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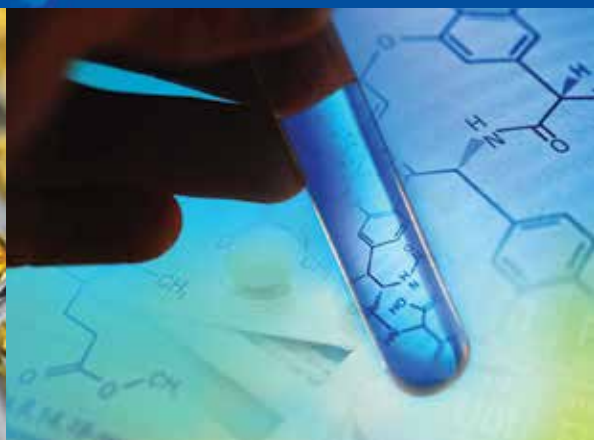

# How to Properly Sample Water Systems • Part 2

by Teri C. "T.C." Soli, PhD
Soli Pharma Solutions, Inc.

Poorly executed sampling is the cause of most excursions from microbial process control trigger values (Alert and Action Levels) and specifications. In Part 1 of this article we learned about the boundary layer phenomenon, how its depth is dramatically affected by water velocity, and how that impacts biofilm thickness. We also learned about the differences in the sampling objectives for Process Control data versus Quality Control data. In Part 2 of this article we will learn how to manipulate the flow velocity (and other factors) to remove the fragile biofilm from the flow path before collecting samples or otherwise using the water. This knowledge allows us to develop a standardized sampling procedure that eliminates most of the microbial count variability currently plaguing most water system operations and causing unnecessary and unverifiable excursions and fruitless investigations. With these false excursions eliminated, the company's investigative resources are unburdened to focus on the real problems, and at the same time avoid unnecessary regulatory scrutiny and maximize product quality where the water is used.

## Recap of Part 1

Since biofilm develops within the laminar sublayer beneath the turbulence above that boundary layer in a flowing pipe, we can know its maximal thickness as a function of flow velocity. Biofilms could develop anywhere that is wet within the water system, including its piping, its valves (upstream and downstream surfaces of sample ports as well as use point valves), and within poorly maintained connectors such as hoses or permanently connected hard piping between the water system and process equipment. Depending on the water flow velocities, the biofilms could be relatively thin and very tenacious (in high flow rate piping) or thickly colonizing the internal surfaces of infrequently used valves or downstream connecting piping. A high flow velocity across these surfaces can shear off the fragile tops of biofilms growing in these areas. A vigorous standardized water flush before sample collection essentially eliminates the microbial contribution from these formerly stagnant surfaces. Sometimes this pre-flush is appropriate and sometimes it is not, depending on how the data is used and routine POU valve use practices, as will be discussed below.

## Ideal Sampling Technique for Microbial Process Control Data

In the case of process control sampling, the water of importance is the water within the system – in other words, the water behind the valves. Knowing that this water could pick up substantial microbial contaminants as it exits through the valve and perhaps also from a hose attached to it before it enters a sample container, every effort must be made to avoid this additional microbial contribution to the systemic bacteria that are intended to be collected in that sample. Routine, well-defined practices should be instituted to avoid or prevent this additional sample contamination from occurring. The sampling procedure described below should avoid any substantial microbial contribution from the outlet during sampling:

1. Assure that valves used for microbial sampling are of a sanitary design (don't retain water downstream of the sealing surfaces and all upstream surfaces can be reached by sanitizing agents when in the closed position).
2. Sanitize the external and internal surfaces of the valve, particularly if the lumen is narrow (1/4 inch or less), regardless of orientation, and susceptible to water retention by surface tension phenomena. Be sure to thoroughly saturate all surfaces with alcohol and allow adequate contact time (at least 30 seconds to 1 minute). It may be necessary with small lumen valves to inject alcohol directly into the downstream side of the valve using a long cannula and syringe.
3. Aseptically attach a sterile or recently sanitized hose (and gasket) to the outlet to be able to direct the water flow and minimize the splashing/spraying of water from a bare outlet.
4. Direct the end of the hose to a suitably-sized* flush bucket or drain and open the valve sufficient to achieve at least an 8 ft/sec flow velocity through the widest part of the valve/hose assembly. For convenience and consistency between samplers, specify a fully open valve for at least 30 seconds.
   * *Never reduce the flush rate to accommodate a convenient bucket capacity – adjust the bucket capacity to the needed flush rate. Also assure that the drain or flush collection funnel have the capacity to accommodate the needed flushed water flow rate. Do not compromise this flow rate since it provides the needed shear forces to remove the fragile portion of the biofilm that may be colonizing the valve and flow path of the water.*
5. After this initial 30 second full-force flush that sloughs off biofilm down to about 40 - 50 microns thick, throttle back the flow rate to a manageable sampling flow rate and allow an additional 30 seconds of flush time. This lower flow rate now moves the boundary layer and turbulence to far above the surface of the remaining biofilm allowing very little of it to slough off into the sample container.
6. Aseptically collect the water sample and close the valve. *Please note that after the valve has been opened for pre-sampling flushing, never close and reopen the valve to resume the sampling procedure. Just leave it open until after the sample is collected. Closing the valve after flushing – but before sample collection – could slough additional biofilm organisms off the sealing surfaces within the valve and release them into the sampled water.*
7. Detach the hose and gasket, and set them aside to be resanitized and/or properly stored for full drainability and drying.
8. Inject alcohol all the way up into the downstream valve lumen again with a cannula and alcohol-filled syringe to displace any retained water within this downstream portion of the valve.
9. If the valve is in an environmentally compromised location, cover the outlet side with a porous Tyvek or equivalent cover to reduce interim environmental contamination prior to the next use.

If personnel compliance with this procedure is enforced, the vast majority of sampling variability will be eliminated.

## Ideal Sampling Technique for Microbial Quality Control Data

If microbial sampling for QC or water release could be done by the above procedure for Process Control sampling, it would also be ideal for and would eliminate the vast majority of outlet or hose-sourced contaminations, **but that is not the objective of this sampling process**. The process of QC sampling must exactly simulate the same procedure and materials utilized when the water is used so that any valve or hose or other delivery-related contaminants are similarly collected in the QC sample. That is because the objective of QC sampling is to duplicate the quality of water that is being used by manufacturing. Manufacturing's water use technique may not be ideal and may allow outlet biofilm organisms to contaminate the water when it is used. QC must know this, so the QC sampling must also capture these potential water contaminants from the end of the hose or other connector from the water system where the water enters the manufacturing process (the true "point of use"). This sampling process should reveal the same levels and types of organisms that are likely to be


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present in the water when it is used in washing or in formulations or whatever its manufacturing purpose might be.

Therefore, the "ideal" QC sampling technique must exactly duplicate the water use technique, which may not be ideal from a microbial perspective! This means that:

- The sampled water must be collected from the same point of use employed by the water user.
- It must utilize the same outlet sanitization practices employed by the water user, if any.
- It must utilize the very same hose or hard-piped connection from the outlet to the point of use employed by the water user.
- It must utilize the same pre-use flushing and/or outlet sanitization practice employed by the water user, if any.
- And after collecting the sample, it must utilize the same post-use outlet procedures employed by the water user, if any.

Basically, the QC sampling procedure utilizes the same "everything" that the water user employs – not just similar – THE SAME.

## Impact of Bad Sampling

For process control sampling, poor sampling technique will invariably lead to inconsistent test results between samplers, between outlets, and between sampling days. The data will be quite variable because of this inconsistent removal of intra-outlet and hose biofilm with some values perhaps randomly exceeding process control triggers or even quality specifications.

So a great deal of effort will be wasted investigating spurious and non-repeatable excursions, creating not only an avalanche of paperwork and lost resources, but also stimulating ineffective CAPAs that don't appear to correct the problem, potentially incriminating your whole training program if you continually blame "employee error" as the root cause. Numerous deviations, especially a backlog of unresolved ones, are a regulator's clue that the water system may be out of control and that you do not understand your system well enough to know how to correct it, inviting unwarranted regulatory scrutiny.

Does any of this sound familiar in your shop? Do you have sampling procedures that only specify a pre-flushing time or gallonage but no indication of an exactly reproducible flow rate parameter? All of these problems are purely because of improperly executed sampling (and a vaguely written sampling procedure). Fortunately, these are simple fixes.

So what happens if FDA sees different QC sampling procedures being used at point-of-use outlets than the water users are utilizing? An FDA 483 observation is a certainty! The reason is that the sampling technique being utilized likely employs better flushing and better hoses than manufacturing uses or even no hoses at all. Basically, the sampling data likely gives lower, best case microbial counts compared to the water that manufacturing is using, allowing atrocious water system use practices to continue unabated because the data indicate there is no problem. Very common bad practices include poor hose use, storage, and maintenance, leaving hoses connected, and no pre-flushing before use. These can all promote water contamination and cause product problems, and that is FDA's concern.

If manufacturing were to adopt water system use practices similar to the above ideal pre-sampling practices for process control sampling (e.g. fresh hoses, specified vigorous pre-use flushing, etc.), then the samplers could use these better practices for QC sampling as well. This would allow the data to consistently look as good as the utilized water actually is, plus much fewer excursions and much less regulatory scrutiny and concern over product quality.

## Conclusions

Poorly executed sampling for microbial Process Control testing leads to highly variable, inconsistent, and unrepeatable test results, unnecessary "false" excursions, wasted investigational resources and possible over-reaction to what appears to be water system problems, but in reality are not. It may also give an inspector the impression that the water system is out of control and the company is incompetent in its investigational process and water system understanding and maintenance.

Poorly executed sampling for microbial Quality Control testing also gives highly variable, inconsistent and unrepeatable test results, but since this sampling is often done with better materials and practices compared to manufacturing's water use practices, it provides a better reflection of the quality of the utilized water than reality. This false impression can lead to inaction when remedial action is warranted, putting product at risk as well as guaranteeing an FDA 483 observation if noticed during an inspection.

All of these scenarios can be avoided by sampling and use procedures employing, among other details, well maintained hoses and definitive pre-flushing parameters specifying flushing rates and times of at least 8 ft/sec linear velocity (or fully open) for at least 30 seconds before sampling and/or use.


T.C. has been the Owner and Principal Consultant at Soli Pharma Solutions for 11 years, specializing in water system and product microbial control troubleshooting and training. He has 36 years of pharmaceutical industry experience and served 18 years on PhRMA's Water Quality Committee. He has been on USP Expert Committees for the past 15 years and is currently a member of the USP Chemical Analysis Expert Committee (responsible for pharmaceutical waters). He holds BS and MS degrees in Microbiology from Texas A&M University and a PhD in Microbiology and Immunology from the University of Arizona. T.C. is a frequent presenter at Pureflow's educational seminars and symposiums.

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*- Henry Ford*

Pureflow inc.

CORPORATE OFFICE
1241 Jay Lane | Graham, NC 27253
Phone (336) 532-0300
Fax (336) 532-0310

Serving the Southeast

Toll-free (800) 242-9430

www.pureflowinc.com