Proposed Changes to Test Limits for USP Sterile Water Monographs
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In May 2012, the United States Pharmacopoeia (USP) proposed changes to the monograph for Sterile Water for Injection, as well as potential changes to other Sterile Water monographs and related test chapters ⟨645⟩ Water Conductivity and ⟨643⟩ Total Organic Carbon. These proposals were published in the bi-monthly Pharmacopeial Forum to solicit public comment and feedback. After the review of public comment, if these changes are approved by the USP Chemical Analysis Expert Committee, they would become official in the first supplement of USP36-NF31 (latter part of 2013). This article provides more details regarding the changes and potential impact to you.

Introduction

Since the adoption of ⟨645⟩ Water Conductivity and ⟨643⟩ Total Organic Carbon (TOC) tests for USP Purified Water (PW) and USP Water for Injection (WFI) in 1996, there have been slow but steady advances by other major pharmacopeia (US, EU, Japan, India, China, and Brazil to name just a few) to harmonize the respective monographs for PW and WFI. The benefits of having harmonized tests and specifications for raw materials, APIs, drug products, etc., are well-established. However, due to the common use of water, the harmonization of bulk waters such as PW and WFI is of upmost value to the pharmaceutical and life sciences community, since these raw materials (and sometimes ingredients) are utilized in every manufacturing facility.

Yes, there are some differences in the details of monographs and tests among the major pharmacopoeia. The EP conductivity limits for PW are higher than their conductivity limits for WFI, whereas other pharmacopeias have the same conductivity limits for both water types. USP and JP are less restrictive about allowable production methods for WFI compared to most other pharmacopeias. There are differences regarding the requirement for heavy metals and nitrates testing. And there are more differences.

These differences and others notwithstanding, the adoption of conductivity and TOC based tests for the detection of ionic and organic impurities by most pharmacopoeias has been the universal point of agreement, i.e., harmonized strategies for measurement and control of these types of impurities. The details sometimes vary, but more often do not. As a result, the PW and WFI monographs and the tests contained therein are partially harmonized. Considering that prior to 1996 dozens of qualitative chemical tests (for each pharmacopeia) were required (and their details did vary), the conversion to two quantitative chemical tests is a remarkable benefit to the industry.

Sterile Waters

What about packaged sterile waters such as Sterile Water for Injection (SWFI)? These are the waters that are used as an ingredient in individual injections or intravenous administration. They could also be used in the administration of an inhaled asthma

medicine, i.e., Sterile Water for Inhalation. Today, for these types of waters, many pharmacopeia have a range of tests, usually some combination of chemical tests for chloride, sulfate, ammonia, CO_2, calcium, etc. Starting in 2008, USP deleted these qualitative chemical tests for the aforementioned sterile waters, and replaced them with the current two-tiered conductivity limit, depending on the container volume.

- For containers with a nominal volume of 10 mL or less, if the conductivity is not greater than 25 µS/cm, the water meets the requirements.
- For containers with a nominal volume greater than 10 mL, if the conductivity is not greater than 5 µS/cm, the water meets the requirements.

Though the Oxidizable Substances (OS) test was replaced by the TOC test for the bulk PW and WFI waters in 1996, the OS test was retained for testing sterile waters, even as the other chemical tests were being replaced in 2008. The retention of the OS test was due, in part, to the difficulty to determine an appropriate and safe instrumental test method and limit for organic impurities that would arise from packaging and packaging processes. A TOC or other analytical test for sterile waters was not adopted at that time.

Proposals

USP has published and proposed two primary changes to sterile water monographs and related general test chapters in Pharmacopeial Forum Volume 38(3) in May 2012. The monographs that would be impacted are Sterile Water for Injection, Sterile Purified Water, Sterile Water for Inhalation, and Sterile Water for Irrigation, and the two general test chapters that would be impacted are ⟨645⟩ Water Conductivity and ⟨643⟩ Total Organic Carbon. The two changes for each of these waters are:

1. These waters shall continue to meet the two-tiered conductivity test described in ⟨645⟩ Water Conductivity. However, based on discussions within the Pharmacopeial Discussion Group, it is proposed to lower the conductivity limit to 15 µS/cm (from 25 µS/cm) for containers with a nominal volume of 10 mL or less.
    a. There is no proposed change to the conductivity limit for containers with a nominal volume greater than 10 mL.
    b. Also, there is additional text to clearly indicate to the analyst to “vigorously agitate the package to homogenize the water sample.” This is to assure that any sample measurements are homogenous and they are treated as the water is used.
2. A TOC test has been added to the monographs. However, it is specified in each monograph as an alternative to the OS test (you may perform either method), with intentions to delete the OS test in upcoming years (USP38 in 2015). The key contents in ⟨643⟩ Total Organic Carbon are the following.
    a. The proposed sterile water TOC limit is 8.0 mg C/L (8.0 ppm).
    b. An SST test with sucrose and p-benzoquinone at 8.0 ppm.
    c. The use of reagent water (to make the SST solutions) at 0.50 ppm.
    d. An instrument detection limit at 0.10 ppm.
    e. None of these changes are applicable to USP Purified Water and WFI.

These are proposals with intentions to make them official in the first supplement of USP36-NF31 (latter part of 2013). Depending on the public comment, the proposals could be approved and made official by the USP Chemical Analysis Expert Committee, or withdrawn or amended.

Note: There are no proposed changes to the conductivity and TOC requirements for USP Purified Water and WFI. These proposed changes apply only to the USP sterile water monographs.

For all the details, you can go to the USP website (www.usp.org) and access Pharmacopeial Forum for free.