Pharmaceutical Water Sampling, Process Analytical Technology (PAT), Instrumentation

Anthony Bevilacqua, Ph.D., Principal Scientist, Mettler-Toledo Thornton, Inc.

Brian Pochini, MBA, Principal Engineer, Sanofi

Disclaimer

We are speaking here representing ourselves, not our employers or USP

- All of the presentation points are prepared based on
  - 1) publicly available information,
  - 2) non-confidential discussions, or
  - 3) opinions or representation of available information
- If you have any specific "USP water-related questions", we encourage you to go to www.usp.org and look at the FAQs

Keys to Compliant Sampling Programs

A compliant sampling program ensures that the water used in the manufacturing process is suitable for use.

- Samples must be representative of the water used in manufacturing processes
- In-line/on-line monitoring removes exogeneous contamination potential of “grab samples” used for offline testing
- Process Control (PC) sampling reflects water within the water system (within the distribution system).
- Quality Control (QC) sampling reflects water quality as it is collected at the true point of use (where delivered for use).
  - QC sampling must use the same delivery path and components as used during water transfer during manufacturing usage.
- The type of impurity also impacts “how to collect samples” and “use for PC vs QC”
  - e.g., chemical (conductivity and TOC), microbial, endotoxin, particulate (for Sterile Water products)
  - Improper collection could result in inaction when remediation is required or vice versa.
- Non-monograph attribute sampling falls under Process Control sampling and is still important to reliable operation
  - Examples in pretreatment system include Hardness, Chlorine, Endotoxin, Silica

Process Analytical Technology (PAT)

October 2004 FDA issued Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.

- "Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance."
- "The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."
- During a joint FDA/EMA meeting in the early 2000s, in a private discussion, the USP CEO said "of course this is quality by design, it is not 'quality by accident'."

20 years since this Guidance for Industry was released many companies have still not adopted online TOC and Conductivity, and many continue to perform offline testing where online instruments are available.

- Question: If your online TOC and Conductivity instruments have been qualified and have been calibrated, what value does offline testing bring?

The Role of Instrumentation in Pharmaceutical Water Systems

The role of the instrumentation (of any water system or any process) is to provide data to assure compliance and control

- When your online chemical instrumentation fails (not calibrated, not meet SST, etc…), this does NOT mean your water is out of compliance
  - Same is true for your offline lab instruments
- When your chemical instrumentation needs to be serviced for an extended period of time (hours to days/weeks), this does not mean your water system is out of service
  - Same is true for your offline lab instruments

By the way, 30+ years ago, when virtually all quality measurements were done offline in a lab, and 1 L of water was sampled out of the 500 or 50,000 L produced that day, the company is flying ‘blind’ >99.99% of the time.

- It just means you have less data (more uncertainty)

But testing <0.05% of material produced in the ‘well-respected lab’ is considered state-of-the-art, while online sampling is considered risky by some.

- **Why is that?**

Sampling for Quality Control

USP <1231> tells us QC samples shall be representative of the quality of water used in Production

6.1.2 QUALITY CONTROL SAMPLING

QC sampling is intended to reflect the quality of water that is being used. These samples should be collected at the true point of use; that is, where the water is delivered for use, not where it leaves the water system. QC sampling must utilize that same delivery path and components utilized for a water transfer during actual water use. This includes the same valves, hoses, heat exchangers, flow totalizers, hard-piped connections, and other components utilized during water use.

In addition to the water transfer components, QC sampling must also use the same water transfer process employed during water use, including the same pre-use outlet and delivery path flushing procedure and the same outlet, fitting, and hose sanitization practices employed during actual water use. The water delivery process and components used for QC sampling must be identical to manufacturing practices at every system outlet for the QC sample to mimic the quality of water being used by accumulating the same chemical and microbial contaminant levels it would during actual use from that outlet location.

Sampling for Quality Control

USP <645> tells us that QC sampling may be done online or offline

⟨ 645 ⟩ WATER CONDUCTIVITY

INTRODUCTION

Electrical conductivity in water is a measure of the ion-facilitated electron flow through it. Water molecules dissociate into ions as a function of pH and temperature and result in a very predictable conductivity. Some gases, most notably carbon dioxide, readily dissolve in water and interact to form ions, which predictably affect conductivity also. For the purpose of this discussion, these ions and their resulting conductivity can be considered intrinsic to the water.

Water conductivity is also affected by the presence of extraneous ions. The extraneous ions used in modeling the conductivity specifications described below are the chloride and ammonia ions. The conductivity of the ubiquitous chloride ion (at the theoretical endpoint concentration of 0.47 ppm when chloride was a required attribute test in *USP 22* and earlier revisions) and the ammonium ion (at the limit of 0.3 ppm) represents a major portion of the allowed water ionic impurity level. A balancing quantity of anions (such as chloride, to counter the ammonium ion) and cations (such as sodium, to counter the chloride ion) is included in this allowed impurity level to maintain electroneutrality. Extraneous ions such as these may have a significant effect on the water's chemical purity and suitability for use in pharmaceutical applications.

The procedure in the section *Bulk Water* is specified for measuring the conductivity of waters such as *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*. The procedure in the section *Sterile Water* is specified for measuring the conductivity of waters such as *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*.

The procedures below shall be performed using instrumentation that has been calibrated, has conductivity sensor cell constants that have been accurately determined, and has a temperature compensation function that has been disabled for *Bulk Water* Stage 1 testing. For both online and offline measurements, the suitability of instrumentation for quality control testing is also dependent on the sampling location(s) in the water system. The selected sampling instrument location(s) must reflect the quality of the water used.

Sampling for Quality Control

USP <643> tells us QC sampling may be done online or offline

⟨ 643 ⟩ TOTAL ORGANIC CARBON

INTRODUCTION

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, from biofilm growing in the system, and from the packaging of sterile and nonsterile waters. TOC also can be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system. A TOC measurement is not a replacement test for endotoxin or microbiological control. Although there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.

A number of acceptable methods exist for analyzing TOC. This chapter does not endorse, limit, or prevent any technologies from being used, but this chapter provides guidance on how to qualify these analytical technologies as well as how to interpret instrument results for use as a limit test.

Apparatuses commonly used to determine TOC in water for pharmaceutical use have in common the objective of oxidizing the organic molecules in the water to produce carbon dioxide followed by the measurement of the amount of carbon dioxide produced. Then the amount of carbon dioxide produced is determined and used to calculate the organic carbon concentration in the water.

All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved carbon dioxide and bicarbonate, and the carbon dioxide generated from the oxidation of organic molecules in the sample. The discrimination may be accomplished either by determining the inorganic carbon and subtracting it from the total carbon (the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. Although purging may entrain volatile organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

PROCEDURES

1. Bulk Water

The following sections apply to tests for bulk *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*.

1.1 Instrumentation requirements: This test method is performed either as an on-line test or as an off-line laboratory test using a calibrated instrument. The suitability of the instrument must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg/L (0.05 ppm) or lower of carbon.

When testing water for quality control purposes, ensure that the instrument and its data are under appropriate control and that the sampling approaches and locations of both on-line and off-line measurements are representative of the quality of the water used. The water purification process, distribution, and use should be considered when selecting either on-line or off-line measurement.

Sampling for Process Control - Chemicals

- USP <1231> tells us that QA samples, a.k.a., samples for process control, assure us that the sample is representative of the process
- For chemical impurities in a closed loop recirculating water system, *chemical impurities tend to be homogenously distributed*
- This allows a single measurement point to potentially support QC (for release) as well as QA (for process control)

6.2.1 CHEMICAL ATTRIBUTES

Dissolved chemical contaminants detected by conductivity or TOC testing tend to be uniformly distributed in the water throughout the water system. However, there are exceptions where localized chemical contamination sources can occur, such as from a coolant-leaking heat exchanger in a sub-loop, or at a point of use, or within a dead leg. These chemical contaminants may only be seen at the associated outlets and not systemically. However, in the absence of localized contamination influences, chemical attributes are candidates for on-line testing at fixed strategic locations within the distribution system, such as near a circulating loop return, and are generally reflective of the same chemical quality at all locations and points of use within the distribution system. Nevertheless, the suitability of the on-line locations

of these instruments for QC release purposes must be verified as being representative of the use-point water quality. This is usually done during water system validation.

Sampling for Process Control – Microorganisms

- This slide contains almost the *EXACT opposite message* as the previous slides.
- Microbial uniformity is NOT assured; in fact, it virtually guaranteed to be non-homogenous

6.2.2 MICROBIAL ATTRIBUTES

The same uniformity scenario cannot be assumed for microbial attributes. Planktonic organisms in a water sample could have originated from biofilms in the purification or distribution systems releasing more or less uniform levels of planktonic organisms into the circulating water, as detectable in samples from all outlets. However, a local biofilm developing within a water delivery conduit (e.g., a use-point outlet valve and transfer hose) in an otherwise pristine biofilm-free water system could release planktonic organisms detectable only in water delivered through that conduit. Therefore, QC release samples for assessing the quality of water that is delivered by the system during water use must be collected after the water has traversed the same fluid conduit (including the same preparatory activities such as outlet sanitization and pre-flushing) from the water distribution system to the specific locations where the water is used.

On-line microbial water sampling/testing has value in pharmaceutical water systems only for PC purposes unless the water is taken from the point of use in the same manner as routine water usage, in which case the data can also have a QC release purpose. Microbial counts detected from strategic sampling ports continue to have PC and investigational value, but generally cannot be substituted for QC release testing except in certain scenarios, as described in *6.1.2 QC Sampling*.

Instrumentation – Process Control or Quality Control?

Online / In-Line / At Line

- Temperature
- Pressure
- Level
- Conductivity
- Total Organic Carbon (TOC)
- Hardness
- Chlorine
- pH

Offline

- Rapid Microbial Monitoring (RMM)
- Conductivity
- Total Organic Carbon (TOC)
- Hardness
- Chlorine
- pH
- Ozone

What is missing?
What is incorrect?

Instrumentation – Process Control or Quality Control?

Online / In-Line / At Line

- Temperature
- Pressure
- Flow/velocity
- Level
- Conductivity
- Total Organic Carbon (TOC)
- Online Water Bioburden Analyzer
- Hardness
- Chlorine
- pH
- Ozone

Offline

- Bacterial Endotoxin
- Rapid Microbial Monitoring (RMM)
- Total Organic Carbon (TOC)
- Hardness
- Chlorine
- pH
- Ozone

What is missing? Particles, Turbidity
What is incorrect? Flow/velocity

Online / In-line / At-line vs. Off-line

Online / In-line / At-line Pros

- Higher frequency of data collection
  - Essentially real time
- Not influenced by sampling method
- Not influenced by exposure to environment
- Encouraged by Pharmacopeia and Regulatory agencies

Online / In-line / At-line Cons

- Expensive, especially on large systems
- Must be qualified (during PQ typically)
  - Requires doing offline testing
- Routine maintenance/Calibration activities
- Not all compendial parameters currently available in-line/on-line/at-line
  - Microbial & Endotoxin

Off-line Pros

- All compendial parameters available offline
- Lower costs especially on smaller systems with established labs.

Off-line Cons

- Lower frequency of data collection
- Can be easily contaminated
- Does not necessarily represent condition in water system (delays in testing)
- More manpower required (sampling, testing)

Benefits and Weaknesses of On-line vs At-line

Benefits of On-line

- No false positives
- No sampling costs
- Real-time decisions / actions
- Use for PC and QC
- Conductivity - no water consumed (?)
- Encouraged by global regulators

Neutral – impact both equally

- Calibration time/cost
- Service downtime

Weakness of on-line

- One time installation costs
- TOC - more water consumed
- Supports only 1 “loop”; costs for more loops

Loop Outlet vs Point of Use

USP FAQs: Water for Pharmaceutical and Analytical Purposes

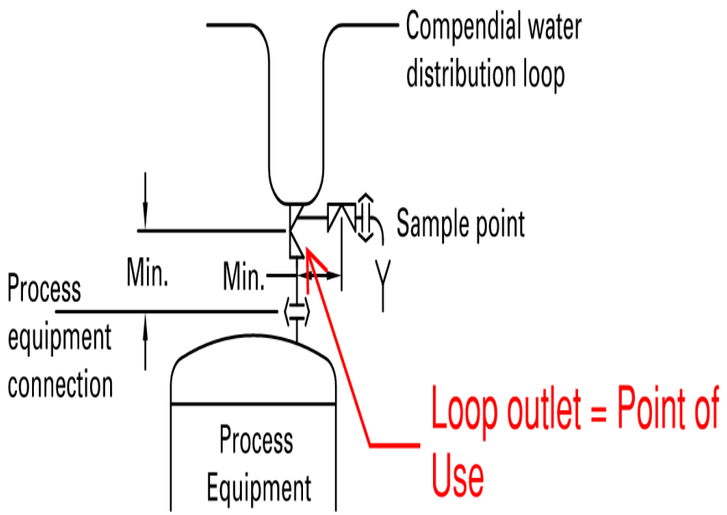
17. Is the outlet on the water distribution system, sometimes called a point of use outlet, considered to be the point of use?

No. The destination of that water where it will be used for product formulation or cleaning or where it enters a manufacturing process is the true point of use. The quality of water at the true point of use, as delivered by manufacturing (or by a sampling process identical to the manufacturing water delivery process) must be known at all points of use receiving water from the system. The water quality at the true point of use is where the water must be "fit for use", i.e. pass your water specifications.

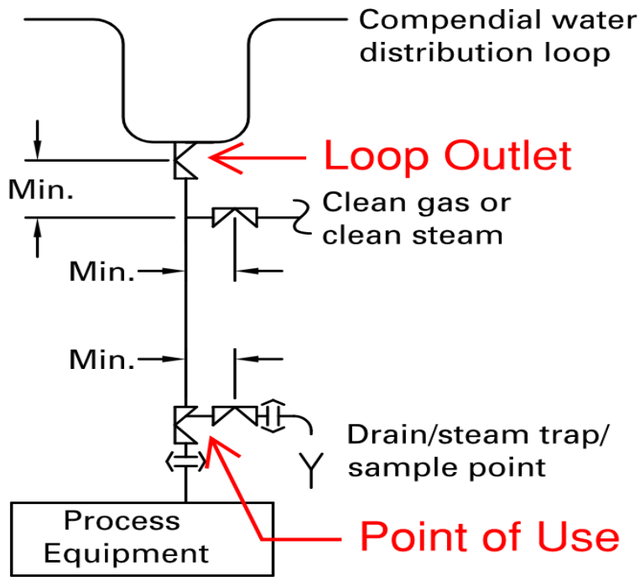
https://www.usp.org/frequently-asked-questions

Loop Outlet vs Point of Use con’t.

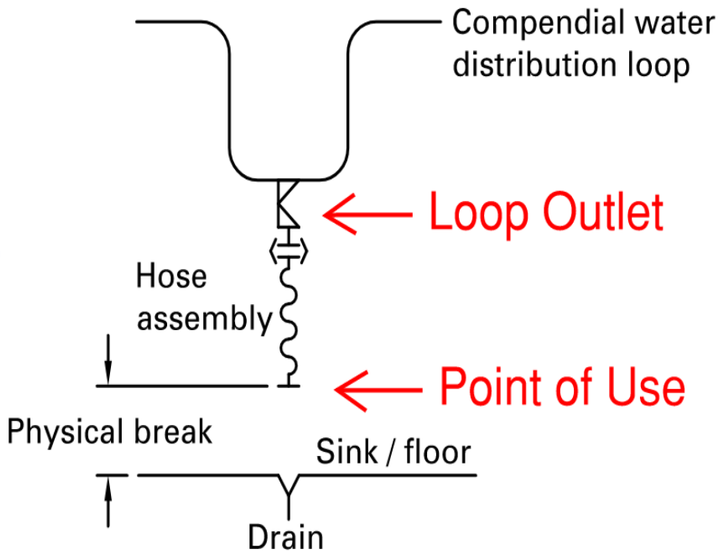
ASME BPE 2024 Point of Use Designs (SD-4.1.2.1-1)



(b) Direct Connect to Equipment



(a) Hard Piped to Equipment



(e) Hose

Can a TOC instrument be used to measure microorganisms? And vice versa

USP <643>

⟨643⟩ TOTAL ORGANIC CARBON

INTRODUCTION

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, from biofilm growing in the system, and from the packaging of sterile and nonsterile waters. TOC also can be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system. A TOC measurement is not a replacement test for endotoxin or microbiological control. Although there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.

A number of acceptable methods exist for analyzing TOC. This chapter does not endorse, limit, or prevent any technologies from being used, but this chapter provides guidance on how to qualify these analytical technologies as well as how to interpret instrument results for use as a limit test.

Online Water Bioburden Analyzer

Process Control or Quality Control?

References

- ASME Bioprocessing Equipment (BPE) - 2024
- USP <1231> Water for Pharmaceutical Purposes
- USP <85> Bacterial Endotoxin Test
- USP <643> Total Organic Carbon
- USP <645> Conductivity

Thank You

To all for attending.

A special Thank You to the following:

- Brian Hagopian for bringing a water program back to the ISPE Boston Education sessions.

- Alnylam for hosting this educational session and opening their doors to the ISPE Boston community.