# "Concept paper on the need for revision of note for guidance on quality of water for pharmaceutical use (H+V)"

## A comment by Fritz Röder and Ruven Brandes

5 min. reading time

*by Fritz Röder and Ruven Brandes*

The highly anticipated modification of the "Water for injection (WFI)" monograph (0169) got the ball rolling in the past year. On 1 April 2017, the revised monograph has come into effect. From that date onwards, it is possible to produce WFI by employing other methods than distillation. Membrane methods will also be accepted, as this has been allowed in the US and Japanese pharmacopoeia for quite some time. The announcement of the modified monograph immediately resulted in various questions being raised concerning the detailed design of such a water treatment system. Consequently, the EMA created a Q&A document to make clear its position in this regard. However, this also resulted in new questions (see LOGFILE 36/2016). The issuing of the final version of the Q&A document is to be anticipated for April 2017.

However, this modification regarding the topic of "WFI" is to be generally appreciated, and represents a milestone in the international harmonisation of pharmacopoeias. As a consequence of the modification, EMA is required to adapt various further regulations. "Note for guidance on quality of water for pharmaceutical use" is the first document connected to the modification. Now, this document is to be revised correspondingly. The EMA published a concept paper of the planned modifications that can be commented on until 6 June 2017 (Concept paper on the need for revision of note for guidance on quality of water for pharmaceutical use (H+V)).

The concept paper calls for the elimination of the "Highly Purified Water (HPW)" monograph, no. 1927, which was established in 2002, and its removal from all regulations as far as possible, including the "Note for Guidance".

As this water quality will be unnecessary in the future, it would be logical to delete this monograph. However, in this connection the authors think that it would not be clear what has to be done with registration documents that contain HPW. This would, in principle, require the modification of all the affected files. It is probably the case that there will be a transition period; although this remains to be seen.



 

Furthermore, in this connection many users want to know how the transition and requalification from a HPW system to a WFI system will take place. It is clear that the transition is to be notified to the authority. This is specified in monograph 0169. Due to these ambiguities, also with regard to the Q&A document, the HPW monograph will presumably remain in the European pharmacopoeia for some time.

In 2012, a new "Water for preparation of extracts" monograph (2249) was published in version 7.4 of the pharmacopoeia. As of now, this monograph is also to be considered in the "Note for Guidance".

A third significant modification refers to the topic of endotoxins. In 2014, the "Guidelines for using the test for bacterial endotoxins", EP chapter (5.1.10.), were published in the European monograph and they should be included into the provisions for WFI accordingly (which actually would also require another revision of the WFI monograph 0169). This would result in a significant modification:

With the new monograph there is no traditional specification of a limit value for endotoxins, but the general chapter 5.1.10 will be applied. Thus, the endotoxin limit would have to be calculated on a product-specific basis (as far as endotoxins are relevant at all) and would need to be determined by the pharmaceutical company itself. In this respect, it is interesting to ask if such a modification is also applied to e.g. the existing WFI monograph. In such a case, the limit should be calculated for all manufactured products, as the calculation refers to the finished medicinal product. Such a risk-based approach is to be welcomed in that the operator may now determine its own limit value, although it slightly counteracts the international efforts for harmonisation.

In summary, the proposal for the elimination of "Highly Purified Water" from all regulatory documents is to be seen as being logical. At the time, the HPW water quality was only considered to be a temporary solution; the further continuation of its use would result in regulatory problems in the long term. However, the successful elimination of HPW also includes the joint answering of the pending questions from the world of industry on WFI production using membrane technology. It is ultimately the case that the conversion of an HPW system into a WFI system requires transformation work and adequate re-qualification.

The risk-based approach to the determination of limit values regarding endotoxins is a logical consequence with regards to the standardisation of various water qualities. The endotoxins are not specified in the monograph on purified water so that the revision of such a guideline should establish clarity regarding the content of endotoxins. The harmonisation of water qualities and their use would therefore appear to be reasonable.

Presumably, answering the pending questions may only be done in cooperation between the world of industry and the authorities, as the know-how of both parties is required.

As soon as new information is available on this topic, we will inform our readers as usual.

## Sources:

**Note for guidance on quality of water for pharmaceutical use:**

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003394.pdf, retrieved on 21 March 2017



 

**Concept paper on the need for revision of note for guidance on quality of water for pharmaceutical use (H+V):**
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500222390.pdf, retrieved on 14 March 2017

**Q&A document on new WFI monograph:**
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211657.pdf, retrieved on 14 March 2017

**Questions on Q&A document, editorial in LOGFILE 36/2016 of 27 September 2016:**
https://www.gmp-verlag.de/de/leitartikel-gmp-logfile/gmp-aktuell/gmp-logfile-36-entwurf-ema-qa-wfi-herstellung.html, retrieved on 16 March 2017

## Authors:

**Fritz Röder**
Allergan plc, Weiterstadt
E-mail: roederfritz@googlemail.com

**Ruven Brandes**
Wirtschaftsgenossenschaft deutscher Tierärzte eG (WDT), Garbsen
E-mail: brandes@wdt.de



 