



# ISO 22519

## Purified Water and Water for Injection Pretreatment and Production Systems

*PDA Israel  
New Developments in Water Systems  
Tel Aviv, May 2019*

*Shlomo Sackstein  
Biopuremax - CEO*



Biopuremax has over 20 years of experience in the design, supply, installation, validation and operation of high quality Biopharmaceutical water systems.

Biopuremax specialty is water systems - Purified Water (PW) and Water-for-Injection (WFI) systems, with cutting edge water production technologies.

Developed the revolutionary Biopuremax process of media and chemical free RO pretreatment.

## **Purified Water and Water for Injection pretreatment and production systems**

- Introduction of the standard: what is the aim, whom is the standard for
- Scope: design, materials selection, construction and operation of PW and WFI pretreatment and membrane based production
- Selecting materials, methods and system components
- System design, selection table based on feed water
- Operation: production, idling when storage tank full, sanitization

## **Compilation of the standard**

- ISO is an independent, non-governmental organization made up of members from the national standards bodies of 162 countries.
- Active participation in the meetings: Austria, India, Israel, Japan, Korea Republic, Netherlands
- Member bodies voting: Austria, Bahrain, Canada, China, Egypt, Ethiopia, Finland, France, India, Iran, Ireland, Israel, Japan, Kenya, Korea, Mongolia, Netherlands, Portugal, Rwanda, Spain, United States, Vietnam

## **Compilation of the standard**

- ISO/Technical Committee 282/Work Group 03
- Convenor (Chairman): Shlomo Sackstein, Standards Institute of Israel (SII)
- [shlomo@biopuremax.com](mailto:shlomo@biopuremax.com)
- Secretariat: JISC, Support Secretariat: SII
- ISO Technical Program Manager (TPM): YU Limei
- ISO Editorial Program Manager (EPM): Hamaoka Ritsu

Stage	Description	Target date	Started	Status
10.00	Proposal for new project registered		2017-02-21	CLOSED
10.20	New project ballot initiated	2017-02-22	2017-02-22	CLOSED
10.60	Close of voting	2017-05-17	2017-05-19	CLOSED
10.99	New project approved		2017-06-01	CLOSED
30.00	Committee draft (CD) registered		2018-01-29	CLOSED
30.20	CD study/ballot initiated		2018-01-29	CLOSED
30.60	Close of voting/comment period		2018-03-23	CLOSED
30.99	CD approved for registration as DIS		2018-05-31	CLOSED
40.00	DIS registered		2018-06-13	CLOSED
40.20	DIS ballot initiated	2018-08-15	2018-08-15	CLOSED
40.60	Close of voting	2018-11-08	2018-11-08	CLOSED
40.99	Full report circulated: DIS approved for registration as FDIS		2019-01-22	CLOSED
50.00	Final text received or FDIS registered for formal approval	2019-02-28	2019-02-05	CLOSED
50.20	Proof sent to Secretariat or FDIS ballot initiated: 2 months	2019-03-08	2019-03-08	CURRENT
50.60	Close of voting -- Proof returned by Secretariat	2019-05-03		AWAITING
60.60	International Standard published			

FINAL  
DRAFT

INTERNATIONAL  
STANDARD

ISO/FDIS  
22519

ISO/TC 282

Secretariat: JISC

Voting begins on:  
2019-03-08

Voting terminates on:  
2019-05-03

---

**Purified water and water for injection  
pretreatment and production systems**

RECIPIENTS OF THIS DRAFT ARE INVITED TO  
SUBMIT, WITH THEIR COMMENTS, NOTIFICATION  
OF ANY RELEVANT PATENT RIGHTS OF WHICH  
THEY ARE AWARE AND TO PROVIDE SUPPORTING  
DOCUMENTATION.

IN ADDITION TO THEIR EVALUATION AS  
BEING ACCEPTABLE FOR INDUSTRIAL, TECHNO-  
LOGICAL, COMMERCIAL AND USER PURPOSES,  
DRAFT INTERNATIONAL STANDARDS MAY ON  
OCCASION HAVE TO BE CONSIDERED IN THE  
LIGHT OF THEIR POTENTIAL TO BECOME STAND-  
ARDS TO WHICH REFERENCE MAY BE MADE IN  
NATIONAL REGULATIONS.



---

Reference number  
ISO/FDIS 22519:2019(E)

© ISO 2019

### **What is the aim, whom is the standard for?**

- The only ISO standard to cover PW and WFI production
- The standard is to provide a benchmark that can be used by the industries that use PW and/or WFI
- For national governments, state authorities and regulatory bodies to use the standard to evaluate the design and operation of new or existing PW/WFI systems.



## **In Scope**

- PW and WFI Generation design/configuration
- Materials selection
- System construction
- Operation of Purified Water (PW) and Water for Injection (WFI) pretreatment and membrane based production systems

### Not in Scope

- PW and WFI specifications, these are covered by Pharmacopeias (EP, USP, JP)
- Selection of the appropriate compendial water definition, e.g. PW, WFI or other
- Thermal process for production of PW or WFI
- Storage and distribution
- Pure steam generation and distribution
- Laboratory water
- Validation

## **Recommended System Components**

- Pretreatment Ultra Filtration - membrane process for removal of suspended solids, bacteria, TOC. Operation with reject and regular back wash.
- Multi Media Filters – removal of coarse particulates. Operation with back wash.
- Chlorination – Hypochlorite dosage in range of 0.2 ppm - 0.5 ppm for control of incoming and system bacteria levels.
- Softeners – replacement of magnesium-calcium with sodium to reduce scale precipitation. Needs down stream resin trap.

### **Recommended System Components**

- Anti Scalant – dosage of chemicals to RO inlet to defer scale precipitation. Operation with permeate removal validation.
- Electrolytic Scale Reduction (ESR)– resin free electrolytic precipitation of scale to stop hardness precipitation. Non sacrificial anode and cathode.
- Degassing CO<sub>2</sub> contact membrane (degasser) – water contact membrane for reduction of CO<sub>2</sub> gas in water.
- Ultra Violet (UV) Lamp – irradiation of the water for dechlorination.

## **Recommended System Components**

- Single/double Pass Reverse Osmosis – membrane based process for reduction of: ions, TOC, bacteria and endotoxin. Always operated with a reject stream.
- Continuous Electro De-Ionization (CDI/EDI/CEDI) – for reduction of water ion levels downstream of Reverse Osmosis (RO) using electrically regenerated resin.
- Polishing Ultra filtration - Is a membrane based process using molecular weight cut off for reduction of endotoxin, TOC and bacteria post CDI/EDI/CEDI.

## **Materials and Construction: Piping**

- All components in the PW/WFI system, not in contact with product, shall be manufactured from: Stainless Steel (SS) 316/316L.
- All PW/WFI contact parts to be fabricated only from SS 316L, including: piping/tubing, tanks, pumps, heat exchangers, valves, instruments and other accessories.

## **Materials and Construction: Piping**

- SS tubing dimensions per 3-A Sanitary Standard Inc, ASME BPE, Japanese Industrial Standards division G (JIS-G), Japanese Industrial Standards (JIS) 3459, ISO 1127 and EN 13057 or other relevant piping standard.
- Tubing may be seamless or welded with seam.
- Piping and fittings must meet system pressure requirements, specifically for the high pressure RO feed and concentrate.
- Welding shall be performed with TIG/GTAW, >99.97%, argon shield gas to be used.

### **Materials and Construction: Non Final Product Contact Piping**

- SS 316L: Only butt welding for piping/tubing welding shall be used.
- Butt-welding may be manual or by orbital welding machine.
- Inspection with borescope and passivation is not required.
- Piping/tubing standards shall be 3A/food grade with flange or Tri Clamp (TC) connections.
- Piping/tubing internal finish may be polished or standard mill surface finish.



## **Materials and Construction: Non Final Product Contact Valve**

- Valves installed may be of the following types:

ball valve

angle valve

diaphragm valve

needle valve

butterfly valve

- Threaded connections shall not be used.

### **Materials and Construction: Product Contact Piping**

- SS 316L: Butt-welding by orbital welding where ever possible, a minimum of 70% of automatic welds shall be inspected and 100% of manual welds.
- Minimum acceptable ID polish shall be  $Ra \leq 0.6$  micron.
- Welding shall be performed with TIG/GTAW, 99.997% argon shield gas.
- Test coupons shall be performed every start of work per day and per piping/tubing diameter.
- Weld logs shall record all the piping/tubing welds in the system.

## **Materials and Construction: Product Contact Piping**

- Passivation shall be performed during commissioning/start up.
- Only certified welders shall be used.
- Piping/tubing connections shall be Tri Clamp (TC) or other sanitary style connection.
- Threaded or flanged connections shall not be used.

## **Materials and Construction: Additional materials**

- EPDM
- PTFE-Teflon
- Fluoroelastomers (FKM PEEK)
- PFA
- High grade (low impurity) fused quartz
- Other non-corroding, hot water resistant, non-particle shedding and non-leaching materials can be acceptable.

## **Materials and Construction: Additional materials**

- Elastomers and plastics shall be compatible with any of the following:

USP Class VI

FDA CFR 21 177.2600

WHO TRS970

### **Operation: Production**

- The PW/WFI Pretreatment and Production system shall operate/circulate constantly 24/7, no stoppage of the pump or flow.
- The constant operation/circulation shall keep the water moving without stagnation.
- There is no objective criterion of minimum flow or minimum speed. Minimum flow or turbulent flow may be defined per system.

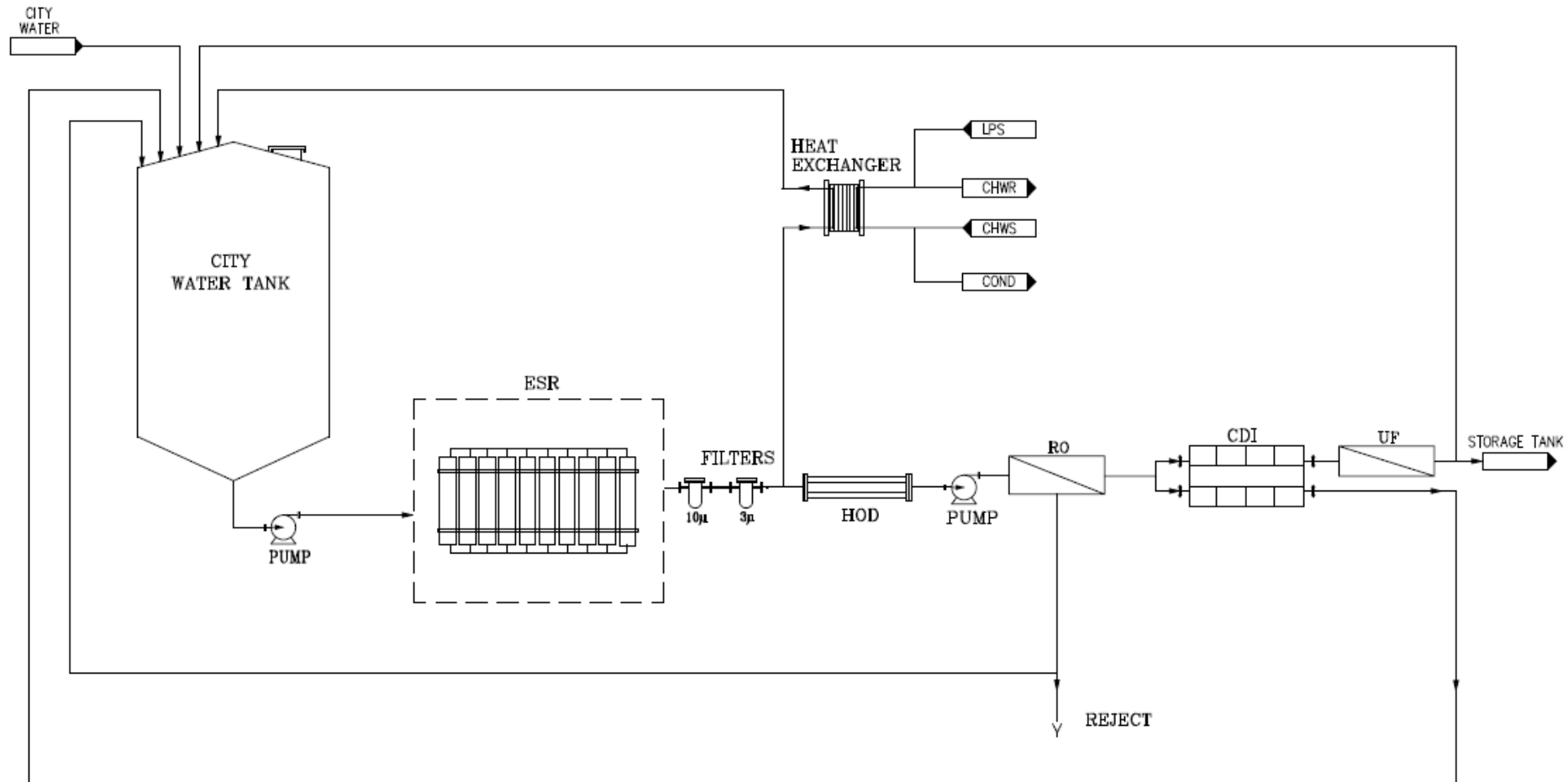
### **Operation: Production**

- Savings may be realized by throttling or return of the concentrate and lowering speed of pumps when storage tank full.
- A system with Electrolytic Scale Reduction (ESR) and UV dechlorination will continuously reduce bacteria while operating.
- Areas of the system that do not have constant flow, as in CIP return lines and bypasses, shall be gravity drained between uses.

### **Operation: Recirculation when storage tank full**

- When the PW/WFI storage tank is full, the PW/WFI Production shall shunt the product water back to the raw/supplied water inlet of the PW/WFI Pretreatment.
- The production system shall not operate Start/Stop when the storage tank is full. The production system should continue to operate continuously.





### **Operation: Sanitization**

- Hot Water Sanitization shall be the method for keeping the systems clean of microbial contamination.
- To prevent buildup of scale on the heating surfaces, water used shall be soft (less than 20 ppm as  $\text{CaCO}_3$ ).
- Appropriate temperature, time and cycle shall be determined, for example:  
A periodic heat sanitization shall be performed so that the lowest temperature in the system is  $80^\circ\text{C}$  for at least 30 min

### **Operation: Sanitization**

- All equipment units in the PW/WFI Pretreatment and Production shall be compatible with Hot Water Sanitization (HWS).
- This includes the Electrolytic Scale Reduction (ESR), UV, filters, Reverse Osmosis (RO), CDI/EDI/CEDI and UF units.
- If Activated Carbon Filter (ACF) is used it shall be sanitized at least twice a week with steam. If hot water is used, the minimum sanitization temperature shall be 85°C for one hour at least.

## **Sampling Principles**

- Provision for sampling the water upstream and downstream of all components that could affect the microbial or chemical quality of the water.
- Zero dead leg sample valves: on non PW/WFI piping and on PW/WFI piping.
- The sample valves shall be installed on short outlet tees as not to contaminate samples by bioburden growing in the fitting.
- The sample valves shall be above a tundish drain with sufficient clearance to allow insertion of standard sample bottles.

## Sampling for Conductivity

- If an online conductivity instrument is installed, **there is no need** for samples to be taken for off line second or third stage conductivity testing if the online conductivity has already met stage 1 criterion.

## Bioburden Reduction

All production systems must steadily improve the operating parameters from stage to stage, e.g.:

Feed water	500 cfu/ml
After Softening/Antiscalant/ESR	200 cfu/ml
Feed to RO	100 cfu/ml
RO Permeate	20 cfu/ml
CEDI outlet	5 cfu/ml

#	Parameter	RO Feed	After RO	PW	WFI
1	Hardness (PPM CaCO <sub>3</sub> )	≤feed water	<1	<1	<1
2	TOC (ppb)	≤feed water	<500	<500 (online)	<500 (online)
3	Endotoxin (EU/ml)	NA	NA	NA	<0.25
4	Microbial total count (cfu/ml)	<500	<200	<100	< 10 cfu/100 ml
5	Free Chlorine (ppm)	<0.05	<0.05	<0.05	<0.05
6	Pseudomonas (cfu/100ml)	<10	<1	<1	<1
7	E. coli (cfu/100ml)	<1	<1	<1	<1
8	Total coliforms, Fungus, (cfu/100ml)	<1	<1	<1	<1
9	Conductivity (μS/cm@25°C)	Like feed water	<10	<1.3 (online)	<1.3 (online)

## Informative Annexes

- Annex 1: Examples of water feed PW production – PFD's of typical systems
- Annex 2: Examples of feed water categories – High bioburden/organics, high hardness, high silica/iron/manganese
- Annex 3: System selection table – per feed water, recommendation of system configuration
- Annex 4: Configuration of typical integrity test - for UF membrane

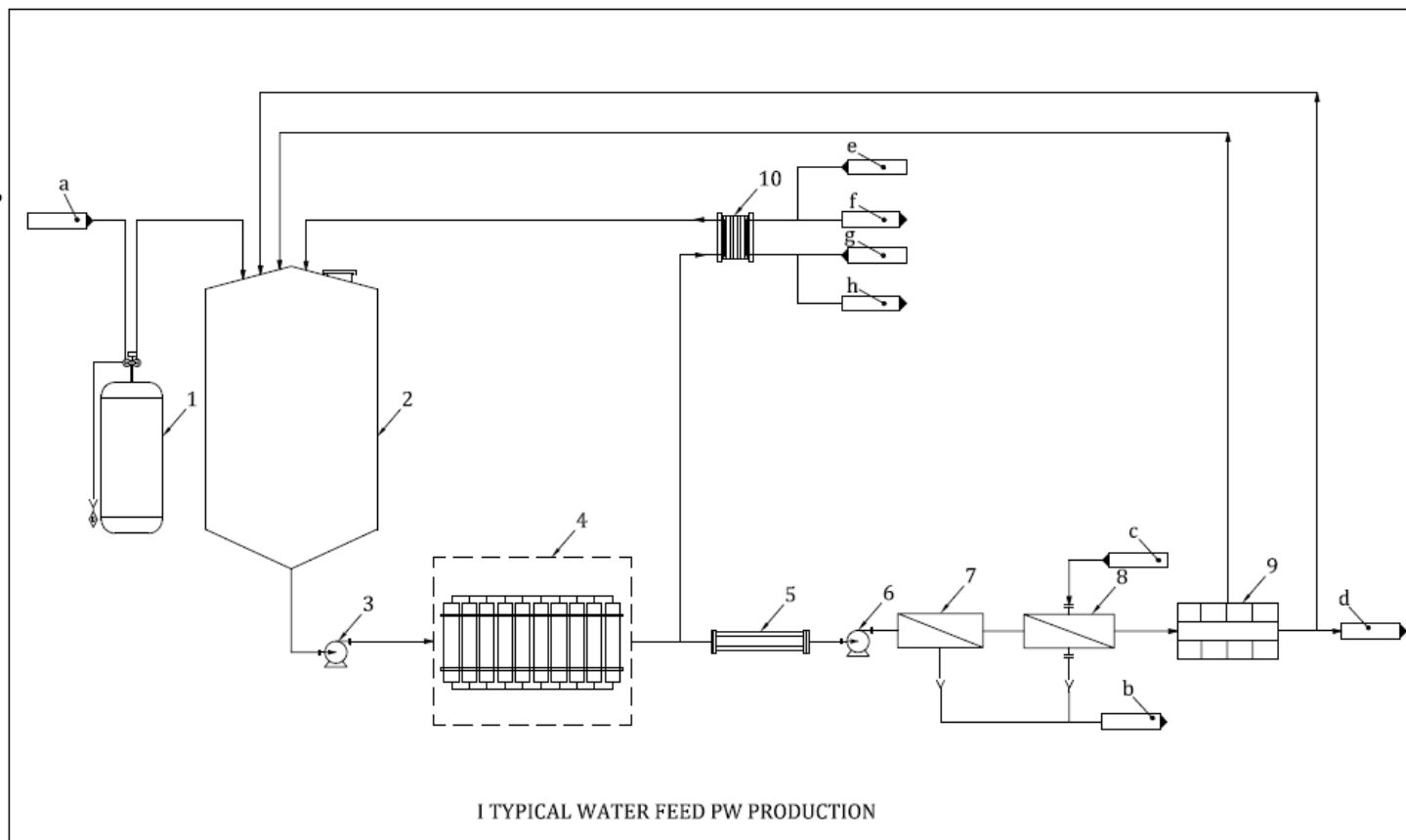


## PFD for Typical Water Feed PW Production

KEY:

1. MMF/FILTRATION
2. BREAK TANK
3. CIRCULATION PUMP
4. ESR
5. HOD (UV)
6. HP RO PUMP
7. RO
8. CO<sub>2</sub> DEGASSER
9. CDI
10. HEAT EXCHANGER

- a. Supplied water  
b. Drain  
c. Compressed air  
d. To Storage tank  
e. Steam  
f. Chilled water  
g. Chilled water  
h. Condensate

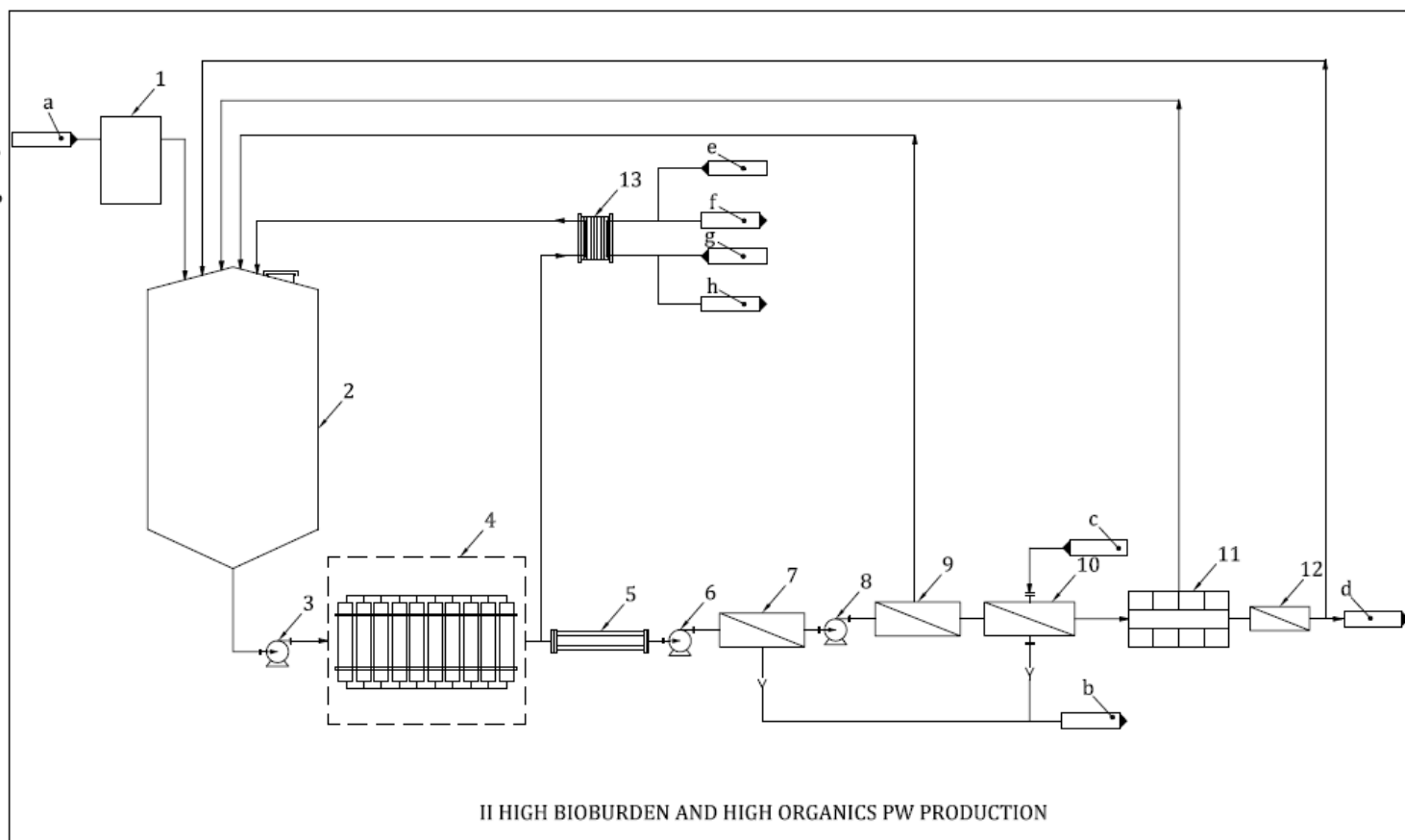


## PFD for High Bioburden And High Organics PW Production

### KEY:

1. UF PRETREATMENT
2. BREAK TANK
3. CIRCULATION PUMP
4. ESR
5. HOD (UV)
6. HP RO I PUMP
7. RO I
8. HP RO II PUMP
9. RO II
10. CO<sub>2</sub> DEGASSER
11. CDI
12. POLISHING UF
13. HEAT EXCHANGER

- a. Supplied water
- b. Drain
- c. Compressed air
- d. To Storage tank
- e. Steam
- f. Chilled water
- g. Chilled water
- h. Condensate

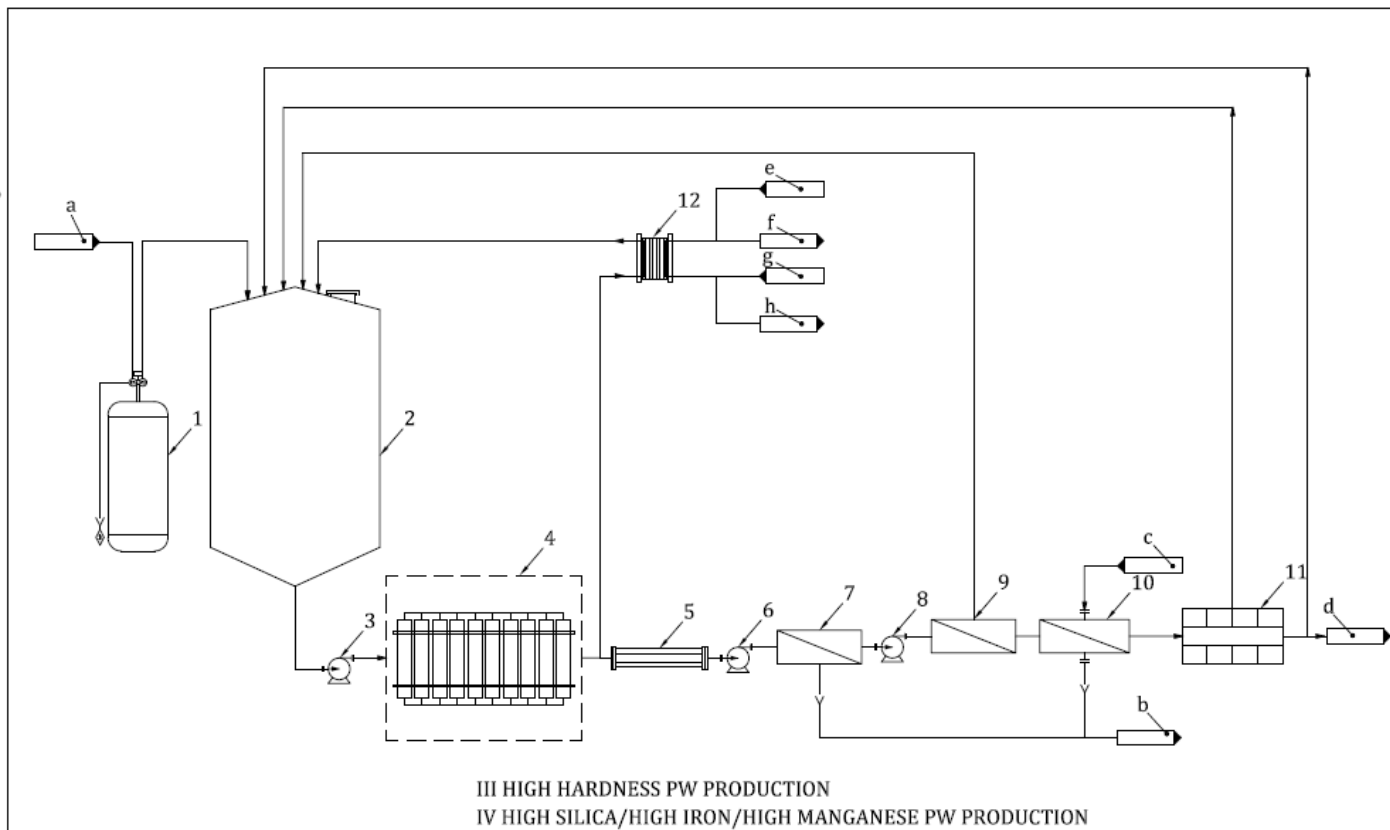


## PFD for High Hardness PW Production High Silica/High Iron/High Manganese PW Production

**KEY:**

1. MMF/FILTRATION
2. BREAK TANK
3. CIRCULATION PUMP
4. ESR
5. HOD (UV)
6. HP RO I PUMP
7. RO I
8. HP RO II PUMP
9. RO II
10. CO<sub>2</sub> DEGASSER
11. CDI
12. HEAT EXCHANGER

- a. Supplied water  
b. Drain  
c. Compressed air  
d. To Storage tank  
e. Steam  
f. Chilled water  
g. Chilled water  
h. Condensate



Water parameter	Typical	High bioburden and high organics	High hardness	High silica/high iron/high manganese
TOC	≤30 ppm	> 30 ppm	≤30 ppm	≤30 ppm
pH	≤8.0	≤8.0	≤8.0	≤8.0
Conductivity (@25°C)	≤600μS/cm	≤600μS/cm	>600μS/cm	≤600μS/cm
Hardness	≤300 ppm CaCO <sub>3</sub>	≤300 ppm CaCO <sub>3</sub>	>300 ppm CaCO <sub>3</sub>	≤300 ppm CaCO <sub>3</sub>
Microbial Total Count	<500 cfu/ml	≥500 cfu/ml	<500 cfu/ml	<500 cfu/ml
Total Coliforms, Pseudomonas, E. coli, Fungus	<1cfu/100ml	>1 cfu/100ml	<1cfu/100ml	<1 cfu/100ml
CO <sub>2</sub> level	≤30ppm	≤30ppm	>30ppm	≤30ppm
Total Silica	<12ppm	<12ppm	<12ppm	≥12ppm
Iron	<0.2ppm	<0.2ppm	<0.2ppm	≥0.2ppm
Manganese	<0.01ppm	<0.01ppm	<0.01ppm	≥0.01ppm

Water may be characterized on the basis of one criterion or more. The high range of measured parameters shall always be used.

Process:		Sanitant		Initial Filtration			Anti-Scaling			Sanitant Removal			Production		CO <sub>2</sub> Reduction		Polishing	
Feed	Final product	CL <sub>2</sub>	CD	FS/DF	UF/MF	MMF	Softener	AS	ESR	ACF	SBS	UV	SPRO	DPRO	NaOH	Degassing	CEDI	UF
Typical (Annex A.1)	PW	P	P	P	P	R	P	P	R	NR	P	R	R	P	P	R	R	P
	WFI	P	P	P	P	R	P	P	R	NR	P	R	NR	R	P	R	R	R
High Bioburden and high organics (Annex A.2)	PW	P	P	P	R	P	P	P	R	NR	P	R	P	R	P	R	R	R
	WFI	P	P	P	R	P	P	P	R	NR	P	R	NR	R	P	R	R	R
High Hardness (Annex A.3)	PW	P	P	P	P	R	P	P	R	NR	P	R	P	R	NR	R	R	P
	WFI	P	P	P	P	R	P	P	R	NR	P	R	NR	R	NR	R	R	R
High Silica/High Iron/High Manganese (Annex A.3)	PW	P	P	P	P	R	NR	P	R	NR	P	R	P	R	P	R	R	P
	WFI	P	P	P	P	R	NR	P	R	NR	P	R	NR	R	P	R	R	R

**Key**

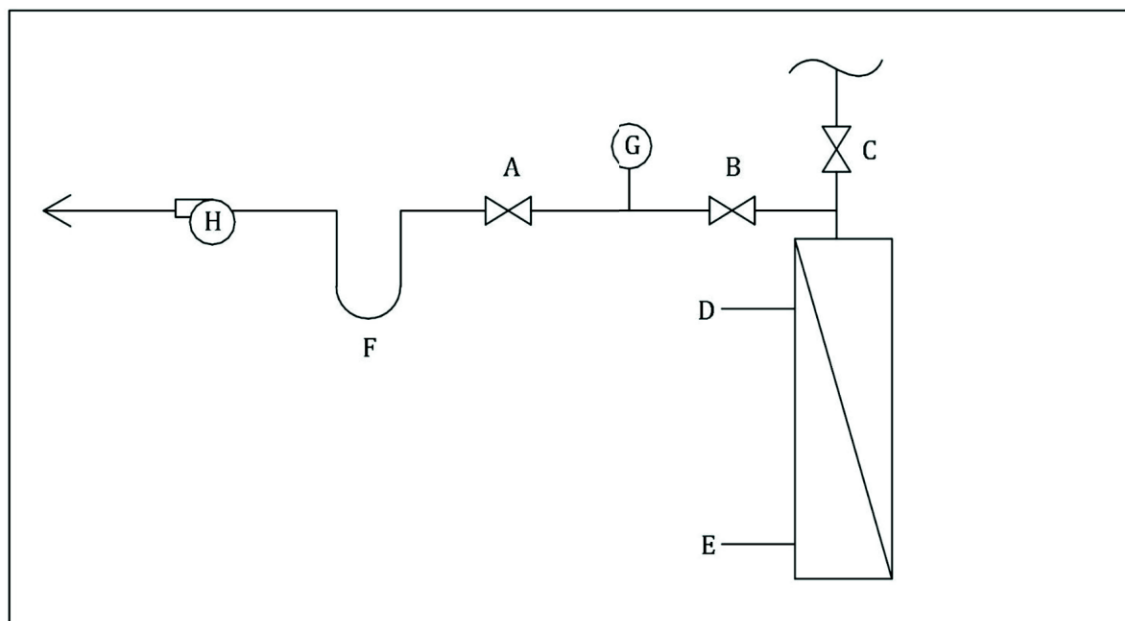
A, B, C: Isolation valves

D, E: Feed/concentrate (open)

F: Water trap

G: Vacuum gauge

H: Vacuum pump



## **Main Points**

- Point 1: Minimum of environmental impact.
- Point 2: Minimum of microbiological build up.
- Point 3: Continues Bioburden Reduction after every stage.
- Point 4: Sanitization with Hot Water.
- Point 5: All components in the PW/WFI system, Stainless Steel 316/316L.
- Point 6: The system shall not stop when storage tank full.



**Shlomo Sackstein**  
shlomo@biopuremax.com  
+972-54-4951150  
+972-9-9716111