CRITICAL UTILITY DESIGN AND MAINTENANCE

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MSD SINGAPORE

Agenda

- Type of utilities system
- Regulatory requirement
- Design approach
  - Design principle and strategic
  - GEP
  - System boundaries
- Maintenance plan
  - Rouging
  - Filter integrity testing
  - Contamination / microbial control
- Industry trend - PAT
Critical utilities system
– Gas system
– Pure steam
– Water system

Non-critical utilities system
– Chilled water
– Plant steam
– Instrument air
– Potable water

**Critical utilities system**

**Definition**

- **Direct impact system (process system)**
  – Contact the product
  – Direct impact product quality
  – Contact materials that ultimately become part of product

- **Depend on process, can be raw material, component or process aid (excipient)**

- **Application example:**
  – N2 for vessel blanketing
  – Pure steam SIP
  – WFI for compounding
Critical utilities system

Equipment that use critical utility:

– Blow-fill-seal (BFS) packaging machines
– Compounding system
– Filling line
– Freeze-drying (lyophilization)
– Part washer
– Autoclave
– SIP skid

Gas system

Nitrogen
– Storage tank
– Distribution loop

Sterile air (filtered air)
– Generation (compressed air)
  • Oil free type
– Distribution loop
  • Buffer tank
  • Air dryer
  • 0.2μ filter
Critical utilities system

**Pure steam**

- Generation
- Distribution loop

**Key feature**

- Feed water from PFW
- Use plant steam for distillation process

- Removal of endotoxins and other impurities via multiple separation stages
- For process sterilization purpose

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**Critical Utilities System**

**Water system**

**Purified water system (PFW)**

- Generation
- Storage and distribution

**Water For Injection (WFI)**

- Generation
  - Feed water from PFW
- Storage and distribution
Storage and Distribution System

**Key components**

- Tanks
- Pumps
- Heat exchangers
- Valves
- Sample Valves
- Instrumentation
  - What’s critical?
  - Location

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**PFW Generation**

*Schematic*
• The softened and chlorinated water is fed to a multi-media filter unit (MMF).
• Remove particulate present within the feed water supply.
• After filtration, the water flows to a break tank for storage.

• Feeds into break tank
  – The MMF water
  – Water re-circulated back from final filter

• The It consist of
  – spray ball
  – heated vent filter
  – bursting disc
  – level sensors
The activated carbon filter removes
- light weight organics
- any residual chlorine

**Daily backwash cycle**
(Auto or manual)

To remove up to 90 - 98% of inorganic ions together with all large contaminants and organic molecules contained in the feed water.

A twin pass RO unit protect the system from bacteria and pyrogens.
PFW Generation

Continuous Deionisation (CDI) Unit

- RO permeate is fed to the CDI unit for polishing.
- Uses high purity resins materials to remove all ionic materials from the water effectively.
- Give a maximum resistivity of 18.2MΩ-cm (25°C).

PFW Generation

Water quality

<table>
<thead>
<tr>
<th>Micro-siemens/cm</th>
<th>µS/cm@25°C</th>
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<tbody>
<tr>
<td>0.055</td>
<td>0.1</td>
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<tr>
<td>18.2</td>
<td>10</td>
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</table>

<table>
<thead>
<tr>
<th>Mega-ohms/cm</th>
<th>MΩ/cm@25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
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</tbody>
</table>

USP 29
• Conductivity < 1.3 µS/cm at 25°C
• TOC < 500ppb (0.5 mg/l)
## Conductivity of different water

<table>
<thead>
<tr>
<th>Pure water</th>
<th>Purified Drinking water</th>
<th>Brackish water</th>
<th>Sea water</th>
</tr>
</thead>
</table>

### Conductivity $\mu S/cm$

<table>
<thead>
<tr>
<th>LOW</th>
<th>MEDIUM</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
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<td>10</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>1000</td>
<td>10000</td>
<td>100000</td>
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</table>

### Resistivity MΩ/cm

<table>
<thead>
<tr>
<th>LOW</th>
<th>MEDIUM</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>10</td>
<td>1.0</td>
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<tr>
<td>0.1</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>0.001</td>
<td>0.0001</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

## PFW Generation

**Final Filter**

- The water is passed through 0.2 $\mu m$ before entering into storage tank.
- Bioburden reduction
- Removal of particulate contamination down to 0.2 $\mu m$.

**Microbio limits:**
- drinking water $< 500$ cfu/ml
- PFW $< 100$ cfu/ml
- WFI $< 10$ cfu/ml
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What might a regulator want?

For people to understand the intent of regulations, and then implement programs to meet that intent.
FDA has recently focused attention on critical utilities.

End users and their qualification and quality assurance personnel must demonstrate that the facility complies with 21 CFR 211.65(a) which states:

“Equipment shall be constructed so that surfaces that contact components, in-process materials or drug products, shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.”

PIC/S is the abbreviation and logo used to describe both the - Pharmaceutical Inspection Convention (PIC) - Pharmaceutical Inspection Co-operation Scheme (PIC Scheme)

The main differences between the PIC Scheme and PIC are:

<table>
<thead>
<tr>
<th>PIC Scheme</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme</td>
<td>Convention</td>
</tr>
<tr>
<td>An informal arrangement</td>
<td>A formal treaty</td>
</tr>
<tr>
<td>Has no legal status</td>
<td>Has legal status</td>
</tr>
<tr>
<td>Between Health authorities</td>
<td>Between countries</td>
</tr>
<tr>
<td>Exchange of information</td>
<td>Mutual recognition of inspections</td>
</tr>
</tbody>
</table>
PIC/S develop guidance “The Aide-Memoire – Inspection of Utilities” for GMP inspectors

- For training and preparation of inspection
- Checklist for critical utility on water, steam and gases

Improved standard and guidelines such as

- ASME Bioprocessing Equipment standard (BPE-2012)
- ISPE Baseline@ Pharmaceutical Engineering Guides
- International Standard ISO 8573 Compressed Air

have driven the quest of quality in pharmaceutical industry.

- Vary of interpretation by different regulators
EMEA reaffirms rejection of RO for WFI production in EEA

Reflection Paper on 5 March 2008

EP requirement for WFI be produced only by distillation

Refer RO membranes as "bacterial fermenters" and production of WFI RO would not be “as safe as water prepared by distillation”

Mandatory for manufacture of all products shipped into the European Economic Area

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Regulatory requirement

**USP**

- Recognized and used in > 140 countries
- Guide to produce medical products
- Specify standard for PFW and WFI

**Example:**
- Conductivity @ temperature (USP <645>)
- TOC (USP <643>)
- Bacteriological Purity Total Aerobic Count (CFU/MI)
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Design approach

**Factors**

Design approach affect by following factors:

- Validation
- Quality
- Process
- Timeline
- Budget
- Automation
- Safety & Environment
- Feed Water Quality
- Specification

Critical Utility Design
Design principle and strategic

**Design and project workflow**

- **Qualify**
  - Direct-impact systems only
  - Quality-critical requirements only

- **User Requirements**

- **Commission**
  - Engineering Specifications

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**User requirement specification**

- Set the standard and specifies your requirements
- Document the functions you want
- Used as a live document up until the DQ is completed and approved
- Traceability of PQ and OQ functionality testing (RTM)
- Part of procurement process e.g. tender document
GEP

Risk assessment

Objective

- Minimize project expenditures, streamline validation, and forgo unnecessary processes or mechanical design options
- Serve to qualify the use of certain system and component attributes that affect cost and performance
- Determine what operations of critical utilities classified as critical and non-critical
- Determine the scope and extend of validation
Risk assessment tool

Failure Mode Effects Analysis

- Assessment tool to determine their potential value for process design techniques
- Cause & effect analysis
- Assign each risk 1-10 for occurrence / severity / detection
- \( RPN = \text{Occurrence} \times \text{Severity} \times \text{Detection} \)

Example:

Microbial development in the WFI storage tank

- Surface finish on tank < 20 (Ra)
- Temp > 80 °C

With rating 0-10:

\[
RPN = O \times S \times D \\
= 1 \times 10 \times 2 \\
= 20 \text{ (low risk)}
\]
## Risk Assessment & FMEA

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>FMEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured by System Quality Attributes (SQA)</td>
<td>Structured by process steps</td>
</tr>
<tr>
<td>Begins with identifying hazards to SQA's</td>
<td>Begins with identification of potential failure modes</td>
</tr>
<tr>
<td>Controls are assessed based on design features and procedures</td>
<td>Controls are grouped as prevention and detection controls</td>
</tr>
<tr>
<td>Used to identify controls that must be incorporated into the user requirements</td>
<td>Used to identify and prioritize risks of a given process</td>
</tr>
<tr>
<td>Used to establish acceptance criteria for validation</td>
<td></td>
</tr>
</tbody>
</table>
“I don’t know how to explain them, but I know them when I see them.”

Apply to all critical utility from design to operation stage:

- **Projects**
  - design
  - construction
  - commissioning
- **Standards & Practices**
  - drawing control
  - equipment change management
  - documentation
- **Operations**
  - maintenance
  - calibration
  - safety and environmental
Good Engineering Practice (GEP)

General rule

- Allow provision for future expansion
- Utilities should be routed from plant room to process area
- Process utility systems are designed to satisfy the requirement of facility
- Meet regulatory requirements and expectations pertaining to equipment
- Drawing for utility systems must be approved and updated.

Good Engineering Practice (GEP)

Good Equipment Layout

- Keep design as simple as possible
- Provide good spacing for equipment
- Follow process flow
- Ease of access for operation and maintenance
- Operators review equipment layout during design stage
- Equipment and piping labeling
Good Engineering Practice (GEP)

System “Qualification Drawing” requirements:
- show the plant layout, with service connections and, as appropriate:
  - All isolating-, drain-, vent-, control-valves, and items served, complete with tag numbers where used.
  - Any critical items, such as filters, outlets, sample points etc.
  - The quantity, quality and direction of flow of the working fluid.

Component tagging
- Main components should be tagged or labelled, to ensure that there are unique references for items to use in:
  - Commissioning records
  - Maintenance records
  - SOP’s
  - Asset registers

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Quality Critical Attributes

URS → Engineering Specs → Design Details → SAT / Commissioning → FAT → SAT / Commissioning → Design Details → Engineering Specs → URS

EQ

GMP

GEP

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System boundaries
System boundaries

**Design criteria**

- Product
- Regulatory
- Dosage form

- Pressure
- Temp
- Flow rate
- Demand
- Auto/manual

- Storage
- Future capacity
- Generation rate
- Feed water Quality

**Utility quality**

**Use point criteria**

- Product quality
- Regulatory
- Dosage form

- Pressure
- Temp
- Flow rate
- Demand
- Auto/manual

**System criteria**

**Re-evaluate system design boundaries and constraints**

**Detailed system design**

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**Compressed air to sterile air**

- Galvanized piping
- Non critical
- Critical
- SS piping
- Sanitary valve
- Sanitary sampling point
- 0.2 μm sterile filter
Critical utility design

Standard requirement

Basic requirement includes:

- Eliminate dead legs where possible
- Sanitary design for component
- N2 seal storage tank or vent filter (0.2 μm)
- Piping material - SS316L
- Orbital welding and inspection
- Sampling point for distribution loop
- Instruments for trending (TT / FT / PT)
- Standby pump for water distribution loop
- ISO/DIN type of gasket / seal e.g. PTFE, EPDM, Viton® and Silicone

Why Stainless Steel 316L

L indicates low carbon – but note that the specification limits for 316 and 316 L overlap

<table>
<thead>
<tr>
<th>316</th>
<th>C</th>
<th>Mn</th>
<th>Si</th>
<th>P</th>
<th>S</th>
<th>Cr</th>
<th>Mo</th>
<th>Ni</th>
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<td>3.0</td>
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<td>3.0</td>
<td>14.0</td>
<td>0.10</td>
</tr>
</tbody>
</table>

SS 316L used when there is a danger of corrosion in the heat-affected zones of weldments
Why Stainless Steel 316L

Many reasons:

• Availability of tube and sheet material
• Availability of valves and fittings
• Corrosion resistance
• Weldability

• ASTM A269 (unpolished ID and OD) and A270 (polished ID and OD)
• Tolerances are generally tighter for ASTM 270

 Orbital Welding

• The standard approach is to use closed head orbital welding
  – Automated repeatable quality welds
  – Protection from oxidation on both sides by purge gas
  – Weld parameters (primary / background values of pulsed welding current, primary / background pulse times and rpm), controlled by the power supply, which determines the surface travel speed of the tungsten electrode.

• Orbital welding provides precise control of the heat input into the weld results in better corrosion resistance than manual welding

• Ensure sample welds (coupon) are produced for all heat combinations.
Orbital Welding – test coupon

Test coupons that conform to the specification on the actual materials to be used before the start of the job

Others:
- lines were labeled with the heat number of the tubing
- date of welding
- weld number on the ISO drawing
- piping system number
- weld log for future reference

Standard requirement

Water system

Air gap for drain point (min. 50mm)

Eliminate microbial contamination from common drain line

ASME 112.1.2:
The minimum required air gap shall be twice the diameter of the effective opening
**Dead Leg definitions**

A dead leg is any area in a piping system where water can become stagnant and where water is not exchanged during flushing.

Bacteria in dead-end pipe lengths / crevices are protected from flushing and sanitization procedures and can recontaminate the piping system.

**Zero deadleg valves** were used to minimize deadlegs in critical areas of the piping system.

Modern piping design limits the length of any dead-end pipe to 6 times the pipe’s diameter (even shorter dead legs are preferred).

This is the six diameter rule (6D).

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**Dead Leg guideline**

As per ASME BPE 1997: "For Bioprocessing systems, L/D of 2:1 is achievable with today's design technology for most valving and piping applications."

If deadlegs exist in a system, some provision should be made for flushing them through routinely.
Case Study - Dead leg

Carbon filter manifold in operation

- Dead leg section during normal operation
- Promotes microbial growth and formation of bio-film
- Affects performance of carbon filter

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Case Study - Dead leg

Carbon filter manifold during back-washing

- Dead leg section, collects ‘dirty’ backwash water
Case Study - Dead leg

Carbon filter manifold in operation

After improvement

Keep deadlegs between valves to minimum

Case Study - Dead leg

Carbon filter manifold during back-washing

After improvement

Keep dead legs between valves to minimum
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Maintenance challenge

- Maintenance always link to reliability / availability
  - 24hrs X 365 days
- Maintain the validated state
- Contamination / microbial control
Rouging

- A form of surface corrosion – reddish / brownish
- Common problem in WFI / pure steam systems
- High temperatures and dissolved gases accelerate corrosion and formation of iron oxides
- Iron oxide can break away from SS surfaces and flow through the entire water system downstream (migratory rouge)

**Effect**

- Cr-oxide dominated passive-layer is changing to Fe-oxide enriched corrosion layer

- Influencing parameters:
  - Alloy quality
  - Surface treatment
  - WFI quality
  - Temperature
  - Exposition time
  - Gas content (type and quantity)
Rouging

• Typically found in:
  
  – Pump impellors and internal housing
  – Vessel spray balls
  – In-line filters and housings
  – Storage vessel surfaces (usually above water line)
  – PTFE surfaces e.g. tri-clamp gaskets and valve diaphragms

Example

Pump volute from WFI system

Spray ball WFI storage tank

Pump impeller from WFI system
Rouging

Example

Rouging on a PTFE tri-clamp gasket

Rouge discoloration found on a point of use 0.45 μm filter membrane

Rouging

Example

Rouge can be wiped off and can move throughout a system. The rouge layer consists of heavy-metal-oxides, preferably Fe-Oxides. The rouge-layer consists of particles of heavy-metal-oxides which can leave the surface based on stream conditions.

Wipe test of a production vessel

Wipe test of a WFI pipe
Rouging control

• **Removal of rouging**

• Generate an oxide film that covers and protects the surface of the SS surface by **nitric acid or citric acid**

• Recirculation through distribution loop (2 hrs)

• Post passivation – PFW water flushing till pH 6 to 8

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**Before / After Derouging**

**before Derouging**

**after Derouging**
Rouging control

**Monitoring**

- Schedule inspection to check components in the loops for sign of rouge
- Establish baseline and identify possible problem area
- Establish SOP for derouging / repassivation process
- Routine sampling of water quality
  - Conductivity
  - TOC
  - Heavy metals
  - Nitrate

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**Filter integrity testing (FIT)**

- **Filter type:**
  - Air / Gas filtration
  - Water filtration
  - Vent filtration for storage tank
- **Purpose:**
  - Sterile boundaries
  - Protect from contamination (bacteria retention)
- **Maintenance:**
  - Routine schedule replacement
  - FIT (before and after)
Filter integrity testing

• What is FIT?
  A measure of the ability of a filter element to work as designed through multiple cycles, is a sensitive process parameters that requires qualified testing

• Factors influencing FIT
  - Temperature
  - Upstream Volume
  - Wetting Agent

Potential integrity breaches underscore the need for FIT

Breaches may occur as a result of...
• Factory defects
• Shipping damage
• Improper maintenance
• Structural creep
• Chemical degradation
• Age

Breaches can occur in many locations...
• Seals and O-rings
• Membrane potting
• Fibers (broken or punctured)
Type of FIT

- Water intrusion test (gas)
- Forward flow (water)
- Bubble point filter test

Water intrusion test (gas / vent)

The resistance to water flow is overcome by a specific pressure

For hydrophobic gas filters
Forward flow (water)

- An integrity test measuring air diffusion
- Measurement of diffusive (diffusional) flow of a gas through a wetted filter.
- Measured under pressure and evaluated by comparing the results to a limit value.

Contaminants in water

Dissolved inorganic

Dissolved organics

Micro-organisms

Particulate matter
Sources of Microbial Contamination

- Source supply water or feedwater
- Unprotected Vents / unsealed tanks
- Faulty air filters
- Contaminated use points/sample points
- Unsatisfactory drain air breaks
- Replacement carbon/resin/sand
- Contaminated chemical additions
- Improper sampling

Contamination control

**RO membrane cleaning**

- Cleaning is activated by
  - fall in permeate
  - dramatic rise in permeate conductivity
  - rise in 1st pass differential pressure

- Acid clean - remove hardness scale and is effective in removing iron precipitates.

- Alkaline clean - remove biological material, colloid, silica etc.
Contamination control

Cleaning removes debris, scale, and resin foulants from the module that can severely reduce performance.

It is very important to follow cleaning guidelines in the CDI O&M manual:
- for cleaning to be effective
- to avoid damaging the module

Microbial Control and Biofilms

There are a number of measures that control microbes:

1. Avoid or minimise dead legs
2. Continuous re-circulation of water
3. Avoid stagnant ambient temperature water
4. Allow for drainage of pipework
5. Use sanitary valves & suitable gaskets selection
6. Use suitable construction materials
7. Maintain system water temperature at > 70*C
8. Regular sanitation or sterilization
9. UV radiation
10. Air break for drains
Microbial Control

1. Continuous re-circulation of water
2. Avoid stagnant ambient temperature water
3. Allow for drainage of pipework and storage tanks
4. Use sanitary valves
5. Avoid or minimise dead legs

The above measures discourage bacteria from:
  • Lingering longer and reproducing to larger numbers
  • Settling to establish biofilms
  • Good drainage of unused pipes and tanks allows drying which prevents bacteria from multiplying, although they may remain dormant for periods of time

Microbial Control

1. Use suitable construction materials
2. Maintain system water temperature at > 70*C
3. Regular sanitation or sterilization
4. UV radiation

The above measures are designed to facilitate the killing of bacteria:
  • Most, if not all water system bacteria are vegetative forms (do not have spores) and therefore killed at temperatures above 60*C. 70 – 80*C is recommended to allow for cooler spots in systems.
  • Stainless steel is better for withstanding temperatures and providing better surface finish to prevent biofilm establishment.
Microbial Control

1. Regular chemical treatments can become expensive to get a system back under control
2. Chemical treatments have to be applied at correct concentrations and allow sufficient contact time for effectiveness. Handling of chemicals would require safety assessment
3. Heat at sufficient temperature is a more effective sterilizing agent
4. UV radiation is effective but
   • Need to be certain there is no shading of bacteria (requires direct exposure to bacteria)
   • Need ensure UV intensity is maintained over time. Can still have a blue light when UV energy is insufficient

Microbial control

Sanitization

Sanitization are performed periodically to control the microbial growth

Weekly sanitization of the PFW
- Generation
- Distribution loop

FDA – over 65 degrees C is considered self sanitizing

EU – stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70 degrees C
Microbial control

On request when intrusive maintenance:

After the distribution loop or storage tank is opened, altered or exposed for maintenance / calibration

After replacement of the filter element for the final filter or heated vent filter

After the distribution loop or storage tank has remained out of service for > 4 hours

Case study – microbial contamination

Scenario:

Total Viable Count (TVC) results for water which was sampled and tested on 1st Oct 12 hit action limit for PFW generation system (after 5-7 days incubation).

Purified water (sampling point: SP-123 Final filter outlet): 25 cfu/100ml

Alert limit – 1 cfu/100ml
Action limit – 10 cfu/100ml
Distribution loop is maintained at 80deg C
**Case study – microbial contamination**

**Immediate Action:**

- Notified production to stop using water and perform impact assessment
- Lab to conduct internal investigation e.g. SOP, personnel, human error, contamination during sampling, ID test, trending, etc.
- Informed system owner to check water system condition
  - PM record, daily log sheet (fact finding)
  - Root cause analysis
  - Review trending and alarm log from PLC
  - Recovery actions as per SOP

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**Case study – microbial contamination**

**Cause & effect diagram**
Typical recovery actions:
- Flushing and initiate sanitisation cycle on water generation & distribution loop
- Dismantle and inspect final filter, internal parts and O-ring before replaced
- Inspect U.V Steriliser
- “Chlorine shock” on inlet of MMF filter
- Chemical cleaning & sanitisation of RO membrane & CDI unit
- Chemical sanitization of incoming feed water pipe
- Inspect internal water pipe for any sign of biofilm build up and leakage
- Inspect chorine dosing pump for abnormality

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**Process Analytical Technology**

**Definition**

**FDA – Center for Drug Evaluation and Research**

“a system for designing, analyzing, and controlling manufacturing through timely measurements, (i.e., during process) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.”

How:
On-line release using qualified Analyzers with a validated process

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**FDA for PAT**

**Guideline**

**PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance**

**FDA PAT Initiative**

“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.”

These tools and principles should be used for process understanding and to meet regulatory requirements for validating and controlling the process
USP

Guideline

USP Chapter <643> on TOC states …

“On-line TOC measurements for bulk-produced water…have the advantage of providing real-time measurements and opportunities for real-time process control and decisions, in addition to recording the TOC quality attribute for release of water to production…off-line measurements of bulk waters have the disadvantage of being impacted adversely by the sampling method, sample container and uncontrollable factors, such as organic vapors.”

PAT drivers

Goal: 100% understanding and control

• Improve Assurance
• Improve Process Controls
• Improve Understanding
• Improve Quality

In line sampling port

WFI or PFW loop

SCADA system

TOC analyzer
Utilities / Maintenance
• Equipment Owner
• Execution of SOPs and protocols

QA/QC
• Input to SOPs and Protocols
• Surveillance & inspections of equipment & components
• Technical support
• Release documentation

Moving to PAT – A company effort

Engineering
• Equipment choice
• Sampling conformity to design of water system (installation)
• Review of as-builds
• Functional testing (Commissioning, IQ,OQ)

Validation
• Master plan creation and owner
• Documentation review
• Validation testing (PQ) execution
PAT benefit

**TOC and conductivity**

- Eliminate sampling errors
- Reduced water system downtime and sanitization
- Release water and product faster
- Increase profits
- Better control of the process
- Reduce sampling cost

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**On-line TOC vs. Laboratory TOC**

<table>
<thead>
<tr>
<th>On-line</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate measuring low ppb</td>
<td>LOD above most water systems</td>
</tr>
<tr>
<td>No sample contamination</td>
<td>Grab sample contamination</td>
</tr>
<tr>
<td>No sample handling</td>
<td>Sample tracking protocols</td>
</tr>
<tr>
<td>Low cost-of-ownership</td>
<td>High cost-of-ownership (labor intensive)</td>
</tr>
<tr>
<td>Trending information</td>
<td>No trending information</td>
</tr>
<tr>
<td>Real-time data</td>
<td>Delayed data</td>
</tr>
<tr>
<td>Continuous monitoring</td>
<td>Infrequent results</td>
</tr>
<tr>
<td>Measure in own environment</td>
<td></td>
</tr>
<tr>
<td>Data for valuable information</td>
<td></td>
</tr>
</tbody>
</table>
Grab sample testing

**Lab sampling**

- **Sample cost**
  - Materials
  - Time
  - Labor

- **Laboratory analysis cost**
  - Time
  - Equipment maintenance

10 Points x 1 TOC x 365 days = 3,650 samples

10 Points x 1 conductivity x 365 days = 3,650 samples

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**TOC / Conductivity comparison**

- **Off-Line Testing (TOC & Conductivity):** USP <643> and <645>
  - Sample testing Turnaround Time = 1 to 2 Business Days
  - Operator time to sample = ~30 minutes per day
  - Analyst time to test = ~1 hour per sample
  - Review Time = ~15 minutes/day
  - Instrument set-up (Daily & Weekly) = ~6 hours

- **On-Line Testing**
  - Sample testing Turnaround Time = Real Time
  - Operator time to sample = None
  - Analyst time to test = ~1 hour per sample
  - Review Time = ~15 minutes/day
  - Instrument set-up (Daily & Weekly) = ~2 hours
Estimate of samples taken in 24 hours

- Increased process control & improved product quality
- Eliminate sampling errors
- Faster product / water release
- Increased profits

Industry direction – PAT for critical utility

FDA launches Pharmaceutical cGMP’s for the 21st Century: A Risk Based Approach

Specific Goals
- Most up-to-date concepts of risk management and quality systems approaches are incorporated into manufacturing
- Encourage manufacturers to use latest scientific advances
- FDA
  - submission review and inspection to improve
  - Risk based approach encourages innovations
- Regulations and manufacturing standards rapidly applied
Summary

• **Critical utility**
  - Type of utility

• **Regulatory**
  - FDA / Standard / USP

• **Design**
  - Applying of GEP will ensure reliable equipment without compromise the cGMP expectation

• **Maintenance**
  - Rouging / FIT / Contamination & Microbial control

• **Industry trend - PAT**
  - FDA risk based approach and PAT increase auditor confidence

Questions?