

USP/EP Purified Water and Water for Injection Systems – Case Histories

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Case History No. 1

USP/EP Water for Injection System – High Conductivity

- Feed Water Supply
 - Large Municipal Treatment Facility
 - Source Water: Surface Supply
 - Feed Water Conductivity: 125 $\mu\text{S}/\text{cm}$
@ 25°C
 - Feed Water Total Organic Carbon: 3.0-
3.5 mg/l

USP/EP Water for Injection System – High Conductivity

- **Feed Water Supply**
 - **Feed Water pH: 8.5 – 9.5**
 - **Feed Water Primary Treatment:
Chlorination**
 - **Feed Water Distribution System
Disinfecting Agent: Chloramines**

USP/EP Water for Injection System – High Conductivity

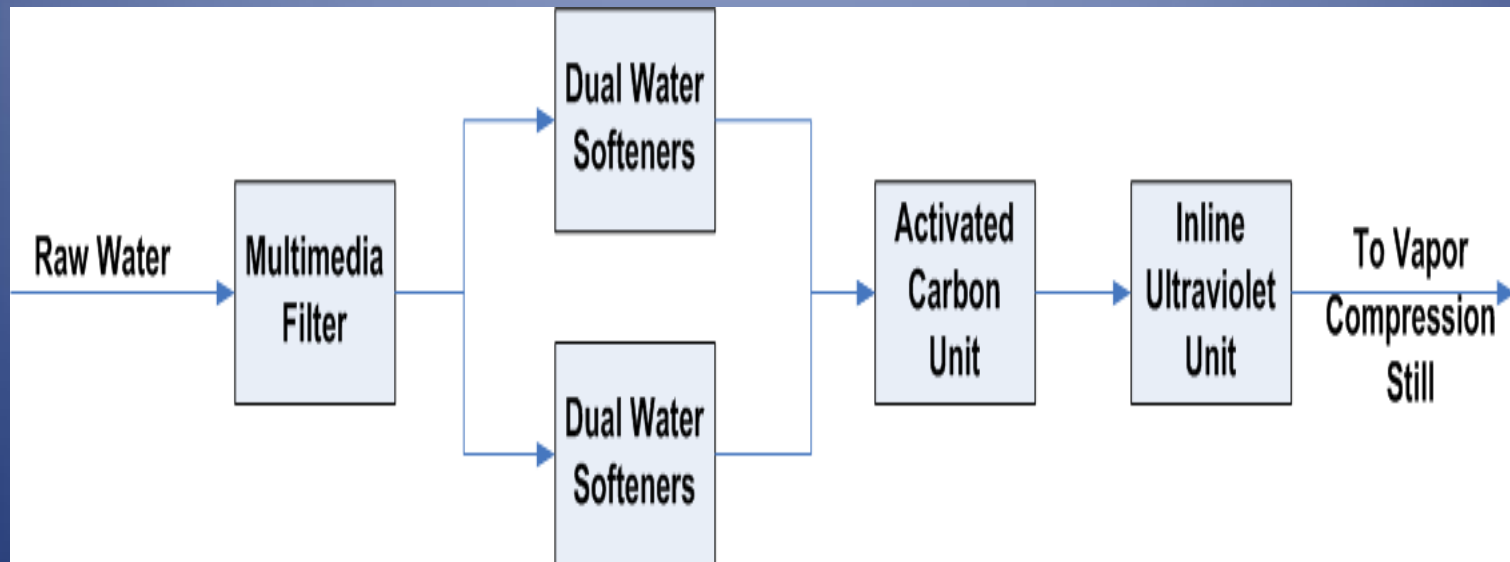
- Feed Water Supply
 - Feed Water Total Trihalomethane Concentration: 20-35 $\mu\text{g/l}$
 - Feed Water Residual Chloramine Concentration: 2.2 – 2.5 mg/l
 - Feed Water Temperature: 3 - 27°C

USP/EP Water for Injection System – High Conductivity

- **System Design - Pretreatment**
 - **Multimedia Filtration Unit**
 - **Dual Water Softening System**
 - **Activated Carbon Unit**
 - **Inline Ultraviolet Sanitization Unit**

USP/EP Water for Injection System – High Conductivity

Figure A



USP/EP Water for Injection System – High Conductivity

- **System Design – Distillation Unit**
 - Feed Water Tank
 - Feed Water Pump
 - Vapor Compression Distillation Unit

USP/EP Water for Injection System – High Conductivity

- System Design – Storage and Distribution
 - Sanitary WFI Storage Tank
 - Distribution Pump
 - Main Recirculation Loop Temperature:
85°C

USP/EP Water for Injection System – High Conductivity

- **System Design – Storage and Distribution**
 - Sub Loop Temperature: 25-30°C (one shift per day – hot balance of time)
 - Hot WFI Feed to Pure Steam Generator

USP/EP Water for Injection System – High Conductivity

- Problem

Upon system start-up the inline conductivity value of distilled product water and recirculation Water for Injection exceeded the USP and EP Conductivity Specification. Stage 2 USP Conductivity readings were 5.1 – 6.3 $\mu\text{S}/\text{cm}$ @ $25 \pm 1^\circ\text{C}$.

USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations
 - TOC of WFI product water: 0.015 – 0.036 mg/l (anticipated)
 - Organic scan of WFI indicated Chloroform (THM) at a concentration of about 0.002 µg/l (anticipated)
 - **Problem not related to organic contamination**

USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations
 - Total Viable Bacteria <1 cfu/100 ml (MF, R2A, 120 hours, 30-35°C)
 - Bacterial Endotoxins <0.25 IU/ml
 - **Problem not related to microbial or contamination or biofilm**

USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations
 - Problem must be inorganic in nature
 - Since distillation is employed (phase change), contaminant must be gas that dissolves in water to produce ionic material.
 - Ammonia and carbon dioxide will exhibit these attributes
 - pH of feed water directs focus to ammonia

USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations

Consider monochloramine removal by activated carbon:



Where: C* = Represents the activated carbon surface and CO* represents a surface oxide on the activated carbon.

USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations

Ammonia is a gas that will dissolve in water and ionize, in an equilibrium reaction, to produce the ammonium ion and the hydroxide ion as follows:



USP/EP Water for Injection System – High Conductivity

- Resolution – Design Considerations

As pH increases, the relative concentration of ammonia gas to ammonium ion increases.

Subsequently, the feed water to the distillation unit contains ammonia gas which, along with steam, is condensed. In the distilled product water, at lower pH, the ammonia gas concentration is small, producing ammonium ion and highly electronically mobile hydroxide ion.

USP/EP Water for Injection System – High Conductivity

- Resolution – System Enhancement

The ammonium ion must be removed. This can be accomplished through ion exchange. The pretreatment system to the distillation unit was enhanced to include:

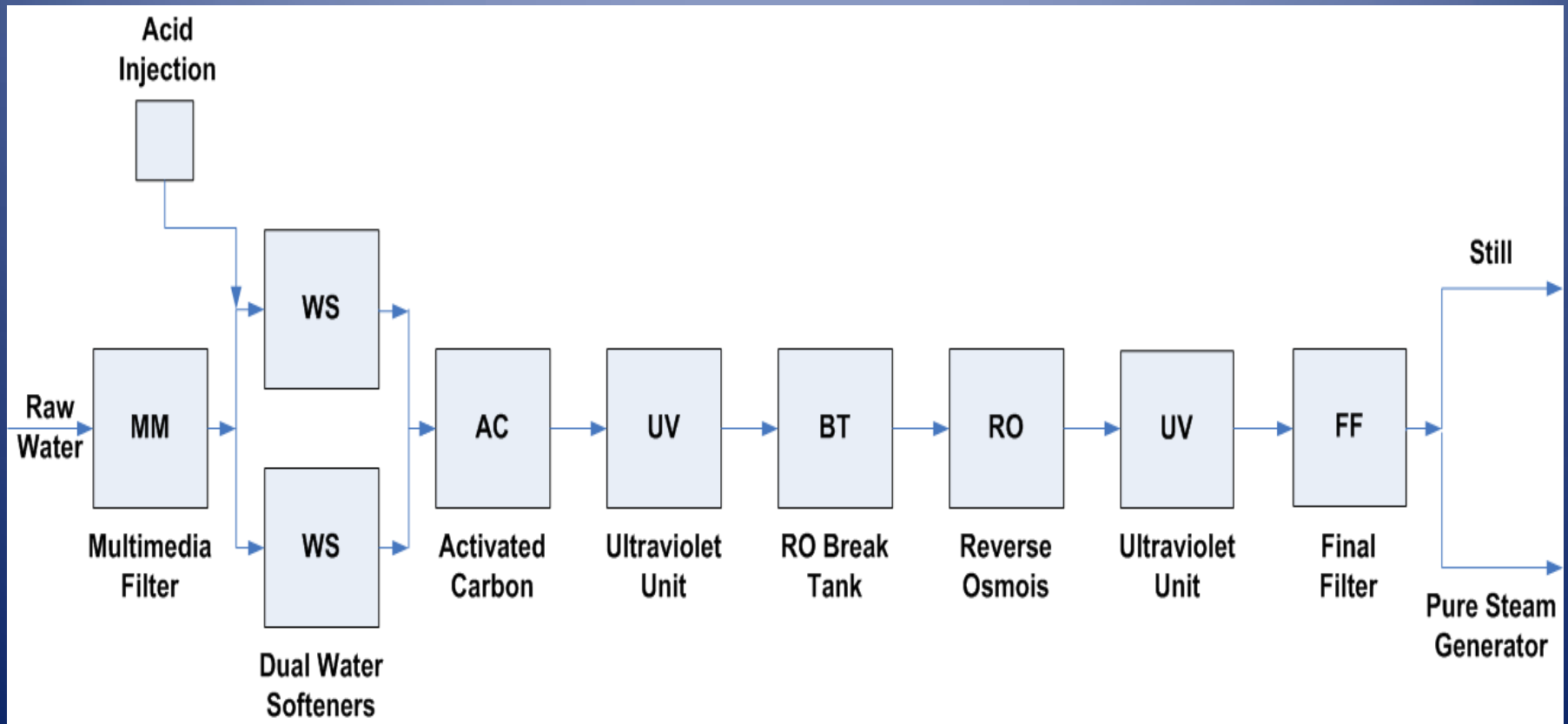
- Multimedia Filtration Unit
- Acid Injection (pH=8.0)
- Dual Water Softeners
- Activated Carbon Unit

USP/EP Water for Injection System – High Conductivity

- Resolution – System Enhancement (continued)
 - Inline Ultraviolet Sanitization Unit
 - RO Break Tank
 - Reverse Osmosis Unit
 - Continuous Electrodeionization Unit
 - Inline Ultraviolet Sanitization Unit
 - Final Filtration System

USP/EP Water for Injection System – High Conductivity

Figure B



USP/EP Water for Injection System – High Conductivity

- Results
 - Both distilled water and WFI distribution loop conductivity values decreased to meet the Stage 1 USP and EP limits.
 - Since deionized feed water was available, Pure Steam Generator feed was changed from WFI to pretreated source.
 - The blowdown volume for both the vapor compression distillation unit and Pure Steam Generator were reduced by about 50%.

Case History No. 2

USP Purified Water System – Objectionable Material in Final Product

- Pathogenic bacteria are detected in final product. The USP Purified Water employed for manufacturing has an established total viable bacteria monitoring program. Historical bacteria are not detected in point-of-use samples (1 ml, HPC, PCA, 72 hours, 30-35°C)

USP Purified Water System – Objectionable Material in Final Product

- Investigation - Laboratory
 - Evaluation of Laboratory Procedures
 - Duplicate Sampling for TVB Determination by Contract Laboratory
 - Results using same enumeration method are similar
 - No bacteria detected in 1.0 ml sample

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Design
 - Multimedia Filtration
 - Activated Carbon
 - Mixed Bed Deionization
 - USP Purified Water Storage Tank
 - Distribution Loop – Sanitary 316L Stainless Steel

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Design (continued)
 - Distribution Loop Inline Ultraviolet Sanitization Unit
 - Distribution Loop Final 0.2 Micron Filtration System

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Operation
 - Municipal Feed Water
 - Chloramine Residual Disinfecting Agent
 - TOC = 250-370 mg/l
 - Conductivity = 0.9-1.1 $\mu\text{S}/\text{cm}$ @ 25°C
 - Mixed Bed Units Rechargeable Canisters

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Operation
 - Storage Tank and Distribution Loop Sanitization Method
 - * Hot Water @ 85°C for 4 hours
 - * Frequency = Yearly

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Operation
 - Loop Membrane Filter Change
 - * Frequency = yearly
 - * No integrity testing
 - * Frequency based on TVB data

USP Purified Water System – Objectionable Material in Final Product

- Investigation – Return to Laboratory Data
 - Sanitization Frequency and Filter Change – Do Not Support Observations
 - Continue Use of Contract Lab and Duplicate Samples
 - Change Enumeration Method – MF (100 ml), R2A, 120 hours, 30-35°C

USP Purified Water System – Objectionable Material in Final Product

- Investigation – Return to Laboratory Data
 - Results for All Samples in 5 Day Period Indicate < 1 cfu/100ml
 - **Samples From All Points in the “Generation System” Indicate <1 cfu/100ml**

USP Purified Water System – Objectionable Material in Final Product

- Investigation – System Operating Log/Action
 - Review of the System Operating Log indicates that activated carbon change frequency is once/two years.
 - Municipality had changed from chlorine to chloramine use within the last 10 months.
 - Replaced activated carbon media with catalytic activated carbon

USP Purified Water System – Objectionable Material in Final Product

- Investigation – Point-of-Use Resample
 - Reinitiated sample program – 100 ml
 - Contract Laboratory and Internal Laboratory indicate TNTC after 48 hours!
 - Stopped production

USP Purified Water System – Objectionable Material in Final Product

- Corrective Action
 - Chemically sanitized water system piping.
 - Because distribution system biofilm was obviously present, chemically sanitized the storage and distribution system with 1% Peracetic Acid & Hydrogen Peroxide in dynamic/static/dynamic mode for 16 hours, flushing all points-of-use repeatedly.

USP Purified Water System – Objectionable Material in Final Product

- Corrective Action
 - Revised TVB monitoring program to MF (100 ml), PCA, 72 hours, 30-35°C.
 - Added *P. aeruginosa* presence/absence testing of 100 ml.
 - Continued use of Contract Lab for two weeks

USP Purified Water System – Objectionable Material in Final Product

- Corrective Action
 - TVB results indicate <1 to 5 cfu/100 ml
 - No “objectionable organisms noted.
 - *P. aeruginosa* absent in 100 ml.
 - Initiated weekly hot water sanitization program with monthly chemical sanitization program

USP Purified Water System – Objectionable Material in Final Product

- Corrective Action
 - Initiated “fast track” design program for RO based system.
 - Replaced 0.2 micron final filters (loop) with 0.05 micron disposable ultrafiltration cartridges with monthly change (prior to chemical sanitization).

USP Purified Water System – Objectionable Material in Final Product

- Corrective Action – Interim Specification
 - TVB Alert Limit = 5 cfu/100 ml
 - TVB Action Limit = 10 cfu/100 ml
 - Absence of “Objectionable Organism” in 100 ml sample
 - Absence of *P. aeruginosa* in 100 ml sample

Case History No. 3

USP Purified Water System – High Conductivity in Ozonated System

- A USP Purified Water System employing ozone for microbial control, experiences a gradual increase in distribution loop conductivity with increasing feed water temperature from spring to summer months. The increase requires collection of point-of-use “grab samples” for USP “Stage 2 and Stage 3” measurement.

USP Purified Water System – High Conductivity in Ozonated System

- **Feed Water Supply**
 - Privately Owned Treatment Facility
 - Source Water: Surface Supply (River)
 - Feed Water Conductivity: 350 $\mu\text{S}/\text{cm}$ @ 25°C
 - Feed Water Total Organic Carbon: 3.5-4.4 mg/l

USP Purified Water System – High Conductivity in Ozonated System

- **Feed Water Supply**
 - **Feed Water pH: 7.1 – 7.8**
 - **Feed Water Primary Treatment: Chlorination**
 - **Feed Water Distribution System Disinfecting Agent: Chlorination**

USP Purified Water System – High Conductivity in Ozonated System

- **Feed Water Supply**
 - **Feed Water Total Trihalomethane Concentration: 65+ $\mu\text{g/l}$**
 - **Feed Water Residual Chlorine Concentration: 0.5-1.0 mg/l**
 - **Feed Water Temperature: 2-30°C**

USP Purified Water System – High Conductivity in Ozonated System

- **System Design - Pretreatment**
 - **Multimedia Filtration Unit**
 - **Activated Carbon Unit**
 - **Inline Ultraviolet Sanitization Unit**
 - **Dual Water Softeners**

USP Purified Water System – High Conductivity in Ozonated System

- **System Design – Ion Removal**
 - RO Break Tank
 - Reverse Osmosis Unit (HWS)
 - Continuous Electrodeionization Unit (HWS)
 - Inline Ultraviolet Sanitization Unit
 - Final 0.1 Micron Filtration

USP Purified Water System – High Conductivity in Ozonated System

- **System Design – Storage & Distribution**
 - Ozonated Storage Tank
 - Distribution Pumps
 - Ozone Destruct Ultraviolet Unit
 - 316L Stainless Steel Distribution Loop

USP Purified Water System – High Conductivity in Ozonated System

- **Investigation**
 - **Feed Water Trihalomethane (THMs) levels a concern**
 - **Collected samples throughout system for THM analysis**

USP Purified Water System – High Conductivity in Ozonated System

- Investigation – THM Results ($\mu\text{g/l}$)

	Chloroform	Dibromochloro-methane	Bromodichloro-methane	Bromoform
Feed Water	35	8.0	19	0.69
Activated Carbon Product Water	18	4.6	6.6	0.33
Reverse Osmosis Product Water	7.8	ND	2.8	ND
CEDI Product Water	9.0	ND	3.1	ND
Distribution Loop	7.9	ND	2.3	ND

USP Purified Water System – High Conductivity in Ozonated System

- **Investigation – Data Evaluation**
 - THMs oxidized by ozone to carbon dioxide
 - Carbon dioxide reacts with water to produce the bicarbonate ion and an extremely mobile hydronium ion

USP Purified Water System – High Conductivity in Ozonated System

- Investigation – Data Evaluation



USP Purified Water System – High Conductivity in Ozonated System

- **Investigation – Data Evaluation**
 - The ions produced increase the conductivity
 - Literature search indicates that select activated carbon will remove THMs

USP Purified Water System – High Conductivity in Ozonated System

- **Investigation – Resolution**
 - New activated carbon media installed
 - Loop Conductivity decreases below Stage 1 levels.
 - THM resample

USP Purified Water System – High Conductivity in Ozonated System

- Resolution – THM Results (µg/l)**

	Chloroform	Dibromochloro-methane	Bromodichloro-methane	Bromoform
Feed Water	42	8.3	17	0.35
Activated Carbon Product Water	2.0	ND	0.7	ND
Reverse Osmosis Product Water	ND	ND	ND	ND
CEDI Product Water	ND	ND	ND	ND
Distribution Loop	ND	ND	ND	ND

USP Purified Water System – High Conductivity in Ozonated System

- **Investigation – Resolution**
 - **New activated carbon media replaced every 3 months during warmer months**
 - **Loop Conductivity remains below Stage 1 levels.**

Thank you!

Questions?