13 May 2019

Submission of comments on *Guideline on the quality of water for pharmaceutical use* – EMA/CHMP/CVMP/496873/2018

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA  |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

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

1. 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)* |
| --- | --- | --- | --- |
| General |  | 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. |  |
| Sec 2, L 62 |  | **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. |  |
| Sec 2; L67/68 |  | **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 Reference section. |  |
| Lines 75-79 |  | **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 |  |
| Sec 4.1; L 93 |  | “ *confirm the quality of the water. Potable water may be used in* API production 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 use instead 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) |  |
| Sec 4.3 L 110 |  | *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 |  |
| Sec 4.4 L 114 + |  | **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 with Ph.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. |  |
| Sec 5.1 L 154 |  | **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. |  |
| Sec 5.2 L 160 |  | **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 |  |
| Table 3 (All) |  | **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 |  |
| Table 3 L 162Header Row (Row 0) |  | **Deletion suggested:**Header: ~~Minimum a~~ Acceptable quality of waterRationale: 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 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)
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| Table 3 (All) |  | **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 |  |
| Table 3 L 162Row 6,12; Col 3 |  | **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. |  |
| Table 3 L 162Row 6, Col 1 |  | **Deletion suggested:** Delete the example in col. 1*T*y*pe 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 |  |
| Table 3 L 162Row 6, Col 3 |  | **Suggest** **to change** Col. 3 “acceptable quality…”*~~Purified Water~~* Potable WaterRationale: 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..” |  | **Delete.:** “*~~(biological)~~…*”Rationale: 1. 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
2. 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?
3. 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.
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| Table 3 L 162- Row 12,Col. 2+3 |  | **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:1. 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.
2. Please also refer to our previous comment regarding the suggested removal of “Biological”
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| Table 3 L 162Row 14 (last row), Col. 1 +3 |  | **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 rowsHowever, A2)In line with previous comments, if accepted, this line is then redundant with row 12 and may be deleted1. Alignment w previous comments
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| Sec 5.3; L 178-180 |  | **Change:**“In general, the final rinse used for equipment, containers/closures should use the same quality of water as used in 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. |  |
| Table 5, L 183Row 2,Col. 2“Product type” |  | **Change:**“Intermediates and Active Pharmaceutical Ingredients*~~AS~~*”Rationale: In line with previous comments. |  |
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