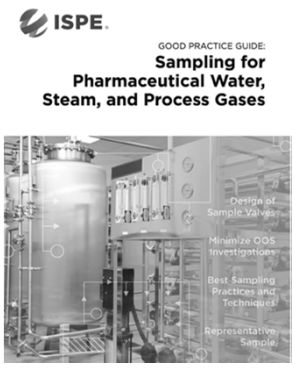
SHIFTING PARADIGMS IN PHARMACEUTICAL WATER AND STEAM:
CRITICAL UTILITY SAMPLING;
ISPE'S NEW GPG:
PHARMA WATER CHAPTER

Joe Manfredi
GMP Systems, Inc.



ISPE GOOD PRACTICE GUIDE: SAMPLING FOR PHARMACEUTICAL WATER, PHARMACEUTICAL STEAM, AND PROCESS GASES
WATER SAMPLING CHAPTER

- **Two primary groups to monitor and control**
  - Chemical contaminants
  - Biological contaminants
- **To understand; two topics must be discussed**
  - Distribution of contaminants within the water purification and distribution system
  - Overall purposes for sampling

WATER SAMPLING CHAPTER

- **Purpose of Sampling**
- **Sampling Attributes of Importance**
- **Sampling for Process Control Purposes**
- **Sampling for Quality Control Purposes**
- **Determining Sampling locations**
- **Developing Sampling plans**
- **Sample Valve Design**
- **Sampling Techniques**
- **Handling of Samples**
- **Parametric (Real-time) Release**

PURPOSE OF SAMPLING

- **Obtain samples that accurately reflect contents of the system and/or to ensure water of suitable quality is used for manufacturing or other designated purposes.**
- **Points Identified & documented for each location:**
  - Early in the design process
  - Justify and document the requirement (tabulate)
  - Identify the reason for a particular point
- **Reasons for installing a sampling point:**
  - Quality Control
  - Process Control
  - Technical, Investigational or Diagnostic

PURPOSE OF SAMPLING

The purpose of a proposed sampling location will define:

- Impurities of interest at that point
- Valve & accessories suited for that location
- When (routine and/or event based) sampling should be performed
- How the sample should be collected
- How the sample should be handled to preserve the attributes of interest

PURPOSE OF SAMPLING

Data from sampling can have varied uses

- Quality Control of raw material (Regulatory)
- Process Control of purification and distribution systems
- Special sampling, for investigative or diagnostic purposes
- To create a baseline for the system for future reference

<u>It is crucial that the purpose of sampling is understood</u>

- Appropriate limits or action/alert trigger values
- Appropriate frequency of sampling

SAMPLING ATTRIBUTES

If sampling for Quality Control

- Attributes (and limits) are those required to comply with regulatory or compendial requirements (such as USP, EP, JP, etc.)
- Additional in-house and/or regulatory requirements

If sampling for Process Control

- May be the same as for Quality Control but with tighter alert and action levels
- Alternate attributes may apply with trigger levels related to the performance and maintenance of particular unit operations

SAMPLING ATTRIBUTES

Impurities

Chemical impurities, particulates, and insoluble constituents are typically distributed homogeneously. Sampling can be performed at a limited number of locations provided there is no likelihood of added downstream contamination

- Homogeneous impurities my be continuously monitored if validated to be predictive at all points of use
- When validated, data could be used for quality control or water release purposes
- Homogeneously distributed impurities include:
    - Ionic impurities: electrical conductivity or resistivity
    - Organic impurities: Total Organic Carbon (TOC)
    - Nitrates (EU requirement)
    - Heavy metals (EP requirement if applicable)

SAMPLING ATTRIBUTES

Important notes:

- The potential for contamination introduced downstream of a particular point
  - Ex:, components after POU valves, such as hoses, gaskets or heat exchangers.
- Chemical contamination in sub-loops, parallel loops or other portions of the system could affect only that portion. The purity in sub-loops and their POU's may not be accurately reflected by samples in the main distribution system. For sub-sections, additional instrumentation or manual testing may be required.

SAMPLING ATTRIBUTES

Impurities

- Biological impurities (bacteria and endotoxin) are typically not evenly distributed in a distribution system (or its associated purification)
  - 99.9% of the bacteria present exist in biofilms
  - Planktonic (free-floating) organisms originate from a biofilm
  - The release of planktonic organisms from biofilms is episodic
  - Planktonic organisms are easily destroyed by sanitants (i.e.: heat, ozone) or inactivated by UV
- Biofilms grow more quickly in low flow zones and may add contamination via shear from hydraulic shock

SAMPLING FOR PROCESS CONTROL

- Monitor for routine PC by following trends of actual or related attributes
  - Points should be strategically located. Ex: start and end of distribution, at or near critical POU. Except POU, points not typically used by/for manufacturing
  - When sampling for PC, avoid local contamination so as to not unduly affect the test results
- Monitoring PC trends helps identify functions not working as intended. Investigations and remediation can bring the process back under control before failure. PC trigger values, (Alert & Action Levels) identify when the process is deviating.

SAMPLING FOR PROCESS CONTROL

Alert Levels

- Based on analysis and trending and set near the top edge of normal data. Occasional slight excursion may be an expectation, although may be early indication of growing control problem
- Responses to excursions should include notification of quality, manufacturing, and maintenance
  - Closer attention paid to the routine data
  - Values higher than Alert but less than the Action should be considered uncharacteristic or “out of trend”
  - Frequent excursions above the Alert Level are considered “out of trend”.
  - Evaluate need for resampling
  - Need for investigation and remediation

SAMPLING FOR PROCESS CONTROL

Action Levels

- Established based on data trending and water specifications. Set above the normal data trends and indicative of PC beginning to fail, but far enough from the specification so remediation can bring the process under control before failure.
- Any data value could be caused by a sampling problem
  - Resampling and retesting
  - Notification of appropriate parties
  - Determine if conditions are indication of PC problem
  - Remediation activities to restore control.
  - Determine root cause and implement corrective action to avoid recurrence.

SAMPLING FOR QUALITY CONTROL

- **Sample the quality of water used for manufacturing**
  - Collect samples at routine intervals or
  - Time the collection of samples when the water is drawn for manufacturing
- **Duplicate the procedures utilized by manufacturing (to duplicate the water delivered to manufacturing)**
  - Use of the same outlet sanitization practice
  - The same hardware and attached devices
  - The same outlet flush procedure

SAMPLING FOR QUALITY CONTROL

- **Challenges to sampling that duplicates how water is used by manufacturing**
  - Hard piped or permanent connections between the water system and manufacturing equipment
  - Large size, automated valves, etc.
- **Engineering solution may be appropriate**
  - Divert valve may be installed at the manufacturing equipment
  - Sample port on or near the equipment
  - Disconnect the interconnecting piping for sampling
- **Utilization of use point valves with a built-in upstream sample port is generally unacceptable for sampling for QC purposes**
  - Essentially samples the water within the distribution loop
  - Unable to test for contaminants in the interconnecting piping

SAMPLING FOR QUALITY CONTROL

- **For any excursion of a specification or limit value**
  - Investigation is necessary
  - Determine the cause of the excursion
  - Implement corrective action
  - Prevent recurrence in the future
  - For an out-of-specification (OOS) investigation the impact of water on the product is assessed
    - Good PC using effective and trend-derived Alert and Action Levels, control over water use practices, and proper sampling become important OOS-avoidance programs assuring continuous compliance with QC Specifications.

ISPE. Connecting Pharmaceutical Knowledge ispe.org

DETERMINE SAMPLING LOCATIONS

- **Risk Assessment (RA) performed for any new or renovated water system**
  - Identify locations that pose a risk of contamination to determine critical sampling locations
    - RA can provide a rationale for selection and help define the intended purpose based on the CQA's and CPP's
    - *If a sample point is defined in the system design it does **not** automatically imply it must be sampled routinely. Diagnostic sample ports, not routinely used, should be designated as such and properly maintained.*
- **Sampling locations in appropriate sections of the system including source water, pretreatment, primary treatment, final treatment, storage & distribution, and any special point of use treatment**

DETERMINE SAMPLING LOCATIONS

Source water

- Must meet local drinking water standards
- Typically potable water supplier is responsible for quality to the property boundary, where responsibility is transferred to the property owner/operator. Pharmaceutical manufacturers are responsible for end-product quality, including assuring water quality at system inlet

Treatment Unit Operations (Pre, Primary & Final)

- Sampling should occur before and after each unit operation
- Sample ports after a unit operation can often be used to test prior to next unit operation
- Attributes sampled should assure best performance of equipment
- On-line instruments may eliminate or minimize manual sampling

DETERMINE SAMPLING LOCATIONS

Storage & Distribution (Main and sub loops)

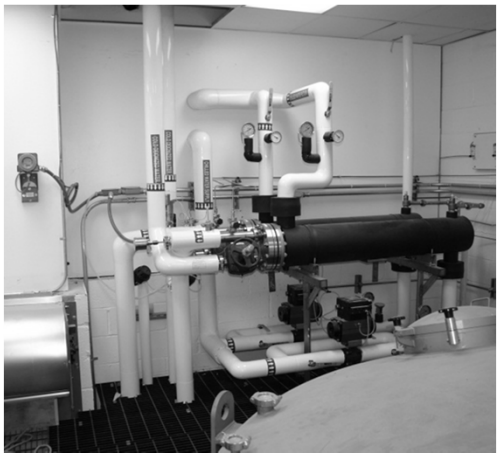
- QC sampling in distribution should be at use points, with identical methods as used by manufacturing. PC sampling should be before the first and after the last point of use. Systems with multiple return loops should have sampling locations in each return
- Consider sites of possible contamination
- All valves in the distribution should be sanitary. Sample points located in a purification train and used for PC may not need to be sanitary
- Obtaining representative samples
  - POU valves, inaccessible once permanently connected, can be included in Initial Sampling prior to connection and compared with data from a substitute sampling point for confirmation of suitability

DETERMINE SAMPLING LOCATIONS

Points of Use (POU)

- Defined as the location where water, from the distribution system, is used. For sampling, the POU may not be the valve. Sampling a "POU" must include any pathway that the water travels to reach the process.
- Sample as close as possible to the process equipment. POU sampling for QC, should mimic the way the water is used for manufacturing
- If a POU cannot be sampled, the next most representative location should be identified including a rationale in the risk assessment. Validation and/or routine monitoring should conclude the replacement location is representative of the POU
- Direct sampling of water as normally used eliminates the need for additional locations since the POU serves both

DETERMINE SAMPLING LOCATIONS

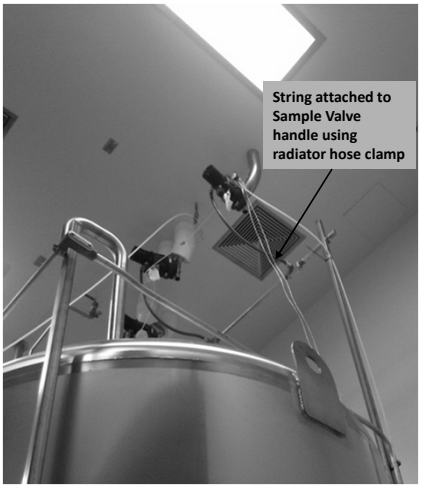


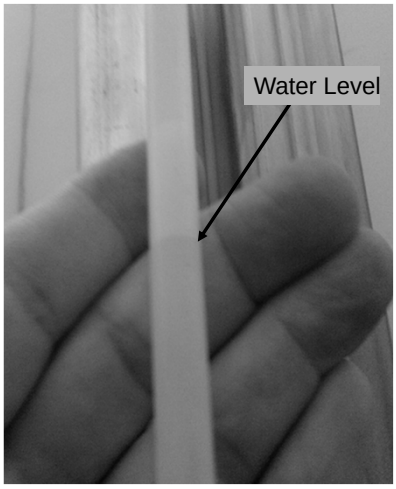
DETERMINE SAMPLING LOCATIONS

Physical installation of sample points (SP)

- Must allow samples representative of the water tested
- Restricted or limited utility, may impede proper sampling, result in safety concerns, yield data with a high degree of variability, and result in increased OOS findings
- Must afford suitable accommodations for samplers and materials. Adequate space to facilitate proper activities and minimize interference (ie: pipe insulation)
- Should be considered during design including the disposal of waste from flushing, location relative to HVAC, etc. Design in consultation with stake-holders for sampling of both QC & PC
- Water flushed from sample valves is often significant and may be hot, hence disposal cannot be overlooked. Sampling in clean environments may be complicated by the lack of accessible drains and other issues

SAMPLING LOCATIONS





DEVELOPING SAMPLING PLANS

- **Sampling provides details of critical quality attributes when properly performed**
- **Plans should assess quality attributes on a defined schedule at locations within the system**
- **Sampling plans (frequencies, locations and durations) generally parallel the phases of validation**
- **Sampling plans define locations to be sampled, attributes to be tested, frequency at which samples are needed, and the purpose of the resulting data**
- **Sampling plans are required for both new and renovated systems**

DEVELOPING SAMPLING PLANS

- **Background philosophy**
  - Sample plan should be based on the expected sampling required during the system life cycle
  - Sampling guidance is provided in new Sampling GPG
  - Automated monitoring
    - Conductivity and TOC
      - **Minimization or elimination of manual chemical testing**
      - **Confirm readings are representative especially if used for release**
  - Water may be delivered at various temperatures at a single point of use. Sampling should be the worst case temperature for microbial control. Water delivered at both 65°C and 20°C should be sampled at 20°C

Table 2: Examples of Suggested Source Water and Equipment Testing and Frequencies (Note A)

Equipment Sample Location	Suggested Commissioning and Pre-validation Tests and Frequencies	Suggested Initial Phase Tests and Frequencies	Suggested Intermediary Phase Tests and Frequencies	Suggested Extended Tests and Frequencies (Note B)
Potable Source Water Supply at Inlet to Pre-Treatment	Qualification of a new water source in the facility may involve initial and periodic testing of the source water to verify and ensure continuing compliance with potable water requirements. If the water is from a reliable source, at a minimum, obtain and review testing certificates from the supplier to establish full compliance with appropriate potable water regulations. Based on a risk assessment, it may be necessary to verify, via testing, the supplied water entering the facility complies with all potable water requirements. Local/country requirements should also be followed for water used in the manufacture of products sold in those areas.			
Media Filter	Confirm Silt Density Index (SDI) reduction	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Organic Scavenger Bed	Confirm TOC reduction	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Water Softener	Confirm Hardness reduction	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Carbon Filter for dechlorination	Confirm Free and Total Chlorine reduction Monitor microbiological levels	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water. Monitoring microbial levels may be important as needed for process control purposes		
Chemical feed for declorination	Confirm Free and Total Chlorine reduction Confirm sufficient dosage without overdosing (Note H)	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		

ISPE. Connecting Pharmaceutical Knowledge ispe.org

Table 2: Examples of Suggested Source Water and Equipment Testing and Frequencies (Note A)

Equipment Sample Location	Suggested Commissioning and Pre-validation Tests and Frequencies	Suggested Initial Phase Tests and Frequencies	Suggested Intermediary Phase Tests and Frequencies	Suggested Extended Tests and Frequencies (Note B)
Continuous Electrodeionization (CEDI) or other Deionization Process as a final treatment	Confirm Conductivity reduction Confirm chemical reduction (Note D) Monitor TOC and microbiological levels	• Conductivity and TOC daily or online (Note C) • Chemical testing daily (Note D) • Microbiological testing daily (Notes E,F)	• Conductivity and TOC at a frequency between daily and weekly or online (Note C,J) • Chemical testing between daily and weekly (Note D,J) • Microbiological testing between daily and weekly (Notes E,F,J)	• Conductivity and TOC at regular intervals or online (Note C), typically at least once per week • Chemical (Note D) and microbiological (Notes E,F) testing at regular intervals, typically at least once per week
Ozone as part of the purification system (Notes F,G)	Monitor ozone and microbiological levels	Ozone levels online daily Microbiological testing daily (Notes E,F)	Ozone levels online Microbiological testing between daily and weekly (Notes E,F,J)	Ozone levels online Microbiological testing at regular intervals, typically at least once per week (Notes E,F,J)
Ultraviolet treatment for microbiological control or TOC reduction (Note F,K)	Confirm microbiological reduction	Microbiological testing daily (Note E)	Microbiological testing between daily and weekly (Notes E,F,J)	Microbiological testing at regular intervals (Notes E, F), typically at least once per week
Ultraviolet treatment for ozone destruction (Note F)	Monitor ozone levels	Quarterly or online for process control purposes, or at a frequency commensurate with the criticality of the process to the production of the desired grade of water.		
Ultrafiltration for endotoxin control (Note F)	Confirm absence of detectable endotoxin (Note L)	Endotoxin testing daily	Endotoxin testing between daily and weekly (Note J)	Endotoxin testing at regular intervals, typically at least once per week
Microbially retentive filtration (Note F)	Confirm acceptable microbiological levels	Microbiological testing daily (Note E)	Microbiological testing between daily and weekly (Notes E,F,J)	Microbiological testing at regular intervals (Notes E,F), typically at least once per week

NOTES TO TABLE 2

Notes to Table 2:

Note A: This table lists several of the most commonly used treatment processes and may contain treatment steps that are not present in all systems. There may also be treatment processes in use that are not listed in this table. In all cases, the extent and frequency of sampling should be commensurate with the criticality of the process to the production of the desired grade of water.

Note B: The frequency and extent of sampling during the Extended Phase of the Performance Qualification typically serves as the initial frequency and extent for future validation maintenance testing, but is subject to adjustment based on a review of accumulated data and the use of risk analysis tools.

Note C: Verification of the equivalency of on-line readings to those obtained from sampling should be established in order to utilize on-line readings as suitable for quality control release.

Note D: Chemical testing may or may not be required as determined by applicable pharmacopoeias.

Note E: Microbiological identification testing may be performed to provide a profile of the resident micro flora within the water system.

Note F: Depending on the criticality of the process to the desired impurity/contaminant content of the water, less frequent sampling and testing may be performed for processes determined to be less critical.

Note G: Refer to the ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems for a more complete review of ozone and its use in the pharmaceutical industry

Note H: A slight excess is desirable, but overdosing may create undesirable and unintended side effects.

Note I: In the event that ultrafiltration is used for microbial reduction, testing should reflect the impurity/contaminant reflects process operation.

Note J: Testing frequency dependent on criticality.

Note K: When an ultraviolet treatment unit is used for TOC reduction, organic molecules are oxidized and converted into molecules that actually increase the conductivity of the water. Typically, the increase in conductivity is not monitored because there is an ion exchange process immediately downstream of the ultraviolet treatment unit that removes the oxidized organic material, reducing both the conductivity and the TOC.

Note L: The limit of detection shall be commensurate with the level of endotoxin appropriate for the process.

DEVELOPING SAMPLING PLANS

Regulatory Requirements:
Monitoring Frequency and Extent

- No well-defined regulatory requirements exist regarding routine sampling frequency and duration.
  - Various pharmacopoeias provide specifications for microbiological and chemical constituents but no definition of sampling frequency or duration

DEVELOPING SAMPLING PLANS

- **Commissioning and Pre-validation**
  - Sampling during commissioning:
    - Assist development of O&M practices/procedures
    - Provide baseline information for system performance
- Duration based on system size/complexity (e.g.: 1-5 days)
- After system operational start, each unit operation monitored/tested at least once to provide baseline values
- Extended pre-validation micro sampling for process knowledge and system robustness assurance
- Equipment determined as non-critical tested during commissioning as part of the C&Q/Verification

DEVELOPING SAMPLING PLANS

- **Sampling for Performance Qualification/Verification**
  - Document water quality is delivered from the system during:
    - **Typical Use (Nominal)**
      - Include period of normal or simulated normal operation to demonstrate compliance. Usage defined with rationales.
    - **Worst Case Use (Testing System Limits)**
      - Defined as the most extreme situations during operation
        - No water use
        - Maximum instantaneous use
        - After maintenance or service procedure
    - **Special Scenarios**
      - Occur during normal use as unplanned or planned activities. Special scenarios are inconvenient when they occur, making it advantageous to pre-validate.
        - Power failure
        - Unanticipated emergency or unplanned procedures where pre-validation is not practical

DEVELOPING SAMPLING PLANS

Validation Sampling

- **Initial sampling (intensive)**
  - Typically 2 to 4 weeks. Monitoring and testing daily (all sample & use points in the distribution and selected points) based on RA. 10 to 20 consecutive working days
  - If operationally consistency, organism populations may be identified. Typically, a few distinct types of organisms (e.g. five or less) will make up the resident population
  - Demonstrate production and delivery consistently meets specifications. Starts after final IQ & OQ report approval. Demonstrate consistent quality before start of next phase
- **Intermediary sampling (less intensive)**
  - Similar duration as initial sampling. To further demonstrate consistent production and delivery of water of required quality when using SOPs
  - May provide additional worst case data since use points are not as frequently active
- **Extended Sampling:**
  - Not less than the remaining balance of one year. Typically reduced sampling frequency, from initial and intermediary.

DEVELOPING SAMPLING PLANS

- **Performance Qualification (PQ) Protocol sampling**
  - The protocol should describe the purpose, scope and strategy (including rationales). The plan and data described with prerequisites and acceptance criteria. Adjustments as appropriate for production (e.g. no production or significant variations)
  - Stakeholders review and comment
  - Communication and information-sharing. Feedback (e.g. missing samples) must be communicated and documented in a deviation.
- **Performance Qualification Reporting**
  - At conclusion of Intermediary Sampling, a summary report should be prepared including recommendations for the Extended Sampling plan.
  - At conclusion (all portions) the final report including any recommendations should be made available to participants as well as to current and future users
  - At least annually, data generated from sampling should be reviewed to observe seasonal trends, modify sampling frequency and adjust alert/action levels previously established

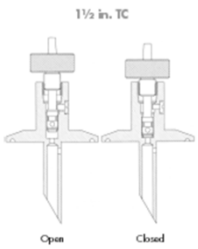
SAMPLE VALVE DESIGN

- Cannot allow contamination of the sample, must be functional internal & external. Consider method of connection, length of the flow path, water retention upstream and water in the exit path after closure.
- Post-valve hardware may pose a risk of contamination introducing contaminants not representative of the system water. Capping sample ports can lead to entrapment of moisture and microbial growth. Alcohol introduced after sampling removes water, but may increase the risk of organic contamination/high TOC.
- Sample valves must be appropriate for the pressure, temperature, flow and selected based on location.
- Acceptable materials, suitable finish, and system-compatible method of connection based on their location. Industrial sample valves likely to compromise microbial sampling.
- Sanitary diaphragm valves are well-accepted although other designs also accepted. Typical connection for valves in the sanitary portion of the system is sanitary clamp, whether used for chemical or microbial sampling.
- Sanitary component use becomes critical after final purification and in the distribution.

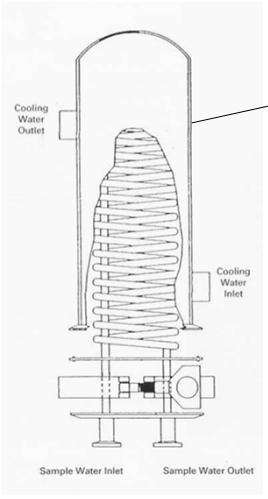
SAMPLE VALVE DESIGN

- Selection & placement should ensure minimized; contamination, ergonomic difficulty and safety concerns
- Use point sampling may be a challenge based on size, pressure, and flow. Addition of a suitably clean adapter can aid if it does not compromise the sample or create a dead-leg
- Sample valves available in straight and angle-body configurations. Sizes and styles vary widely with various inlet and outlet connection types
- Design and selection should account for issues such as temperature. Handles made of stainless steel may conduct heat creating an unsafe condition
- Mounting should be via short outlet or flush-mount fittings. When desirable to take a sample further into the water stream, valves with an extension that protrudes into the process stream may be considered but may pose a challenge for cleaning & alignment
- When sampling hot water and pure steam it may be necessary to reduce the temperature for safety or compatibility with containers, etc. Cooling reduces safety concerns and simplifies sampling but adds a risk of contamination necessitating suitable equipment and methods.

SAMPLE VALVE TYPES



FIXED & PORTABLE SAMPLING



SAMPLING TECHNIQUES

Appropriate sample containers

- Containers must not add or subtract measurable amounts of contaminant (ie: several containers may be needed)
  - Scrupulously clean glass for TOC (plastics impart extractables)
  - Pre-sterilized for bacteria
  - Pyrogen free for Endotoxin
  - Plastic containers for conductivity
- Sample container materials should be non-additive, non-reactive, and non-absorptive. Containers may need to allow samples collected in aseptic manner minimizing splashing and aeration, have adequate sealing mechanism and provide means to record information
- Container materials determined by the attributes tested. Impact is typically time-relate based on contact

SAMPLING TECHNIQUES

- **Sampling Technique**
  - For production, water should be flushed (eg: at least 30 seconds & at least 8 FPS) through the outlet and connectors to remove bacteria. Repeatability of flushing (both time and rate) is extremely important for data consistency. It may be more practical to specify the outlet be fully opened for at least 30 seconds. Alternatively, flush at the maximum possible rate for an extended but specified period
- **When hoses are involved**
  - When the sampling location is challenging, hoses may be employed but should be installed immediately before sampling and removed immediately after or within a qualified period. (i.e.: autoclave, clean, or hang between use or employ single-use disposables)
- **Training**
  - Personnel must be trained on proper technique since vast majority of variations in results can be traced to inconsistent techniques.
- **Use of common sampling points for PC & QC**
  - PC Sampling: accurately reflecting the quality of water flowing through the pipe.
  - QC Sampling: accurately reflecting the quality of water used by production.
  - In some cases, a single sampling location may be used for both
- **Sampling from sinks**
  - Sink use point sampling should represent the actual use of that matching the procedural use of the sink, including any flushing requirements and attachments or hoses

SAMPLING TECHNIQUES

- **Sample point preparation before taking samples**
  - Samplers must understand that preparation of a point for one analysis may introduce contamination for a subsequent sample. The order of sampling must be defined and reasons understood.
  - Preparation of the port permits taking an accurate bacteria and/or endotoxin sample. Hence, samples for bacteria and endotoxins should be taken last.
- **Sample point treatment after taking samples**
  - If the sample point is used to collect samples for bacteria or for endotoxin, treating the valve after sampling may be prudent if water can become trapped downstream of the valve closure.
  - It may be prudent to dry the valve and outlet path using alcohol or other suitable disinfectant which is allowed to evaporate. Valves that allow for sanitant to be “charged” into the valve and capped, retaining the sanitant, may be considered.
  - Samplers must be observant and let appropriate parties know if the sample valve is in need of service or repair

SAMPLING ACCESS

HANDLING OF SAMPLES

- Samples performed by in/on-line instruments are transferred directly to the analyzer and don't experience chemical and microbial contamination hazards unless the sample is stagnated or delayed before being analyzed.
- Off-line Samples may be exposed to external contamination by any of several routes:
  - Improper manual sampling
  - Transfer between the water system and sample container
  - Transport to the laboratory
  - Storage, prior to testing
  - Container opening for testing and re-closure (if applicable)
  - Transport, re-storage or reopening if additional tests are needed

PARAMETRIC RELEASE (REAL-TIME)

- **Chemical Attributes**
  - For 20 years, USP has facilitated use of on/in-line monitoring of TOC and Conductivity for satisfying compliance with PW and WFI monographs with the caveat that the data from these instruments is representative of attributes measured at points of use. If used solely for process control there is no need to establish this point of use equivalence.
  - If potential for non-equivalence exists, due to complex system design/construction, then additional sampling points may be required.
- **Microbiological Attributes**
  - Microbiological attributes are not homogeneously distributed, rendering rapid on-line microbial testing, and conventional spot microbial testing from any sampling port an inaccurate representation of the microbial quality of the water. Similar concerns exist with bacterial endotoxin. However, the extremely high level of microorganisms required to produce a significant change in the level of endotoxin and the special conditions to release that endotoxin into the water, it is uncommon for a well-designed and maintained system to exhibit varying endotoxin levels at different points of use.

PARAMETRIC RELEASE (REAL-TIME)

- **Grab-Sampling Versus On-Line/At-Line Monitoring**
  - If rapid on/at-line technologies were installed for microbial and endotoxin testing at a single point in the distribution system, the resulting data may be valuable for process control but not for product release. Point of use testing is required for release. Alternatively, if these instruments were installed at **all points of use** they could be validated for release. Portable versions of these technologies could be moved to different points of use, as needed, reducing the cost

RAPID MICROBIAL DETECTION TECHNIQUES & RMM

- Rapid detection techniques primarily categorized as either destructive or non-destructive
  - In destructive analyses, the cell is killed and can not be identified, possibly important for QC or Release testing. Lethality is not important for PC
  - Rapid microbial techniques not needing amplification are generally much quicker. Some of these techniques kill the cells and some do not
- Most RMM's have some delay in data availability. On-line technologies, claiming instantaneous data, are actually a rolling sum of many hours of prior sampling from the limited side stream flow. The quickest techniques to generate data, in 1-2 hours, invariably are destructive. Many of the slower techniques are non-destructive, but take 1-3 days. Even the best technologies do not give instantaneous data akin to Conductivity or TOC testing

RAPID MICROBIAL DETECTION TECHNIQUES & RMM

- **Rapid Endotoxin Detection Techniques**
  - The detection of endotoxin in WFI can currently only be accomplished by molecular amplification process employing Limulus Amebocyte Lysate (LAL) reagents. Analogs and chemical modifications of the reagents have allowed endotoxin to be quantitated photometrically in as little as 15 minutes. The LAL technology has traditionally been laboratory-based, but has now been commercialized as a rapid portable version that can be easily employed at-line. This technique is grab sample based with the associated limitations, but is sufficiently rapid and performable with minimal training to make it a near-real-time at-line test, rivaling the test result turnaround time of some on-line TOC instruments

RAPID MICROBIAL DETECTION TECHNIQUES & RMM

- **Future of Real Time Release (RTR) for Pharmaceutical Water**
  - The formation of biofilm between distribution loop outlets and actual points of use dictates testing at the point where the water is delivered. So, from an on-line instrument perspective, RTR of the water for microbial attributes is still in the distant future. For systems where endotoxin levels are an important attribute, the use of portable endotoxin testing is essentially real-time
  - Only microbial attributes are not currently able to be tested in near real-time. Sampling must still be from the point of use, making on-line measurement costly. RMM's are available for use with grab samples. Test results are available rapidly (about an hour). These are destructive tests, that does not matter with zero counts. 1-3 day delay in result availability is not suitable for a parametric or real time release approach.

Thank You!

GMP Systems

GMP Systems, Inc.
14 Madison Rd.
Suite F
Fairfield, NJ 07004
973-575-4990 ph.
973-808-9201 fax.
sales@gmpsystem.com
Joe Manfredi