ISPE Newsletter - Monitoring

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Pharmaceutical Water and Steam Workshop on

Monitoring

ISPE rCoP D/A/CH Chapter

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Chapter 1

Pure Steam

The third workshop of the Pharmaceutical Water and Steam rCoP took place from November 5th – 6th, 2007.
After introductory presentations, a number of workshops were held on the following subjects:

- Pure Steam
- Online/Offline
- Failure of online/offline analyzers
- Warning and Action limits
- Sampling
- TOC

About 30 professionals from fields such as OEM, planning, regulatory agencies, instrument manufacturing, service industry, consulting, QC and pharmaceutical manufacturing took part. All participants actively contributed to the workshops.
This newsletter presents the discussion points and results from the workshops. These can be used as suggestions and/or guidelines. The following statements are observations, experience and considerations regarding possible causes or solutions. Pertinent scientific studies might have been initiated but are currently not complete.

Pure Steam systems in the pharmaceutical industry- Regulations and Standards:

- Pure Steam is defined by the USP 30 (2007) or the current version of the monograph „Pure Steam“.
- In accordance with WHO-specifications, the feed water must meet drinking water specifications. Purified Water may also be used as feed water.

Further regulations include:

- EU-GMP Guidlines: the steam used for sterilization must not contaminate products and equipment.
- EN 285: is a European Norm for large-scale steam sterilizers which are predominantly used in the healthcare industry for the

sterilization of medicinal products or accessories. This norm also describes the quality tests for steam.

- HTM2010: UK Health Technical Memorandum 2010, Part 3 „Validation and Verification - Sterilization“ covers the validation and periodic monitoring of various sterilization processes which are practiced in hospitals, laboratories and other health care institutes.
- ISPE Pharmaceutical Engineering Guideline, Baseline Vol. 4 „Water and Steam Systems„ (2001), Chapter : Pharmaceutical Steam
- DIN EN 13060 „Small Steam Sterilizers“ (formerly DIN 58946) and DIN 58950 „Sterilization - Steam sterilizers for pharmaceutical products“ includes definitions of steam qualities such as industrial steam, sterilization steam and pharmaceutical pure steam.

Recommended Monitoring in pure steam systems and pure steam quality requirements

The manufacturer specifications of the pure steam generator should be fulfilled.

Typical recommendations for the minimum feed water quality for pure steam generators include:

- Absence of amines and chlorides
- Maximum Silicate ≤ 1 ppm
- Dissolved CO2 ≤ 0,2 ppm
- Heavy metals ≤ 0,1 ppm
- Nitrate ≤ 0,2 ppm
- pH 5-7
- Conductivity at 25 ℃ (± 1 ℃) ≤ 5,0 µS/cm
- TOC ≤ 500 ppb
- Bacteria max. 100 CFU/ml
- No further contaminants which could lead to scale

When the aforementioned feedwater quality is met, the product quality of the Pure Steam generator can be defined as follows:

Parameter	***USP 30 Specification***	**Measurement**
Conductivity	meets test criteria (Stages 1 – 3) USP <645>/Ph.Eur: 0.6 - 3.1 µS/cm 0 -100 ℃	Inline/offline measurement in the Pure Steam condensate
TOC	≤ 0.5 mgC/l / 500 ppb	Offline or online measurement with TOC analyzer
Endotoxines	< 0.25 EU/ml	Offline
Non-condensable gases*	Specifications should be set dependent on the application	Offline** using the Büretten method (see EN 285 p.27)

* Are not required for pharmaceutical pure steam systems in the pharmacopeia. However, the EN285 requires that the volume percentage of non-condensable gases in steam sterilization of medicines does not exceed 3.5 Vol-%

** Online measurement is possible but requires a larger investment in the automation and controls.

The actual conductivity of Pure Steam is strongly dependent on the quality of the feed water used and the temperature of the pure steam distillate when using an uncompensated measurement.
The pure steam condensate meets the current requirements of the USP and Ph. Eur. for "Water for Injection". Suggested sampling points can be found in the chapter “Qualification of Pure Steam Systems“.

The influence of non-condensable gases

A membrane degassing unit can be used to meet the stringent requirements of EN 285 and HTM 2010 for the inert gas content in pure steam (≤ 3.5 % as volume).
The presence of non-condensable gases can negatively influence the thermal transfer from steam because the steam condensation at surface interfaces is inhibited. Therefore the sterilization process using steam with non condensable gases is less effective than sterilization at the same temperature using steam without non condensable gases.
For example: Saturated steam at 2 bar has a temperature of 120.23℃. If we assume that 3.5% of the vapor is noncondensable gas, then the partial pressure of the steam is 1.93bar and the partial pressure of the non-condensable gases is 0.07 bar (2 bar total pressure). Consequently, we would measure 2 bar pressure but the temperature resulting from the steam pressure would only be 118.99℃.

Since many steam systems are controlled by pressure, the presence of the non condensable gases could lead to lower steam temperature even though the overall pressure meets specification. This being said, most systems also monitor the temperature. Therefore the non-condensable gases specification ensures that heat transfer is consistent and it minimizes fluctuations and local effects such as air pockets within sterilizers.
For this reason, limiting the concentration of non-condensable gases can be beneficial.

When the percentage of inert gases (predominantly N_2 and O_2) in the feedwater is less than 11% by volume, the non-condensable gas limit in the pure steam of ≤ 3.5% by volume can be met using degassing.

Qualification of pure steam systems: PQ

Methods of sampling and microbial monitoring of new systems are described in the FDA Guide to Inspection of High Purity Water Systems (see Phase 1-3 below). The USP Monograph <1231> also includes guidance on sampling.

Phase 1: Sampling after each purification step and at all use points daily for 2-4 weeks until the system is stable and SOPs are complete.
Phase 2: Sampling after each purification step and at all use points daily for 2-4 weeks.
Phase 3: Monitoring for over a year to encompass seasonal influences, less frequent sampling compared to phase 1 and 2

Suggested sampling regime during regular operation and after completion of qualification:

Sampling intervals during regular operation are similar to Phase 3 but can be adjusted with further operating experience.

Chapter 2

Online / Offline

Starting point:

If critical instruments are installed to monitor a clean media system, these must be qualified in accordance with GMP. Critical instruments are measuring instruments that monitor parameters, which can influence the quality of the clean media.
Generally there is no regulatory requirement for the use of online instrumentation. This means that the monitoring of the system can be conducted using different types of measurements. The economic aspect plays a significant role since the use of qualified engineering and laboratory personnel, the investment costs for online instrumentation, the existence of an internal laboratory, the analysis costs, and the size of the factory and the clean media system (number of sample points) all must be taken into account.

An adequate monitoring system consists of a combination of instrumentation, visual inspection, manual documentation and laboratory analyses.

Online / Offline:

The definition of online/offline analysis must be clearly defined and understood between the end user and the engineer so that no misunderstandings take place in the planning, procurement and execution of the clean media system. We define these terms as follows:

1. Online: A physical / chemical parameter is measured by an instrument located on the water plant. The value can be used in the control panel as a setpoint, control point or alarm message. It can be registered or transferred to a SCADA system. The sensor is permanently installed in the water plant and is serviced and calibrated regularly. If the sensor is located directly in the product (water or pure steam) piping, then it is also called an “Inline” measurement. If a side stream is taken from the product sent through a measurement and then sent to drain, then we call this an online but not an inline measurement.
2. Offline: An offline measurement refers to a measurement which is not directly on or in the clean media system, and the data is used in electronic or paper form. Samples which are analysed in the laboratory for conductivity, pH, TOC or bacteria load are all offline measurements. Since there is no regulatory requirement regarding online measurements, monitoring of a clean media system can theoretically be completely offline. This would however complicate setting the monitoring intervals (validation/PQ) and in the case of an OOS result documenting and defining the necessary steps.

Scope of a monitoring program:

A monitoring program can include online measurements and/or it consists of various activities which are usually carried out by several different qualified people.

1. Online instrumentation with transmittal of the signal to control functions, information or alarm messages (service and calibration)
2. Offline „instrumentation“ in the laboratory (service and calibration)
3. Analytical sampling in the inhouse lab or at an external audited lab
4. Visual inspection of clean media systems and documentation with checklist and log book
5. Service and maintenance including calibration
6. Defining the procedure and the release criteria for putting the system

back in to operation after repair, service and calibration.

Monitoring Parameters:

The following instruments should be considered as a minimum. These parameters play a considerable role in the function of the system and the supply of the clean media to the points of use. They are involved in meeting the critical quality parameters:

- Temperature after the generation system
- Conductivity after the generation system
- Temperature in the loop return
- Conductivity in the loop return
- Pressure in the loop return if a minimum flow is monitored using pressure
- Water level in tank
- TOC measurement in the loop return or offline

Fundamental considerations:

- Conductivity: Conductivity limits for purified water and WFI are specified in the USP. If the conductivity is measured online with an inline sensor, then both the non-temperature compensated measurement and the temperature should be recorded.
- TOC: The TOC limit is specified in the USP. The TOC is often measured online at the outlet of the water generation system and/or in the ring main return. The measurement is most frequently found in the ring main return whereby no offline analysis is needed. When these analysers are used, special attention must be paid to the instrument accuracy, display accuracy, measuring method and calibration.
- pH: Is no longer specified in the USP due to the low conductivity of purified water and WFI. Depending on the water purification process online pH measurements may be found in the generation system.
- Ozone: Ozone is commonly used for sanitization of cold storage and distribution system and to prevent microbiological growth, however this is not a requirement of the USP. Precaution must be taken to ensure that neither the quality nor the yield of the end product is negatively influenced when it comes into contact with water which had been ozonated. It is recommended that an ozone analyser monitor the ozone concentration after the tank, after the UV (ozone destructor) and in the ring main return, depending on the operating state of the storage and distribution system.
- Flow / flow velocity: A flowmeter can monitor the pipe velocity in a distribution system. Microbial growth can be prevented or reduced

	by maintaining a minimum velocity. A continuous measurement is not necessary. It is recommended that the velocity is checked during the qualification phase of the OQ under consideration of the actual water consumption situation. – Temperature: Monitoring of the temperature is recommended for systems which are thermally sanitized. The successful sanitization can be recorded and documented. – Pressure: The pressure conditions in a distribution system are not critical. The guarantee of supply to machines which are connected to the distribution system must be upheld. Furthermore contamination of the clean media through connected end users must be avoided (positive pressure in the loop). This also applies to connected apparatus' that cannot be protected against back-contamination by pressure peaks (pressure in the machine is higher than in the water loop). – Level: A continuous level measurement in the storage tank is not required. Level measurements serve as information, ensure security of supply and show the capacity for planned system expansions.

	The following matrix can be used as a recommendation for the scope of the measuring equipment and the basis for the risk analysis with regard to critical parameters. Example: Instrumentation of a Highly Purified Water / WFI-USP generation system.

GEP = Good Engineering Practice
GMP = Good Manufacturing Practice

Parameter	**Relevance**		**Display**		**Recording**		**Alarm**	
Description	**GEP**	**GMP**	**Local**	**Control box**	**Data storage**	**Data Logger / Printer**	**Single**	**Common Fault**
Flow feedwater inlet, upstream of the first system components	X		X	X				
Pressure feedwater inlet, upstream of the first system components	X		X					
Pressure downstream of prefiltration	X		X					
Water hardness post softener	X		X	X				X
Pressure in front of the filter in the RO feed	X		X					
Pressure after the filter in the RO feed	X		X					
Flow in the RO feed	X		X					
Pressure in front of the RO feed pump	X			X				X
Pressure after the RO feed pump	X			X				X
Flow in the RO permeate	X		X	X				X
Pressure in the RO permeate	X			X				X
Conductivity in the RO permeate (temperature compensated)	X			X		X		X
Pressure after any subsequent treatment steps	X			X				X
Conductivity after any subsequent treatment steps (not temperature compensated)		X		X		X		X
Flow after any subsequent treatment steps except after the final treatment step	X		X					
Conductivity after the ultrafiltration (not temperature compensated)		X		X		X		X
Temperature after the ultrafiltration		X				X		X
Flow in relevant concentrate waste streams	X		X					
Pressure of additional components that are critical for a technically flawless operation	X			X				X
Level of necessary dosage tanks	X							X

	Example: Instrumentation of a storage and distribution system for Highly Purified Water / WFI-USP

Parameter	**Relevance**		**Display**		**RECORDING**		**ALARM**	
Description	**GEP**	**GMP**	**Local**	**Control panel**	**Memory**	**Recorded**	**Single**	**Aggregate**
Level Storage Tank (current level, ON/OFF Water System)	X			X		X		X
Level High Overflow protection	X							X
Level Low Pump / Vacuum protection	X							X
Pressure downstream Loop Pump	X		X					
Temperature in Loop Return		X		X		X		X
Temperature downstream Heater / Cooler	X			X				X
Conductivity in Loop Return (uncompensated for temperature)		X		X		X		X
Flow in Loop Return		X		X		X		X
Pressure in Loop Return		X		X				
TOC in Loop Return		X	X	X		X		X

Interval for Sampling / Lab Analysis:

The location of the sampling ports should be determined together with the user at an early stage. This avoids technical deviations in the water system after installation and during PQ due to missing sampling ports.
The following criteria shall be considered for the definition of sampling valves , the sampling interval in PQ1 ... PQ3, the subsequent analysis and stipulation of the monitoring routine program,: (execution can be similar to a risk based analysis)

- Quality of feed water, its deviations and already implemented monitoring
- Dosage and quality of „added substances“ between individual purification technologies (acid, caustic, salt, chemicals)
- Impact / Change and quality of the substance respectively up- and downstream of the purification step
- Technical design of the entire system (sanitary design) and primarily with regard to design and execution of points of use and sampling
- Concept for sanitization of the entire water purification systems as well as the storage and distribution systems (chemicals, heat, ozone)

	Examples: 1. Water system in sanitary design → sampling up- and downstream of circulation pump can be excluded; a negative impact on the water quality is not possible 2. In the loop system diaphragm valves with zero-dead-leg design are installed at all manually operated usepoints → extensive or even daily sampling can be skipped in the first PQ-phases, since a negative impact on the water quality by the water system itself can be excluded (the water circulating in the loop has continuously the same quality) → test results that are not in agreement can be traced back to inappropriate sampling or sample handling by almost 100%. 3. The water purification system operates in continuous mode (internal re-circulation when being in „stand-by“ and storage vessel is filled) → Sampling between the individual purification process equipments of the water system can be reduced. 4. Storage and distribution system executed in sanitary design, without additional purification processes and equipped with online instrumentation for critical parameters → chemical / physical change almost impossible, thus the interval for sampling shall be related to predominantly microbiological tests. 5. Hot storage and distribution („self-sanitizing“) or daily sanitization using ozone → Significant reduction of samples from PQ1/PQ2 to PQ3 should be the goal. 6. A sampling port in the return section of a loop or ringmain has in most system designs the same value as the last point of use → eliminate in sampling plan. 7. Food for thought: Elimination of sampling points in sampling plan if these are equipped with manually operated zero-dead-leg diaphragm valves?

Chapter 3

Hardware failure of On- / Offline Instruments

The possibility of hardware failure(s) or non-reliable readings of instruments should be discussed in the risk analysis for each individual measurement point. The required action in this case should be outlined in detail. Furthermore and particularly for product relevant measurements – i.e. conductivity and TOC measurements in accordance with USP and EP; depending on the application other parameters are possible – a reasonable SOP should be installed.
This SOP should include but is not limited to the following action items:

1. System should be brought into a failsafe operation mode or should confirm this mode despite the failure of the (online) measurement
2. Replacement with spare sensor and/or instrument
3. Repair of the measurement system
4. Periodical use of offline instruments for data acquisition during repair / replacement period
5. Evaluation / Validation of previous data by applying a plausibility check

The following serves as an example of what a detailed analysis of these points could include:

1. System should be brought into a failsafe operation mode or should confirm this mode despite the failure of the (online) measurement

The failure or defect of an instrument used for water quality monitoring (product relevance) does not necessarily mean a deterioration in the quality of the produced water as long as the water system still operates normally. Nevertheless, appropriate practical measures on how to handle a situation like this should be considered.
The approach is different for measurements that are critical for the system operation like control parameters for Reverse Osmosis, EDI or Distillation units. These can also be physical parameters which are less significant for the water quality such as temperature, tank level, pressure or flow.
In case of a failure or defect of a measurement that is critical for safe operation, the system should automatically switch to a safety mode to help prevent damages or additional component failures and thus long shut down times. Usually, the system or at least the respective component shuts down. These automatic modes and safety functions can be tested on a new system during a FAT (Factory Acceptance Test) and SAT (Site Acceptance Test) by simulation of measurement failures. This is standard practice nowadays for qualified water system fabricators.
If a measurement was categorized in the risk analysis as being noncritical with regard to both system operation and produced water quality, a formal acknowledgement of the failure can be sufficient, while following a defined action plan. Sufficient documentation in which the actions are explained is recommended as it enables reconstructing of events at a later point in time.
In case of failure of a measurement that is clearly relevant to the water

quality like conductivity or TOC, it is advantageous to define appropriate procedures in advance and strictly carry these out.

2. Replacement with spare sensor and/or instrument

Malfunction or complete failure of an instrument can happen at any time (and can never be completely ruled out). Thus the goal should be to define appropriate actions in advance that enable a rapid and uncomplicated replacement without disturbing the operation of the entire system. Although having a spare part on stock can be helpful, it should be considered in relation to the criticality of the measurement in the overall system.
The periodic and regular replacement of an instrument or sensor due to expected wear or required calibration within the scope of system maintenance can be practical, but should be discussed in the risk analysis. The cost for spare instruments and/or sensors in relationship to securing the system operation should be estimated and taken into account.

The design of the installation should allow appropriate space for a quick and uncomplicated replacement.
In addition, the supply of spare or replacement parts is usually easier when the process connection of a probe is standardized, such as TriClamp®, common Aseptic Connections in accordance with DIN 11 864, etc., since standardized components are more rapidly available than customized parts. This can help reducing lead times for spare parts.

3. Repair of the measurement system or its components

If a measurement system or one of its components requires repair or an upgrade, it is essential to document accordingly. What was repaired and why? What was the result of the analysis at the manufacturer (Root Cause Analysis)?
If a repair was successful and economically justifiable, the same component can be used and installed after inspection while observing that

- quality relevant measurements have a valid calibration certificate,
- noncritical measurements relevant for system operation must work flawlessly.

4. Periodical use of offline instruments for data acquisition during repair / replacement period

In case of failure of a quality critical online instrument, the periodical use of an offline instrument (for instance one which is already in house or leased) can be considered during the repair or service intervall. Such an offline instrument should meet the requirements related to measurement range, technical specification, intended use and application. Valid calibration documents are crucial, too.
Data like instrument type, serial number, etc. of the offline device should be recorded for completion of validation documentation.
In general, this repair case scenario should be discussed in the risk

analysis based on economical requirements as well as system operational needs.

5. Evaluation / Validation of previous data by applying a plausibility check

Online technology allows for an almost continuous monitoring of system parameters. For important and, especially, for quality critical parameters, a trending of recorded data can support the decision making process whenever an error or failure of an instrument occurs and a resulting action needs to be taken.

If a data trend does not indicate a system error or a deterioration of the water quality, the system can be operated without the online system and data trending for some time. In current pharmacopoeial monographs, there are no binding statements on continuous monitoring, although its advantages are listed and explained.

Chapter 4

Alert and Action Limits

Alert and action limits should be defined for all important monitored parameters and their trends,. For example, such parameters of importance could mean that the parameter is regulated by one or more public authorities (EPA guidelines, national/international Pharmacopoeia,...) and is used to finally release the water for production.

The action limit can only be as high as the limit regulated by law or pharmacopoeia. The action limit may not exceed this statutory defined range.

The action limit doesn't necessarily have to be the same value as the statutory limit. A stricter action limit might be used dependent on the application or if the long-term evaluation of the water system shows that the parameter is continuously significantly below the statutory limit.

In addition to defining action limits it is also recommended to define alert limits. These alert limits should be set so that appropriate measure(s) can be launched prior to reaching the action limit.

The monitoring trend results should be checked and evaluated from time to time. The frequency of this periodical evaluation can be defined in an SOP.
The resulting reaction if an alert or action limit is exceeded should also be defined in an SOP. This document should further cover the procedure for multiple limit violations. The USP Monographs can support the definition of appropriate measures that need to be taken in the case of a limit violation.

Monitoring data should be evaluated periodically. At the same time, the alert and action limits for monitored parameters and their trends should be checked to see if an adjustment may be required.

Chapter 5

Sampling

Water quality testing can be executed using online measurements or by taking water samples off the system. Since these samples are used to assess the quality of the pure water system, special care is required with regard to the following aspects:

a) Planning of sampling points

In order to accurately be able to test the water quality, the necessary sampling points must be considered in the planning phase of a system. In general, these include sampling points for the raw water (feed water used for water purification sytem), within the water purification system, in the storage and distribution system and the points of use.
In addition, sampling points can be differentiated into „Monitoring Sampling Points“ and „Technical Sampling Points“.
When planning sampling points, the different modes of system operation should be considered (sanitization, shut-down procedures, standard operation,...).

The following sampling points have proven successful:

Location
Feed to water system
After each individual water purification step
System outlet
Storage Vessels
Loop return section
At Pumps (when replacing pumps)
Point of Use

The following relates to sampling of the water purification system and monitoring of the water quality:
A water purification system is designed to handle a defined feed water quality. Deviations in the feed water quality outside the design range can have an impact on the functionality of the system. It is not sufficient to only evaluate the water analysis of the water source (eg. City Water Supply), since the distribution network in the manufacturing facility can also influence the water quality. Therefore, periodical analysis of the feed water quality is recommended. The collected data also provides a better process understanding about the system operation with changing feed water quality.
The purification stages of the system improve the water quality stepwise until the desired quality is reached at the water system outlet. Even though the relevant quality is that which is measured after the final purification stage, it is a reasonable approach to take samples between the individual purification stages. These samples help identify deviations

in the system early and allow for a timely reaction. The sampling points should be defined for each water system individually. In addition, these sampling points should be understood as points for status definition of the system operation rather than as points for regular monitoring following GMP requirements. The following sampling points should be considered (non-exhaustive list):

- Feed to water system
- After softener
- After a mixed bed ion exchange column
- After an activated carbon filter
- After an UV-disinfection unit
- After a reverse osmosis skid
- After an EDI Unit
- After an ultrafiltration skid
- At outlet of distillation unit

b) Design

Sampling points should be planned and designed so that the sampling can be executed without hazard for personnel or quality of the sample. Hence, the sampling points should comply with the technical requirements of the water system, especially regarding draining and rinsing of the sampling pipe. When sampling, the pipe needs to be rinsed with the water that is to be tested. Thus, appropriate drain(s) should be existent that also can handle the real water temperature (if hot water is to be sampled).
The sampling point should represent the unaltered water quality of the respective location in the system. It should be designed so that the same conditions apply to the sampling procedure as they apply to normal consumption of the process and disruptive environmental effects (such as dust, fumes of solvents or disinfection reagents,...) can be excluded. When not being used, the sampling point may not change in its qualitative characteristics (no corrosion, no stagnant water or microbial proliferation of residual water in pipe). It may be necessary to drain the sampling line by forced ventilation to enable a complete water discharge. During sampling the water flow should be adjustable by the person collecting the sample, for example by using a diaphragm valve. Sampling points should be readily accessible and safely operated, especially when sampling hot water.

c) Flexible Connections

When vessels are connected with the water system using flexible connections, the sample should be taken at the end of the flexible line or hose. Hence, the quality of this flexible line or hose as well as the connection itself is incorporated in the system assessment. Special care should be taken during planning and design of sampling points with flexible connections (no stagnant water) and the sampling personnel should be trained intensively.

d) Taking a Sample

Sampling, transport and conditioning of the sample should not have an impact on its quality. Samples should be tagged to be able to clearly identify the location in the water system from which the sample was taken. Thus the following requirements result for the sampling procedure:

e) The Sampling Container

The container should not have any impact on the quality of the sample. It needs to be inert related to its chemical and physical characteristics. The cleaning, sterilization and sealing of the container may not contaminate the sample. It should be clearly tagged and reference the sampling point and time.

f) Sampling Personnel

With respect to their qualification, training, the environment and their clothing, the sampling personnel should be able to take a water sample without contamination. Therefore, gloves should be worn during sampling (to avoid contaminationof hand cream or dandruff) and personnel should not speak (to avoid contamination with saliva droplets). The sampling container should only be opened as long as the sampling procedure requires.

g) Transport

The sample should be analyzed as soon as possible. The quality should not be influenced during transport. Mistakes should be avoided by tagging the containers appropriately.

h) Analysis

The sample should be analysed using appropriate procedures and techniques. The respective analysis results should be linked to each sample without any doubt. In case sampling errors were identified, corrective action should be taken to eliminate the cause(s) and avoid future mistakes.

Chapter 6

TOC-Measurement

The measurement of TOC of pharmaceutical water needs to comply with regulatory requirements as given in international Pharmacopoeias (USP/EP). Based on these minimum requirements the following items should be considered and discussed:

- A System Suitability Test (SST) of the instrument used for online or offline testing should be performed periodically. During this test, the oxidation method of the instrument is evaluated and the results are documented. Reasonable SST intervals can be: 1-2 times per year (combined with a calibration), but at least prior and after maintenance activities that can have an impact on the oxidation method (eg. UV lamp replacement). A higher frequency of SST's (shorter intervals) can be defined by the user.
- When selecting a TOC-instrument the aptitude of the technology

	for the desired application should be evaluated and proven. If the instrument should be used for different water qualities, the aptitude for this operation should be ensured and documented respectively. – In case, a TOC-Instrument shall be used for the USP/EP-relevant TOC measurements in Purified Water (PW) or Water for Injection(s) (WFI), the selected technology should comply with the current Monographs in USP <643> and/or EP 2.2.44. The versions of both Monographs should always be used in their current form or edition.