Bulk Pharmaceutical Water Monitoring and Testing

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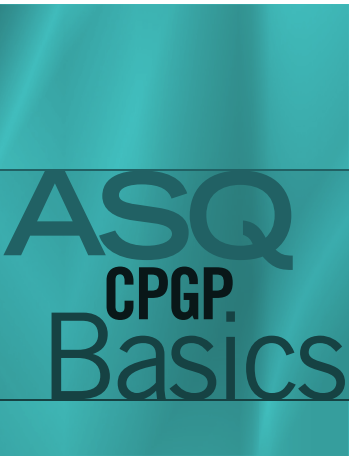

"ASQ CPGP Basics" discusses various good manufacturing practice (GMP) topics from the American Society for Quality (ASQ) *Body of Knowledge* for the Certified Pharmaceutical GMP Professional (CPGP) program. This column provides basic theory and application of GMP topics useful to quality professionals and is a valuable resource for daily work applications.

Reader comments and suggestions are requested. Please send your comments and suggestions to column coordinator Alice Krumenaker at alice.krumenaker@gmail.com or to journal managing editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- Bulk pharmaceutical water serves either as a pharmaceutical component in product formulations or a material that decontaminates, cleans, or sanitizes product-contact equipment.
- Total organic carbon (TOC) and water conductivity make up the common tests prescribed by the United States Pharmacopeia (USP), PharmEuropa (EP), and the Japanese Pharmacopeia (JP). Water for injection (WFI) additionally requires the bacterial endotoxin test (BET).
- Heavy metals or other specific ion testing of the pharmaceutical waters is required by EP.
- EP suggests a total aerobic microbial count.
- Both US Food and Drug Administration and USP guidance provide recommendations on sampling frequency and locations.
- Pure steam when condensed should satisfy WFI specifications.
- Water conductivity monitoring and testing may be performed offline or inline. Inline systems require automatic diversion systems if out-of-specification (OOS) test data occur.
- The TOC compendial test for bulk pharmaceutical water is harmonized among the USP, EP, and JP.
- BET testing may be accomplished by multiple methods and have different requirements.
- Water systems are basic to compliant regulated manufacturing, and appropriate sampling and testing are fundamental to control of these systems.

PHARMACEUTICAL GMP PROFESSIONAL CERTIFICATION BODY OF KNOWLEDGE

III. LABORATORY SYSTEMS

A. Compendia (US, Europe, and Japan)

5. Biological, microbiological, chemical, and physical test methods
   Identify and interpret results from compendia identification tests, quantitative analysis, qualitative analysis, and other tests or studies for biological, microbiological, chemical, and physical tests.

INTRODUCTION

This discussion addresses the monitoring and testing of bulk (not packaged) pharmaceutical water. Bulk pharmaceutical water serves either as a pharmaceutical component, a manufacturing material that is later completely evaporated or sublimated, or a material that decontaminates, cleans, or sanitizes product-contact equipment. It is produced and distributed by a system that undergoes initial qualification and must forever be monitored. Thus, bulk pharmaceutical water is a utility, a process material, an excipient, or all three.

TESTING AND SAMPLING PHARMACEUTICAL WATER

Total organic carbon (TOC) and water conductivity make up the common tests prescribed by the United States Pharmacopeia (USP), PharmEuropa (EP), and the Japanese Pharmacopeia. Water for injection (WFI) additionally requires the bacterial endotoxin test (BET) with a specification of not more than 0.25 Endotoxin Units/ml (International Units/ml in Europe). The *Japanese Aseptic Processing Guidance Appendix A2, Pharmaceutical Waters* (1) states, "Whenever water quality is monitored and controlled by conductivity and TOC testing, it is not usually necessary to monitor individual metals or inorganic ions." Therefore BET, TOC, and water conductivity may be considered sufficient process control and monitoring tests for maintaining a pharmaceutical water storage and delivery system in control.

For quality control monitoring tests of pharmaceutical water, neither USP nor JP require heavy metals or other specific ion testing of the pharmaceutical waters because the US Environmental Protection Agency (EPA)'s National Primary Drinking Water Regulation has sufficiently tight specifications to preclude their retesting in the more purified water. Unfortunately, EP is not in harmony with USP or JP by the requirement of the tests shown in the Table.

TABLE: EP tests and specifications for the principal pharmaceutical waters.

Pharmaceutical water ▶ QC release test ▼	Purified water	Water for injection in bulk
Nitrates	0.22 ppm	0.2 ppm
Heavy metals	0.1 ppm	0.1 ppm

Though not a compendial specification, EP (2) suggests a total aerobic microbial count (TAMC) action limit of 10 CFU/100 ml in its WFI monograph, which agrees with the 1993 FDA *Guide to Inspections of High Purity Water Systems* (3). EP and the 1993 FDA guide give a TAMC action limit of 100 CFU/ml for purified water. USP general chapter <1231> explains that microbial specifications would be inappropriate for a continuously produced material such as bulk pharmaceutical water and for such a validated process. The microbial incubation time lag inherently defeats the real-time production and usage of bulk pharmaceutical water.

The EP TAMC action limit statement, in both the purified water and WFI monographs, specifies the use of agar medium S, which is R2A media. Neither USP nor JP specifies an agar for TAMC of bulk pharmaceutical water, permitting different process validation results to dictate appropriate medium.

Two guides exist for the frequency and location of bulk pharmaceutical water sampling for monitoring and testing offline. The 1993 FDA guide (3) also created the generally accepted sampling frequency and sampling locations within a bulk pharmaceutical water distribution system. It recommends daily sampling (except during shutdown) from a minimum of one point of use, with all points of use tested weekly. *USP* <1231> states that "sampling frequencies should be based on system validation data and should cover critical areas including unit operation sites. . .samples should be collected

from use points using the same delivery devices, such as hoses, and procedures, such as preliminary hose or outlet flushing, as are employed by production from those use points."

Pure steam is manufactured such that, when condensed, it satisfies WFI specifications. Guidelines for monitoring pure steam are less well defined to nonexistent compared to those for bulk pharmaceutical waters. Providing it is manufactured from a system that already passes TOC and water conductivity, it is presumed not to deviate significantly from its source pharmaceutical water. In addition, pure steam is inherently self-sterilizing such that TAMC is highly unlikely to provide trends on the steam but only on incorrectly sampled condensate. BET results on pure steam that use points or sampling points provide enough assurance against grossly contaminated (by Gram negative bacteria) draw-off valves.

Water conductivity monitoring and testing may be performed offline or inline. Inline conductivity monitoring inherently prevents the progression to Stage 2 or Stage 3 of the USP or EP water conductivity test. The distribution system must be designed such that an out-of-specification (OOS) (based on conductivity versus water temperature) automatically results in either diversion to drain or recirculation into the water generation system. If using the offline pharmacopeial water conductivity test, stages 2 or 3 must be performed if the prior stage fails. No OOS investigation per FDA OOS guidance (4) or stoppage of the conductivity or any multi-stage compendial test may occur between stages. *USP* <645> requires an electronic calibration of the conductivity meter by replacing the conductivity sensor with a nationally traceable resistance device (e.g., Wheatstone Bridge).

The TOC compendial test for bulk pharmaceutical water is harmonized among the USP, EP, and JP. The apparatus for measuring TOC, like water conductivity, is either inline or offline. The periodic suitability testing of the apparatus is specified as employing both a standard solution of compendial sucrose and a system suitability standard solution of 1,4-Benzoquinone. The diluent or solvent is reagent water having a TOC of not more than 0.10 mg per liter.

A monitoring test required for, and applicable only to, WFI and pure steam is the BET. The test, being highly dependent on the particular Limulus Amebocyte Lysate (LAL) and corresponding test equipment and instruments, is not a candidate for compendial test suitability verification, but must undergo complete method validation for parenteral products. The LAL reagent used in the BET has been classified as a biologic and is licensed by the Center for Biologics Evaluation and Research (CBER). FDA requires that a finished parenteral pharmaceutical manufacturer operating in the US or shipping to the US use "an LAL reagent licensed by CBER in all validation, in-process, and end-product LAL tests (5)."

Portions of the BET general chapter have been harmonized among the three compendia. USP, EP, and JP permit and describe the following six methods:

- Gel-clot method: limit test
- Gel-clot method: semi-quantitative test
- Turbidimetric end-point method
- Turbidimetric kinetic method
- Chromogenic end-point method
- Chromogenic kinetic method.

All three compendia contain similar wording that, "in the event of doubt or dispute, the final decision is made based upon method A (Gel-clot method: limit test) unless otherwise indicated in the monograph (for a specific finished parenteral pharmaceutical)."

IMPLICATIONS FOR COMPLIANCE PROFESSIONALS

This brief introduction to water sampling and testing from the CPGP *Body of Knowledge* is a recommended starting point for discussion on bulk pharmaceutical water systems.

The quality of pharmaceutical water is critical in manufacturing facilities. Sampling and testing are vital to validation and ongoing monitoring. Compliance professionals must be familiar with these topics and assure that their areas of responsibility meet regulatory requirements. Aseptic manufacturing areas are often well-controlled regarding these considerations. Non-aseptic areas perceived to be of lesser risk may not be adequately controlled. Water systems are somewhat less visible in the manufacturing environment (i.e., manufacturing water comes from the spigot). Water systems must not be taken for granted.

Pharmaceutical water systems must not be a "black box" in the manufacturing environment. These systems comprise multiple equipment including pre-treatment

systems, ion exchange and reverse osmosis equipment, distillation, clean steam, storage tanks, circulating loops, and distribution equipment. These systems must be well understood and appropriately tested and maintained for compliant operation.

Systems preparing and supporting purified water supplied to manufacturing must not receive lesser attention. Sampling and testing, followed by thorough review of data including ongoing monitoring and trending, is a necessity. Areas with unreliable or variable sources of input water should be tested at higher frequency commensurate with risk. Water systems are basic to compliant regulated manufacturing, and appropriate sampling and testing are fundamental to control of these systems.

CONCLUSIONS

Bulk pharmaceutical water is a critical material in pharmaceutical manufacturing. It serves either as a pharmaceutical component in product formulations or a material that decontaminates, cleans, or sanitizes product-contact equipment. Sampling, testing, and ongoing monitoring of test data from pharmaceutical water enables maintenance of water quality. Required tests are identified and specified by the respective compendia. FDA guidance and USP provide recommendations on sampling frequency and locations. Pure steam when condensed should satisfy WFI specifications. The importance of pharmaceutical water to the manufacturing site behooves compliance professionals to be familiar with these systems and be vigilant regarding monitoring and trending of test data.

REFERENCES

1. JP, *Japanese Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing*, Appendix A2, Pharmaceutical Waters, Japanese Pharmacopeia, 2005.
2. EU, *Guidelines to Good Manufacturing Practice; Medicinal Products for Human and Veterinary Use*, Annex I, Manufacture of Sterile Medicinal Products, PharmEuropa, 2008.
3. FDA, *Guide to Inspections of High Purity Water Systems*, FDA, 1993.
4. FDA, *Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, FDA, 2006.
5. FDA, *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*, FDA, 1987.

GENERAL REFERENCES

USP, Monograph on Purified Water, *United States Pharmacopeia/National Formulary.*

USP, Monograph for Water for Injection, *United States Pharmacopeia/National Formulary.*

USP, Monograph for Pure Steam, *United States Pharmacopeia/National Formulary.*

USP, <85> Bacterial Endotoxins Test, *United States Pharmacopeia/National Formulary.*

USP, <643> Total Organic Carbon, *United States Pharmacopeia/National Formulary.*

USP, <645> Water Conductivity, *United States Pharmacopeia/National Formulary.*

USP, <1231> Water for Pharmaceutical Purposes, *United States Pharmacopeia/National Formulary.*

EU, Monograph for Purified Water, *PharmEuropa*

EU, Monograph for Pure Steam, *PharmEuropa* **GXP**

ARTICLE ACRONYM LISTING

ASQ	American Society for Quality
BET	Bacterial Endotoxin Test
CBER	Center for Biologics Evaluation and Research
CPGP	Certified Pharmaceutical GMP Professional
EP	PharmEuropa
FDA	US Food and Drug Administration
GMP	Good Manufacturing Practice
JP	Japanese Pharmacopeia
LAL	Limulus Amebocyte Lysate
OOS	Out of Specification
TAMC	Total Aerobic Microbial Count
TOC	Total Organic Carbon
USP	United States Pharmacopeia
WFI	Water for Injection

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