Changes in USP <1231>: Water for Pharmaceutical Purposes

8 min. reading time

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The informational USP chapter <1231>: "Water for Pharmaceutical Purposes" is currently in the process of being amended. The new draft amendment was published for annotation in version 43 (2) of the USP Pharmacopeial Forum. The amendments that have been made are not very grave but several new advices have also been added. Here is an overview.

The current version of USP chapter <1231> was published in May 2016 and has been valid since December 1, 2016. The last amendment was very comprehensive which is why we published a detailed explanation of the guideline at that time in a pdf download entitled **The new USP <1231>: Water for Pharmaceutical Purposes**. The USP guideline is a very comprehensible and comprehensive directive on how to design, operate and monitor a water system. There is no comparable directive on the subject of high-purity water amongst European Regulations which is why all persons engaged in GMP should make a point of reading USP <1231>. The new draft can be found under www.usppf.com in Forum 43 (2) and downloaded free of charge (registration required). It is open for comment until the end of July 2017. It has been supplemented with two new subjects, whilst two other subjects have been changed. Additionally certain terms have been more precisely defined. With this article we would like to draw your attention to the new and changed items.

Sampling Hold Times for Chemical Tests

One of the two new subjects concerns the sampling hold times for chemical tests. Basically it is advisable to conduct chemical tests immediately after extracting samples, since impurities may dissolve in water once the sample has been bottled. These impurities may be caused by contamination from ambient air or by the walls of the sample container ("leach-out"). In both cases the longer the samples are stored, the greater the potential to be adversely impacted by containers or conditions, in the worst case creating a false positive result. The proper container should be one that does not contaminate the sample during storage/hold time, eliminating the possibility that leach-out impacts certain parameter, i.e. glass bottles for the TOC assessment, plastic bottles for the measuring of the conductivity. Irrespective of the material of the container, where possible the sample should be stored cool and only for a short time in order to obtain representative results.

Elemental Impurities

The second new subject "Elemental Impurities" also contains useful tips. You will remember that the old heavy metal test on pharmaceutical products was replaced by this new concept. The old testing method was too nonspecific. Modern techniques are now being employed to conduct this test. Based on toxicological findings, various metallic elements have been categorised according to how hazardous or critical they are to health i.e. categories 1, 2A, 2B und 3. Maximum

permitted daily doses ("PDE values") are specified for each element. Those with the least acceptable daily admitted exposure are lead, mercury, arsenic and cadmium and belong in category 1. In the case of high-purity water a patient absorbs the highest proportion of heavy metals via high-volume injection substances (USP <1231> assumes a concentration based on a daily dose of 2000 ml). To analyse your own situation as operator or quality assurer, you must focus first on your drinking water. As USP <1231> only quotes the WHO and the US EPA threshold values, the following table shows the currently valid specifications in Germany and the threshold values for heavy metals in pharmaceutical products and in drinking water respectively.

Element	**USP <232> [µg/ml]**	**WHO [µg/ml]**	**ICH Q3D [µg/ml]**	**98/83/EC Drinking Water Directive EU [µg/ml]**	**TWVO Germany [µg/ml]**	**US EPA Drinking Water Requirements [µg/ml]**
Regulation for	medicinal products	medicinal products	medicinal products	drinking water	drinking water	drinking water
Mercury (Hg)	0.0015	0.006	0.001	0.001	0.001	0.002
Lead (Pb)	0.0025	0.01	0.0025	0.01	0.01	0.015
Cadmium (Cd)	0.001	0.003	0.001	0.01	0.003	0.005
Arsenic (As)	0.0075	0.01	0.0015	0.01	0.01	0.01

Table 1: Threshold Values as stipulated in Various Regulations for Heavy Metals for the Parenteral Absorption of Medicinal Products (Volume 2000 ml)

You will find information on the subject of "Elemental Impurities" in chapters 2.4.20 and 5.20 of the European Pharmacopoeia. However, no PDE values are given for the above-mentioned elements. Therefore, the following specifications have been taken from the ICH Q3D-Guidelines (Table A.2.2, page 22).

Based on the table, it is established that as a general rule the threshold values in finished medicinal products are never more than factor 10 lower (therefore more severe) than the threshold values in drinking water. USP <1231> assumes that the removal of heavy metals in common water-treatment plants (irrespective of whether it is a membrane or vaporisation process) are around factor 100 to 1000. This provides a valid risk justification to adhere rigidly to the newly required threshold values. Furthermore, the described case represents "worst-case" conditions (2 litres parenteral dispensed). An analysis of your own drinking water may show that no heavy metals can be detected. And there should be no source of contamination in the pipeline leading from the sampling point to the water-treatment plant (lead pipes are supposedly no longer used). To be on the safe side, the user can conduct an exemplary analysis of the high-purity water in the distribution system in order to detect any of the above-mentioned heavy metals.

The reader may add as an attachment to his risk analysis on the subject of elemental impurities the results of these additional analyses and assess his high-purity water accordingly. Inhalations and oral medicines are subject to other PDE values and absorption volumes. The case assumed here is meant as a „worst-case" scenario.

The two amended sections of the USP chapter are on the subject of microbiology and critical process parameters in the distributor system.

Microbiology

As in the case of the chemical tests, the new guideline adds advice on hold times for the microbiological examination of water (chapter 8.5.1). It points out that the results of incubation during a lengthy holding time may go either way, even unintentionally improving the sample or being detrimental to it. Germs found in very clean samples (and containers) will tend to decrease over time, whereas those in an impure sample are prone to increase. Thus, the risk of false positive/negative results increases during a lengthy holding time. Therefore, the sample should be cooled during a holding time of over two hours. Incubation should take place within 24 hours. In situations where even 24 h is not possible (such as when using off-site contract laboratories), it is particularly important to qualify the microbiological sample hold times and storage conditions to avoid significant changes in the microbial population during sample storage.

Critical Processing Parameters in the Distributor System

Last but not least, the potentially critical processing parameters in the distributor system have been changed. One new factor is the temperature of the hot water required to be able to monitor the sanitising process (and basically the storage temperature too). In addition the previously recommended measurement of particles in the distributor system has now been eliminated. This makes sense since any particles that may be in the drinking water will certainly be gradually separated out during the filtration process. The reverse osmosis membrane, with a molecular weight cut-off value of approximately 100 Dalton, only lets the tiniest particles through, hardly detectable by any measuring method. The only conceivable entry of particles is via the vessel ventilation which is generally fitted with a particle filter. Nevertheless should any particles get into the distributor system, they, if in polar form, will be detected by the conductivity test.

In conclusion, it remains to say that the amendments to the guideline do not really mean new demands on the user. Already existing requirements are more clearly defined and assistance given. The final version of USP <1231> will appear in the first Supplement USP 41 – NF 36. Publication is not expected until 2018.

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