ISPE Boston Area Chapter

Serving All of New England

Take the Guesswork out of your Water Purification System

Brian Hagopian, CPIP

Chemist and President

CLEAR WATER CONSULTING
EXPERTISE YOU CAN COUNT ON

brian@clear-water-consulting.com

(978) 888-3082

2 THINGS BEFORE WE START

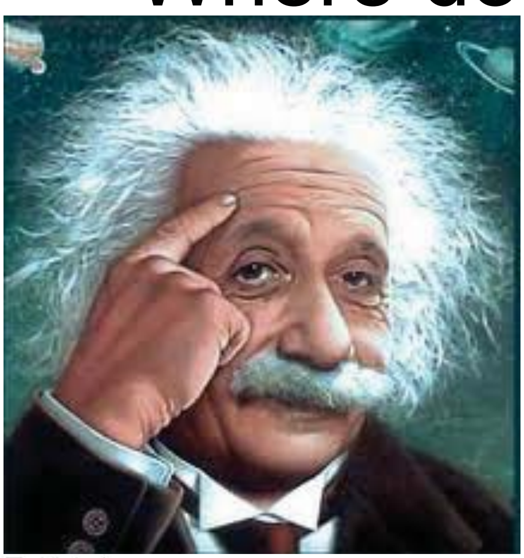
Everyone comes at water purification from a different perspective.

There will be time at the end to cover your questions

WATER PURIFICATION
DOESN'T HAVE TO BE COMPLICATED

But a lot of people like to make it seem "wicked" complicated

Where do we start?



Answer 3 Simple Questions

1. What is our starting point?
2. Where do we need to end up?
3. How do we get there?

Translating that to Water Purification

1. What is our starting point?
2. Where do we need to end up?
3. How do we get there?

1. What is our starting (incoming) water quality?
2. What is the final water quality that we need?
3. What treatment processes are available and what does each process do?
4. How can we get the water from the point where it is produced to the points where it is used (without picking up contamination along the way) ?

Question #1: What is our starting water quality?

To produce pharmaceutical grade water, the starting point is assumed to be potable water

What public information is available from the local municipality?

Contaminant Detected	Unit	MCL	MCLG	Level Detected	Range of Detection	Major Sources	Violation
Regulated Contaminants							
Nitrate	ppm	10	10	0.34	N/A	Runoff from fertilizer use; leaching from septic tanks, sewage; erosion from natural deposits.	NO
Flouride *(see below)				1.17	0.88 to 1.17	Water additive that promotes strong teeth.	NO
* State (MCL)	ppm	2	none				
* EPA (MCL)	ppm	4	none				
Sodium	ppm	none	none	34.3	N/A	Erosion of natural deposits; road salt, and water treatment chemicals.	NO
Chlorite	ppm	1.0	0.8	0.50	0.21 to 0.50	By-product of drinking water disinfection.	NO
Turbity (see note)	NTU	1.0	TT=100%	0.17	0.06 to 0.17	Soil runoff.	NO
TT= Lowest percentage of monthly samples <0.3 NTU **Note:** Turbidity is a measure of the cloudiness of the water. We monitor it because it is a good indicator of the effectiveness of our filtration system.							
Disinfectant residual	ppm	(MRDL) 4	(MRDLG) 4	.97	0.42 to .97	By-product of drinking water disinfection.	NO
Perchlorate	ppb	2.0	none	0.33	N/A	Rocket propellants, fireworks, munitions, flares, blasting agents. Aged water treatment disinfection chemicals	NO

What public information is available from the local municipality?

Contaminant Detected	Unit	MCL	MCLG	Level Detected	Range of Detection	Major Sources	Violation
Volatile Organic Contaminants							
(TTHM)	ppb	80	0	(50)	0.5 to 50.0	By-product of drinking water chlorination.	NO
[Total Trihalomethanes]				(Highest Runing Annual Average)			
Disinfection By-Product Contaminants							
(HAA)	ppb	60	0	(20.7)	0 to 20.7	By-product of drinking water chlorination.	NO
[Halo-acetic Acids]				(Highest Runing Annual Average)			
Unregulated Contaminants							
MTBE	ppb	none	none	N/D	N/D<0.05	Gasoline Additive.	NO
Chloroform	ppb	none	none	15.1	3.9 to 15.1	By-product of drinking water chlorination.	NO
Bromodichloromethane	ppb	none	none	7.3	2.2 to 7.3	By-product of drinking water chlorination.	NO
Chlorodibromomethane	ppb	none	none	2.5	N/D<0.6 to 2.5	By-product of drinking water chlorination.	NO
Sulfate	ppm	none	none	5.0	5.0	Mineral and nutrient	NO

Unregulated contaminants are those for which EPA has not established drinking water standards. The purpose of un-regulated contaminant monitoring is to assist EPA in determining their occurrence in drinking water and whether future regulation is warranted.

What public information is available from the local municipality?

Contaminant Detected	Unit	MCL	MCLG	Level Detected	Range of Detection	Major Sources	Violation
Radionuclides							
Gross Alpha	pCi/l	15	0	0.5 (+-1.1)	N/A	Erosion of natural deposits	NO
Radium 228	pCi/l	5	0	0.1 (+-0.6)	N/A	Erosion of natural deposits	NO
Contaminant	Unit	MCL	MCLG	Level Detected	Range of Detection	Major Sources	Violation
Lead	ppb	15	0	.001	0 of 50	Corrosion of household plumbing systems. Erosion of natural deposits.	NO
Copper	ppm	1.3	1.3	0.04	0 of 50	Corrosion of household plumbing systems. Erosion of natural deposits; Leaching from wood preservatives.	NO

Finished water pH ranged from 7.5 to 8.3

Here is a list of the contaminants that we really need to know about in our source water supply

Ammonia
Bacteria
Barium
Bicarbonate Alkalinity
Boron
Calcium
Carbon Dioxide
Carbonate Alkalinity
Chloride
Chlorine/chloramine
Fluoride
Hardness
Iron
Magnesium
Manganese
Nitrate
Particle Content
Potassium
Silica
Silt Density Index
Sodium
Strontium
Sulfate
Total Organic Carbon

Let's understand classes of contaminants or impurities are in the water to start with

- **Particles or Suspended Solids**
- **Dissolved Solids**
  - **Ionized**
  - **Non-ionized**
- **Colloidal Materials**
- **Dissolved Gases**
- **Bacteria and other living organisms**

All Contaminants / Impurities have the potential to introduce variability !!

Particles or Suspended Solids

- These are materials that do not dissolve in water
- They can be any shape
- They are generally thought of as hard, spherical particles
- Moving water has the ability to keep more particles from settling out
- Larger and more dense particles will settle out by themselves
- Smaller particles may never settle

Dissolved solids, Ionized

- These materials will dissolve in water
- Once dissolved, they split into positive and negative ions.
  - Adds positive and negative charges to a solution in equal amounts
  - Solution remains electrically neutral
- The ionized solids content changes how much electricity the water can conduct
- Direct relationship between the abundance of ions and the conductivity of the water

Dissolved solids, Non-Ionized

These materials also dissolve in water

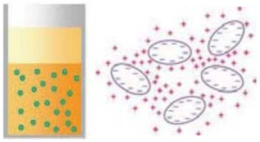
Once dissolved, they do not form ions in solution, so they don't add any charge to the solution

No change in the conductivity of the solution

Cannot measure abundance by measuring conductivity

Presence is more difficult to detect

Colloidal Materials or Suspensions



These materials are organic and contain carbon

Colloidal materials are tiny in size, but relatively large in molecular weight (10,000-5,000,000 MW)

All colloidal materials have a slightly negative charge

Somewhere between suspended and dissolved

- Too small to settle by themselves
- Held in solution by size and charge repulsion

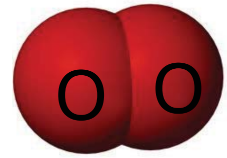
Almost impossible to detect presence by conductivity

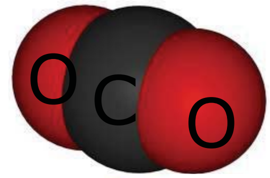
Measure abundance by silt density index

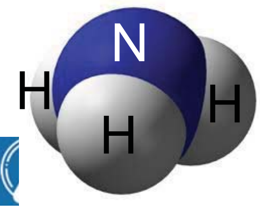
Can quickly clog and gum up purification processes

Dissolved Gases

- Nitrogen, oxygen, carbon dioxide, ammonia
  - Not removed by most purification processes
  - More dissolved gases in solution at lower temperatures (opposite of dissolved solids)
  - Least understood and least studied contaminant
  - Carbon dioxide is troublesome because it adds conductivity when it dissolves into solution
  - Ammonia can be troublesome to some purification processes in waters treated with chloramine
  - Measured in clean steam as non condensible gases

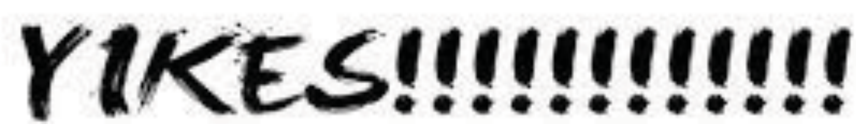




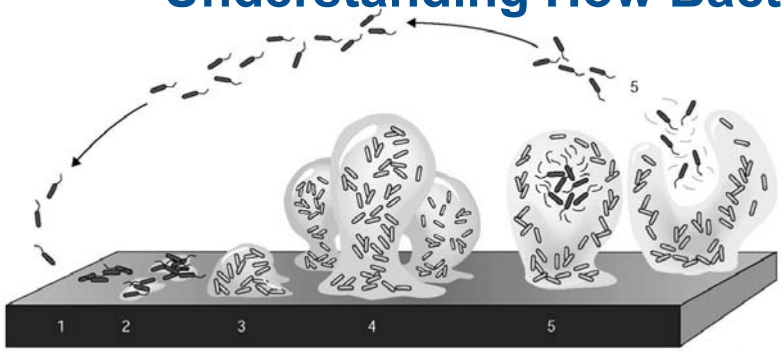


Bacteria and other living organisms

- Not uniformly distributed in a water system
  - Exist in equilibrium with their environment
  - More food = more bacteria
  - Less than 1% of bacteria in a system is free floating and detectable
  - Bacteria is a big concern because bacteria competes for nutrients with cells we're growing
  - Bacteria can replicate every 30 minutes
    - Mammalian cells replicate every 24 hours
    - That's a ratio of 2800 trillion to 1
  - Vast majority is found in biofilm which we can't detect



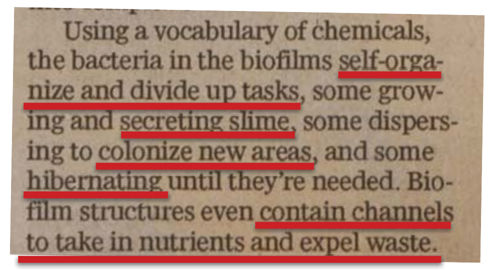
Understanding How Bacteria Work



Attach **Colonize** **Biofilm Development and Growth** **Send out scouts**

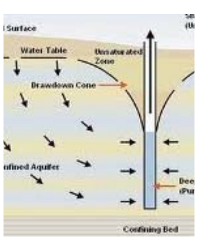
Not uniformly distributed like other contaminants

Regular sterilizations or nutrient deprivation for best control


Using a vocabulary of chemicals, the bacteria in the biofilms self-organize and divide up tasks, some growing and secreting slime, some dispersing to colonize new areas, and some hibernating until they're needed. Biofilm structures even contain channels to take in nutrients and expel waste.

Boston Globe, June 29, 2016

Where does our water come from? How do it properties vary?



Well Water

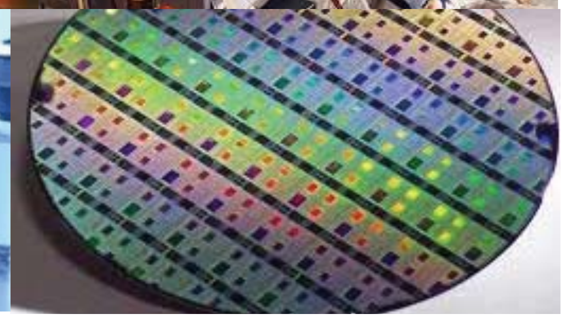
Low Suspended Solids
High Dissolved Salts
Low Colloidal Content
Some Dissolved Gases

Surface Water

High Suspended Solids
Low Dissolved Salts
High Colloidal Content
High Dissolved Gases

Question #2 What is the end use of the water ??



What water quality do we really need ?

It depends !

Where are we in the product's life cycle ?

Research

Pilot Scale

Clinical Trials

Drug Discovery

Full Scale Manufacturing

Labs use CAP/CLSI, ISO or ASTM specifications for purity

Characteristic	CAP and CLSI Type		
	I	II	III
Specific conductance, µmhos/cm	0.1	0.2	0.5
Specific resistance, MW · cm	10	2.0	1.0
Silicate, µg/L	50	100	1,000
Bacterial growth, cfu/mL	<10	10	—

Labs use CAP/CLSI, ISO or ASTM specifications for purity

From:
ISPE Baseline Guide for Water and Steam Systems, Volume 4, Third Edition

Organization / Reference	ISO3696 (1995) Water for Analytical Laboratory Use		
Water Grade or Type	Grade 1	Grade 2	Grade 3
Specified Source and Purification Approaches	Grade 2 Source; RO+0.2um Filt, or DI+0.2um Filt, or Re-Dist (in glass)	Multiple-Dist or DI or RO+Dist	Single-Dist or DI or RO
pH value at 25°C (inclusive range)	*	*	5.0 to 7.5
Conductivity µS/cm @25°C, max	0.1	1.0	5.0
Temperature Compensated Conductivity Measurement?	YES	YES	YES
Oxidizable matter O_2 content mg/L, max	*	0.08	0.4
Absorbance at 254 nm and 1 cm optical path length, absorbance units, max	0.001	0.01	*
Residue after evaporation on heating at 110°C, mg/Kg, max	*	1	2
Silica (as SiO_2) mg/L, max	0.01	0.02	*
Particulate and Colloids	Implied limitation by 0.2 µm filter	*	*

Labs use CAP/CLSI, ISO or ASTM specifications for purity

From:
ISPE Baseline Guide for Water and Steam Systems, Volume 4, Third Edition

Organization / Reference	ASTM D1193 (2018)[1] Standard Specification for Reagent Water				ASTM D5196 (2013)
Water Grade or Type	Type I	Type II	Type III	Type IV	Standard Guide for Bio-Applications Grade Water
Specified Source and Purification Approaches	Distillation or equiv + mixed bed DI + 0.2µm Filtration	Distillation	Distillation, DI, EDI, and/or RO + 0.45 µm Filt	Distillation, DI, EDI, and/or RO	Drinking Water Source; Suitable process(es)
pH value at 25°C (inclusive range)	*	*	*	5.0 to 8.0	*
Conductivity µS/cm @25°C, max	0.0555	1.0	0.25	5.0	*
Resistivity MΩ-cm @ 25C, min	18	1.0	4.0	0.2	18.2 ± 1 [2]
Temperature Compensated Conductivity Measurement?	YES	YES	YES	YES	YES
TOC (as C), max	50 µg/L (50 ppb)	50 µg/L (50 ppb)	200 µg/L (200 ppb)	*	20 µg/L (20 ppb)
Total Silica µg/L, max	3	3	500	*	*
Sodium µg/L, max	1	5	10	50	*
Chloride µg/L, max	1	5	10	50	*
Heterotrophic Bacteria Count cfu/mL, max	Type A: 0.01 (10cfu/1000mL) Type B: 0.1 (10cfu/100mL) Type C: 10 (100cfu/10mL)	Type A: 0.01 (10cfu/1000mL) Type B: 0.1 (10cfu/100mL) Type C: 10 (100cfu/10mL)	Type A: 0.01 (10cfu/1000mL) Type B: 0.1 (10cfu/100mL) Type C: 10 (100cfu/10mL)	Type A: 0.01 (10cfu/1000mL) Type B: 0.1 (10cfu/100mL) Type C: 10 (100cfu/10mL)	1 (100cfu/100mL)
Bacterial Endotoxins EU/mL or IU/mL	Type A: 0.03 Type B: 0.25 Type C: *	Type A: 0.03 Type B: 0.25 Type C: *	Type A: 0.03 Type B: 0.25 Type C: *	Type A: 0.03 Type B: 0.25 Type C: *	0.01
Particulate and Colloids	limitation by 0.2 µm filter	*	limitation by 0.45 µm filter	*	*
Nucleases, Proteases	*	*	*	*	Limited as needed for certain applications

Footnotes:
* Not Specified, Not Required, Not Applicable, or No Limit
(1) Water may be produced with alternate technologies if specifications are met and water is appropriate for the application.

Dialysis has their own requirements

Table 11-13 AAMI/ANSI Water Quality Standards	
Contaminant	Suggested Maximum Level, mg/L
Calcium	2.0
Magnesium	4.0
Sodium	70
Potassium	8.0
Fluoride	0.2
Free Chlorine	0.5
Chloramines	0.1
Nitrate (N)	2.0
Sulfate	100
Antimony	0.006
Copper, barium, zinc	0.1 each
Arsenic, lead, silver	0.005 each
Beryllium	0.0004
Chromium	0.014
Cadmium	0.001
Selenium	0.09
Aluminum	0.01
Mercury	0.0002
Thallium	0.002
Bacteria	<100 (cfu/mL)
Endotoxin	0.25 EU/ml
Note: "meq/L" = milliequivalent/liter	

Pharmaceutical Water Quality

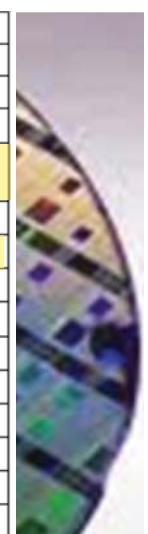
PARAMETER	USP PURIFIED	USP WFI
Total Organic Carbon (ppb)	500	500
Conductivity	<1.3 @ 25°C	<1.3@25°C
Bacteria	None given, but recommended to be 100/ml	None given, but recommended to be 10/100 ml
Endotoxins	----	<0.25 EU/ml

Hey, Why Is Injectable Grade Water Allowed To Have Bacteria ??

Microelectronics requirements are unbelievable !

Table 11-14 ASTM D5127-13 / SEMI F63-0701 Electronics Grade Water Standard

Parameter	Grade			
	E-1	E-2	E-3	E-4
Resistivity at 25°C	18.1	16.5	12	0.5
Total Organic Carbon, TOC, max. (μg/L)	5	50	300	1,000
SiO_2 (total), max. (μg/L)	5	10	50	1,000
Viable bacteria, max.	5/100 mL	10/100 mL	50/100 mL	100/100 mL
Copper, max. (μg/L)	0.05	1	2	500
Zinc, max. (μg/L)	0.05	1	5	500
Nickel, max (μg/L)	0.05	1	2	500
Sodium, max. (μg/L)	0.05	1	5	1,000
Potassium, max. (μg/L)	0.005	2	5	500
Chloride, max. (μg/L)	0.1	1	10	1,000
Nitrate, max. (μg/L)	0.1	1	5	500
Phosphate, max. (μg/L)	0.1	1	5	500
Sulfate, max. (μg/L)	0.1	1	5	500



When Type E-1 is not good enough

Table 11-14 ASTM D5127-13 / SEMI F63-0701 Electronics Grade Water Standard

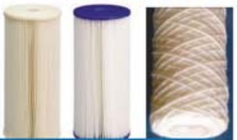
Parameter	Grade						
	E-1	E-1.1	E-1.2	E-1.3	E-2	E-3	E-4
Resistivity at 25°C	18.1	18.2	18.2	18.2	16.5	12	0.5
Total Organic Carbon, TOC, max. (µg/L)	5	2	1	1	50	300	1,000
SiO_2 (total), max. (µg/L)	5	3	1	0.5	10	50	1,000
Viable bacteria, max.	5/100 mL	3/100 ml	1/100 ml	1/10 L	10/100 mL	50/100 mL	100/100 mL
Copper, max. (µg/L)	0.05	0.02	0.002	0.0001	1	2	500
Zinc, max. (µg/L)	0.05	0.02	0.002	0.001	1	5	500
Nickel, max (µg/L)	0.05	0.02	0.002	0.0001	1	2	500
Sodium, max. (µg/L)	0.05	0.02	0.005	0.001	1	5	1,000
Potassium, max. (µg/L)	0.005	0.02	0.005	0.001	2	5	500
Chloride, max. (µg/L)	0.1	0.05	0.02	0.005	1	10	1,000
Nitrate, max. (µg/L)	0.1	0.05	0.02	0.005	1	5	500
Phosphate, max. (µg/L)	0.1	0.05	0.02	0.005	1	5	500
Sulfate, max. (µg/L)	0.1	0.05	0.02	0.005	1	5	500

Question #3
What water purification processes are available?
What does each one actually DO?

- Particles or Suspended Solids
- Dissolved Solids
  - Ionized
  - Non-ionized
- Colloidal Materials
- Dissolved Gases
- Bacteria and other living organisms

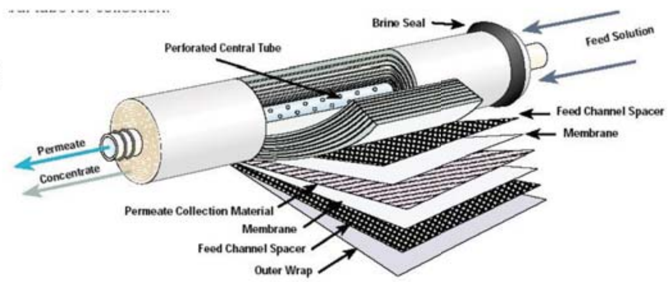
Suspended Solids Removal

Particle filters remove contaminants based on their size



Nominally rated filters
80-95% removal efficiency
Sizes down to ~ 1 micron
Compression or flat gasket seals

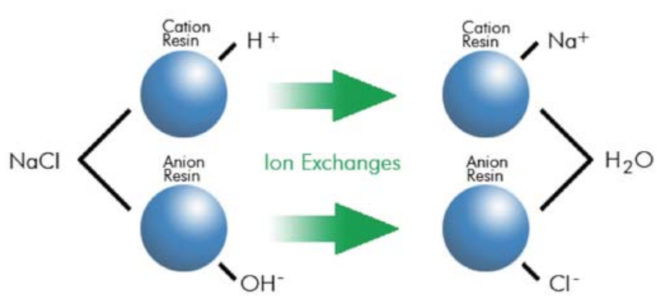
Most are absolute rated filters
95-99.9999% removal efficiency
Sterile filtration
0.1 to 0.8 micron size
O-ring seals primarily



Ultrafiltration
~99% removal efficiency
5,000-500,000 MWCO
Tangential Flow
A reject stream

Reverse Osmosis
90-99% removal efficiency
200-500 MWCO

Ion exchange removes contaminants based on their electrical or ionic charge in solution

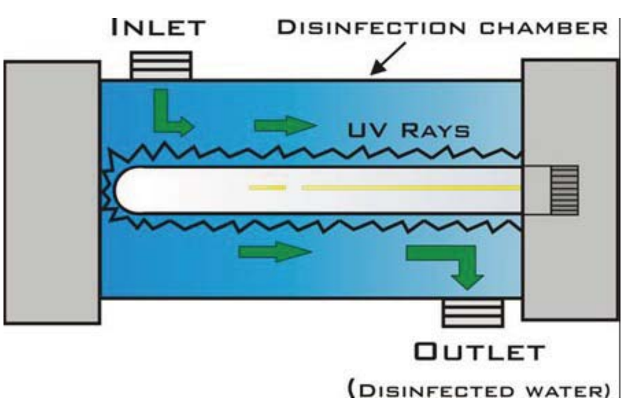


Carbon filters remove small (below 1,000 MW) non polar molecules

Remove disinfectants from drinking water

Protects chlorine sensitive reverse osmosis membranes

Ultraviolet units come in two basic flavors

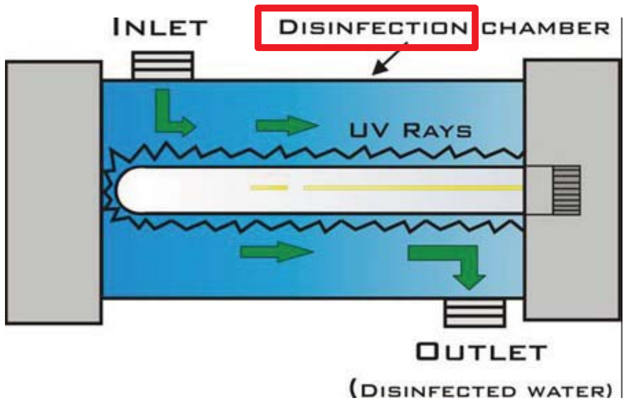


Single wavelength units (254 nm) for bacterial control

Dual wavelength units (185 & 254 nm) for organics (TOC) and bacteria control

Dual wavelength units (185 & 254 nm) increase the conductivity of the water, so location is extremely important

Commonly Misused Words



Sanitize
10^3 reduction

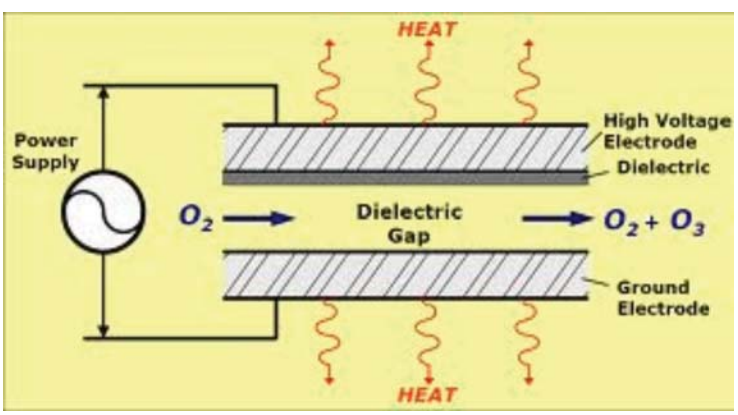
Disinfect
10^5 reduction

Sterilize
10^6 reduction

These words are used almost interchangeably by equipment manufacturers

But these words mean very different things

Ozone Generators are becoming more popular



- **Oxidizes organics**
- **Kills bacteria**
- **Consumes biofilm**
- **Ozone is NOT considered an added substance**

Mis-application and misuse of ozone technology has led to compatibility and other under and over dosing problems, making many users reluctant

Distillation is the only water treatment process that removes the water from the contaminants

Considered the gold standard for producing Water-For-Injection (WFI) grade water

Dissolved gases and some chemicals can carry over into distillate (product water)

Sequencing of Unit Processes
Varies between equipment manufacturers

- **Remove Particles first**
  - **Suspended Solids**
  - **Colloidal materials**
- **Remove dissolved ions next**
- **Remove trace materials**
  - **Ions, organics, particles**
  - **System generated impurities**
- **Remove bacteria throughout but definitely as one of the last steps**

Question #4 - How to get the water from the mechanical room to points of use without its quality degrading?

Design of Pharmaceutical Distribution Piping Systems

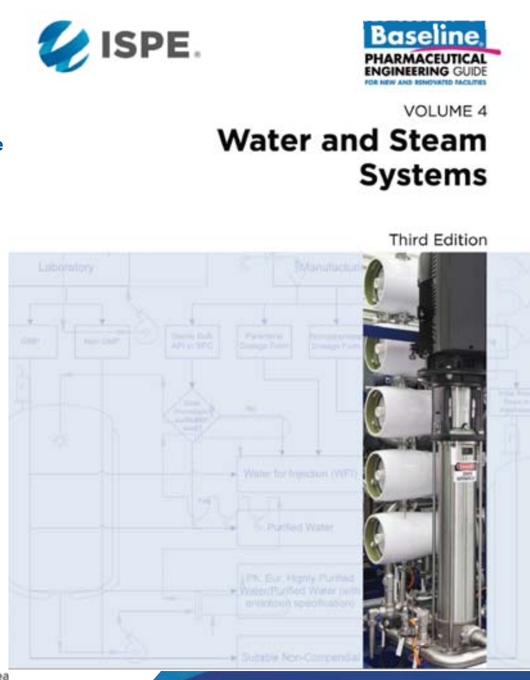
- **Design to 5 feet per second (FPS) velocity**
- **Design to 3 FPS in return with use points active**
- **No dead legs (2D to 6D rule)**
- **WFI water almost always piped in stainless steel**
- **Purified water can be piped in SS, PP, PVDF**
- **Distribution piping slopes for drainability**
- **The pumping system and the size and length of the piping system must be considered together**

Where can we get a more complete discussion on pharmaceutical water and steam systems ???

Over 250 Pages of Guidance

Just Updated in 2019

Members of the Boston Chapter are underlined




ISPE Baseline® Guide:
Water and Steam Systems

Acknowledgements

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Nissan Cohen	Biopharmaceutical Water Doc	USA
Brian Pochini, CPIP	Sanofi	USA
Gary Zoccolante	Plymouth Rock Water Consultants	USA

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Core Team

The following individuals took lead roles in the preparation of this Guide:

Jamie Evans	GC Biotherapeutics	Canada
Michelle Gonzalez	Amgen Inc. (retired)	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Joseph Manfredi	GMP Systems, Inc.	USA
Brian McClellan	Aqua-Chem Inc.	USA
Chris Peterson	AbbVie	USA
T.C. Soli, PhD	Soli Pharma Solutions Inc.	USA
Philip E. Sumner	Pfizer Global Engineering	USA
Steve Wisniewski	CAI	USA

Other Contributors

The Team wish to thank the following individuals for their significant contribution to the document.

Robert M. Augustine	Eli Lilly and Company	USA
Andrew Baird	Jacobs Engineering	USA
Anthony Bevilacqua, PhD	Mettler-Toledo Thornton Inc.	USA
Robert C. Coleman	IHL Consulting Group, Inc.	USA
Martin Emery	AveXis	USA
Diana Fischer	Bausch & Lomb, Inc.	USA
W. Roderick Freeman	Kite Pharma	USA
Ariel Kehati	Omrix, Johnson & Johnson	Israel
Shlomo Sackstein	Biopuremax Ltd.	Israel
Ian Shanahan	MECO Ireland Ltd.	Ireland
Roland Thoendel	Takeda	Austria
Anders Widov	Wiphe AB	Sweden
John Walker	VWS/Elga	United Kingdom
Paul Whitehead, PhD	VWS/Elga (retired)	United Kingdom

Where can we get a more complete discussion of all of these sampling related issues???

120 Pages of Guidance

An Industry Benchmark

Members of the Boston Chapter are Underlined

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GOOD PRACTICE GUIDE:

Sampling for Pharmaceutical Water, Steam, and Process Gases

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The authors and contributors to this Good Practice Guide are listed below, but the following people deserve special recognition for their extensive involvement in developing and vetting the content for this guide: Joseph Manfredi and Teri C. Soli, PhD for the Water Chapter, Brian Pochini, CPIP for the Steam Chapter, and Ruby Ochoa for the Process Gas Chapter.

Chair		
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Chapter 1: Introduction		
Brian Hagopian, CPIP (Chapter Lead)	Clear Water Consulting, Inc.	USA
Chapter 2: Pharmaceutical Water		
Michael Baumstein	Pfizer, Inc.	USA
Rod Freeman	Beckman Coulter, Inc.	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Jeppe Kjems	CU Engineering	Denmark
Joseph Manfredi (Chapter Lead)	GMP Systems, Inc.	USA
Aravind Palinvelu	Roche	Singapore
Teri C. Soli, PhD	Soli Pharma Solutions, Inc.	USA
Michael Tomaselli	Filters, Water, and Instrumentation, Inc.	USA
Chapter 3: Pharmaceutical Steam		
Michael Baumstein	Pfizer, Inc.	USA
Andre Gill, PE	Andre Gill Engineering	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Joseph Manfredi	GMP Systems, Inc.	USA
Brian Pochini, CPIP (Chapter Lead)	Sanofi	USA
Teri C. Soli, PhD	Soli Pharma Solutions, Inc.	USA
Philip Sumner, PE	Pfizer, Inc.	USA
Nancy Tomoney	West-Ward Pharmaceuticals	USA
Anders Widov	Wiphe AB	Sweden
Chapter 4: Process Gases		
Michael Baumstein	Pfizer, Inc.	USA
Brian Hagopian, CPIP	Clear Water Consulting, Inc.	USA
Ruby Ochoa	Trace Analytics, LLC	USA
Aravind Palinvelu	Roche	Singapore
Michael Vestermark	Novo Nordisk Biopharm	Denmark
Peter Vishton (Chapter Lead)	Independent Consultant	USA
Glossary		
Michelle Gonzalez, PE	Amgen, Inc. (retired)	USA

THANK YOU

Brian Hagopian, CPIP

CLEAR WATER
CONSULTING
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brian@clear-water-consulting.com

(978) 888-3082