be used for one batch, as stated in the revised draft GMP Annex 1. The time criterion is derived from GMP Annex 1. The guideline has also been rephrased for clarity.
257	22	Comment: Change sentence "If a sterilising filter is used for more than one working day or is re-used for additional batches, the…" Proposed change (if any): While typically not recommended, if a sterilising filter is used for more than one working day or is re-used for additional batches, the…." I believe inclusion that filter re-use is typically not recommended helps to harmonize this with the equivalent FDA Guidance Note (Guidance for sterile drug products produced by aseptic processing). It is also a difficult thing to validate as per cGMP so it is my opinion that we should not encourage this practice.	Partly accepted. A filter is expected only be used for one batch, as stated in the revised draft GMP Annex 1. The guideline has also been rephrased to increase the readability.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
257-258	4	Comment: Filtration time could be linked with filling time (Point of Use Filter) and can be > a working day (24h) for large batch size. Bacterial Challenge validate this duration. For pre filtration that reduce bioburden and other filtration not linked to filling operation, the 24 hours limit can be applied. Proposed change: If a sterilising filter**, other than the Point of Use Filter**, is used for more than ...	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
257-259	1	Comment: Please clarify requirements and acceptability in case manufacturing of sterile products is done in campaigns. Please confirm that within the same campaign re-sterilisation before re-use is not required.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
257 - 260	10	Comment: The proposals to re-use and re-sterilise filters, in the context of campaign aseptic batch manufacture should be reviewed to ensure they are sufficient and consistent with GMP.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
257-264	3	Comment: PDA proposes the following changes for clarification. Proposed change: "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~~ **and the filtration process validated to show performance robustness**. If re-	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		used, the filter should be dedicated to ~~a single~~ **one** product, **thoroughly cleaned and** sterilised before re-use. **The cleaning and sterilization of the filter must be validated. The process validation of the filter should include bacteria retention studies with the product or a challenge fluid as close to the product composition as possible using the actual operating parameters. The validation study should encompass the maximum filtration, cleaning and sterilization cycles the filter is subjected to.**	
257-264	18	**Comment:** Again these GMP documentation are available e.g. in the validation dossiers and is the subject of GMP inspections as well. In addition providing this information in the registration dossier may lead to unnecessary variations in the case of change of filter or changes being effected on the process. We feel that providing documentation in duplicate or triplicate is efforts and resources demanding and increases the level of administrative burden. **Proposed change:** Please modify these sentences to read: "Suitable evidence of the bacterial retention capability after challenging the filter system to simulate exposure during a campaign should be provided **on request if required to assess the quality of the product with regards to GMP conditions**. This simulation **could** ~~**should**~~ include	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.”	
258	22	Comment: If re-used, the filter should be dedicated to a single product and sterilised before re-use. Proposed change (if any): If re-used, the filter should be dedicated to a single product and cleaned and sterilised before re-use. If a filter will be re-used, it is important to perform cleaning of the filter between batches.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
259	4	Comment: In the case of 2 batches without dismantling the terminal filter… Proposed change: **Thank you to remove these words** "… and sterilized before re-use."	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
259-260	1	Comment: For campaign manufacturing, integrity test “after use” may be performed just at the end of the campaign and not necessarily after each batch produced (e.g: when the execution of the FIT is not ensuring that the downstream side of the filter remain sterile) Proposed change (if any): Its integrity should be tested before and after use.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
260	4	Comment: In case of 2 successive batches without dismantling the terminal filter… each use is an issue. Proposed change: Its integrity should be tested before and after **use or at least at the end of the campaign.**	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
260-261	22	Comment: Suitable evidence of the bacterial-retention capability after challenging the filter system to simulate exposure during a campaign should be provided. Proposed change (if any): Propose that an additional sentence should be added to clarify the definition of "campaign" in this context. For example "Suitable evidence of the bacterial-retention capability after challenging the filter system to simulate exposure during a campaign should be provided. Under these circumstances, a campaign refers to the total amount of batches that a filter will be used for before being discarded". As it currently reads, it is unclear if a campaign means one batch, or the entire number of batches to which the filter will be used.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
261 - 263	22	Comment: The sentence "This simulation should include any physical handling of the filter during its use, such as maximum combined sterilisation time …" could create issues for the end-user in attempting to	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		validate the maximum combined sterilisation time. As per regulatory expectations, during microbial retention studies, 47-mm filter discs are typically used, which are not intended to be sterilised multiple times. Proposed change: Potentially modify paragraph to indicate that the end user would be responsible for providing used process filters that had been exposed to the entire multiple use campaign (including multiple sterilisation cycles).	GMP issue. This aspect is covered in the revised draft GMP Annex 1.
262	4	Comment: Simulation performed at filter supplier level do not include all maximum working conditions. Remove "such as maximum combined …" Proposed change: **Any physical handling of the filter during its use, such as sterilisation time and temperature, integrity testing, mechanical handling and maximum filtration volume at maximum pressure should be considered in the simulation**	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
263 - 264	22	Comment: With reference to the sentence "…and maximum filtration volume at maximum pressure", perhaps reword to indicate that worst-case processing conditions should be included in the simulation, with consideration given to maximum filtration volume, pressure and/or flow rates.	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): It is suggested that the re-worded sentence (above) will allow the end-user to carefully design their microbial retention studies based on their actual process runs where there may be pressure gradients etc involved. The way this sentence currently reads implies that maximum pressure would be needed for the entire simulation run, which may not be an accurate portrayal of the process in question.	
264	4	Comment: Lines 257 to 264 describe filter re-use but not pay attention to the behaviour of the DP components during filter resterilisation (DP impregnated in the membrane) appropriate procedure as rinsing and /or evidence of no degradation products in the following batches should be provided Proposed change: **Thank you to remove these words"** …and sterilized before re-use…" and "…after…."	Partly accepted. The section on use of a filter for several batches has been deleted from the guideline since this is considered to be a GMP issue. This aspect is covered in the revised draft GMP Annex 1.
265	4	Comment: Is holding time applicable between1st and 2nd sterile filtration or between preparation and 1st filtration? Proposed change: **Each** maximum holding time between bulk solution preparation **and filtration and between filtration if applicable** should be stated, and appropriately supported by data.	Partly accepted. Both types of holding time mentioned are considered.
265 - 266	1	Comment:	Partly accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please clarify what is expected in case there are multiple filtration steps in a row i.e. 0.45 µm for particle reduction and 2 sterilising grade filters in a row.	Clarification is provided in the guideline.
265-266	5	Comment – bulk solution preparation can mean many different things. Perhaps a modification to the text to clarify what is meant by the term "bulk solution preparation" – is this the expiry of the bulk or is it a different time period that is related to sterile filtration (for example removing bulk from a refrigerated condition and allowing it to come to room temperature prior to sterile filtration)? Additionally, there should be no requirement to minimise this time period if data is available to cover the time period; The maximum holding time between bulk solution preparation and sterile filtration should be stated minimized and appropriately supported by data.	Partly accepted. Further clarification has been provided. In line with GMP any holding times should be justified and supported by data.
266 and 274	4	Comment: Remove the notion of minimized time. Proposed change: Please delete: The times should be minimised.	Not accepted. The requested data is in line with GMP Annex 1.
267	2	Comment: The terminology "immediately" is too vague and should be replaced with "within 24 hours". Proposed change: "….not filled within 24 hours into… ".	Accepted.
267	22	Comment: The sentence "If a sterile bulk solution is not filled immediately into the final product	Partly accepted. Different wording.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		containers…" needs definition of the word "immediately" for clarity. Proposed chane: "If a sterile bulk solution is not filled immediately (i.e. within 24 hours) into the final product containers…" needs definition of the word "immediately" for clarity.	
267-268	1	Comment: Please clarify what is expected in case after sterile filtration of the bulk solution several manufacturing steps (under aseptic conditions) are required to yield the product	Accepted.
267-268	18	**Comment:** The meaning of "immediately" in this sentence is unclear. The notion of immediate is very vague and subject to interpretation. In addition, the sterile filtration process is carefully validated by the companies. In the case a holding time is envisaged, all measures are taken to preserve the sterility of the product. This holding time is part of the validation exercise and has been demonstrated to be safe. **Proposed change:** Please delete this sentence and modify to have: "~~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~~. **The maximum holding time between sterile bulk solution and filling should be stated, minimised and appropriately supported by data**".	Partly accepted. The guideline has been amended with a time limit. The need for holding times above 24 hours should be justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
268	22	Comment: With respect to the sentence "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." If the bulk is re-filtered using a second filtration step, consideration should be given to potential filter extractables (essentially, this could double filter extractables into the final bulk). Proposed change (if any): Include a further sentence to indicate that if a second sterile filtration step is performed, consideration must be given to the impact on the final bulk solution (e.g. filter extractables).	Partly accepted. Further clarification on data requested for different types of filters has been provided.
272	4	Comment: add barrier technologies and/or closed systems should be strongly recommended to minimize microbial contamination from the most important source i.e. operators Proposed change: Most important source of microbial contamination is operators, it is recommended to use barrier technologies **(isolators and RABS closed in operation) and/or closed systems.**	Accepted.
272	4	Comment: It is not contamination (operation which contaminates) but contaminants Proposed change: ...without adding any **microbiological contaminants**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
273-274	4	Comment: By consistency please replace limit by acceptance criteria Proposed change: Hold time between washing and sterilization of equipment used in aseptic processing also needs to have an established (validated) **acceptance criteria.**	Not accepted. The text discussed was not found in the guideline
273-277	1	Comment: Please clarify how this shall be handled in case sterile API is used for drug product manufacturing and only aseptic processing is performed.	Partly accepted. In this case only the filling time is relevant. In exceptional cases when the same container of sterile substance is used on several occasions, that holding time would also be relevant.
273 – 277	6	Comment: Holding times should be limited based on risk and process needs. A pre-defined limitation for "not more than 24 h" is arbitrary and not risk-based.	Partly accepted. Minimisation of holding and filling times is important. Longer times than 24 hours are not prohibited, but need to be justified by risk analysis.
274 – 377 388	6	Comment: Ph. Eur. specifies two alternative but equivalent methods to obtain terminally sterilised products: Current chapter 5.1.1 of Ph. Eur. in the section "Steam sterilization (Heating in an autoclave)" explicitly mentions that – beside the reference cycle (121 °C / 15 minutes) - "other combinations of time and temperature may be used for steam sterilization, provided that it has been satisfactorily demonstrated, that the chosen process delivers an adequate and reproducible level of lethality when operating routinely within the established tolerances".	Not accepted. The Ph. Eur. states that "Sterilisation process conditions are chosen to achieve the highest level of sterility assurance compatible with the drug product". Thus, even though different sterilisation cycles are accepted, they are not considered equivalent and the method with the highest level of sterility assurance should be chosen. Cycles using the reference conditions achieve the highest level of sterility assurance and are thus the first choice. As stated in the guideline, GMP requirements are generally not described (such as general validation requirements), but only the requirements that needs to be elaborated upon in the dossier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Other combinations of time and temperature" are accepted, if "procedures and precautions employed are such as to give a SAL of 10E-6 or better". With the introduction of the "Sterility Assurance Level of SAL 10-6 or better" besides the established "reference cycle of 121 °C / 15 minutes" Ph. Eur. has outlined in principle two alternative but equivalent pathways to obtain sterile products. Ph. Eur. does not limit the choice for the alternative cycle for any reason. The current valid EM(E)A paper "Decision tree for the selection of sterilization methods" finalized in 1999 and slightly modified in 2000 did not take into account the two compendial and equivalent moist heat sterilization cycle approaches. In the draft guideline "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" (line 203- 309), in line with Ph. Eur. requirements. But the upper part of the decision tree has not changed from the previous version of the guideline, although the concept has changed substantially to demonstrate sterility for moist heat sterilisation processes. Using other than reference cycles conditions require more data, but reference cycle shall	In addition, the concept of post-aseptic processing terminal heat treatment (previously called terminal microbial reduction process) has been further elaborated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not be made the primary method of choice of sterilisation process development. "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 are not required. In all other cases physical and biological validation of the sterilisation cycle should be provided to demonstrate a SAL of 10E-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" (line 140 – 144). Proposed change : Can the medicinal product be sterilized by moist heat to achieve SAL of 10E-6 or better? In case **YES**, the applicant shall use the most appropriate moist heat sterilisation process selecting the appropriate sterilisation condition in the range between reference cycles and minimum requirements of a Fo >= 8 minutes and a sterilisation temperature >= 110 °C. Depending on the process chosen, the documentation submitted shall vary (see 4.1, lines 140 to 144). Minimum documentation shall be required for the reference cycle.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In case **NO**, the option sterile filtration also in connection with microbiological reduction processes shall apply.	
275 - 276	7	Comment: The low risk of microbial contamination should be stated instead of stating that contamination is not possible. No method of processing is capable of eliminating all contamination risk. Proposed change: Modify the sentence (delete and insert underlined where noted) as follows: "The grounds for holding times longer than 24 hours should be justified and evidence should be provided demonstrating that <u>there is a low risk of</u> microbial contamination ~~is not possible~~ during processing, (e.g. tightness of tanks, plumbing, any transportation of storage tank and storage conditions)."	Partly accepted. The section has been re-written to state that longer holding and filling times should be supported by a risk assessment.
276	22	Comment: Referring to "tightness of tanks" seems a bit ambiguous and could not really be demonstrated. Proposed change: Perhaps replace "tightness of tanks" with "integrity of sealing / structure".	Partly accepted. The section has been re-written to state that longer holding and filling times should be supported by a risk assessment.
278	4	Comment: The media fill simulation is suitable to validate filling times during interventions in the filling area, but not holding times in closed vessels as sterility assurance is related to individual vessel	Partly accepted. The section has been re-written to state that longer holding and filling times should be supported by a risk assessment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		tightness after each set-up and can only be confirmed by appropriate physical testing covering each use on production batches. Proposed change: It should be confirmed that the results of the media fills support the proposed filling times **including interventions and activities in filling area. Holding times in closed vessels and systems should be based - after each set-up and sterilization – on appropriate physical protection (maintained and alarmed overpressure) or testing (tightness, leak testing) covering the use on production batches.**	
279	5	Comment: There is an acceptance for aseptic processing that media fill results fall within the field of GMP which is somewhat in contrast to the description and level of detail requested for sterile filtration. Have we thought carefully for sterile filtration what data/information falls within the field of GMP and what are necessary for the regulatory submission?	Partly accepted. The full evaluation of media fills should be performed in relation to on-site inspections, since it is not possible to evaluate by the assessor. However, in order to assess acceptable holding and filling times some information may be necessary to include in the dossier.
282	1	Comment: Please provide more information regarding expectation on sterile primary packaging materials	Accepted.
282	2	Comment: As explained in line 103 this sterilisation procedure of primary containers needs to be well documented in Module 3.	Not accepted. Repetition of information is avoided in the guideline. In addition, the need for sterile containers in relation to aseptically processed products should be well known to the manufacturers.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please consider to repeat or refer to the information in line 103-104.	
282	4	Comment: as for the holding time of the product the sterility of the primary container should be verified at the point of use Proposed change: ...products. **For ready to use (RTU) primary packaging materials the maintenance of the evidence of integrity to maintain the sterility shall be verified at the point of use.**	Not accepted. This is covered by GMP.
284-285	17	Comment: It is not clear how the bioburden should be controlled. Proposed change: Acceptable limits should be provided.	Not accepted. There should be no bioburden in relation to aseptic processing since the materials that are processed should be sterile. Where established bioburden criteria are available, they are presented in connection with the sterilisation method.
286-301	3	Comment: As written, this section is confusing and seems to require more than GMPs. GMP inspection is not mandatory for active substance manufacturer. Proposed change: Suggest using exactly the text from the current GMPs or providing reference to specific current GMP sections.	Not accepted. A GMP certificate is requested for the site performing the sterilisation of the active substance
286-301	14	Comment: This paragraph is in contradiction to the scope of the guideline, see lines 72- 73: "General GMP requirements are not included." Furthermore,	Partly accepted. Insurance of compliance with relevant GMP requirements is requested in the application.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the sterilisation of an excipient does not fall under GMP guide part I. Proposed change: ~~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.~~	The text has been revised to provide guidance on GMP requirements for Active substance, excipients and containers required to be sterile. Sterilisation of active substances should be performed in compliance with GMP Part 1 and GMP Annex 1. For excipients and containers a GMP certificate should be provided when available. Clarification is provided on the information requested to ensure satisfactory GMP compliance when no GMP certificate is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
286-301	16	Proposed change: ~~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~~ 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 for any active substance manufacturer who performs sterilisation and subsequent aseptic handling of the active substance has to be submitted. Rationale for change: The paragraph is in contradiction to the scope of the guideline, see lines 72- 73: "General GMP requirements are not included." General GMP rules cover this section. Therefore, we propose to delete parts of this paragraph from the drafted guideline at this stage. Please delete/ rework this paragraph. Proposed change: ~~Similarly, for sterile excipients, any sterilisation and aseptic processing should be performed in accordance with GMP for medicinal products with the same~~	Not accepted. Insurance of compliance with relevant GMP requirements is requested in the application. The text has been revised to provide guidance on GMP requirements for Active substance, excipients and containers required to be sterile. Sterilisation of active substances should be performed in compliance with GMP Part 1 and GMP Annex 1. For excipients and containers a GMP certificate should be provided when available. Clarification is provided on the information requested to ensure satisfactory GMP compliance when no GMP certificate is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~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.~~ Rationale for change: This could be misleading because the sterilisation of an excipient does not fall under GMP guide part I. Therefore, we propose to delete this general remark too. Please delete this section.	
288	5	Comment: We make no reference to Drug product intermediates but comment on drug substance and excipients Proposed change: include drug product intermediate	Not accepted. The requirements for the sterilisationof intermediates is in line with those related to the drug product.
288 - 296	5	Comment: The requirements for drug substance to be sterilised in facilities which hold a manufacturing authorisation, and operate according to GMP for drug product manufacture is clearly stated. What is unclear is what, where and how information should be presented in M3 e.g. is the expectation that information on drug substance sterilisation should be placed in the drug product section of the dossier? This has implications on post approval management of the submission. Please clarify expectations. It	Accepted. Clarification has been provided on where in the dossier structure the information should be provided, i.e. if a reference is provided in CTD 3.2.P.3/NtA Part 2, the actual information may be provided in relation to the information on the active substance, excipient or container as applicable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would be preferable for proposal to be consistent with post approval variation guidelines.	
288-296	5	Comment: It would help if a regulatory agency make it clear where they expect the actual information to sit in the dossier. There is good clarification around GMP certificate but no comment on quality modules. Proposed change: Include clarification	Accepted.
288-296	5	Comment: Are we missing an opportunity here – manufacturers who have certificates of suitability for sterile manufacture often make sterile multiple substances/products via similar/identical sterilisation processes and very few parts of the process are different subject to the requirements of the substance/product (e.g. solvents, temperature etc). Would it not be better if the GMP file was routinely updated but only the process steps specific to the product were included in the regulatory file. It could reduce the PAV burden but also encourage better CPV in process improvement? Proposed change: thought for consideration.	Not accepted. This would need a regulatory process similar to ASMF, this is not possible within the EU legal framework.
288-300	1	-how should this be interpreted: If we have an API that is manufactured chemically (non sterile) and then sterilized by irradiation, should the sterilization part be seen as DP production or DS production? Which	Partly accepted. Clarification has been provided in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		guidelines are applicable and what are the expectations?	
290-292	5	Comment: The guidance that the sterilisation & aseptic processing of drug substances is considered to be a step in the manufacture of the medicinal product has already led to confusion concerning where active substance sterilisation info should be presented in M3. AstraZeneca have also received requests to submit drug product variations for changes to sterilisation & & aseptic processing of drug substances. Proposed change: Add clarification that this guidance relates to GMP & that from a M3 & post approval variation perspective, this should be managed as active substance/3.2.S.	Accepted. Clarification has been provided on where in the dossier structure the information should be provided, i.e. if a reference is provided in CTD 3.2.P.3/NtA Part 2, the actual information may be provided in relation to the information on the active substance, excipient or container as applicable.
296	26	Comment: The following sentence should be added*: "Full validation data on sterilisation process is requested in the quality dossier of the applicant/MAH (in cases where there is no further sterilisation of the final product). These data should be included in sections 3.2.P.3 Manufacture for human products or Part 2 B Description of the manufacturing method for veterinary products." *cf. Q&A on Quality, Part 1: Active Substance - Good-manufacturing-practice compliance for sterilisation of an active substance	Partly accepted. Clarification has been provided on where in the dossier structure the information should be provided, i.e. if a reference is provided in CTD 3.2.P.3/NtA Part 2, the actual information may be provided in relation to the information on the active substance, excipient or container as applicable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000071.jsp&mid=WC0b01ac058002c2af and Guideline on ASMF procedure (CHMP/QWP/227/02 and EMEA/CVMP/134/02, foot note to table 2)	
300-301	5	Comment: It would be valuable to add a little more guidance here to reduce duplication of reviews by both EDQM & EU assessors for MAAs/variation applications. AstraZeneca have received requests related to MAA/variations to provide the sterilisation & validation information that has previously been assessed by EDQM. Proposed change: Provide confirmation that where CEPs are available for sterile active substances or excipients, it is not necessary to resubmit the information (to support MAA/variations) concerning sterilisation & aseptic processing of active substances and excipients in Module 3.	Accepted. Even though the sterilisation process is evaluated by the EDQM in relation to the CEP procedure, the sterilisation of the drug substance is considered vital for the quality of the drug product. In order to ensure that the drug product manufacturer has sufficient knowledge to evaluate the sterilisation process for the drug substance in relation to the quality of the drug product, information on the sterilisation process should also be submitted in the authorisation application for the drug product.
302	4	Comment: Title: Selection of sterilisation method What proposed are processes and it is included Aseptic process and Microbial reduction process not allowing to achieve the goals of the sterilization process.	Not accepted. Sterilisation is considered as the superordinate term and should be therefore used in the heading of the chapter. The basis of an aseptic process is that the individual components are sterilised before. The heading of this chapter is maintained.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Modification of the title: "Selection of **microbial reduction process, sterilisation and aseptic process."**	
302-313	25	My question relates to your new draft "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container" http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500204724.pdf When reading the document, especially the 2 first paragraphs of chapter 4.3, my interpretation is that alternative method of terminal sterilization (e.g. ionising radiation) can be considered whatever is the product (aqueous or non-aqueous). But when reading the decision tree for aqueous products, there is no option for ionizing radiation terminal sterilisation, only heat and if not possible, sterile filtration. The option for ionizing radiation is mentioned only in the decision tree for non-aqueous products. So my question : how shall I interpret the absence of ionizing radiation option in the decision tree for aqueous products? Is it possible to consider a terminal sterilization by ionizing radiation (>=25 kGy) for aqueous products? And if yes, where would it appear in the decision tree, just after F0>=8min?	The comment is noted. According to the GMP Guidance irradiation sterilisation will only be permissible if the absence of deleterious effect on the product is demonstrated. Irradiation of aqueous solution leads to radiolysis of water forming hydrogen peroxide. Therefore, in general, irradiation of aqueous solution is not proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
303-309	1	Comment: Paragraph is not in line with Ph. Eur. 5.1.1. since stated requirements are stricter. Please adjust to Ph. Eur. 5.1.1..	Not accepted. Heat sterilisation is the most robust sterilisation method and should thus be used whenever possible.
Section 4.3	18	**Comment:** As it is written and presented, this section, questions the aim of developing a drug product: indeed, up to now, the aim is to develop a stable formulation adapted to the treatment of a given pathology, focused on species, adapted to users; now this guideline asks to develop a formulation to be terminal-sterilised by sacrificing stability, shelf-life, storage conditions, packaging innovation and specificity to veterinary use. This is definitively not the primary aim of the formulation development to target a formulation capable of undergoing terminal sterilisation. At the end of the formulation, the composition of the product is defined leading to one proposal (one stable formula with draft specifications), but there are a significant number of other attributes that are not fixed leaving some flexibility in the next steps of the development: the potential primary packaging, the potential manufacturing processes, and only at this stage the possible methods of sterilisation are checked. At this stage, the sources of API, excipients are not fixed (microbiological quality could depend of the source); manufacturing scale up could show several degradation pathways. Focusing all the attention on a formula for the sterilisation method could lead to a deficient	Not accepted. The request for chosen the best sterilisation method with the highest SAL is not a new requirement. It is requested in Ph. Eur., 5.1.1 and was already stated in the Decision tree for selection of sterilisation methods attached as Annex to GL on pharmaceutical development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		formulation with a product not fulfilling the quality, efficiency and safety attributes. This would also lead to a dangerous workload for timing of development, and with potential necessity to restart all studies due to scale up results. **Proposed change: IFAH-Europe would strongly recommend reviewing section 4.3.**	
306	1	Comment: sterile filtration as an accepted sterilising method is missing here. Aseptic processing is not a sterilisation method (Ph.Eur.5.1.1) Proposed change: When terminal sterilisation by heat is not possible, the application of an alternative method of terminal sterilisation or sterilising filtration ~~and/or aseptic processing~~ may be considered.	Not accepted. The term aseptic processing could include also sterile filtration. Please refer to section 1 "Introduction" where it is stated that sterile filtration and aseptic treatment are closely related and difficult to handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related.
306-309	15	Comment: The current text states, *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.* We agree with this statement; however, further clarification is required – the alternative sterilisation processes should be 'properly designed, validated and controlled', rather than just 'properly validated'.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: 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 designed, validated and controlled.	
310-313	16	Proposed change: 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~~ regulatory advice regarding the scientific acceptability of the method and the documentation required.	Not accepted. Previous phrasing is more general and refers to the possibility to apply for scientific advice by a regulatory authority.
310-313	21	Comment: The Guideline states that "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	Comment is noted. In section 6 "Definition" of the GL, steam sterilisation is defined by reference to the description in the Ph. Eur., 5.1.1. In the current Ph. Eur., section 5.1.1 it is mentioned that superheated water spray can be used to achieve heat transfer in autoclaves intended for the sterilisation of closed containers.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		acceptability of the method and the documentation required". Medicines for Europe would like to highlight that water spray sterilization is not described as one of the listed sterilization techniques and it is not clear if EMA handles steam and hot water spray under the same principle. Proposed change: Please clarify whether steam and hot water spray are handled under the same principle.	
314	5	Comment: Lack of clarity around what substantial efforts mean. Are the authorities looking for companies to carry out actual manufactures to prove terminal sterilisation is viable or would justification via forced degradation work be sufficient? The paragraph reads as if specific studies or actual manufactures are required.	Comment is noted. In the revised GL it is mentioned what substantial efforts means (e. g. selection of optimal pH, choice of excipients, containers, optimisation of sterilisation method and manufacturing conditions). Forced degradation data may be sufficient for highly heat sensitive products, whereas sterilisation trials may be needed for more stable products.
314-319	1	Comment: Please state and clarify what is expected for legacy and/or long established and marketed products.	Comment is noted. The GL is only proposed for new applications (including generics) or variations concerning the change of the sterilisation method. The GL does not apply retrospectively. Please refer to the proposed "Executive summary" where this is laid down.
314 – 319	5	Comment – for a biologic the suggestion/requirement for a "… substantial effort should be made to enable	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		terminal sterilization" only adds to the complexity and expense of the development process. Formulation development should be understood to prioritize drug delivery and stability without compromising manufacturability, which would include sterilization of some type. Terminal sterilization should not be singled out as a preference from the agency if all of the listed sterilization types are acceptable with supporting data.	For highly sensitive biologicals which could not be terminal sterilised this section is not applicable. Please refer to next paragraph of the GL where it is stated "In case of medicinal products containing highly sensitive active substances, (e.g. proteins or other 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 treatment discussed later in section 4.3 may not be needed."
314 - 319	7	Comment: Justifications for not using a terminal sterilisation cycle should be based on a scientific rationale and risk assessment. Manufacturers should have more flexibility to assess the feasibility of the terminal sterilisation cycle. Proposed change: Revise the wording as follows (delete and insert underlined where noted): "During the manufacturer's evaluation of whether a terminal sterilisation cycle is possible, ~~substantial~~ reasonable efforts should be made to enable terminal sterilisation. If the active substance or some key component of the formulation is shown to degrade ~~significantly~~ unacceptably or an impurity ~~limit~~ result is ~~exceeded~~ unacceptable 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."	Not accepted. Wording has been maintained. However, in the revised GL it is clarified what substantial efforts means (e. g. selection of optimal pH, choice of excipients, containers, optimisation of sterilisation method and manufacturing conditions).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
314-319	14	Comment: An addition is considered necessary to make it clear that the evaluation is only necessary at the development stage of a new drug product. Proposed change: During the development of a new drug product, the manufacturers shall evaluate whether a terminal sterilisation cycle is possible, and if so 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 of undergoing terminal sterilisation~~ The results of the evaluation should be presented in the development section of the original MAA.	Not accepted. Please refer to the "Executive summary" where it is mentioned that the GL is only proposed for new applications or variations. The GL does not apply retrospectively.
314-319	16	Proposed change: During the manufacturer's evaluation of whether a terminal sterilisation cycle is possible, substantial efforts should be made to enable terminal sterilisation within the development of a new drug product. ~~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~~	Not accepted. Please refer to the "Executive summary" where it is mentioned that the GL is proposed for new applications (including generics) or variations. It should be evaluated for each marketing authorisation application whether the sterilisation process is suitable for the applied product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~formulation of undergoing terminal sterilisation should be presented in the development section.~~ Rationale for change: This sentence should be completed and the next section deleted because it cannot be applied on the development / manufacturing of generics / hybrids where the demonstration of essential similarity is the pre-condition for receiving a marketing authorisation. The production process is developed not only with regard to the microbiological quality but also to guarantee the necessary chemical-physical and pharmaceutical quality properties of the finished product.	
317-319	18	**Comment:** See comments on section 4.3 above. **Proposed change:** Please also delete this sentence: **~~"the efforts made to develop a formulation capable of undergoing terminal sterilisation should be presented in the development section"~~**	Not accepted. The efforts made to enable terminal sterilisation should be presented in the dossier.
320	2	Comment: proteins are intrinsic heat labile as is the case with other biological products (e.g. vaccines). Proposed change:"… proteins and other heat labile……"	Accepted.
320	5	Comment: should antibiotics also be included in the e.g. class?	Not accepted. Antibiotics in general should not be mentioned here as some antibiotics could be terminal sterilised at least per F0 concept (e.g. Linezolid, Moxifloxacin).
320 - 323	1	Comment:	See the comment to line 320 made by stakeholder 5 above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please confirm that this is also applicable for antibiotics and/or legacy product.	
326	1	Comment: Sterile filtration is missing here. Aseptic processing does not is not a sterilisation method. Proposed change (if any): For products where terminal sterilisation is not possible, filtration through a bacteria-retentative filter is proposed, ….	Not accepted. The term aseptic processing could include also sterile filtration. Please refer to section 1 "Introduction" where it is stated that sterile filtration and aseptic treatment are closely related and difficult to handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related.
326-327	18	**Comment:** In the case of sterilisation of individual components of the formulation for products where terminal sterilisation is not possible, the application of decision trees is not relevant. The decision trees objective is to promote as much as possible the use of terminal sterilisation of the finished product in final packaging and avoid aseptic processing when possible. But, this will never be the case for sterilisation of individual components that will be further used in aseptic processing, and the global manufacturing method should be considered (e.g. for suspensions: sterilisation by filtration of the solubilised excipients before addition of the sterile active substance in the manufacturing tank offers better global SAL than handling of each individual components in the aseptic environment).	Not accepted. Also for aseptic processing, the sterilisation method which has the highest SAL should be used for sterilisation of the individual components or mixture of components of the formulation, if possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please delete this sentence: ~~**"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."**~~	
326 - 333	7	Comment: Reference to a terminal microbial reduction process at the end of an aseptic process (also included in the Decision Trees) may imply that this is preferred from a regulatory point of view. Based on the well-documented successful and safe application of aseptic processing for many years, there is no scientific or risk-based justification for the need for the application of a terminal microbial reduction process or other lethal treatment process after aseptic processing. Accordingly, aseptic manufacture alone can provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated "terminal sterilization" or other lethal treatment conditions. Baxter endorses the revised Decision Trees as proposed by PDA. Proposed change: Modify the paragraph as follows: "For products where terminal sterilization is not	Not accepted. The usage of a terminal heat treatment is not a new request. Terminal heat treatment is already mentioned in Ph. Eur. 5.1.1 and is in accordance with GMP requirements. Please refer to Annex 1 of Guideline to GMP for Humans and Veterinary use, section "Filtration of medicinal products which cannot be sterilised in their final container", point 110 where it is mentioned that "Consideration should be given to complementing the filtration process with some degree of heat treatment". Terminal microbial reduction process (now phrased "post-aseptic processing terminal heat treatment") should therefore be included in this Guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		possible and aseptic processing is proposed, the decision trees should be considered to be applied to the individual components of the formulation. ~~Also, the possibility of applying a terminal microbial reduction process may be evaluated. It is emphasized 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 as additional microbial reduction process. In case of 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.~~"	
326-333	14	Comment: The second part of this section is contradictory to the GMP-requirements and should be deleted. Proposed change: 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~~	Not accepted. See the comment to the same lines by stakeholder 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~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.~~	
326-333	16	Proposed change: 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.~~ Rationale: This section is contradictory to the GMP-requirements and should be deleted. A microbial reduction process cannot be validated, because neither the type nor the quantity of such casual and sporadic contaminants is known. There is	Not accepted. See the comment to the same lines by stakeholder 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		no increase in product quality due to such a further non-validated germ-reduction process.	
327	1	Comment: Sentence applies for drug products only (formulation).	Accepted. See the comment to lines 326-333 by stakeholder 7. The section starts with "For finished products…".
328	18	Comment: Without definition of performance objectives, the application of a "terminal microbial reduction process" has no scientific rationale (see also comments on line 388 and line 394). Proposed change: Please remove any reference to this microbial reduction process in the guidance or clarify the performance objectives.	Partly accepted. See the comment to lines 326-333 by stakeholder 7. The performance objectives have been further defined.
328 and 333	26	Comment: The word "an additional" should be supplemented: "Also, the possibility of applying an additional terminal microbial reduction process may be evaluated."	Not accepted. The terminology has been discussed and compared with definitions of Ph. Eur. and Annex 1 of GMP GL. The term is changed to "post-aseptic processing terminal heat treatment".
333	26	Comment: The word "additional" should be supplemented: "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 additional terminal microbial reduction process."	Not accepted. The whole sentence has been deleted as deviations handling falls under GMP.
331-333	1	Comment: please clarify this statement	The comment is noted. The whole sentence has been deleted as deviations handling falls under GMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
331 - 333	6	Comment: Requirements for deviation handling within GMP are not within the scope of the guideline as laid down in lines 68 to 73 and should be deleted.	Accepted.
334	5	Comment: Paragraph is not helpful – there are examples whereby the shelf life may not cause an issue for EU countries but may cause wider issues in ROW. Would this be a sufficient justification and meet the requirements of the statement 'would cause problems in the use of the product'?	Not accepted. This is not a sufficient justification as this GL is for products applied in Europe and not for other countries in the world.
334-336	1	Comment: sterile filtration as an accepted sterilising method is missing here. Aseptic processing is not a sterilisation method. Respective revision is necessary	Not accepted. The term "aseptic processing" could include also sterile filtration. Please refer to section 1 "Introduction" where it is stated that sterile filtration and aseptic treatment are closely related and difficult to handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related.
334 - 336	18	Comment: The sentence "*unless the new storage condition or shelf-life would cause problems in the use of the product*" is imprecise. For instance shelf lives below 24 months raises logistic issues, making it difficult (or impossible) to have some products marketed oversea and refrigerated storage conditions may be unrealistic with regard to the field use conditions in veterinary practice. These reasons should	Not accepted. Previous phrasing is more general and allows a case by case decision, what changes could be accepted based on the nature of the sterilised product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be clearly accepted to justify the choice of the sterilization process of veterinary products. Proposed change: Please clarify the scope of this sentence to consider the need to have a product with a shelf life consistent with logistic constraints (not only use constraints). A minimum shelf life is defined in the Target product Profile before development. Too much restriction for retaining sterilizing filtration in lieu of heat or irradiation sterilisation could significantly hinder pharmaceutical innovation and development of generics (whereas this technique is well mastered by the industry).	
334 - 336	18	**Comment:** Shelf life and storage conditions are main quality attributes for a medicinal product and they should not be minimised in the choice of sterilising method. Thus, it is not clear why the benefit risk balance would be in favour of a product with shorter shelf-life and stricter storage condition but sterilised in its final packaging, compared to a product sterilised by filtration but with no storage condition and longer shelf life (for instance 18 months between 2 to 8 °C, compared to 36 months without specific condition of storage...). **Proposed change:** Please modify the sentence to read: "A **moderate** change in shelf-life **(i.e. 3 months or less) or a moderate change in** storage conditions **(i.e. restriction from "no condition" to <30°C or from <30°C to <25 °C)** caused by a terminal sterilisation process is not in itself a reason to allow	Not accepted. Previous phrasing is more general and allows a case by case decision, what changes could be accepted based on the nature of the sterilised product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		aseptic processing, unless the new storage condition or shelf-life would cause problems in the use of the product.	
337-340	14	Comment: The referenced ICH Q3B and VICH GL11 guidelines should prevail over this guideline. Proposed change: Aseptic processing can~~not~~ be accepted ~~based solely on an increase in impurity levels upon terminal sterilisation~~ without further justification if an increased level of impurities above the ICH Q3B or VICH GL11 identification or qualification limit ~~does not necessarily~~ precludes 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.	Not accepted. However, the paragraph has been changed clarifying that toxicological or clinical studies are not generally required to qualify an impurity to allow terminal sterilisation of the finished product or sterilisation of the active substance.
337-344	1	Comment: sterile filtration as an accepted sterilising method is missing throughout the entire paragraph. Aseptic processing is not a sterilisation method. Respective revision is necessary Please provide further explanation since sterile filtration is usually applied to sensitive products to	Not accepted. The term "aseptic processing" could include also sterile filtration. Please refer to section 1 "Introduction" where it is stated that sterile filtration and aseptic treatment are closely related and difficult to handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		maintain the assay and keep the impurities at a suitable level for the use in the patient. Please provide explanation on what is expected here for legacy products.	important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related. The GL applies only for new marketing authorisation applications and for variations. The GL does not apply retrospectively. Please refer to the "Executive Summary" where this is stated.
337-344	16	Proposed change: Aseptic processing can~~not~~ be accepted if an increased level of impurities above the ICH Q3B or VICH GL11 identification or qualification limit preclude terminal sterilisation of the medicinal product ~~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. Rationale: The cited ICH Q3B or VICH GL11 must not be considered as subordinate in comparison to this	Not accepted. However, the paragraph has been changed clarifying that toxicological or clinical studies are not generally required to qualify an impurity to allow terminal sterilisation of the finished product or sterilisation of the active substance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drafted NfG or as subordinate compared to the results of performed safety and clinical studies with the product.	
338 - 340	18	**Comment:** The sentence "*An increased level of impurities above ICH Q3D or VICH GL11 identification and qualification limits does not preclude terminal sterilisation of the medicinal product*" is unclear. This calls into question the identification/qualification thresholds of degradation products set in VICH GL11 if, to justify the disqualification of terminal heat sterilization, exceeding these limits should systematically be balanced with the risk on sterility. Indeed, considering the nature of degradation products and the posology of the product in this risk analysis (as recommended) gives uncertainty as to what will be accepted by Authorities at the time of process development. While this risk-based approach is justified for the selection of aseptic manufacture (high risk process), the choice of sterilizing filtration over moist-heat sterilization (based on VICH GL11 impurity thresholds) should be acceptable without further justification, considering that sterilizing filtration followed by aseptic filling is an efficient and well mastered technique. **Proposed change:** Clearly limit the requirement for such a risk analysis to the justification of the choice of an aseptic processing.	Partly accepted. The paragraph has been changed clarifying that toxicological or clinical studies are not generally required to qualify an impurity to allow terminal sterilisation of the finished product or sterilisation of the active substance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
338 - 340	18	**Comment:** For vet products, the need to qualify a degradation impurity for the sole reason to use a terminal sterilisation method that generates this impurity above the VICH qualification threshold is not acceptable and could not be considered as a benefit on quality, safety and animal welfare point (e.g.3R) of views. In addition, the identification and qualification limits are higher for vet products compared to human product and may need to be considered separately. **Proposed change:** Please amend the sentence to read: "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**~~ **while remaining below** the ICH Q3B or VICH GL11 identification or qualification limit does not ~~**necessarily**~~ preclude terminal sterilisation of the medicinal product."	Not accepted. However, the paragraph has been changed clarifying that toxicological or clinical studies are not generally required to qualify an impurity to allow terminal sterilisation of the finished product or sterilisation of the active substance.
340	4	Comment: Could we show that it is possible to work on the formulation to "compensate" the degradation sterilization? For example, overdose after sterilization for the good product concentration. Proposed change: Line 340 :…product. **Work on formulation could compensate degradation.** The risk induced…	Not accepted. An overage to compensate for degradation due to sterilisation may be acceptable provided that the degradation products are qualified from a toxicological point of view. However an overage remaining after sterilisation is normally not acceptable. Overages allowed to compensate for degradation during manufacture or during storage and should be appropriately justified by detailed development and validation data. Other changes may be considered such as pH changes, nitrogen blanketing or change in excipients.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
340-342	17	Comment: "… *should* be balanced…" needs to be specified.	Accepted. The paragraph has been changed clarifying that toxicological or clinical studies are not generally required to qualify an impurity to allow terminal sterilisation of the finished product or sterilisation of the active substance.
340-344	5	Comment: Welcome the reference to risk based approach and the statements imply that the forced degradation studies can be used from a science perspective to help justify sterilisation approaches. It would be helpful though given the strength of the comment if the authorities could be clear as to what their expectations are for the data package as the statements read as to how they expect this to be exemplified.	Partly accepted. See the comments to lines 340-342 by stakeholder 17 above.
345 - 372	1	Comment: Please revise entire section since sterilisation filtration as method of choice and accepted sterilisation method (Ph. Eur. 5.1.1) is not considered throughout the entire section. Again: Aseptic processing is not a sterilisation method. – Aseptic processing may be applied for filling of sterile filtered solution in packaging materials which cannot be terminally sterilised.	Not accepted. Comment is not accepted. The term "aseptic processing" could include also sterile filtration. Please refer to section 1 "Introduction" where it is stated that sterile filtration and aseptic treatment are closely related and difficult to handle separately, since sterile filtration in most cases is followed by at least one aseptic treatment step such as filling. In order to focus on the most important aspect of filtration and aseptic treatment at each section of this guideline, only one of the two steps may be mentioned, even if both steps are related.
345 - 372	10	Comment: The conditions justifying a waiver from terminal sterilisation based on drug product container and presentation should be more detailed to avoid incomplete or inadequate justification. The default should be terminal sterilisation.	Not accepted. Too detailed information is not proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: This section should be reviewed and revised.	
348-354	4	Comment: The plastic can be sterilized, exclusions are they justified? Proposed change: "….**by an item that could not be terminally…"**	Not accepted. The term "item" is not considered as concrete enough.
350-351	18	**Comment:** The examples provided should not be limited to products for human use. **Proposed change:** Please modify: "Containers enabling non parenteral multi-dose preservative free medicinal product formulation ~~**for human use**~~;"	Not accepted. Veterinary preservative free solutions are not desirable due to the environment where they are used.
352	7	Comment: The examples should include pre-mixed infusion bags, which offers a user benefit and cGMP manufacture vs. vials that must be compounded by a pharmacist under aseptic conditions. Proposed change: Add additional example (as underlined text) as follows: "Enhanced ease of administration, for instance the use of a pre-filled pen compared to a vial, or a pre-mixed infusion bag of a medicinal product that would normally require admixture of a vial with a bag of diluent;"	Not accepted. It might be possible that some pre-mixed infusion bags could be autoclaved.
353-354	18	**Comment:** The example is fully true also in veterinary medicines whatever the medicinal product: the veterinary practice really benefits of plastic vials	Not accepted. The current text is considered appropriate.

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		instead of glass vials as handling of large animals may expose the user to delicate situations. Plastic vials conferring better resistance to shocks and lighter weight of the vials compared to glass vials of the same capacity (large vials 100 to 500 ml are widely used for injectable products in veterinary medicine) is particularly appreciated to facilitate and secure handling of vials on the field. **Proposed change:** Please amend this sentence to read: "Safer handling of ~~**toxic**~~ products, for instance plastic vials instead of glass vials for ~~**cytotoxic**~~ medicinal products **e.g. in veterinary medicine for any treatment of large animals**."	
353 - 358	10	Comment: Many glass vials of cytotoxic drugs are now overwrapped (after labelling) in plastic coating material to render them more resistant to breakage and contain any spill if the vial does break, e.g. Cisplatin 1 mg/ml Sterile Concentrate, marketed by Hospira, is packed in "Onco-Tain® vials." Proposed change: For instance, polypropylene is not as sensitive to heat as polyethylene and could allow terminal sterilisation. Safe handling of toxic products in glass vials may be achieved by assembly in plastic to render them more resistant to breakage and to contain any spill, after terminal sterilisation.	Not accepted. This is considered too specific for inclusion in the guideline. The current text is sufficient.
355 - 358	6	Comment: The section of line 355 to 358 is embedded in the discussion of aseptic processing. From the	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		layout it is not clear, if this section is belonging to the first bullet point only (beginning at line 348) or whether it is a general statement. If lines 355 to 358 are belonging to line 348, the lines should be aligned to the paragraph above. Assuming, that the section shall express, that heat-labile primary packaging material is not the justification for an aseptic process instead of terminal sterilization process, mentioning the different sensitivity to heat of polyethylene and polypropylene is misleading. Both materials can be terminally sterilized and polyethylene is well established for terminally sterilised medicinal products for more than four decades with no superior property of polypropylene compared to polyethylene as primary packaging material.	The layout of the paragraph has changed and the specific packaging material examples have been deleted.
356-357	4	Comment: The Polypropylene can withstand terminal sterilization Proposed change: Please to replace "could" by "should" on lines 356 and 357	Partly accepted. The sentence has been changed distinguishing between high and low density polyethylene.
368 - 369	7	Comment: Aseptic processing should be an option for large volume parenterals if justified with appropriate scientific rationale, risk assessment, and demonstration of unmet medical need, to enable manufacturing innovation.	Partly accepted. The wording has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Revise the bullet wording as follows (delete and insert underlined where noted): "The volume to be administered per dose. ~~Large volume parenterals should be terminally sterilised whenever possible.~~ Terminal sterilization is traditionally preferred for large volume parenterals; however, aseptic processing may be justified with appropriate scientific rationale, risk assessment, and demonstration of unmet medical need."	
368-369	18	**Comment:** It is confusing to make the link between the "volume administered per dose" and "large volume parenteral" which is defined in section 6 - definitions as: "An infusion or injection supplied in a container with a nominal content of more than 100 ml". Indeed, in vet practice multidosis vials are commonly used and they often exceed 100 ml of capacity; but the volume administered per dose is rarely above 100 ml. In addition, the definition of "large volume" should not be the same for products for veterinary and human medicine. **Proposed change:** Please modify to have: "The volume to be administered per dose. **For products for human medicine,** large volume parenteral should be terminally sterilised whenever possible."	Partly accepted. The wording has been revised not to mention large volume parenterals.
370 -372	1	Comment: Please clarify what is expected and acceptable for legacy products.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			The GL is only proposed for new applications and variations. The GL does not apply retrospectively. Please refer to the "Executive Summary" where this is stated.
375-377	15	Comment: The current text states, *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.* As explained in our previous comment to lines 53-60, it is inappropriate to allude to a sterility assurance level for aseptic processing. Aseptic processing is not based on known or predictable microbial inactivation kinetics but relies on a series of independent factors that are validated and controlled to prevent contamination of previously sterilised materials, components, formulated bulk etc. during filling of product into a final container. Proposed change - change existing text to: When moving down the decision trees, the methods generally provide a lesser assurance of sterility and therefore the first possible option should normally be chosen.	Accepted. A slight rewording has been used.
376 - 377	1	Comment: Please clarify what is expected and acceptable for legacy products.	Partly accepted. The guideline applies to new marketing authorisation applications or variation applications for medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
378	5	Comment: Reference to biological products alternative approach may be appropriate – what about antibiotics?	Not accepted. Some antibiotics could be terminal sterilised at least per F_0 concept (e.g. Linezolid, Moxifloxacin), thus antibiotics is not a homogeneous group with regards to sterilisation.
380 - 382	1	Comment: 1. limited to drug product 2. sterile filtration not mentioned	Accepted.
380-382	3	Comment: Delete 380-382--this section based on the following presented above: Based on the well-documented successful and safe application of aseptic processing for many years, there is no scientific or risk-based justification for the need for the application of a terminal sterilization or other lethal treatment process after aseptic processing. Accordingly, PDA continues to contend that aseptic manufacture alone CAN provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated 'terminal sterilisation' or other lethal treatment conditions.	Not accepted The usage of a terminal heat treatment is not a new request. Terminal heat treatment is already mentioned in Ph. Eur. 5.1.1 and is in accordance with GMP requirements. Please refer to Annex 1 of Guideline to GMP for Humans and Veterinary use, section "Filtration of medicinal products which cannot be sterilised in their final container", point 110 where it is mentioned that "Consideration should be given to complementing the filtration process with some degree of heat treatment". Terminal microbial reduction process (now phrased "post-aseptic processing terminal heat treatment") should therefore be included in this Guideline and the decision tree.
380-382	15	Comment: The current text states, *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*.	Partiy accepted. The text has been rephrased.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		As explained in our previous comment to lines 375-377, it is inappropriate to allude to a sterility assurance level for aseptic processing. Proposed change - change existing text to: 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 greater assurance of sterility.	
380-382	18	**Comment:** Without definition of performance objectives, the application of a "terminal microbial reduction process" has no scientific rationale. (see also comments for definition, line 394) **Proposed change:** Remove any reference to this microbial reduction process in the guidance or clarify the performance objectives.	Not accepted. The concept of terminal heat process (previously terminal microbial reduction process) has been further elaborated. It has also been rephrased to post-aseptic processing terminal heat treatment.
380-387	14	Comment: Such a combined sterilisation process cannot be validated because neither the quantity nor the quality of the microbial contaminants is known, so that no SAL for the terminal microbial reduction process can be established. The decision tree shall be modified accordingly. Proposed change: ~~For formulations that cannot withstand a complete terminal sterilisation cycle, a method combining aseptic processing and a terminal~~	Not accepted. The usage of a terminal heat treatment is not a new request. Terminal heat treatment is already mentioned in Ph. Eur. 5.1.1 and is in accordance with GMP requirements. Please refer to Annex 1 of Guideline to GMP for Humans and Veterinary use, section "Filtration of medicinal products which cannot be sterilised in their final container", point 110 where it is mentioned that "Consideration should be given to complementing the filtration process with some degree of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~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.~~	heat treatment". Terminal microbial reduction process (now phrased "post-aseptic processing terminal heat treatment") should therefore be included in this Guideline.
380-387	16	Proposed change~~: 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.~~ Rationale: Such a combined sterilisation process cannot be validated because neither the quantity nor the quality of the microbial contaminants is known, so	Not accepted. The usage of a terminal heat treatment is not a new request. Terminal heat treatment is already mentioned in Ph. Eur. 5.1.1 and is in accordance with GMP requirements. Please refer to Annex 1 of Guideline to GMP for Humans and Veterinary use, section "Filtration of medicinal products which cannot be sterilised in their final container", point 110 where it is mentioned that "Consideration should be given to complementing the filtration process with some degree of heat treatment". Terminal microbial reduction process (now phrased "post-aseptic processing terminal heat treatment") should therefore be included in this Guideline. The text in lines 380-382 has been deleted since the purpose of the text is covered elsewhere in the guideline where the development of the sterilisation method is discussed.

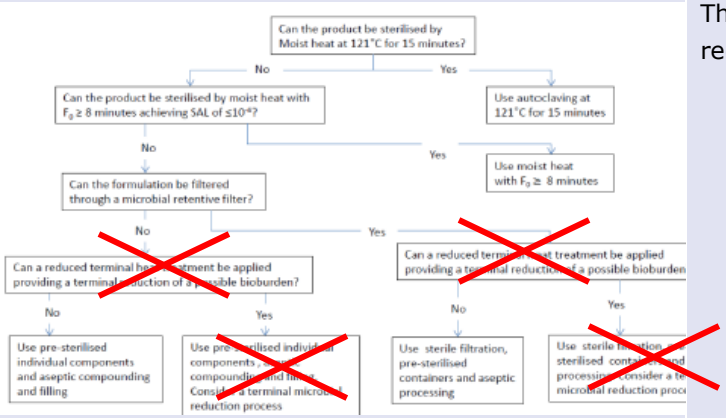
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that no SAL for the terminal microbial reduction process can be established. Furthermore, only the minimum concentration of an antimicrobial preservative sufficient to ensure its antimicrobial efficacy should be used and the level of inclusion has to be justified, see also NfG on excipients in the dossier for application for marketing authorisation for a medicinal product (EMEA/CHMP/QWP/396951/2006). Consequently, the decision trees have to be adapted according to the NfG CPMP/QWP/054/98 Corr "Decision trees for the selection of sterilisation methods", see below.  German Pharmaceutical Indus	
383 - 386	6	Comment: It is acknowledged, that the sensitivity of bioburden is expressed in different D-values. D-values are linked to the composition of the solution (ingredients and concentration), but not necessarily to the presence or absence of a preservative. Proposed change: The correlation of D-value and preservative should be deleted.	Partly accepted. The text has been deleted.
383-386	15	Comment: The current text states, *For solutions containing an antimicrobial preservative or inherent*	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. It is scientifically inappropriate to link a terminal microbial reduction process to a sterility assurance level unless the microbial inactivation kinetics of that process have been investigated and the process validated and controlled in the same manner as that required for a terminal sterilisation process. The document defines a microbial reduction process as 'treatment at conditions that provide a lower lethality than sterilisation'. Proposed change - change existing text to: For a solution containing an antimicrobial preservative or that has inherent antimicrobial properties, the bioburden may be more susceptible to a sterilisation process than for a non-preserved solution. A terminal microbial reduction process could be considered as an adjunct to aseptic processing where filled product in its final container is able to withstand the physical conditions of such a process.	The text in lines 380-382 has been deleted since the purpose of the text is covered elsewhere in the guideline where the development of the sterilisation method is discussed.
383 - 387	18	**Comment:** The sentence is unclear. We understand that it means that, for solutions containing an	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		antimicrobial preservative, it is emphasized that terminal sterilization can be achieved with a reduced stress (F_0, irradiation dose) than would be possible for the same unpreserved solutions. The term "terminal microbial reduction process" seems here inaccurate as this terminal operation is a terminal sterilization as it achieves a SAL of 10^{-6}. How this could be justified in the supportive documentation is also unclear. **Proposed change:** Please clarify	The text in lines 380-382 has been deleted since the purpose of the text is covered elsewhere in the guideline where the development of the sterilisation method is discussed.
388 Decision Tree; aqueous products	3	Comment: PDA recommends the diagram be modified as indicated below **(see attached Decision Tree)** based on the rationale presented for Lines 380-383 above. Additionally, the use of heat treatment should be broadened to include treatment technologies capable of microbiological inactivation besides heat.  Decision Tree PDA _Comments Final.ppt: Proposed change: Please clarify.	Not accepted. For aseptic treatment accidental contamination caused by inadequate technique cannot be reliably eliminated by monitoring, control or validation, thus terminal processes are preferred. Also, the concept of post-aseptic processing terminal heat treatment (previously terminal microbial reduction process) has been deleted from the decision trees, but is kept in the guideline, section 4.1.1, and has been further elaborated.
388 Decision Trees	10	Comment: The text boxes relating to "reduced terminal heat treatment" are unclear as to what is being recommended and why.	Partly accepted. The concept of terminal microbial reduction process (now called post-aseptic processing terminal heat treatment) has been deleted from the decision trees, but is still described in Section 4.1.1 and has been further elaborated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A combination of low heat treatment ($F_o \leq 8$, or hold temperatures below 110°C) and filtration may also achieve a SAL of 10^{-6}. Proposed change: Text box to state: Can SAL of 10^{-6} be achieved by combining aseptic filtration and processing with a terminal low heat treatment ($F_o \leq 8$, or hold temperatures below 110°C)?	
388	19	This amendment proposes that you also adopt the radiation sterilization of the final sterilization method for liquid drug in order to increase the more sterility assurance level. It is already in Japan has been adopted. However, radiation sterilization of the solution will have enough to take into account the influence of the drug. We have to practice to suppress the deterioration due to radiation by free-radical scavenger and frozen. And, we believe that should be filtered through a filter to the case radiation sterilization is not possible. Please see the attached document.	Not accepted. Irradiation of aqueous solution normally leads to radiolysis of water forming hydrogen peroxide. Therefore, in general, irradiation of aqueous solution is not proposed. However, as stated in the guideline, when demonstrated suitable, other sterilisation methods may be accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		 388 Amendment Comments.pptx	
388	22	Comment: Suggest adding Figure numbers to the decision tree titles for clarity	Accepted.
388-389	9	Comment: The Draft Guideline EMA/CHMP/CVMP/QWP/BWP/850374/2015 introduces a new step in the decision tree with the question "can a reduced terminal heat treatment be applied providing a terminal reduction of a possible bioburden?" For this particular case, terminal sterilization is not possible and filtration is (or is not) possible. We understand that filtration alone may not be as secure as a terminal sterilization and that complementing the filtration process with some degree of heat treatment would be more suitable. Nevertheless, the development of such "reduced terminal heat treatment" should be explained in the Guideline: - Are the tests performed on an unfiltered formulation with a bioburden of less than 100 CFU/100ml, or on a specific bioburden population of this formulation?	Partly accepted. The terminal microbial reduction process (now called post-aseptic processing terminal heat treatment) has been deleted from the decision trees, but is still described in Section 4.1.1. The text has been elaborated to provide further guidance on requirements with regards to e.g. bioburden and validation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Should we focus the tests on particular species to provide an appropriate evaluation of the process (if so, which species?) - Which temperature grades and times have to be tested, considering the fact that the product has been demonstrated as being heat labile but that we intend to inactivate micro-organisms? - What are the acceptance criteria to be applied to conclude to a "terminal reduction of a possible bioburden"?	
388-389	14	Comment: Modification of the decision tree for sterilisation choices for aqueous products as commented above. Proposed changes:  	Accepted. The terminal microbial reduction process (now called post-aseptic processing terminal heat treatment) has been deleted from the decision trees, but is still described in Section 4.1.1. The text has been elaborated to provide further guidance on requirements with regards to e.g. bioburden and validation.
388-389	21	Comment: Medicines for Europe	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In some boxes of the decision tree, the guideline advises to make use of a "*terminal microbial reduction process*". Further guidance on the appropriate design of these processes would be welcomed. Proposed change (if any): Please clarify which *terminal microbial reduction processes are considered acceptable.*	
338-390	4	Decision trees (for aqueous and non-aqueous) are not completely exacts. The proposal aims to promote reading and the choice of methods as recommended by the Ph.Eur., to bring together in one single document the main processes of microbial reduction of aqueous pharmaceutical products or not, and improve scientific errors generating sanitary risks. Proposed change (if any): Please see in **Annex Decision tree proposal (enclosed file)**. In consequence the tittle is "**Decision tree for sterilisation choices"**  A3P comments 4.pdf	Not accepted. The proposed decision tree is not considered clearer.
388 - 392	7	Comment: The Decision Tree may imply that regulators expect terminal heat treatments be added	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to the aseptic process. Refer to Baxter's comments on Lines 326 – 333. Proposed change: The decision trees should not include decision points related to use of "reduced terminal heat treatment" as it implies the addition of terminal heat treatment to the end of an aseptic process is preferred from a regulatory point of view.	The usage of a terminal heat treatment is not a new request. Terminal heat treatment is already mentioned in Ph. Eur. 5.1.1 and is in accordance with GMP requirements. Please refer to Annex 1 of Guideline to GMP for Humans and Veterinary use, section "Filtration of medicinal products which cannot be sterilised in their final container", point 110 where it is mentioned that "Consideration should be given to complementing the filtration process with some degree of heat treatment". Terminal microbial reduction process (now phrased "post-aseptic processing terminal heat treatment") is therefore still included in this Guideline, section 4.1.1. It has however been deleted from the decision trees.
388-392	18	**Comment:** Without definition of performance objectives, the application of a "terminal microbial reduction process" has no scientific rationale. (see also comments for definition, line 394) **Proposed change:** Remove any reference to this microbial reduction process in the guidance or clarify the performance objectives. Regarding "Reduced terminal heat treatment" in decision tree, this term needs to be clarified	Accepted. The terminal microbial reduction process (now called post-aseptic processing terminal heat treatment) has been deleted from the decision trees, but is still described in Section 4.1.1. The text has been elaborated to provide further guidance on requirements with regards to e.g. bioburden and validation.
388 - 392	18	**Comment:** 1/ The underlying hypothesis giving the F_0 decision criteria (F_0=15 minutes or F_0=8 minutes) are not clear leading to confusion on how to document the theoretical SAL of moist heat processes. The Sterility Assurance Level (SAL) is calculated based on the bioburden limit and the hypothesis on the maximum D value of micro-organisms. Ph. Eur.	Partly accepted. The concept of post-aseptic processing terminal heat treatment (previously terminal microbial reduction process) is kept in the guideline, Section 4.1.1, and has been further elaborated. It has however been deleted from the decision trees.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		5.1.2 indicates that for moist heat sterilization, the D-value of biological indicators should not be less than 1.5 minutes. Considering the recommended bioburden of 100 CFU/100 mL, a F_0 of 12 minutes will achieve a SAL of 10^{-6}, and a F_0 of 8 minutes will achieve a SAL of 10^{-5} (log reduction: 5.33). Micro-organisms generally found in bulk solutions rather have a D-value between 0.5 and 1.0, but the process should be validated with biological indicators having a greater value (1.5 to 2.5) as prescribed in Ph. Eur. The reasoning need to be clarified and input values (including D-value) to be used in calculations clearly stated, which will also allow calculation of the SAL of non Ph. Eur. moist-heat cycles on the same basis. 2/ In decision trees, when it is found that the product does not withstand terminal sterilization, and that the sterilizing filtration is possible, this should be sufficient, provided that the filtration result in a SAL of 10^{-6}. We don't understand the need for an evaluation step for addition of a terminal microbial reduction at this stage. This evaluation should only be carried out in case filtration cannot ensure a SAL of 10^{-6}. The same comment applies to the second decision tree. **Proposed change:** 1/ - Clarify the reasoning giving the F_0 criteria of 8 and 15 minutes	Also, the text of the revised guideline is in line with the requirements stated in the revised Ph. Eur. 5.1.1 and 5.1.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Clarify how SAL calculation is expected to be performed to document the theoretical SAL of moist heat sterilization processes (min D-value accepted). 2/ Please modify the decision trees in order to delete the request to have a terminal microbial reducing operation.	
390	21	Comment: Please clarify the "dry powder" definition by including it in the "6. Definitions" paragraph (line 394). This request is to understand where the lyophilized powder is included, to avoid different interpretations.	Not accepted. This is not relevant since lyophilised products are not expected to be terminally sterilised.
390-391	12	Comment: On lines 36-37 it is indicated that '…, terminal sterilisation using a reference condition of the Ph. Eur. is the method of choice whenever possible, …'. On line 394 it is also indicated that 'Ph. Eur. sterilisation reference conditions are terminal steam sterilisation at ≥121 °C for 15 min, terminal dry heat sterilisation at ≥160 °C for ≥2 h, and terminal ionising radiation of 25 kGy.' The following order of choice on lines 390-391 (decision tree for sterilisation choices for non-aqueous liquid, semi-solid, or dry powder products) does not appear to comply with the aforementioned:	Not accepted. The text in the Executive summary is a general introduction, the more detailed requirements are stated in more detail later in the document. While sterilisation by heat and sterilisation by ionising irradiation provide the same assurance of sterility, sterilisation by heat has lower risk (e.g. radiolysis impurities) and is more easily controlled than sterilisation by ionising irradiation. For these reasons, heat is given priority over ionising irradiation in the decision trees.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1. Sterilisation by dry heat at 160ºC (Ph. Eur. reference condition). 2. Sterilisation by dry heat at an alternative combination of time and temperature (NOT a Ph. Eur. reference condition). 3. Sterilisation by ionising radiation with an absorbed minimum dose of 25 kGy (Ph. Eur. reference condition). 4. Sterilisation by ionising radiation using a lower validated dose (NOT a Ph. Eur. reference condition). Proposed change: In order to give preference to terminal sterilisation using a reference condition of the Ph. Eur. it is recommended to change the order of choice in the decision tree for sterilisation choices for non-aqueous liquid, semi-solid, or dry powder products as follows: 1. Sterilisation by dry heat at 160ºC (Ph. Eur. reference condition). 2. Sterilisation by ionising radiation with an absorbed minimum dose of 25 kGy (Ph. Eur. reference condition). 3. Sterilisation by dry heat at an alternative combination of time and temperature (NOT a Ph. Eur. reference condition). 4. Sterilisation by ionising radiation using a lower validated dose (NOT a Ph. Eur. reference condition).	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
390-391	12	Comment: On lines 68-71 it is indicated that '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.' On lines 326-327 it is also indicated that '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.' So, the decision trees are applicable to active substances and excipients. However, since active substances and excipients are pure components, the option of using pre-sterilized individual components and aseptic compounding, possibly with a reduced terminal heat treatment, is not available. Therefore, the decision tree for non-aqueous liquid, semi-solid or dry powder products ends, if sterilization through a sterilizing filter is not possible. The decision tree for aqueous products would only be applicable to the excipient water that can be sterilized by moist-heat at 121ºC for 15 min. Hence, this decision tree is not relevant. Proposed change: It is recommended to include a specific decision tree for active substances, excipients	Partly accepted. The decision trees are applicable. If no option in the decision tree is available, a sterile substance cannot be manufactured. A specific decision tree has been introduced for containers.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and primary containers. Such a decision tree may also indicate when gas sterilization can be used.	
390-393	18	**Comment:** Dry heat method is only used in the case of glassware sterilisation. The fact that this method is included in the decision tree for non-aqueous, semi-solids and dry powders is confusing because it seems to suggest that this method could be used to sterilise products in the final primary packaging which is not the case. In addition, no rubber stopper can support those conditions. **Proposed change:** Please modify the decision tree because the conditions 160°C/120min could be possible in tank, for bulk product but not in the terminal sterilisation. Please move this method from the first place of the decision tree to the next step to be studied after the filtration.	Not accepted. A dry powder drug product may be dry heat sterilised if it is not sensitive to heat.
391	1	Comment: Please clarify why sterilisation by radiation (ISO 11137) which is not covered by Ph.Eur. 5.1.1 is more favourable than sterile filtration which is covered by Ph.Eur. 5.1.1. Please also clarify why sterilisation by radiation exposure which in general is related to an increased impurity level and also a higher risk of particulate contamination in drug products is considered more acceptable than sterile filtration.	Not accepted. Ionisation irradiation is covered by Ph. Eur.
391	3	Comment: PDA recommends the diagram be modified as indicated below **(see attached Decision Tree)** based on the rationale presented for Lines 380-	Partly accepted. The guideline describes the information requested in relation to the quality dossier, data requested in relation to GMP is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		383 above. The current decision tree allows the adoption of a 25 kGy sterilizing dose without the requirement for proper validation. PDA recommends adding the requirement to validate all radiation doses per ISO11137. Additionally, the use of heat treatment should be broadened to include treatment technologies capable of microbiological inactivation besides heat.  Decision Tree PDA _Comments Final.ppt	generally not described. Validation data for the Ph. Eur. reference cycle is not requested to be presented in the dossier. The scope of additional post-aseptic processing terminal heat treatment (former terminal microbial reduction process) is not broadened, due to the difficulty to describe relevant acceptance and validation criteria for the other techniques. This does however not imply that other techniques to provided terminal lethal treatment are prohibited.
391 – left column, 2nd cell	15	Comment: The current text states, *Can the product be sterilised by ionising radiation with an absorbed minimum dose of ≥ 25 kGy?* The minimum dose of ≥25 kGy needs to be validated. Proposed change - change existing text to: *Can the product be sterilised by ionising radiation with a validated absorbed minimum dose of ≥ 25 kGy?*	Partly accepted. The guideline describes the information requested in relation to the quality dossier, data requested in relation to GMP is generally not described. Validation data for the Ph. Eur. reference cycle is not requested to be presented in the dossier. The decision tree has however been revised to state ionising radiation once and also deleting the terminal microbial reduction process (it is however maintained in Section 4.1.1).
	15	Comment: The current text states, *Use sterilisation with an absorbed minimum dose of ≥ 25 kGy* The minimum dose of ≥25 kGy needs to be validated.	Not accepted. See the response to the previous issue.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change - change existing text to: *Use sterilisation with a validated absorbed minimum dose of ≥ 25 kGy*	
394	4	Comment: Definition of "Aseptic process " To avoid circular definition could we purpose to delete in the definition each word used in the title. It is not only an assembling. All the materials are not systematically "previously sterilised" (products from blood). It is a cold Microbial Reduction Process that can rarely provide sterility (PNSU not the same quality as PSSM). Proposed change: **Series of actions to prevent** microbiological contamination **in defined conditions and facilities.**	Not accepted. The definition is in line with the definition of aseptic assembly used in Ph. Eur. 5.1.1.
394	4	Comment: Definition of "D-value" According to ISO terminology widely approved D value is a process variable and e.g. : 0,5 or 1 min or 2,3 min is the parameter of this variable. Proposed change: **Time, dose, or other process variable required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions.** D_{121} is the D-value of the relevant spores at 121°C (ISO 11139)	Not accepted. The definition is in line with the definition of aseptic assembly used in Ph. Eur. 5.1.5. It has now also been amended with further clarifications that it is only of significance under precisely defined experimental conditions and that D121 is the D-value of the relevant spores at 121 °C.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
394	4	Comment: Definition of "Fo value" Not limited to saturated steam sterilization process because the thermo biological model is applicable to moist heat. Selected z value shall not be theoretical but is a reference value, for the Fo value, resulting from experimentation on a reference microorganism. Proposed change: Measure of microbiological lethality **delivered by** a **moist heat** sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 121.1 °C with reference to microorganisms with a z value of 10 K (ISO 11139)	Partly accepted. The Definition for F0 value is taken from Ph. Eur.5.1.1. A definition for "steam sterilisation" in line with that of Ph. Eur. 5.1.1 has been added to the Guideline to provide information on what is covered by the expression.
394	4	Comment: Definition of "Large-volume parenteral" ...with a nominal content of more than 100 ml. That excludes 100 ml volume which usually are included. Proposed change: ...with a nominal content **of Non Less Than / NLT 100 ml.**	Not accepted. The concept of Large volume parenterals has been excluded from the guideline
394	4	Comment: Definition of "SAL" PNSU was improperly used long time for sterilization process but now, because the probability to find a non-sterile unit among others is really dedicated to aseptic process, the most often this term is reserved to this process. For sterilization process the international community has regularly adopted Probability of Survival of Single Microorganism (sterility definition), which is more correct and it could be useful to help users with the same definition. The sterilization process reduces	Partly accepted. The definition was copied from Ph. Eur. 5.1.1. However, the definition has been revised in the revised monograph. The definition is thus revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		microorganism from the bioburden in /on an item to the selected SAL. This process is applied for each item. It is possible to extrapolate to the entire load may be one million items if the statistical conditions are respected. Upstream, homogeneity of treatment has to be significantly demonstrated with a reasonable risk. Proposed change: Sterility Assurance Level (SAL). 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 survival of a single microorganism** in this item/unit. (An SAL of 10^{-6}, for example, could denotes a probability of not more than one viable micro-organism in 1×10^{6} sterilized products, **in specified conditions)**.	
394	4	Comment: Definition of "z-value" By consistency with literature, z is lower case letter. Please use definition of the ISO terminology for harmonization. The z value quantifying the temperature difference needed for a variation of 90% of the D value, thereof in the International System of units shall be expressed in Kelvin. Proposed change: Temperature change required to effect a ten-fold change in D value (ISO 11139). **This value shall be in Kelvin**	Partly accepted. The "Z" will be exchanged for "z". There is no difference between centigrades and degrees in Kelvin for a temperature difference, thus the information of Kelvin is redundant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
394	4	Comment: Please add definition of "cold spot" Proposed change: **Load location where measured temperature is less than the sterilization temperature band.**	Partly accepted. A definition for Slowest to heat location has been added.
394	7	Comment: Definition of "Aseptic Process" should be expanded to include other suitable processes to allow innovation in sterilisation processes. Proposed change: Add the following (underlined text) to the definition of 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 or other suitable processes. This is achieved by using conditions and facilities designed to prevent microbial contamination."	Not accepted. The definition is that of Ph. Eur. 5.1.1. However, if an item used in a justified aseptic process is rendered sterile by a novel sterilisation process that is not stated in the definition (but which has been demonstrated to be suitable for its purpose), this would not be a cause for concern in relation to the approval of a medicinal product.
394	15	Comment: The current text states, *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*. It is acknowledged that the definition of 'SAL' is extracted from the Ph. Eur. However, this definition confuses two concepts, i.e. a single item versus a	Partly accepted. The definition was copied from Ph. Eur. 5.1.1. However, the definition has been revised in the revised monograph. The definition is thus revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		single microorganism. A non-sterile item (e.g. an ampoule) in a batch of a million ampoules could have resulted from more than one viable microorganism surviving the sterilisation process in that container. This is different to an SAL of 10^{-6} denoting a probability of not more than one viable microorganism in a million sterilised items. Proposed change: change existing text to: Sterility assurance level – the probability of a single viable microorganism occurring on an item after exposure to a sterilization process	
394	18	**Comment:** The definition of "large volume" should not be the same for products for veterinary and human medicine (see also comments for lines 368-369). **Proposed change:** Large-volume parenteral: "An infusion or injection ~~**supplied in a container with a nominal content of more than**~~ **which volume to be administered per dose exceeds** 100 ml."	Not accepted. The concept of Large volume parenterals has been excluded from the guideline.
394	18	**Comment:** As such, the definition of "microbial reduction process" has no scientific rationale. It should be clarified in terms of required lethality performance. **Proposed change:** Please remove any reference to this microbial reduction process in the guidance or clarify the performance objectives.	Partly accepted. The phrase "microbial reduction process" has been exchanged for "post-aseptic processing terminal heat treatment", which has been further described and defined.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
394	18	**Comment:** Definition of 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…*" The terms "steam" and "dry" refer to the way how heat is applied in accordance to Ph. Eur. 5.1.1 with regard to terminal sterilisation and are connected with the standard conditions 121°C/15min. (steam) or 160°C/2h (dry). However sterilisation of applicable ingredients in an aseptic process is often performed in bulk and not in a number of small volume containers. With regard to heat sterilisation this means that e.g. a bulk solution/liquid is heated by the heating unit of the closed bulk vessel and is homogenised - incl. thermally - by stirring. This is no heating by steam or dry air, but also uses the same germ-killing mechanism of heat. As heat transfer and distribution is fast by direct heating and stirring and as the temperature can be directly controlled in the bulk it is assumed that Ph. Eur. conditions of heat sterilisation by steam and not by dry air can be utilized as a first guidance for aqueous and even oily liquids in bulk. **Proposed change:** • Change in wording of definition, e.g.: …*each of which has been sterilised by heat (steam, dry air or other)…*	Not agreed. A definition for steam sterilisation with a reference to Ph. Eur. 5.1.1 has been added for clarification.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Introduction of guidance/comments for conditions of heat sterilisation of e.g. bulk solutions within aseptic processing (as separate section).	
394	21	Comment: Please include the definitions of cold spot, biological indicators and depyrogenation.	Partly accepted. Definitions for **slowest to heat locations**, biological indicators and depyrogenation have been added.
SAL Definition	3	Comment: PDA recommends use of the definition from ISO 11137 "Probability of a viable microorganism being present on a product unit after sterilization."	Not accepted. The definition in the current Ph. Eur. 5.1.1 is used.
SAL Definition	3	Comment: The SAL mathematical description is incorrect. Proposed change (if any): From: "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." To: "An SAL of $\leq 10^{-6}$, for example, denotes a probability of not more than one viable micro-organism in 1×10^{6} sterilised items of the final product."	Accepted.
Sterility Definition	3	Comment: Survival probability is not determined by organism type (resistance covers this) and environment during treatment. PDA recommends the ISO Definition be used or the guideline definition be modified to conform based on the recommendation below.	Not accepted. The definition is copied from the current Ph. Eur. 5.1.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: 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~~ **level of lethal stress (e.g., F_0, kGy, etc.) to which the organisms are exposed to** during treatment. Or the ISO definition: 2.45 Sterility - state of being free from viable microorganisms. Reference ISO 11139: 2006. NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven.	
Sterilisation	3	Comment: PDA recommends the following definition from ISO 11135: 2014 Definition 3.47 because it is a more comprehensive definition. Proposed Change: ~~A process that inactivates or removes viable micro-organisms in a product until sterility is obtained.~~ "Validated process used to render a product free of all forms of viable microorganisms"	Not accepted. The proposed definition is too wide. For example, sterilisation with respect to viruses is not covered by the guideline. The following definition has been included in the guideline; "A suitably designed, validated and controlled process that inactivates or removes viable micro-organisms in a product until sterility is obtained."