EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2020
EMA/CHMP/CVMP/QWP/230700/2020
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 quality of water for pharmaceutical use' (EMA/CHMP/CVMP/QWP/496873/2018)

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

Stakeholder no.	Name of organisation or individual
1.	A3P Association
2.	AEPSA (Association of Portuguese Companies for the Environment)
3.	AnimalhealthEurope
4.	APIC (CEFIC)
5.	AstraZeneca
6.	BPI e.V. - Bundesverband der Pharmazeutischen Industrie e.V.
7.	Cipla
8.	EFPIA
9.	EGGVP (European Group for Generic Veterinary Products)
10.	EIPG (European Industrial Pharmacists Group)
11.	Gilead Sciences International Limited
12.	Instituto Massone S.A.
13.	ISPE (International Society for Pharmaceutical Engineering)
14.	K+S KALI GmbH
15.	Medicines for Europe
16.	PANPHARMA
17.	Mr SantanuGhosh; AHMEDABAD, GUJARAT, INDIA
18.	SciencePharma (Poland)

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1. General comments – overview

Stakeholder no.	General comment	Outcome
1.	This guideline does not mention anywhere the link with annex 1 under revision	Considering that reference to water is made in different parts of GMP, detailed reference to Annex 1 is not included, whilst general mention to EU GMP vol.4 in the “References”, is added.
1.	This draft guideline does not give any additional information about the evolution of the European Pharmacopoeia regarding methods of production of water for injection without distillation	Reference to the PhEur evolution is already included in section 1”Introduction” of the guideline.
2.	The quality necessary for the production of medicines requires as reference "drinking water", the analysis of parameters – is not used on the Water (potable) Quality Control by private and public water supply systems, at this moment. This situation produce interference on water for pharmaceutical applications, preparation of medicines and in the final product. In our opinion, the presence or absence of water contaminants in trace concentrations may interfere with the product manufacturing, formulation composition, manufacturing process, and drug product control strategy.	Specific reference to Directive98/83/EC, or provisions laid down by the competent authority is already mentioned in the guideline.
2.	Comment: Regarding human risks and drinking water, the WHO reported that "Trace quantities of pharmaceuticals in drinking-water are very unlikely to pose risks to human health. Other studies support this conclusion. EU-level action is clearly justified on this topic as environmental issues are transboundary by nature (Spain and Portugal share five main river basins. Three of these (Duero/Douro, Tajo/Tejo, and Guadiana) are also some of the largest basins in the Iberian Peninsula.): national policies would be more efficient if they were harmonized and coordinated. Technologies for eliminating some pharmaceuticals in wastewater already exist. These solutions need to be incentivized to become mainstream and efforts need to be maintained on research and	Not applicable. The guideline does not deal with specific environmental issues. As concerns drinking-water it should comply with Directive98/83/EC, or with provisions laid down by the competent authority

Stakeholder no.	General comment	Outcome
	innovation in this field. In particular, a specific focus is recommended on issues like the effect of treatment on antibio resistance and the impact of mixtures on receiving bodies through toxicity / ecotoxicity assessment. Not only should pharmaceuticals be treated after use in wastewater, but decentralized treatment must also be considered (treatment at pharmaceuticals production sites, hospitals…). Therefore, sewage sludge is sometimes considered as a channel for pharmaceuticals to spread in the environment notably when used on agricultural fields. AEPSA welcomes the initiative taken by the European Medicines Agency to address p this issue. AEPSA further highlights the prominent role played by wastewater treatment plants as a barrier in preventing pharmaceuticals from spreading or remaining in the environment and we strongly advocates for the harmonization of policies at EU level and for the promotion of existing solutions as well as research incentives on risks raised by pharmaceuticals in the environment.	
3.	AnimalhealthEurope welcomes the opportunity to comment on this Guideline and would like to make the following comments. Some provisions for the use of water in veterinary activities have been introduced. This is very much appreciated. However, some important areas need further clarification. Some suggestions are provided in the specific comments area below. AnimalhealthEurope would be happy to help for any further clarification that QWP might have on veterinary specificities.	Noted.
5.	AstraZeneca generally supports and welcomes the draft guideline on the quality of water for pharmaceutical use. The importance of water selection and control are recognised within the document as well as the stated aim of bringing the document more in line with international pharmacopeias.	Noted.

Stakeholder no.	General comment	Outcome
7.	Kindly include the below topics in this attached guideline, Source Water, Designing of Storage and distribution system for Source Water, Designing of purified water (PW) generation (Final treatment) system, Designing of water for injection (WFI) generation (Final treatment) system, Qualification and Validation, Methodology for Usage of water during validation phase.	Not applicable. The guideline does not deal with specific GMP aspects. In the “References” general mention to EU GMP vol. 4 is included.
8.	General/Introduction: The document is a useful update tied with changes to the pharmacopoeial water grades. The risk-based approach in combination with the setting of requirements for acceptable grades for the quality of water quality is seen as robust and forward looking. Referencing Ph.Eur rather than repetition of specific details defined by Ph.Eur. is helpful. Challenges in this draft edition: Where we do see challenges, major ones, is with the acceptance criteria themselves. The twofold change, i.e. introduction of “biologics” paired with the raising of the minimal water quality to WFI in many cases raises issues of comprehensibility and more important consistency, and finally feasibility.	Acknowledged; table 3 revised to improve clarity.
8.	Quality aspects: We propose that the rationale for setting the acceptable water quality for the production of API (See our comment below to the introduction of “AS”) in the draft) should be determined by its intended use and certainly the purification technologies deployed rather than whether its origin might be from chemical or biological processes. Case in point: A dried, not sterile Active Pharmaceutical Ingredient intended for use in a sterile parenteral product must have the same requirements for water quality in the final isolation and purification regardless of its initial origin, whether biological or chemical.	Partially accepted. Revision of table 3 to take into account chemical/biological issue.

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	Further with the wholesale “raising of the bar” with respect to Water quality the draft misses the opportunity to strengthen rational, fact, and risk-based approaches.	
8.	Environmental aspects and affordability Tightening up the requirements from potable water to purified water and from purified water to WFI will increase environmental burden due to the additional potable water consumed to produce Purified Water and WFI. The environmental impact of purifying water in the amounts used for pharmaceutical fermentation processes is huge with both increased water consumption and CO2 emission. Very large-scale continuous fermentation processes run in the scale of hundreds of m3 per day for a single tank. Increasing the quality of water from potable to purified may increase water consumption by 20% – 40% and the CO2 emission accordingly. The proposed increase in requirements for water quality will increase the consumption of water putting some production sites at risk for insufficient availability of water, indeed already constituting a threat to some sites with the current water consumption. Apart from the extra burden of cost and environmental impact, the blanket adoption of more stringent requirements for water quality will not provide any further benefit to patients regarding safety, quality, efficacy or potency.	Comment noted. Quality and safety considerations are taken into account in this guideline. Use of potable water for fermentation accepted; revised table 3.
9.	The Quality Working Group of the EGGVP has reviewed the contents of this amended Guideline. The initiative to align this with the recently updated Ph.Eur. monograph ‘Water for Injections’ is welcomed, and the Group has no specific comments to be made on the text at this time.	Noted.

Stakeholder no.	General comment	Outcome
13.	What are the challenges in the draft edition • With introduction of 'Biologics' in table 3 (Manufacturing of Active Substance – AS) the requirements for acceptable quality of water has been changed. o Fermentation and cell culture media must as a minimum be manufactured with purified water ▪ Minimum requirement in current edition is potable water. o Final isolation, purification and final purification for a biological AS, not sterile but intended for use in a sterile parenteral product must as a minimum be manufactured with WFI ▪ Minimum requirement in current edition is Purified Water with an endotoxin limit of 0.25 EU/ml and control of specified organisms.	Partially accepted; revision of table 3.
13.	• What is the argumentation for keeping the possibilities to manufacture AS of biological origin with potable water in the fermentation and purified water in the purification of the AS: • Similar requirements for acceptable water quality must be applied for both synthesized and biologics AS. A dried AS, intended for use in a sterile and parenteral DP should require the same water quality regardless of the origin of the AS. o Stricter requirements for higher quality of water used in final purification of biologic AS compared to a synthetic origin product is not scientifically sound. o The proposed differentiation of requirements to water quality for AS of biological origin compared to synthetic origin is not clear. The same unit operations are applied in final isolation and purification steps and the same risk approach	Accepted. Revision of table 3.

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	regarding quality and safety is applied. o The distinction between ”final isolation and purification” and “final purification” is not clear. The final process step in manufacturing the AS may be an ultrafiltration or a column step which may or may not in addition have a purifying effect. In this case the AS is in solution. It may be an isolation of the product by drying - a process which is widely used by some companies for many proteins manufactured by fermentation - in which case the AS is not in solution. o It is important to recognize that an AS of biological origin can be processed and finalized in the same way as an AS of synthetic origin. The downstream process is mainly determined by the molecule, not by the origin of the upstream process. o Risk assessment is an integral part of process design regarding appropriate choice of water quality. Please find in the following our proposal for adjustments of the proposed EMA text	
13.	• Environmental aspects and affordability • Rational • Tightening up the requirements from potable water to purified water and from purified water to WFI will require an environmental burden due to more potable water consumed to produce Purified Water and WFI. Today there is a world-wide focus on manufacturing processes being more environmentally sound leaving as little footprint as possible. EMA has focus on this subject too - the environmental impact of purifying water in the amounts used for pharmaceutical fermentation processes is huge with both increased water	Partially accepted. The additional suggested text not included. Use of potable water for fermentation accepted; revised table 3.

Stakeholder no.	General comment	Outcome
	consumption and CO2 emission. Very large-scale continuous fermentation processes run in the scale of hundreds of m3 per day for a single tank. Increasing the quality of water from potable to purified may increase water consumption by 20% – 40% and the CO2 emission accordingly. • The proposed increase in requirements for water quality will increase the consumption of water putting some production sites at risk for insufficient availability of water, indeed already constituting a threat to some sites with the current water consumption. • The impact of the proposed increase in requirements for water quality will not provide any further benefit to patients regarding safety, quality, efficacy or potency. It will only increase the burden of cost and environmental impact. Proposed changes. Suggested Addition in the document: Based on risk assessment if the company does not need higher standard for water then it is desirable to consider sustainability. The proposed quality of water in the various tables need to incorporate this point. Higher water quality standards are not required than are justified when this also has an impact on sustainability.	
14.	The current draft of the guideline is fundamentally to be welcomed. The proposal that when using purified water in the final isolation and purification step during the manufacturing of active substances, appropriate specifications have to be set for endotoxins and specified micro-organism testing of the active substances as per the relevant Ph. Eur. Chapters, is constructive.	Noted.

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	In fact a risk-based approach should apply for the choice of the quality or type of water (including endotoxin limit) used in the last purification step of nonsterile APIs, but intended for usein sterile, parenteral products. Conclusion: The draft should be published as communicated.	
15.	Medicines for Europe welcomes the draft Guideline on the quality of water for pharmaceutical use and as this is aligned with aligned with the changes in PhEur we have not further observations and comments to this draft.	Noted.
16.	1. INTRODUCTION 'The Ph. Eur. monograph for Water for Injections (0169) was revised in order to allow the production of WFI by a purification process equivalent to distillation, such as reverse osmosis coupled with appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration.' In the cancelled monograph for Water, highly purified (1927), it was allowed to produce HPW with a double reverse osmosis coupled with appropriate techniques such as deionisation or ultrafiltration. Does that mean that it is not allowed to produced WFI with reverse osmosis coupled with a deionisation system? The main concerns around the use of non-distillation methods – reverse osmosis, for the manufacture of WFI relate to the risks associated with microbiological proliferation and/or endotoxins but is it considered as reliable to have a production system with reverse osmosis coupled with a deionisation system and if the storage tank is under Ozone .	Noted. The wording of the WFI monograph is used, so the text is kept as it is in "introduction". "Such as" can be considered "as example".So it does not mean that it is not allowed to produce WFI with reverse osmosis coupled with a deionisation system

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
0	8.	Please re-introduce “Active Pharmaceutical Ingredient (API)” which was replaced by the term “Active Substance (AS)” in the draft in the headers of Sec. 5.2 as well as Table 3 Rationale: This change is confusing because an active substance can include a chemical product in solid form or in solution or be a biological product in solid form or in solution (as e.g. final formulated bulk), whereas an ingredient is (just) an ingredient. Each has different levels of risk with respect to the quality of water used.	Not accepted. The term ‘active substance’ is used in line with EU Directive 2001/83/EC and Regulation 2019/6.
28	1.	Comment: Have the same name for pharmaceutical water Proposed change (if any): “commodities” to be replaced by “utilities”	Accepted.
32	1.	Comment: There is other key parameter than microbiological parameter Proposed change (if any): to mention physical and chemical aspects	Not accepted. The general statement in the guideline: “control of the quality of water” includes also chemical and physical aspects, so no need to specifically mention them.
38 - 43	1.	Comment: Eur. Ph. is used in Europe but depending on export area we should use also some regional regulation (e.g. Chinese, Japanese, Korean regulation … etc.) Proposed change (if any): take into account local regulation	Not accepted. The guideline is intended for products marketed, or to be marketed, in Europe
Lines 48-55	18.	Comment: It is recommended clarifying what reference to the quality of water	Not applicable. In the paragraph regarding the new policy for the

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		for pharmaceutical use has the paragraph regarding the new policy for the test for bacterial endotoxins.	test for bacterial endotoxins there is no specific reference to the quality of water for pharmaceutical use. However, the guideline has reviewed the quality of water used for final processing of non sterile active substances used in parenteral finished products considering the new Ph. Eur policy on bacterial endotoxin tests (no longer included in new monographs for substances for pharmaceutical use) and also the acknowledged possibility for finished product (e.g. parenteral products) of applying a risk based approach to whether a control needs to be applied to a substance. The above has been extended to the quality of water used. Therefore, the text is unchanged.
Sec 2, L 62	8.	Proposed Change:"~~*relevant*~~ *variation application to existing marketing authorisations where there is relevance* to water quality." Rationale: The concern here, further in the guideline, is that not all API are at the same level of risk from the quality of water. All other things being equal a (biological) API that is in powder form should be less at risk than one that remains in liquid form for a long time. The use of purified water rather than WFI might be more readily acceptable for the former.	Not accepted. The proposed change would seem to limit the guideline applicability only to those variations explicitly related to water quality, whilst its applicability is broader(e.g. addition of API manufacturer or others). Therefore, the change is not made.
Sec 2; L67/68	8.	Comment: Reference is made in lines 67/68 to EC guidelines on GMP for ATMPs, but this is not currently included in the Reference section. Proposal: Add the details of this document (EudraLex Volume 4, Part IV) to the	Accepted. "References" amended to include EC guidelines on GMP for ATMPs

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Reference section.	
71-74	3.	Comment: It is not clear if this paragraph exempts any product reconstituted/diluted prior to use by the user (the example given are sheep dips, but premixes for preparation of medicated drinking water could also be envisaged). Does this paragraph mean that whenever such a product is produced, this guideline does not apply? Or does it mean that the water used for reconstitution/dilution is exempt from this guideline? Proposed change: Please change to "This guideline is not intended to cover the water used in situations where medical products…" if the second interpretation was the intention.	Accepted. Proposed change made in final guideline.
Lines 75-79	8.	Comment/Rationale: The EMA Q&A on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies states "This set of questions and answers is intended to provide preliminary guidance until such time the on-going revision of Annex 1 of the GMP guide is complete." The revised Guideline on the quality of water for pharmaceutical use should not refer to the Q&A because the latter is preliminary and not the final location for the information. Recommendation: Instead of the above, the revised Guideline on the quality of water for pharmaceutical use should refer to Annex 1 and publication of the Guide should be held until a final version of Annex 1 is published	Not accepted. Considering that reference to water is made in different parts of GMP, detailed reference to Annex 1 is not included, whilst general mention to EU GMP vol.4 in the "References", is added.
81 - 83	1.	Comment: Annex 1 is under revision Proposed change (if any): take into account the coming new version	Not accepted. Considering that reference to water is made in different parts of GMP, detailed reference to Annex 1 is not included, whilst general mention to EU GMP vol.4 in the "References", is added.

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84	4.	Comment: In the industry it is common/usual practice to use for the production of APIs and pharmaceutical excipients demineralized water. The source of the water is often company owned wells instead of governmental wells. Demineralized water is not suitable for human consumption. Main reason for the use of demineralized water is to avoid corrosion in equipment (e.g. piping, reactors, etc.). Summary: Our suggestion is to include an own “Demineralized water paragraph”. Proposed change (if any): Demineralized water is not covered by a pharmacopoeial monograph but must be of a quality equivalent to that defined in Directive 98/83/EC, or laid down by the competent authority. Testing should be carried out at the manufacturing site to confirm the quality of the water. Demineralized water may be used in chemical synthesis and in the early stages of cleaning of pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher water grades.	Not accepted. The reference to “higher grades of water” in L 95 already allows for use of e.g. demineralised water.
89 - 96	1.	Comment: WHO specifications should be met at least Proposed change (if any): Potable Water World Health Organization regulation to be included	Not accepted. Potable water quality is covered by reference to Directive98/83/EC or provisions laid down by the Competent Authority
92	5.	Comment: Often testing of potable water either chemical or microbiological is carried out by external laboratories on behalf of the manufacturer. Proposed change (if any): consider replacing “Testing should be	Partially accepted. Change: “testing should be carried by the manufacturer to confirm the quality of the water” This implies that the manufacturer remains responsible of controls that, in some cases, may be

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		carried out at the manufacturing site" with – "….. by the manufacturing site, thus allowing an external testing laboratory to be used.	carried out by other external testing laboratories, based on specific agreements.
92	10.	Comment: No guidance on which test should be conducted at the manufacturing Site to confirm potable water quality Proposed change (if any): Specify that the amount of testing and the limits to confirm potable water quality can be determined by a risk based approach (i.e. Total Microbial Count and exclusion of organisms objectionable for the specific manufacturing process) if the source water is certified as suitable for human consumption	Not accepted. Reference to Directive 98/83/EC or specifications as defined by relevant Competent Authority, should be made, as potable water quality is covered by Directive 98/83/EC or provisions laid down by the Competent Authority.
92-93	11.	Comment: the guideline does not explicitly take into account the possibility to perform testing at a certified testing lab. "testing should be carried out at the manufacturing site to confirm the quality of the water". Proposed change: "Testing should be carried out at the manufacturing site, or at a testing laboratory certified by the local competent authorities, to confirm the quality of the water"	Partially accepted. Change: "testing should be carried by the manufacturer to confirm the quality of the water" This implies that the manufacturer remains responsible of controls that, in some cases, may be carried out by other external testing laboratories, based on specific agreements.
Lines 92-93	18.	Comment: The extent to which the tap water should be sampled and examined at the manufacturing site (instead of relying on analyses carried out by the water supplier) is considered to be a GMP aspect. The scope of possible analyzes should result from the risk analysis. Proposed change: *The range of testing ~~should be~~ carried out ~~at the manufacturing site~~ to*	Partially accepted Change: "testing should be carried by the manufacturer to confirm the quality of the water" This implies that the manufacturer remains responsible of controls that, in some cases, may be carried out by other external testing laboratories, based on specific agreements. General mention to EU GMP vol.4 in the

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		confirm the quality of the waterreceivedatthe manufacturing site is a GMP aspect and should result from the risk analysis.	"References", is added
Sec 4.1; L 93	8.	" *confirm the quality of the water. Potable water may be used in*APIproduction as well as*in the early stages of cleaning*." Rationale: A) As argued in the general comments section, we believe that the acceptable water quality for the production of API should be determined by its intended useinstead of "origin/synthetic route" of the Active Pharmaceutical Ingredient. B) In this sense Potable water may also be of a satisfactorily controlled quality to be used in biologicals fermentation, fermentation media, early purification and cleaning of equipment. In particular the applicant needs to offer appropriate documented justification (See also comments regarding "Minimum" water quality)	Accepted. A) Table 3 revised accordingly. B) Use of potable water for fermentation media included in table 3.
93	13.	Comment: we suggest adding use of Potable water for the biologics products as well. Proposed change (if any): Potable water may be used in chemical synthesis, biologics and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water. It is the prescribed source feed water for the production of pharmacopoeial grade waters. Rational: 'biologics' added in line 93 as potable water may as well be of a satisfactorily controlled quality to be used in biologicals fermentation, fermentation media, early purification and cleaning of equipment	Partially accepted. Change proposed by stakeholder not implemented but L93 is updated as follows to remove distinction between chemical and biological active substances; "Potable water may be used ~~in chemical synthesis~~ during the manufacture of active substance and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water.
103	5.	Comment: It is recognised that WFI quality is a key quality factor in	Not accepted. Referenceto 'Compilation of

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		the manufacture of sterile products, however it is not clear as to the rationale of why prior notification to the supervisory authority is required as described in the *Compilation of Community Procedures on Inspections and Exchange of Information.* This appears to be in addition to the normal regulatory filings which would cover such changes. Proposed change (if any): remove requirement	Community procedures on Inspections and Exchange of information' is made in this guideline for information only, however further details on this notifications are outside of the scope of this guideline.
109-110	10.	Comment: There is no indication about endotoxin level requirement for Purified Water intended to feed pure steam generators (different from Draft Annex 1 – line 715-716) Proposed change (if any): Harmonize text with Annex 1 requiring low level endotoxin PW for feeding pure steam generators	Not accepted. Annex 1 is clear. There is no need to repeat information from Annex 1.
Sec 4.3 L 110	8.	*used in the manufacture* of non-sterile dried Active Pharmaceutical Ingredient, intended for use in a sterile parenteral product and *of dialysis solutions.* Rationale: Text added to align with requirement in table 3 for 'Final isolation and purification' in the current edition of the guideline. Please also refer to our other comments regarding table 3	Not Accepted. The Chapters 4.1 – 4.3 are mainly for definition of the water qualities that are referenced to in table 3. Adding the proposed text would be redundant.
110	13.	Comment: We suggest in point 4.3 to align the text with table 3. Proposed change (if any): used in the manufacture of dried biologic AS that is not sterile, intended for use in a sterile parenteral product and of dialysis solutions.	Not accepted. See above.

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		Rational: 'dried biologic AS that is not sterile, intended for use in a sterile parenteral product and' added to align with requirement in table 3 for 'Final isolation and purification' in the current edition of the guideline	
Sec 4.4 L 114 +	8.	Change suggested: "As defined in Ph.Eur. monograph 2249*Water for preparation of extracts is water intended for the preparation of Herbal drug extracts (0765) which complies with the sections Purified water in bulk or Purified water in containers in the monograph Purified water (0008), or is ……. described in ~~the~~ monograph* 2249. Alternatively: Water for preparation of extracts complies withPh.Eur monograph 2249*Water for preparation of extracts … ~~delete intermediate text up to and with (0008)~~ or is water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC which is monitored according to the Production section described in the monograph* 2249. Rationale: The text in draft section 4.4 up to and including "*(0008)*" is a verbatim copy of the 1st paragraph of monograph 2249 which is the relevant requirement. Further: Alternative proposal is shorter/more concise and avoids repetition of wording from 2249.	Not accepted. The text as published in the draft guideline is retained (in line with definition in Ph. Eur. monograph 2.2.49 Water for preparation of extracts).
135	1.	Comment: The table is not complete: missing the words "irrigation solution" and "biologics" Proposed change (if any):	Accepted.

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		"irrigation solution" and "biologics" to be added to fully summarize Table 1	
140	17.	Comment: For Opthalmic product manufacturing – Minimum acceptable quality of water requirements specified –Purified water. Proposed change (if any): Requirement will be –** WFI. ** Reason -Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient (s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. Sterility need to check by the product; for ophthalmic preparation very difficult to do the terminal sterilization and reach the SAL (sterility assurance level) – 12 log reduction, only filtration is the way to remove the viable microbes. So, as per as product sterility complies, WFI will be ideal vehicle than Purified water.	Not accepted. The use of purified water is considered acceptable for ophthalmic products. To be reminded that purified water represents the minimum acceptable quality of water requirements, so WFI can be used as well. The GL in line 136-139 effectively indicates that a higher grade of water, e.g. WFI, may need to be used in some circumstance.
140 - 145	2.	Comment: - The minimum acceptable quality to produce medicines: It should be discriminated, in addition to the typology of medicinal products, by categories of pathology, depending on the possible chemical or inhuman interferences of the patients. Such a situation is very relevant if, in certain clinical conditions, because there is a hypersensitivity to potential trace constituents of the water matrix, persistent after treatment by purification procedures.	Not accepted. This is covered by reference to ‘minimum‘ requirements. The specific criteria mentioned would be addressed during the assessment of the MAA.
Lines 142-	18.	Comment:	Accepted.

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143		The phrase "*with the exception of non-sterile vaccines*" is not entirely clear as the whole paragraph refers to non-sterile dosage forms. For the same reason the annotation "*for non-parenteral use*" does not seem to be necessary here. Reference to "*some nebuliser preparations*" for which WFI should be used is also not entirely clear in view of the fact that – as may be concluded based on the note "**" below the Table 2 (lines 150-151) – these are actually the cases of preparations required to be sterile and non-pyrogenic. For clarity, such cases are recommended to be discussed in the paragraph referring to sterile products (lines 136-139).	Table 2 with associated footnotes explain things clearly, so the sentence on L142 beginning 'with the exception…'; ending '…non-sterile products' is deleted.
145	3.	Comment: Table 2 makes use of purified water mandatory for preparation of oral preparations. However, Table 4 (line 169/170 and footnote in lines 171-173) allows use of potable water for granulation of some veterinary premixes. For consistency, this footnote should also be present here. Proposed change:Please include footnote from Table 4 (lines 171-173) here as well and reference to it for oral preparations	Not accepted. The GL should remain unchanged, potable water should be used for granulation of concentrated premixes only. No footnote to table 2 is needed. Note that table 2 and table 4 have different scope: Table 2 refers to water present as an excipient in the final formulation whilst table 4 is for water used during manufacture of medicinal products but is not present in the final formulation.
Lines 147-149	18.	Comment: According to the outcomes of the risk assessment, WFI may be required in some cases for manufacture of non-sterile vaccines, but generally purified water is proposed to be acceptable. Proposed change: ** According to the outcomes of the risk assessment, WFI may be*	Accepted. Proposed change supported.

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		required in some cases for manufacture of non-sterile vaccines where, ~~WFI is recommended~~ in order to ensure the vaccines' safety and ~~product~~ quality (avoiding introduction of ~~undesirable~~ microorganisms undesirable in the specific finished product formulation), greater microbiological purity of water is needed ~~unless otherwise justified (i.e. for some non-sterile veterinary vaccines for non-parenteral use, purified water might be accepted)~~	
Sec 5.1 L 154	8.	Change suggested: *"For some products ~~such as veterinary teat dips~~, it may be acceptable to use potable water where justified and authorised. The use of potable water should be justified by risk analysis as part of the overall control strategy of the drug product taking account of the variability of the composition and microbiological quality.* Rationale: The example "veterinary teat dips" implies existence of restrictions that –in our view, as stated- do not apply. Further, the proposed changes reinforce the importance of following a risk-based approach.	Not accepted. The text is kept as it was in the previous guideline. The example is considered useful and the term "such as" in the footnote already allows for some flexibility, if adequately justified (and authorised).
155, etc	4.	Comment: API as a worldwide established thermology should not be replaced by AS (Active Substance) Proposed change (if any):	Not accepted. The term 'active substance' is used in line with EU Directive 2001/83/EC and Regulation 2019/6
155-162	11.	Comment:Theguidance does not take into account further processing steps that may occur for the final drug product to achieve sterility. Proposed change (if any): "The minimum acceptable quality of water used for the manufacture of active substance should have a footnote to acknowledge the selection of water type may be influenced by further steps to control for endotoxins or micro-organisms (i.e. sterilization of the DP)."	Not accepted. The quality of the water used during the manufacture of the active substance should not depend/rely on further process steps, including the ones in the manufacture of the drug product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
15	5.	Comment: The words “acceptable” and “heavily” are not required in the sentence. Proposed change (if any):The grade of water will depend on the stage at which it is to be used.	Accepted.
Sec 5.2 L 160	8.	Deletion suggested: *Table 3 summarises the ~~minimum~~ acceptable quality of water for the manufacture of”* Rationale: Replacement to highlight that table 3 gives guidance for choosing the right quality of water; based on knowledge of the manufacturing process and a risk assessment	Not accepted. It is important to highlight that the indicated requirements are the “minimum” ones.
160	13.	Comment: ‘the minimum acceptable’ deleted and replaced by ‘proposed’ to highlight that table 3 gives guidance for choosing the right quality of water is based on knowledge of the manufacturing process and a risk assessment. Proposed change (if any): Table 3 summarises <u>proposed</u> quality of water for the manufacture of active substances	Not accepted. It is important to highlight that the indicated requirements are the “minimum” ones.
162	3.	Comment: Table 3 – Any step excluding final isolation and purification (AS is biological and intended for parenteral use): For fermentation at very large scale, it is impractical and prohibitively expensive to use purified water. Historic data show that use of potable water yielded product of acceptable quality for veterinary use – mainly due to extensive purification after fermentation. Proposed change:Please include a footnote“use of potable water may be acceptable where justified and authorised, taking into account the extent of downstream purification”.	Accepted. While it is preferable that purified water is used, due to the fact that there may be a high variability in potable water quality, potable water is acceptable for use in fermentation media and cell culture media.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
162	3.	Comment: Table 3 – Fermentation media and cell culture media if the AS intended for manufacturing of biologics: For fermentation at very large scale, it is impractical and prohibitively expensive to use purified water. Historic data show that use of potable water yielded product of acceptable quality for veterinary use – mainly due to extensive purification after fermentation. Proposed change:Please include a footnote“use of potable water may be acceptable where justified and authorised, taking into account the extent of downstream purification”.	Accepted. While it is preferable that purified water is used, due to the fact that there may be a high variability in potable water quality, potable water is acceptable for use in fermentation media and cell culture media.
162	4.	Comment: Rows 8 -11 of Table 3 prescribe the water quality required for final isolation and purification of Active Substances (AS) intended for use in non-sterile/sterile and non-parenteral/parenteral products. An implicit intention (mainly from the commentary to line 165) may be interpreted as minimising the potential for AS contamination with micro-organisms and/or endotoxins. The current proposal covers all final stages of isolation and purification of the production process.It is currently not taken into account that microorganisms or endotoxins may be greatly reduced or removed by some processes or process steps in the production process. These steps may be downstream of others that would be considered part of final isolation and purification. If the removal of microorganisms and/or endotoxins can be validated, it seems overly restrictive to require the use of purified water for those steps prior to the process steps with potential removal. Proposed change (if any):	Not accepted. The quality of the water used during the manufacture of the active substance should not depend/rely on further process steps, including the ones in the manufacture of the drug product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Below the table, a further comment should be added to point out that the use of purified water (see table lines 8-11) is only obligatory if there is no safe removal of microorganisms/endotoxins in the final process steps of active substance manufacture or in the further pharmaceutical manufacturing process.Evidence should be provided through a risk-based approach and validation. Below the table, a further comment should be added related to table lines 8-11: “Potable water may be suitable for some final isolation and purification manufacturing stages if downstream microorganism and endotoxin removal has been validated”.	
162, Table 3 (All)	8.	Comment: While lining up the comments to table 3 we of course noticed that acceptance of those same comments would result in some major changes to the table, i.e. deletion of certain rows, because of redundancy. Therefore we copied table 3 from the draft, in edit friendly version and included our suggestions in a separate column for clarity. These are attached as a pdf file	Noted.
Table 3 L 162 Header Row (Row 0)	8.	Deletion suggested: Header: ~~Minimum a~~Acceptable quality of water Rationale: Deletion (if accepted) follows from a previous comment (L 160) In addition and more importantly: • Especially for an API that is e.g. not in solution it may not be necessary (and thus not appropriate) to have WFI as a minimum quality in some lines of the table. Current industry practice is to use Purified Water with a set endotoxin limit as it is proposed in the 12th row: “API is not sterile, but is intended for use in a	Partially accepted There are different requirements for API in solution and not in solution in the revised table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterile, parenteral product". • In addition, such a requirement is very stringent when the API is not claimed to be sterile or low bioburden. So the requirement for the microbiological specification of the water would be well beyond the bioburden specification of the API. • NB: Same negative impact would apply to the requirement for cleaning/rinsing of equipment, containers and closures (chapter 5.3)	
162, Table 3 (All)	8.	Comment: In order to afford a clearer overview of the sum of EFPIA's comments we have attached an annotated version of table 3 for your convenience. SEE EXCEL FILE ENCLOSED.	Noted. Table 3 updated.
162, Table 3 L Row 6,12; Col 3	8.	Change suggested:~~*Purified*~~Potable*Water* Rationale: In fact, it is preferred to use potable water for some of these processes, not at all just for convenience and cost, but because e.g. the minerals that are in the potable water are valuable nutrients for the cells.	Partially accepted. Use of potable water for fermentation media (not vaccines) possible, but not for purification. If significant amount of water is contained in the drug substance (solution), the water quality should be high in earlier steps as well. Revised table 3
Table 3 L 162 Row 6, Col 1	8.	Deletion suggested: Delete the example in col. 1 *Type of manufacture:* *Any step excluding final isolation and purification ~~(e.g. fermentation, initial purification)~~* Rationale:The statement as is, is very clear. Any examples will at worst create confusion here	Accepted.
Table 3 L 162 Row 6, Col	8.	Suggestto change Col. 3 "acceptable quality…" ~~*Purified Water*~~Potable Water	Accepted. Revision of table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3		Rationale: Potable water may be assessed to be of acceptable quality of water for fermentation (See our other comments on potable water)	
Table 3 L 162-Row 12,Col. 2 "Product.."	8.	Delete.: "~~*(biological)*~~…" Rationale: A) As argued in the general comments section, we believe that the acceptable water quality for the production of API should be determined by its intended use B) We believe row 12 and 14 are redundant resp. row 12 is a special case of row 14. What then would be the purpose of the bracket "(biological)" in the Product requirements column? C) More important though, the deciding factor should be the intended purpose. Therefore, this any API in liquid form, regardless of whether or not it is a biological, should be held to the same requirements.	Currently, table 3 states minimum water quality for fermentation media as "purified" – however, potable water (with specifications) may be possible see revision of table 3 A) Accepted; B) Accepted. Revision of table 3 C) Accepted
Table 3 L 162-Row 12,Col. 2+3	8.	Suggestion: Change Col. 2 ~~*AS*~~API~~*(biological)*~~ *is in solution*or dried, *not sterile,but is intended for use in a sterile,parenteral product*. Change Col. 3 ~~*Wfi*~~Purified Water *** Rationale: A) An API intended for use in a sterile parenteral product must have the same requirements for water quality in the final isolation and purification regardless of the initial origin of the API. B) Please also refer to our previous comment regarding the suggested removal of "Biological"	Accepted. Revision of table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table 3 L 162 Row 14 (last row), Col. 1 +3	8.	Suggestion: A) Change Col 1 to: "Final isolation and purification" B) Change Col. 3: ~~*WFI*~~Purified Water*** Rationale: A1) Insertion of "Isolation and" in Analogy with other rows However, A2) In line with previous comments, if accepted, this line is then redundant with row 12 and may be deleted C) Alignment w previous comments	A) Accepted B) Not accepted, since biologicals cannot be terminally sterilised;
162 - Table 3 "Fermentation media and cell culture media"	10.	Comment: Purified water is accepted, without any additional specification Proposed change (if any): It would be better to specify that, in this case, purified water is to be sterilised before use	Not accepted. It is self-evident that entire media are sterilised before use
162 - Table 3 "Final isolation and purification"	10.	Comment: Potable water is accepted or (*) purified water is required only based on greater chemical purity requirements, without considering possible additional microbiological requirements (in case of an AS with a stricter bioburden level). Furthermore, it should be remembered that the AS manufacturer may not know the final destination of the AS Proposed change (if any): It would be better to expand the note (*), including reference to any additional and/or tighter requirements (chemical and microbiological) as determined by the concerned AS	Partially accepted. See revised table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
162	12.	Comment: The Table 3: Water used during the manufacture of Active Substances (AS), at the last line in page 7, says that for the final isolation and purification of an AS which is not sterile, but is intended for use in a sterile, parenteral product, the minimum acceptable quality of water is Purified water, for which appropriate specifications have to be set for endotoxins and specified micro-organism testing. On the other hand, in page 8, last line of Table 3, this new draft adds that for the final purification step of a biological AS intended for parenteral use, WFI is the minimum acceptable quality of water. It is not clear the rationale why Purified water with appropriate specifications for endotoxins and specified micro-organism would not be considered suitable for a biological AS when it is non-sterile, not in solution (i.e., such water not being part of the final formulation of the medicinal product), intended for parenteral use. This would be the case of non-sterile biological AS obtained in dry solid form, by precipitation, which are intended to be used in the manufacture of parenteral products. It should be highlighted that in this case the manufacturing process of the sterile dosage form still needs a further sterilizing filtration after dissolution in WFI. In conclusion, the currently proposed text for the last line in Table 3 is excessively restricting, as according to it, only WFI would be acceptable for the final purification step of *any* biological AS for parenteral products, not considering if the AS is sterile or not and if	Accepted. Revision of table 3

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		it is in solution or solid. The use of purified water with appropriate specifications for endotoxins and specified micro-organisms should be considered suitable for the final purification step of non-sterile, solid, biological AS used in parenteral products, as it was accepted by the previous version of this guideline. Proposed change: a) Revise the Table 3 to include the following case: Type of manufacture: "Final isolation and purification" Product requirements: "AS (biological), dry solid form (not in solution), non-sterile, used for parenteral products." Minimum acceptable quality of water: "Purified Water***" ("***" referring to the currently proposed table footnote in lines 165-166) b) Delete the last line of the table or redefine its scope.	
162 Table 3 row 1	13.	Comment: 'Minimum' deleted according to the above comment (160) Proposed change (if any):~~Minimum~~ acceptable quality of water	Not accepted. Important to highlight that the indicated requirements are "the minimum" ones.
Table 3 row 4	13.	Comment: We suggest for Fermentation media and cell culture media to replace 'Purified water' by 'Potable Water*. Based on risk assessment higher quality of water should be used. Proposed change (if any): *Acceptable quality of water:* Potable Water* *. Based on risk assessment higher quality of water should be used. *Where local quality of potable water cannot be justified to be used	Partially accepted. Revision of table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in process development; a higher quality of water should be used	
Table 3 row 5	13.	Comment: Initial purification is not clear enough we suggest incorporating a definition in a glossary Proposed change (if any): Is initial purification covered by recovery?	Not accepted. Case-by-case.
Table 3 row 7	13.	Comment: we suggest deleting fermentation as example, as potable water could be used for fermentation based on risk assessment Proposed change (if any): Any step excluding final isolation and purification (e.g .~~fermentation~~, initial purification)	Accepted. Table 3 has been revised.
Table 3 row 13-1	13.	Comment: consider adding one row for AS is biological, dried, not sterile, but is intended for use in a sterile, parenteral product Proposed change (if any):Quality of water Purified Water with an endotoxin limit of 0.25 EU/ml and control of specified organisms	Partially accepted. Table 3 has been revised.
Table 3 row 13-2	13.	Comment: we suggest keeping for biologics AS as well and require the same level of quality water as per formulation prior to non-sterile lyophilisation as a dried, not sterile AS intended for use in a sterile parenteral product must have the same requirements for water quality in the final isolation and purification regardless of the initial origin of the AS. Proposed change (if any): AS (biological) is in solution, not sterile,but is intended for use in a sterile,	Partially accepted. Revision of table 3.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		parenteral product. The acceptable water quality could be: Purified Water with an endotoxin limit of 0.25 EU/ml and control of specified organisms	
Table 3 row 13-1 Table 3 row 13-2	13.	Comment: we suggest for biologics AS. To have the same requirement as per chemical API. Proposed change (if any):~~WFI~~Purified Water ***: Appropriate specifications have to be set for endotoxins and specified micro organisms testing of the AS as per relevant Ph.Eur.Chapters	Not accepted. Table 3 was revised to clarify that AS in solution intended for parenteral use have to contain water of WFI standard
165 - 166	1.	Comment: Missing the reference for endotoxins test Proposed change (if any): add the references to the following texts "revision of general chapter 5.1.10 Guidelines for using the test for bacterial endotoxins" and "Substances for pharmaceutical use" (2034)	Not Accepted. Reference of relevant Ph.Eur. chapters already reported in the "references"
Table 4			
Sec 5.3; L 178-180	8.	Change: "In general, the final rinse used for equipment, containers/closures should use the same quality of water as usedin the related manufacturing stage associated with the intermediates or~~final stage of manufacture of~~the API or as used for excipient in a medicinal product." Rationale: In order to avoid confusion for the intermediates.	Accepted. The guideline has been updated.
178-180	11.	Comment:Water to be used in the final stage of manufacture of the AS or used as an excipient in a medicinal product may exceed the quality/type requirements of the drug product, and therefore water with fewer monitored quality parameters may still be appropriate for	Partially accepted. The guideline has been updated to take into account the manufacturing stage associated with intermediates, as well.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		cleaning provided it is still suitable for the AS, drug product, or for use as an excipient. Proposed change (if any): “In general, the final rinse used for equipment, containers/closures should be an appropriate quality of water, such as that used for the final stage of manufacture of the AS orasthatused as an excipient in a medicinal product.”	
178-180	11.	Comment:Additional comment required to account for scenarios where the final rinse is not water (such as an alcohol or aprotic solvent). Proposed change (if any): Add comment “The final rinse may also be an organic solvent where appropriate for the process or where used to facilitate drying.”	Not Accepted. The guideline is specific to the quality of water.
178-180	11.	Comment: clarify wording on the use of water in the final processing steps of AS Proposed change: “In general, if the final rinse used for equipment, containers/closures uses water, it should use the appropriate quality of water such as that used in the final stage of manufacture of AS or as that used as an excipient in a medicinal product”	Partially accepted. The guideline has been updated to take into account the manufacturing stage associated with intermediates, as well
183, table 5	3.	Comment: Final rinse water quality for sterile parenteral products is WFI; in this draft revision no difference is made between human and veterinary parenteral products. Animals are much less sensitive to endotoxins than humans. In the current European Pharmacopeia an explicit difference is made for veterinary drug products: 04/2015:0520 Parenteral Preparations/Injections/Tests/Bacterial endotoxins-pyrogens/Preparations for veterinary use: When the volume to be injected in a single dose is 15 mL or more and is	Accepted. A footnote has been added to table 5 to clarify requirements for certain vet products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		equivalent to a dose of 0.2 mL or more per kilogram of body mass, the preparation complies with a test for bacterial endotoxins (2.6.14) or with the test for pyrogens (2.6.8). At the other hand, a test for bacterial endotoxins is always mandatory for parenteral preparations for human use. Also, product impact is negligible; concerns last rinse water step and therefore no danger for accumulation of contaminants (from the rinse water) into the product; also subsequent sterilization step (e.g. Sterilization In Place (SIP) of vessels, sterilization of materials and utensils) which ensures the killing of potentially higher bioburden loads which may be present in the residual Purified Water (in contrast to Water For Injections) after the final rinsing operation. Proposed change: 1) Cleaning/Rinsing of Equipment, Containers, Closures: Final rinse including CIP of equipment, containers and closures, if applicable Product type: Sterile veterinary parenteral products Minimum Acceptable quality of water: Purified Water 2) Cleaning/Rinsing of Equipment, Containers, Closures: Final rinse including CIP of equipment, containers and closures, if applicable Product type: Sterile veterinary non-parenteral products Minimum Acceptable quality of water: Purified Water	
183, table 5	6.	Comment: Regarding the minimum acceptable quality of water in the cleaning process of non-steriles and AS, there should be a comment: If equipment is cleaned with diluted detergents or/and dried after rinsing with diluted alcohol, the alcohol / detergent should be diluted in Aqua Purificata water. In these cases the final rinse is possible	Not accepted. The water used to dilute detergents should be the same quality of the water indicated for final rinse

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with potable water.	
Table 5, L 183 Row 2,Col. 2 "Product type"	8.	Change: "Intermediates andActive Pharmaceutical Ingredients~~AS~~" Rationale: In line with previous comments.	Not accepted. The term 'active substance' is used in line with EU Directive 2001/83/ECand Regulation 2019/6
188 - 190	1.	Comment: We understand that dilution of the detergent can be performed from the same quality of water used at the final rinse. In our opinion, we can use the same quality as the initial rinse Proposed change (if any): Dilution of detergent should be done by the same quality as used at the initial rinse	Not accepted. The water used to dilute detergents should be the same quality of the water indicated for final rinse
Lines 188-190	18.	Comment: It is recommended to move the lines 188-190 (with general requirements regarding preparation of diluted detergents and alcohol for cleaning/rinsing of equipment, containers, closures) above the Table 5: Water used for cleaning/rinsing. Now the last part of the legend to the Table 5 ("****") is a comment to the final rinse step, which can be confusing, because detergents are not used for this step.	Accepted.
191	1.	Comment: Missing USP reference Proposed change (if any): Add as reference <1231> Water for pharmaceutical purposes (USP)	Not accepted. The guideline is intended for products marketed or to be marketed in Europe, so reference to Ph.Eur. is sufficient.