Pharmaceutical Ultrapure Water Systems -

What Pharma Can Learn From Other Industries?

Igor Gorsky

Pharmaceutical Ultrapure Water Systems –What can we learn from other industries?

- ❑ Sanitization Terms/Definitions
- ❑ Lifecycle Approach to Validation (Design, PQ and Maintenance)
- ❑ Sanitization Methods
- ❑ Other Industries using Pure and Ultrapure Water
- ❑ Rapid Microbial Detection as a tool

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Water System Sanitization

- Sanitization Terms/Definitions

Water System Sanitization

Terms/Definitions

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Water System Sanitization

Water Sanitization – Definitions: Sanitization

"Sanitization is designed to reduce contamination or bioburden by 99.9% or offer 3 log (10^3) reduction.

or

Out of one million microorganisms, a sanitizer will destroy approximately 990,000 of the organisms leaving behind many (10,000) viable microorganisms to reproduce.

Sanitization is accomplished by utilizing heat and chemicals and gels to achieve this level of cleanliness "

Feinstein, S., "How Clean is Clean", ALN Magazine, November 2010

Water System Sanitization

Water Sanitization – Definitions: Disinfection

"Disinfection is designed to reduce bioburden by 99.99% and up to 99.999% or offer up to 5 log (10^5) reduction

or

Out of one million microorganisms, a sanitizer will destroy approximately 999,000 of the organisms leaving behind many (1,000) viable microorganisms to reproduce.

Disinfection is accomplished by utilizing heat, many different chemicals or ultraviolet light "

Feinstein, S., "How Clean is Clean", ALN Magazine, November 2010

Water System Sanitization

Water Sanitization – Definitions: Sterilization

"Sterilization is the statistical destruction of all microorganisms and their spores, by 99.9999% or offer up to 6 log (10^6) reduction

or

Statistically, this definition is accepted as zero viable organisms surviving.

Sterilization is accomplished via several methods including ionized hydrogen peroxide or other hydrogen peroxide based solutions, high heat, ultraviolet light, ozone, radiation, and chemicals (chlorine, formaldehyde, glutaraldehydes, etc.).

Feinstein, S., "How Clean is Clean", ALN Magazine, November 2010

Water System Sanitization

- Sanitization Terms/Definitions
- Lifecycle Approach to Validation (Design, PQ and Maintenance)

Water Systems

Validation Process Lifecycle

Validation Process

Collection and ***evaluation*** of ***data***, from the process ***design*** stage through ***commercial production***, which establishes ***scientific evidence*** that a process is ***capable*** of consistently delivering ***quality product***[1].

[1] ***Process Validation: General Principles and Practices (Revision 1)***, **U.S. Food and Drug Administration, U.S. Government Printing Office: Washington, DC, 2011.**

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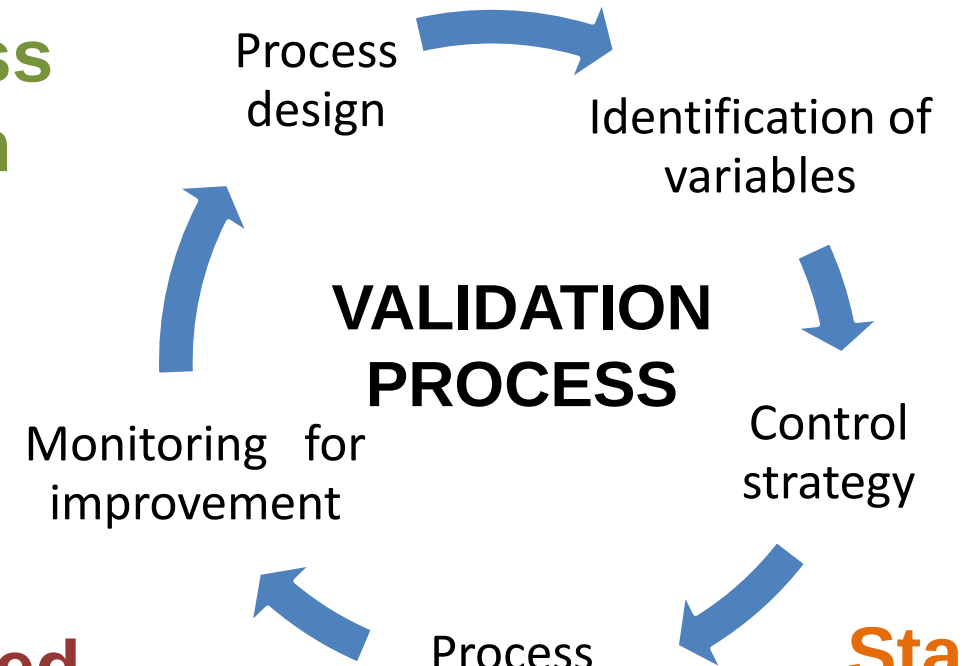
Validation Process Lifecycle

Stage 1 Process Design



Stage 2 Process Qualification

Stage 3 Continued Process Verification

Water System Sanitization

Validation Process Lifecycle

Key Focus - Variation

Understanding

Detection

Response

Control from input through output

"Uncontrolled variation is the enemy of quality." Dr. Edwards Deming

Source: Process Validation GEMcNally, Sept 11, 2012

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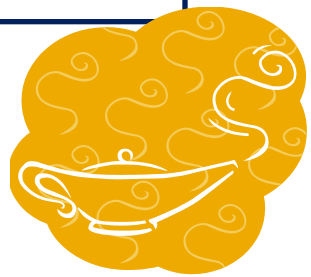
Validation Process Lifecycle



QUESTIONS TO CONSIDER……

- How do I know if my process is in a state of control?
- How variable are my inputs?
- How much variation can be tolerated in my outputs?

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Validation Process Lifecycle:

Stage 1 – Design (Critical Process Parameters vs. Critical Quality Attributes)

Critical Process Operating Parameters	Critical Quality Attributes			
	Total Organic carbon (TOC)	Conductivity	Endotoxin	Bioburden
Operating Temperature				
Sanitization (Temperature, Periodicity, Duration)				
Pressure				
Flow				
Ozone				
Incoming Water Quality				

- Identify Critical Quality Attributes (CQA) and Critical Process Parameters (CPP)
- Establish correlations between CQA and CPP
- Basis for future monitoring and understanding of variability

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Validation Process Lifecycle:

Stage 1 – Design: Cold, Hot or Ambient Temperature

Cold, Hot or Ambient Selection Matrix Example			
Temperature	**Cold (2 to 8°C)**	**Hot ≈80°C**	**Ambient ≈22°C**
Storage	Low Microbial Count, Will Not Prevent Biofilm, Periodic Chemical Sanitization is Recommended	Low Microbial Count, Will Not Prevent Biofilm, Periodic Chemical Sanitization is Recommended	Hot Sanitization is Recommended at Least Once a Week
Recirculated Loop	Low Microbial Count, Will Not Prevent Biofilm, Periodic Chemical Sanitization is Recommended	Low Microbial Count, Will Not Prevent Biofilm, Periodic Chemical Sanitization is Recommended	Hot Sanitization is Recommended at Least once a Week
Points of Use	If Operation Requires Ambient Temperature Water Need a Heat Exchanger or Several Heat Exchangers at the Points of Use if Different Temperature Water is Needed	If Operation Requires Ambient Temperature Water Need a Heat Exchanger or Several Heat Exchangers at the Points of Use if Different Temperature Water is Needed. Advantageous if Hot Water is Needed.	Advantageous if Ambient Temperature Water is Used in Operation, Heat Exchanger or Multiple Heat Exchangers are Required if Hot Water Required for Operation

Water Systems

- Sanitization Terms/Definitions
- Lifecycle Approach to Validation (Design, PQ and Maintenance)
- Sanitization Methods

Water Sanitization Methods

- Heat (Water and Steam)
- Ozone
- Hydrogen Peroxide Solutions
- Chlorine
- Peracetic Acid
- Formaldehyde
- Glutaraldehyde

Water Sanitization Methods:

Few Points to Consider

Use Risk Management (Q9):

- Patient risk
- Product/Business risk
- Equipment risk

Water Sanitization Methods:

Few Points to Consider

- Must be effective short and long term
- Must fit for use
- Must not be additive
- Must be removed effectively, if a chemical
- Must not damage equipment (membranes, filters, surfaces, etc.)

Water Sanitization Methods

Heat:

- **Hot System: Continuous Sanitization (FDA Guidance for Inspection of High Purity Systems)**
- **Ambient/Cold System: Periodic Sanitizations using heat exchangers, heating to 85°C to 90°C, for 1 to 4 hours usually daily to weekly at the end of last shift, on off shift or end of the week.**
- **Understand Hot Sanitization Impact**
- **How often? What temperature? Duration?**

Water Sanitization Methods

Ozone:

- **Ozone (O_3), an unstable allotrope of oxygen, reacts rapidly with most hydrocarbons to effectively destroy biofilms, microbes, and organic residue material within these films.**
- **As the strongest commercially available oxidant, it has a disinfecting strength 3000 times that of chlorine. At appropriate concentrations, ozone injected in water destroys all microorganisms, viruses, oocysts, and pyrogens, and reduces Total Organic Carbon (TOC) by chemical oxidation.**
- **2 ppm Ozone levels for 30 minutes are shown to reduce bioburden by 6 log (10^6) or a 99.9999% reduction.**

Water Sanitization Methods

Ozone:

- **The results indicate that ≥ 5 minutes exposure to ozonated water at concentrations of 0.5 ppm, 2.0 ppm, or 5.0 ppm ozone is sufficient to produce surface sterilization.**

- **Ozone removal, instruments show detection at 1 ppb.**

U.S. Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit (PEL) of 0.1 µmol/mol (100 ppb)(29 CFR 1910.1000 table Z-1), calculated as an 8 hour time weighted average.

Erika Hanley-Onken and Nissan Cohen, The Efficacy of Ozonated Water in Biofilm Control in USP Purified Water Circulation and Storage, Pharmaceutical Engineering, ISPE, November/December 2013, Vol. 33, No 6

Water System Sanitization

- Sanitization Terms/Definitions
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- Other Industries using Pure and Ultrapure Water

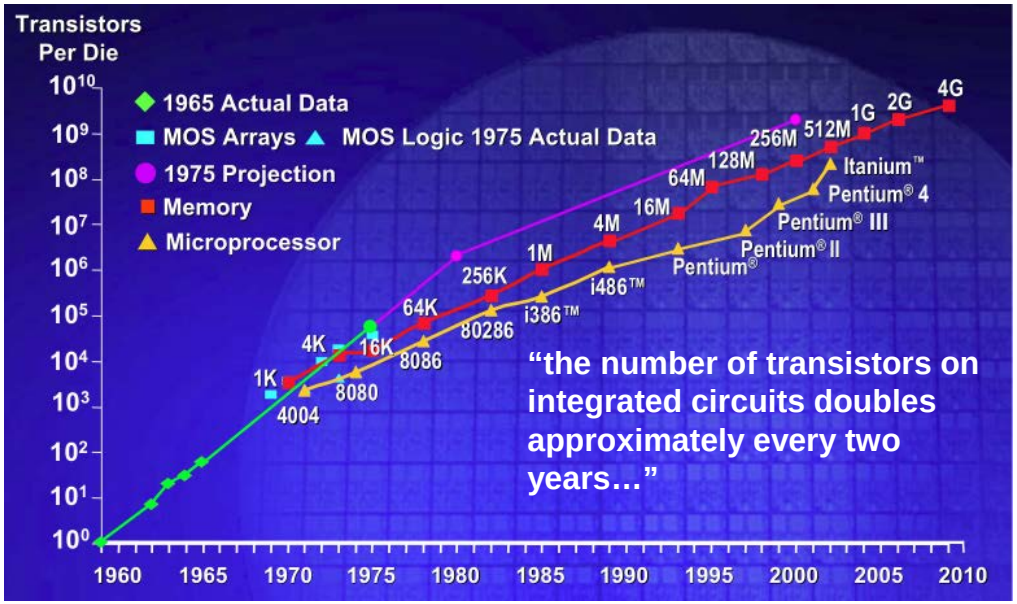
Water Systems

Moore's Law and UPW Technology in Semiconductor

It is the observation that, over the history of computing hardware, the number of transistors in a dense integrated circuit doubles approximately every two years. The law is named after Gordon E. Moore, co-founder of Intel Corporation, who described the trend in his 1965 paper.

Specifics of the Industry

- **Predictable Technology Cycles**
- **Fast paced industry**
- **Exponentially growing demand**
- **Time-to-market is key**
- **Uncompromised reliability and quality require rigorous risk management**



Vyacheslav (Slava) Libman, Ph.D. (Air Liquide Electronics U.S. LP, Balazs NanoAnalysis, Fremont, California) "Ultrapure Water – Quality and Technology to Support Advanced Industries' Needs" Interphex 2014 Presentation

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UPW Technology for Semiconductor Processing
20-30 Years Retrospective

- **Past**

- Quality – 18 MΩ-cm, 25 ppb TOC, Particles 1 µm
- Distribution - PVC/SS
- DI - Deionization by IX
- IX tank liners – rubber
- Quality Monitoring – Resistivity (focus)
- Low consumption ~ 100 gpm
- No/limited reclaim

- **Present**

- Quality – 1 ppb TOC, Particles 0.01 µm, metals 1 ppt
- UPW – IX/RO/EDI
- Distribution – PVDF/PFA
- IX tank liners – ETFE, ECTFE
- Quality Monitoring – TOC, boron, particles, SPC (focus)
- High consumption ~ 1000 gpm
- Extensive reclaim

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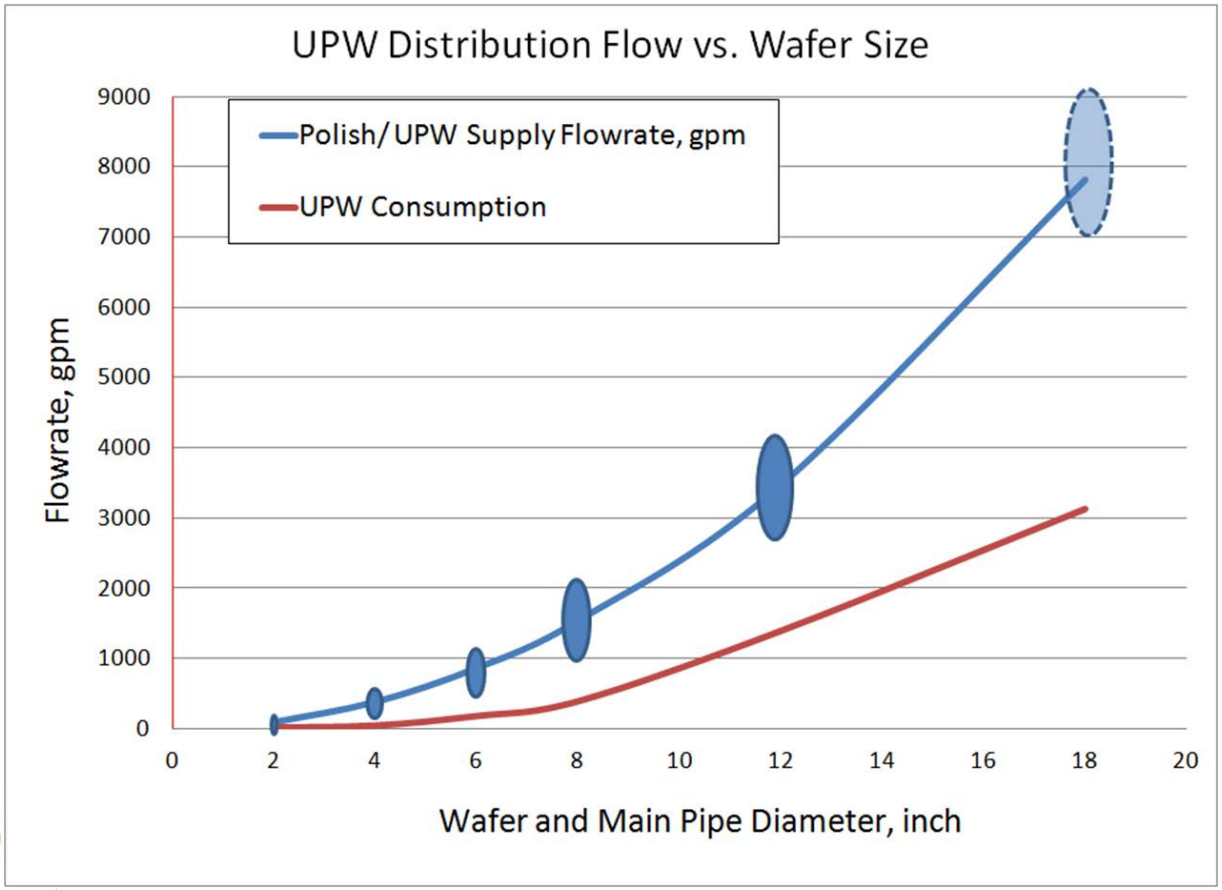
UPW Technology for Semiconductor Processing
Supply Flow Rate and Consumption vs. Pipe Diameter



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Water System Sanitization

SEMI and Pharma: Common and Different

- **Pharma**

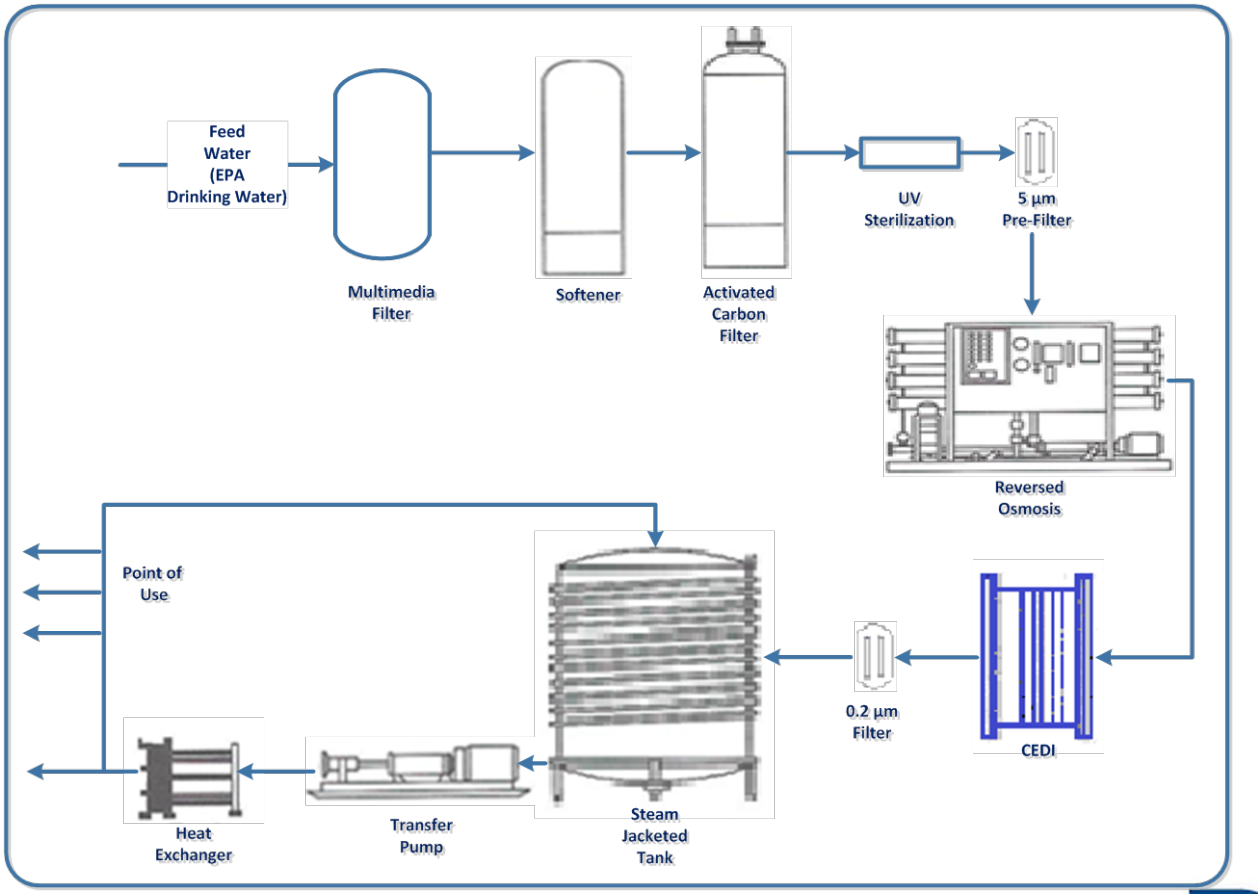
- **UPW Quality is Critical**
- **Tight Bacteria Control**
- **Quality Control is Driven by Regulation (FDA, EMA, etc.)**
- **Microbiological control via sterilization**
- **Material choice is driven by sterilization requirements**

- **Semiconductor**

- **UPW Quality is Critical**
- **Tighter Bacteria Spec**
- **Quality Control is Driven by Manufacturing Performance**
- **Microbiological control by high purity and tight filtration**
- **Material choice is driven by purity requirements**

Vyacheslav (Slava) Libman, Ph.D. (Air Liquide Electronics U.S. LP, Balazs NanoAnalysis, Fremont, California) "Ultrapure Water – Quality and Technology to Support Advanced Industries' Needs" Interphex 2014 Presentation

Conventional Pharma Water System

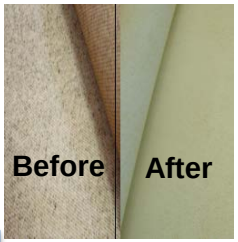


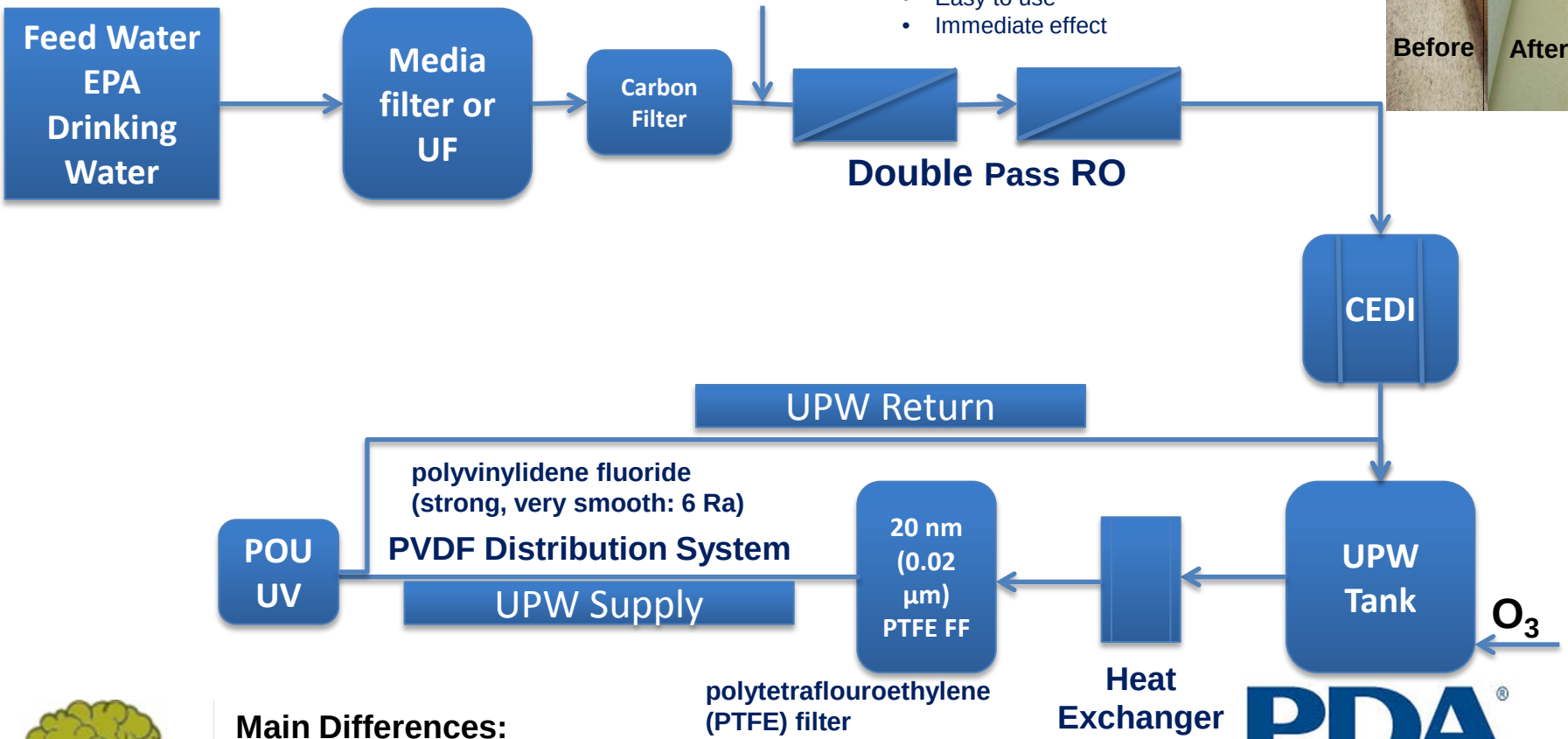
Water Systems - Semi

Semi Concept Pharma UPW

DOHS (Direct Osmosis High Salinity) Cleaning:

- Reversed flow backwashes the membrane
- **Osmotic pressure kills bacteria**
- No interruption
- Easy to use
- Immediate effect





Main Differences:

- Straight forward low COO pre-treatment
- **No need of heat sanitization and anti-rouging treatment Polish**
- Bio-control is ensured by low TOC, filtration, and ozonation – no downtime

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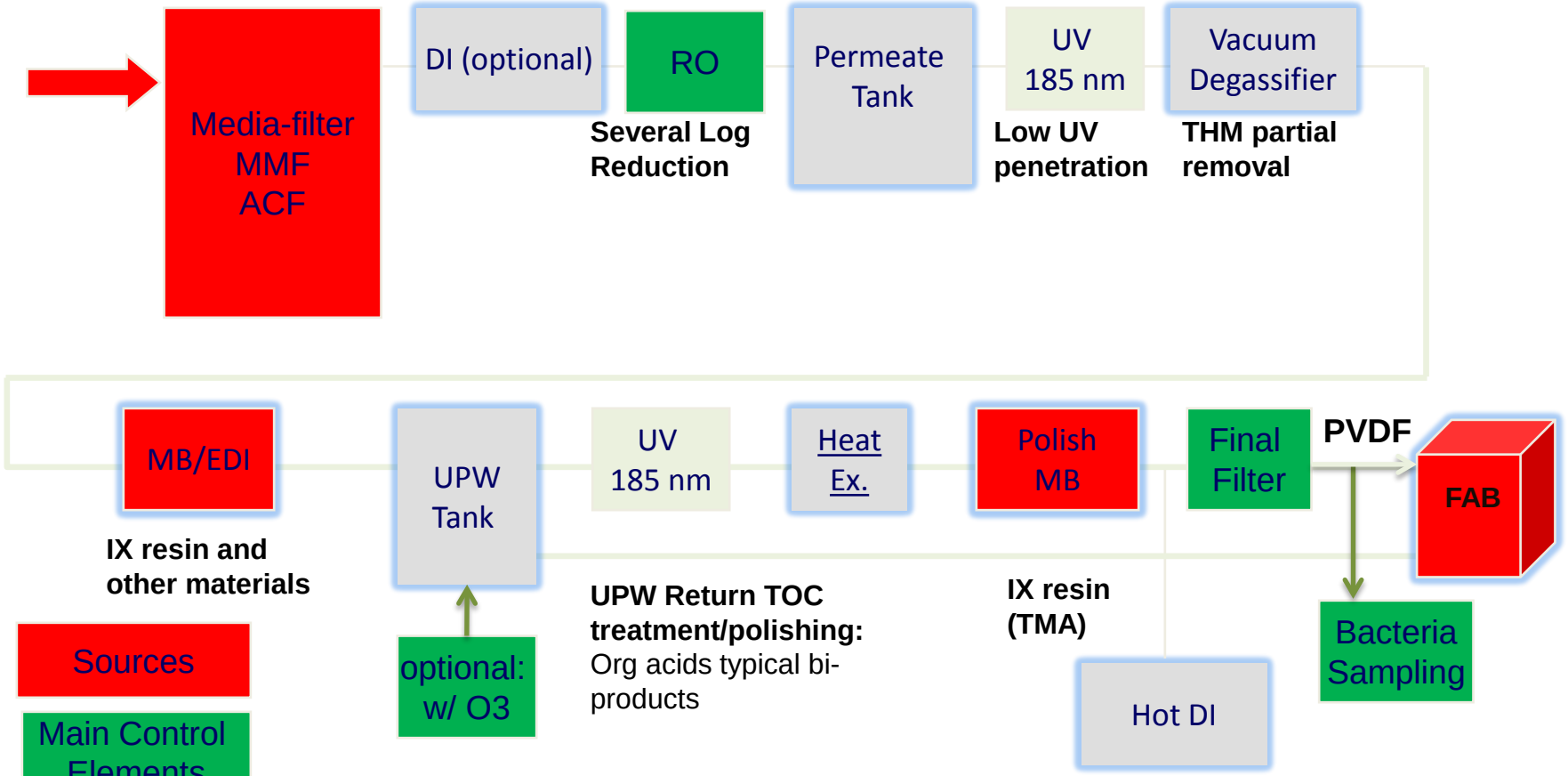

Philosophy:

1. no food – no bugs = tight TOC control + high purity piping
2. Tight filtration guarantees ND bacteria

Microbiological Control in Semiconductor

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Opportunities for Pharma

- Cost/effort reduction by changing operating/design philosophy
  - 2-pass RO - inexpensive TOC control
  - Limiting food is less expensive than “killing”
- Systems design for tighter quality control provide more reliable performance
- Particle removal provides effective microbiological control

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- Trending and Rapid Microbial Detection as a tool

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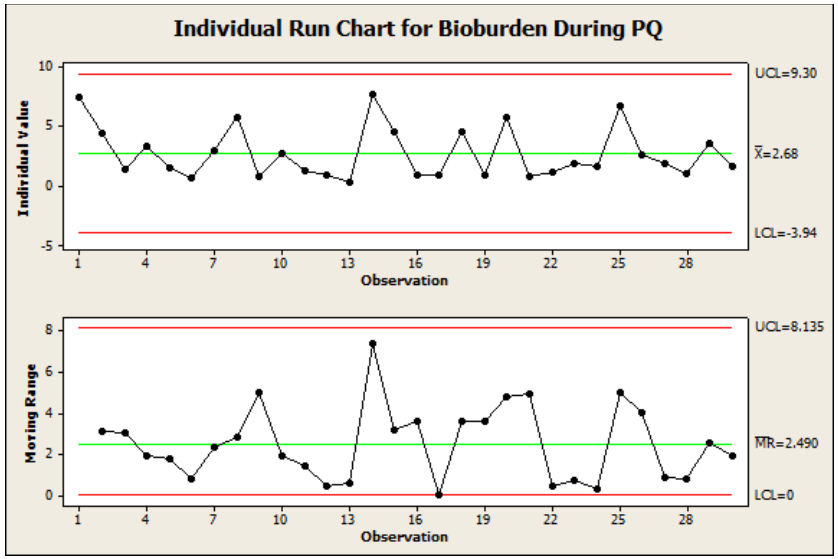
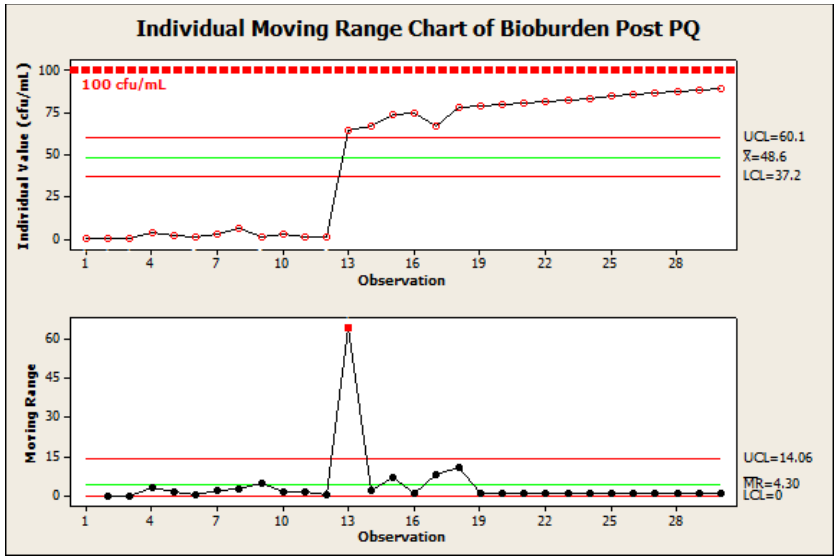
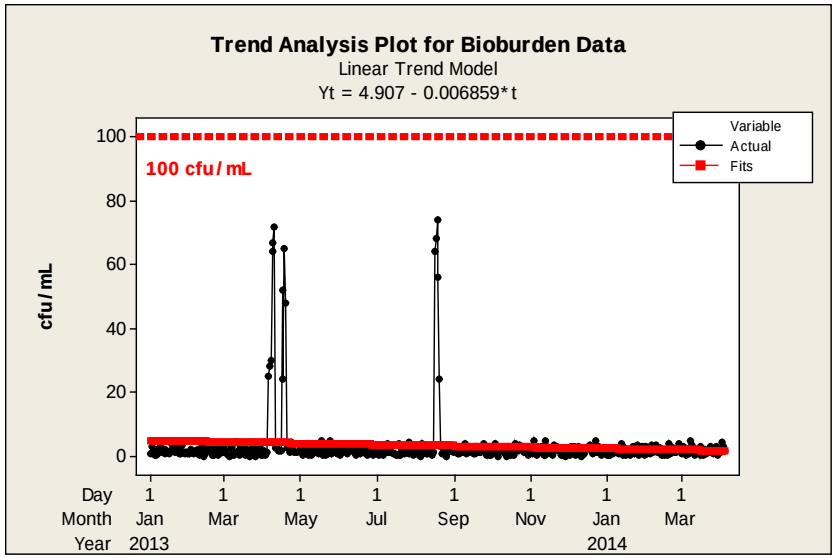
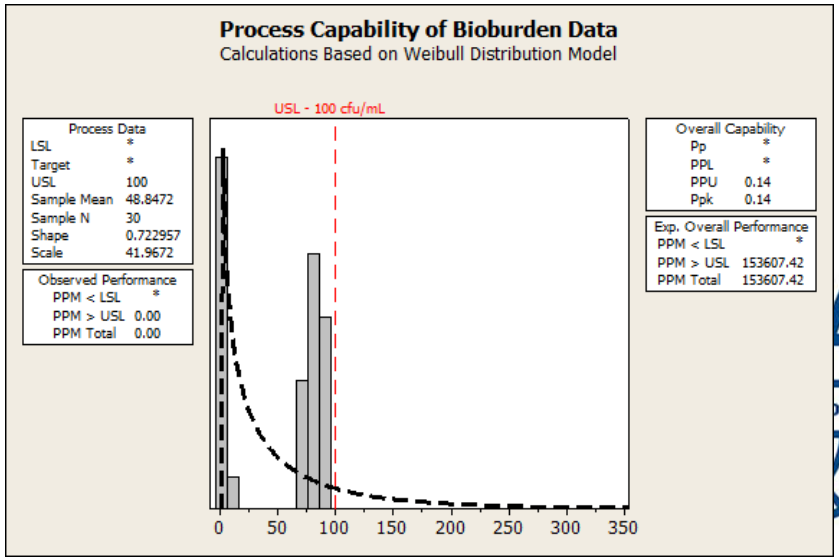
Water Systems

Trend! Trend! Trend!









Water System Sanitization

Data Collection, Evaluation and Trending Point to Consider: Rapid Bacterial Detection

Enablers:

- **USP General Chapter <1223>** ***Validation of Alternative Microbiological Methods***

- **PDA Technical Report 33 (Revised 2013) –** ***Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods***

Example:

Laser Induced Fluorescence (LIF), 40 year old technology.

Water System Sanitization

Conclusion:

- Design (Technology, Materials, Detection)
- Qualification
- Continued Verification/Trending

✓ Concentrate on prevention of bioburden growth and biofilm

Water Systems

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