10 May 2019

Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

	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.
	  ○ Fermentation and cell culture media must as a minimum be manufactured with purified water
	  ▪ Minimum requirement in current edition is potable water.
	  ○ 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.	

	• **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:**	

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	• 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.
	  ○ Stricter requirements for higher quality of water used in final purification of biologic AS compared to a synthetic origin product is not scientifically sound.
	  ○ 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 regarding quality and safety is applied.
	  ○ 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	

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	manufactured by fermentation - in which case the AS is not in solution. ○ 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. ○ 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	
	• **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	

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	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. • 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	

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	on sustainability.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
93		**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	
110		**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. **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	

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160		**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 proposed quality of water for the manufacture of active substances	
162 Table 3 row 1		**Comment**: 'Minimum' deleted according to the above comment (160) **Proposed change (if any):** ~~Minimum~~ acceptable quality of water	
Table 3 row 4		**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 in process development; a higher quality of water should be used	
Table 3 row 5		**Comment**: Initial purification is not clear enough we suggest incorporating a definition in a glossary	

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		Proposed change (if any): Is initial purification covered by recovery?	
Table 3 row 7		**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)	
Table 3 row 13-1		**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	
Table 3 row 13-2		**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	

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		sterile, but is intended for use in a sterile, 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		**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	

Please add more rows if needed.