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The New USP <1231>

Water for Pharmaceutical Purposes – a detailed Overview

GMP-Special

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The New USP <1231>

The New USP <1231>: Water for Pharmaceutical Purposes – a detailed Overview

Fritz Röder

The new version of USP 1231 will go into effect on 01 December 2016. The final version has been available in the relevant editions of the pharmacopoeia since 01 June. With 37 pages the new USP <1231> is very lengthy, but at the same time it contains concise instructions for action.
What has changed compared to the last version? Are there new requirements that did not previously exist? Can some things be omitted in the future?
The following article takes a look at these questions while giving a compact overview of the contents of the chapter.

Note: For copyright reasons the original text of USP <1231> is not included in this document.

1 Short Overview – What is USP<1231> and what is new?

Chapter <1231> is very detailed and describes diverse **aspects of construction, operation and monitoring of water systems**. "USP <1231> Water for Pharmaceutical Purposes" is "non-binding" (as are all USP chapters from <1000> onwards). However, when a water system is monitored there are repeated references to it. Moreover, the regulations also coincide with diverse other regulations and recommendations that exist concerning this topic (e.g., U.S. FDA Guide to inspections of high purity water systems, ISPE Guide Water & Steam Systems, WHO-Technical Report 970 (2012) water for pharmaceutical use (Technical Report Series, Annex 2), USP 85/643/645/797).

Another point - and that is the most important one – is that USP <1231> offers an extensive and very useful **guide for action to control water systems**. By following these tips it becomes possible to recognise potential problems early on. In practice, the topic of biofilm formation in particular frequently gives rise to questions to which the monograph can supply a number of answers.

The document has been completely revised and restructured. The old version had a narrative style with large text bodies. The new version contains many layout changes and makes greater use of chapter numbers and lists. A very welcome change is that all **procedural topics** are explained in terms of content, then they are dealt with separately with regard to **"areas of concern"** and the **corresponding control mechanisms**. Both topics were already included in the old version, but now they are more clearly organised. This makes the document easier to understand.

One new part is given in **Performance Qualification**: In the future it will be possible to use the water, at a risk, as soon as phase 1 of the PQ has been completed. However, exceeding the action level would render batches produced during phase 2 unsalable.

The **recommended temperature in hot sanitising** has also changed. The previous recommendation of at least 80 °C has been lowered to 65–80 °C. Now temperatures far in excess of 80°C are advised against.

From the "Sampling" chapter onwards the guideline has been reorganised and completely rewritten. This includes the chapters on "Chemical Tests", "Microbiological Tests" and "Alert and Action Levels". The key items remain the same in content, although they have generally been moved to other locations and new aspects have been added. That is welcome insofar as the previous guidelines on the topic of **"Sampling and Water Monitoring"** were not overly detailed. For example, the following references are new:

- Sampling plans for validation
- Sampling plans for routine operations
- Differentiation and explanation of the sampling concepts for drinking water, process water, purified water, water for injections and for sampling outside of the routine

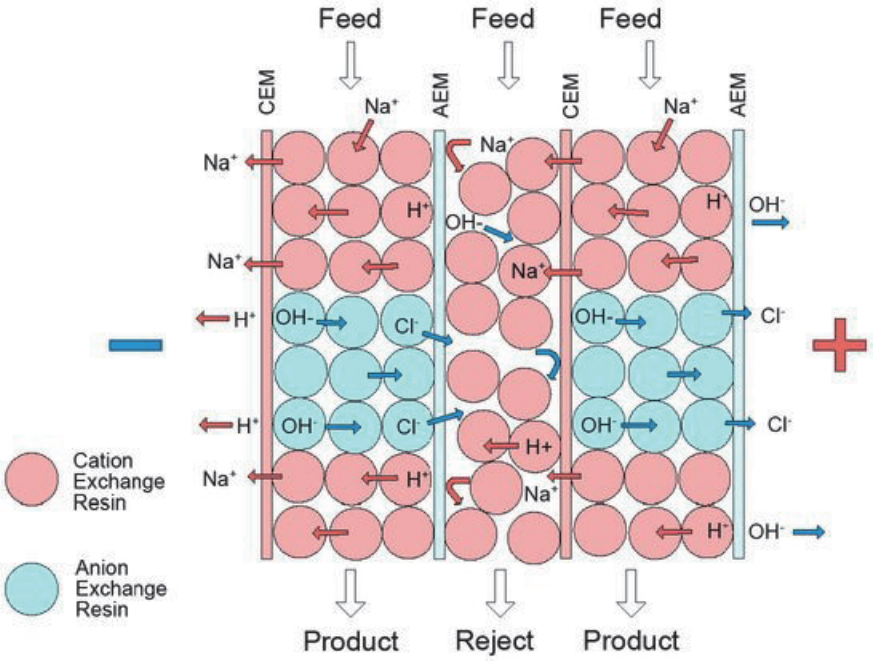

Figure 1 *Figure 1: Principle of the EDI process (source: GMP MANUAL, Chapter 5.B.6)*

eration is recommended. UV systems can be employed to prevent biofilm formation. For this purpose, the quality parameters (conductivity, bacteria count) are to be monitored before and after the EDI. In combination with an adequate sanitisation concept, reliable system control is possible.

When ion exchangers are used, special attention should be paid to rechargeable canisters, which can be a significant source of contamination after long or improper storage.

Reverse osmosis

Purpose: to remove substances in water

This method employs semipermeable membranes that allow for only the smallest molecules to pass through. As water molecules permeate the membrane, virtually all other substances are retained. Technically speaking, this results in a separation rate of 98% for substances and even higher for micro-organisms.

The above-mentioned pre-treatment of the water is crucial for operating a reverse osmosis system. Hardeners must have been either removed (softening) or hydrolysed in advance by hardness stabilisers. Furthermore, USP 1231 points out that chlorine compounds that could be contained in the source water must be removed beforehand to prevent damage to the membrane.

As a rule, a single step of reverse osmosis (RO) does not suffice to produce water that meets the requirements of the pharmacopoeia. It is possible to install either a two-step system or other RO technologies downstream, such as an EDI system.

Microbiological monitoring should be closely scrutinised. Biofilms can form on the membranes and compromise water quality. Nowadays, improved membrane materials for reverse osmosis systems allow for hot-water sanitisation, which facilitates microbiological control.

There are not many changes from the previous version of USP 1231. Only one paragraph referring to yield was removed and the section now features a new structure.

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Fritz Röder is a renowned expert in the field of purified water and ultrapure media technologies. In addition to this specialisation he can look back on a wide range of experience in the GMP environment. The various stages of his career have imparted to him a profound understanding of different company perspectives.

With experience not only in facility engineering, but also from the standpoint of procurement or operations, Mr. Röder is familiar with the problems inherent to the acquisition of facilities. He also possesses expertise in the field of solid, semi-solid and liquid (sterile) drug forms. In recent years he has participated in diverse audits and inspections.

Following completion of his studies, Fritz Röder acquired the necessary technical background and practical experience at a manufacturer of ultrapure water systems. Afterwards he was employed as responsible operator and procurer for all water systems at a drug product manufacturer for solid forms (now Allergan plc).

The next phase of his career brought Mr. Röder to Bayer AG in Grenzach, where he managed various larger projects relating to semi-solid and liquid sterile drug product forms and where he participated in a major FDA inspection. He has been active as Project Manager at Allergan plc since 2015.