ASAHI/AMERICA

Life Science Application and Validation Guide

High Purity Piping Systems
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Section One
Introduction

This guide contains many possible applications but its main focus is on High Purity Water. High Purity Water Production is perhaps the most visible and important system in a Biopharmaceutical manufacturing facility. As a critical system evaluated for facility licensing, the water system's importance cannot be overstated. The FDA utilizes the water system as a benchmark indicator of a facility's current Good Manufacturing Practice (cGMP) suitability because it is an universal component, regardless of the intended application.

The major goal of this application guide is to provide a high purity water design philosophy to economically improve the quality, reliability, and broaden the utilization of Purified Water (PW) systems in pharmaceutical manufacturing. Too much emphasis has been placed upon the "regulatory perceptions" of pharmaceutical water systems at the expense of the water quality. PW systems must fulfill their role as the primary water source for most pharmaceutical applications, and expensive Water For Injection (WFI) should be relegated only to applications as defined by the name; water for injection.

The conceded microbiological integrity of WFI comes at a price; high cost, low purity and high metals content. Too often, WFI grade water is chosen to meet all facility applications, without regard to quality, to avoid regulatory scrutiny. This is costly both technically and economically. WFI water is not a high grade of water. WFI grade water is in contact with the atmosphere and, when piped in stainless steel, has an alarming metals content (see graph on page 2). Rouging has been treated as an unfortunate byproduct of pharmaceutical water quality and not recognized as the gross contaminant that it is. Hot WFI water, recirculating in 316 L Stainless Steel pipe, will consistently contain Iron, Molybdenum, Tungsten, Chrome, Nickel and Cobalt, as well as Copper, Zinc and traces of other heavy metals.

- Metal laden WFI water, which has a significant carbon dioxide content, is not suitable for most laboratory, research or chromatographic applications. The water quality varies and is difficult to reproduce from facility to facility. There is a concern that this water impairs some cell culture processes as well.
- Hot WFI water can be 10X more expensive than the higher quality DI alternative.
- Hot WFI requires expensive utilities support and poses safety risks due to its high temperature.

High purity DI water should replace low purity WFI water in all applications except the final purification of parenterals.

A high purity or DI water system should meet the following objectives:

1) Economically provide high purity water of exceedingly high quality, suitable for all applications.

2) Provide water without disruption 24/7/365

3) Provide water of suitable quality and consistency so as to eliminated water as a variable in research and manufacturing.

High quality Purified Water will fulfill virtually all of the technical water requirements of the BioPharm industry. PW quality should not be measured by the minimal regulatory definition of PW, but be defined as the standard of quality routinely delivered by a DI water system.

- The water should have a TOC less than 50 ppb, preferably less than 10 ppb.
- The microbial activity should be less than one colony forming unit (cfu/ml), and typically much less.
- The water should have no detectable endotoxin.
- The water should exceed 17.5 MegOhm resistivity and there should be no detectable fluctuations in quality, day to day, year to year.
- The DI water contains no detectable ions to one part per billion.
- The water should require no heating or cooling to maintain quality.
- The water quality is reproducible from facility to facility and is easily scaled up.
- The DI water must be piped in thermoplastic materials and be provided on an instantaneous basis, suitable for all applications, including the feed source of the WFI make up.

PW should comprise the bulk of a facility's water use with WFI utilized on an "as directed" basis. This approach provides high quality water on demand with considerable savings on utility infrastructure and support, operating expense and capital equipment savings. This application guide is provided to assist pharmaceutical engineers to apply these concepts based upon a wealth of real world application and experience. The goal is to improve pharmaceutical water quality, reliability and efficiency. This application guide will also investigate other functions in the facility where thermoplastic products can be applied to increase productivity and improve quality.

Asahi/America - The Company

Asahi/America pioneered the development of corrosion resistant thermoplastic fluid flow products in the United States. As a leader in thermoplastic fluid flow products, Asahi/America offers expertise in product, system design and installation. This approach is the Total Systems Approach. With a focus on high purity and DI water applications, Asahi/America's knowledge in the application is the foundation for products to meet the challenges of the industry. An Asahi/America system is specified with confidence.

With superior product design and ISO 9001 manufacturing, Asahi/America has remarkable product breadth. Valves and pipe are offered in numerous thermoplastic materials, and range from ¼" to 24". Offerings include pneumatic and electric actuators, thermoplastic compressed air and ventilation/exhaust systems, and extensive custom fabrication.

Products are available through one of the industry's largest distributor networks, nearly 1000 locations nationally and throughout Latin America. Customer support comes from knowledgeable distributors and from a sales and engineering staff dedicated to thermoplastic system design.

Please feel free to contact the Asahi/America experts with any questions about its products and how they fit your pharmaceutical and biopharmaceutical applications. ***Asahi-America - The Wet Process People***

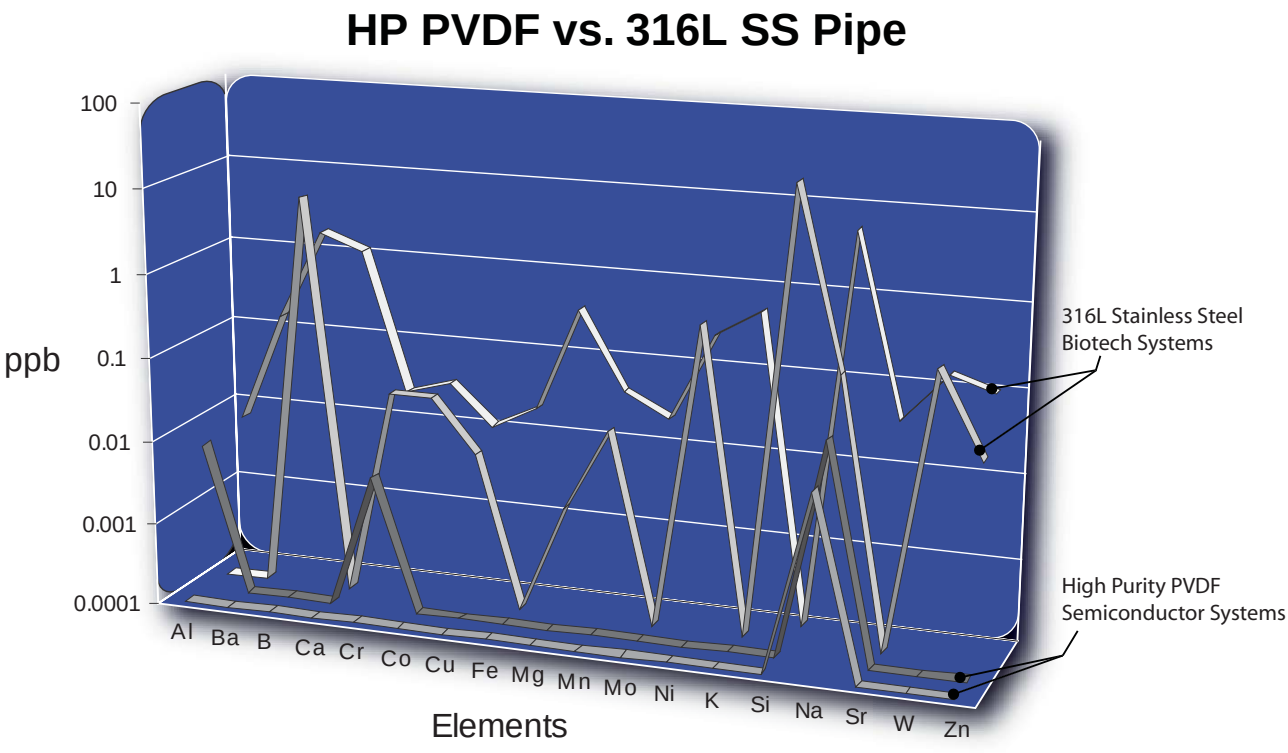

FIGURE 1.A: ION CONTAMINATION COMPARISON BETWEEN FOUR ACTUAL HP INSTALLATIONS. ION CHROMOTOGRAPHY MEASUREMENTS TAKEN ON DYNAMIC WATER SAMPLES DEPICT EXPECTED PURITY LEVELS BETWEEN POLYMER AND STAINLESS SYSTEMS.

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1.1 PURPOSE OF THIS GUIDE

This guide is presented in a unique format, a total stand alone document which answers questions for the design, construction, commissioning and validation of a pharmaceutical PW system or process application. It is a combination handbook and textbook to guide you through the entire process from conception to successful operation.

This guide is a source of information for pharmaceutical and biopharmaceutical managers who need to make critical decisions in regard to process systems. It is directed to high purity applications and takes you through conception, validation and successful operation.

It is organized in such a way to lead the user through the steps in the design and construction of an engineering project.

Asahi/America is prepared to assist you in all phases of a project from start to finish to make your planning and installation as smooth as possible.

1.2 HOW TO USE THIS GUIDE

The following is a suggested approach to a typical project:

1. Select your application from the following categories or create a new possible application:

    - USP Purified Water
    - Water for Injection (WFI)
    - Solution and Buffer Preparation
    - Fermentation or Cell Culture Media Preparation
    - Clean in Place Systems (CIP)
    - Pure Air and Gasses
    - Equipment Hook-up

2. Refer to our generic designs which are shown in Sections 4 and 5. Section 4, (USP Purified Water) includes a basic list of equipment, valves, piping and instrumentation. Also included is information on recommended materials of construction.

3. Define the project including a schedule.

4. Create a preliminary Process Flow Diagram (PFD)

5. Create Specifications (Refer to the Section 8 for the specifications of our products).

6. Prepare a Process and Instrumentation Drawing (P&ID).

7. Prepare Equipment and Materials List.

8. Prepare a validation plan.

9. Order the equipment and materials.

10. Prepare construction and piping drawings including isometrics.

11. Prepare construction schedule.

12. Startup and commissioning

13. Validation

14. Operation

Section Two
Applications and Design USP Purified Water

As stated in the introduction the major goal of this application guide is to provide a high purity water design philosophy to economically improve the quality, reliability and broaden the utilization of Purified Water systems in pharmaceutical manufacturing. Purified Water systems must fulfill their role as the primary water source for most pharmaceutical applications. Expensive WFI water should be relegated only to applications as defined by the name, Water for Injection.

Based on the premise that Purified Water (PW) systems should be the major water source in a manufacturing and lab facility, it then needs to be economical and reliable. Proper utilization of thermoplastic piping systems from Asahi/America is part of the equation. The design options provided in section 4.1 are provided to better understand PW systems and the use of thermoplastics within these systems.

2.1 USP Purified Water (USP 25)

This is the most common type of high purity water used in the pharmaceutical and biopharmaceutical industries. It may possibly be the most important system in the facility, considering so much importance rides on the quality of the purified water and its relation to the success of the validation and licensing of a manufacturing facility. Problems with a PW system invite more scrutiny on the quality of the rest of the manufacturing process. PW systems that vastly exceed expectations emphasize the quality of the enterprise as a whole.

Purified Water is frequently misunderstood. It is technically a relatively low grade of high purity water at one MΩ, 500 ppb TOC (Total Organic Carbon) and a liberal bacteria count of 100 cfu/ml.* The designation PW quality, is a regulatory designation, and often higher product water quality is actually desired. It is important not to confuse or combine regulatory specifications with product water quality requirements. From a design viewpoint,

**The Pharmaceutical Industry usually utilizes a WFI product water specification of 10 cfu's/ ml by convention. Actually there is no bacteria specification in the Pharmacopoeia for either Purified or WFI water, but the FDA still enforces USP 22 microbiological requirements.*

Classification	Purified	WFI	Standard RO/DI	Suggested Levels
Resistivity (MΩ/cm)	< 1	< 1	17.5	18.1
Conductivity (µS)	< 1	< 1	0.057	0.056
TOC (ppb)	< 500	< 500	< 50	< 5
Bacteria* (cfu/100ml)	< 10,000	10	< 100	< 10
Endotoxin (EU)	NA	< 0.25	< 0.25	< 0.03

TABLE 2.1 WATER QUALITY COMPARISON

higher water quality is actually required to maintain microbial control. Any credible thermoplastic (RO/DI) water system design should make water that is 17.5 MΩ (0.055 uS), TOC < 50 ppb and bacteria at about 1 cfu/ml. By properly utilizing TOC UV lamps in the design, the water should be less than 10 ppb TOC, and bacteria at considerably less than one cfu/ml.

2.2 System Design

2.2.1 Design Philosophy

Generally speaking, it is not recommended to utilize a chemical addition approach to water treatment. Sequestrants, dispersing agents, chlorine addition and bisulfite additions all add chemicals that eventually have to be removed again. The pretreatment should rely upon backwashable filter media for suspended solids removal, not cartridge filtration alone. A high purity water system should be based upon reverse osmosis, for economic and technical reasons. If ion exchange resins and a TOC UV light unit are properly utilized, there is no reason the system cannot provide the following design goals:

1. Exceedingly high quality Ultra Pure Water (see Suggested Levels for Table 2.1)
2. No detectable product water quality fluctuations.
3. Reduced capital investment
4. Minimal operating costs
5. Virtually no maintenance except for one scheduled maintenance day per year.

These goals are routinely achieved in the semiconductor industry and have become more common in the biopharmaceutical water systems. With the use of proper design and thermoplastic materials truly remarkable water quality is becoming routine.

It is exceedingly difficult, if at all possible, to constrain microbiology in the pretreatment vessels and in storage tanks. A microbiological control strategy is to allow normal levels of microbiological activity in the pretreatment and storage tanks, but to prevent inoculation of the distribution loop, and retard growth of organisms in the product water.

Pretreatment of bacteria prior to the RO have virtually no relation or effect upon bacteria levels after the RO unit due to the almost impenetrable RO membrane. Microbiology in plastic storage tanks should stabilize at no more than 20 cfu/ml, and are typically in the 1 cfu/ml range. There should be no or just barely detectable slime layer under the water line of a DI storage tank. One should be very concerned with effective microbial control after the storage tank. Control microbiology in the distribution loop by preventing the inoculation of the distribution loop with a 3 stage barrier to microbes (post treatment) and by making the product water inhospitable to by operating at less than 10 ppb TOC in the distribution loop. Bacteria will always be present in a distribution loop, but if there is no food (i.e.; TOC) in the distribution loop, bacteria may survive, but they cannot thrive. Microorganisms should stay almost irreversibly attached to the hydrophobic surfaces of plastic pipe, resulting in virtually no detectable bugs in the bulk phase product water.

2.2.2 System Sizing

Water systems are best sized by their distribution loops (typically 1", 1 ½", 2.0 " or 3.0 " for USP systems). You first must know approximately how much water you need to provide, on an instantaneous basis, and on a daily basis/shift. Instantaneous water usage should not exceed 1/3 the distribution loop flow rate for semiconductors, and 1/2 the distribution flow rate for Bio-Pharm where pressure and flow stability are not as critical. The instantaneous usage sizes the required post treatment and distribution loop or loops. The daily usage sizes the RO make up capacity and the storage tank(s).

Pipe Size mm (inches)	Flow Range (gpm)	System Length (ft)	Pressure Drop per 100ft	
			PVDF	PP
32 (1)	10-15	500	2.16 - 4.57	2.70 - 5.72
50 (1½)	25 - 35	1,500	1.11 - 2.08	1.64 - 3.49
63 (2)	50 - 70	2,000	1.17 - 2.18	1.93 - 3.60
90 (3)	65 - 90	3,000	0.25 - 0.49	0.75 - 1.22

TABLE 2.2 SUGGESTED SYSTEM FLOW RATES AND SIZES

In addition to the Table 2.2, please refer Asahi/America's Engineering Design guide for complete listings of pressure drops and fluid velocities based on total flow through a pipe diameter.

The storage tank should be sized proportionally with the RO unit to provide design balance. A rule of thumb is the RO unit should be capable of filling the tank in no less than an hour and no more than 3 hours. The RO sizes the required pretreatment and feedwater piping and heating (if used) requirements. You can then figure out utilities, electrical, floor drains and room sizing.

2.3 Process Design

The design of a Purified Water system can be broken down into four sections of design consideration:

1. Feed Water
2. Pretreatment
3. Purification
4. Post Treatment

Each of these categories can be further broken down into the details of the equipment utilized and specific piping layout.

2.3.1 Process Design: Feed Water

The feed water is either city water or on site well water. The feed water must meet EPA potability standards, or the system must address any feed water quality deficiencies. The feed may be surface water or well water, or a combination. Surface waters are often characterized by low salt content and suspended solids that foul RO units. Well waters are often free of suspended solids, but have a high salt content that consumes mixed bed polisher life after the RO.

The municipal treatment plant, phone numbers, treatment process and chemical additions supplied in the drinking water should be known and taken into consideration when designing a water system. The presence of chloramines, elevated pH and chemical coagulants all may cause considerable problems if not addressed from the beginning.

Following the initial feedwater, standard RODI water system design is best divided into three stages. They are conveniently classified as: Pretreatment, Purification and Post Treatment.

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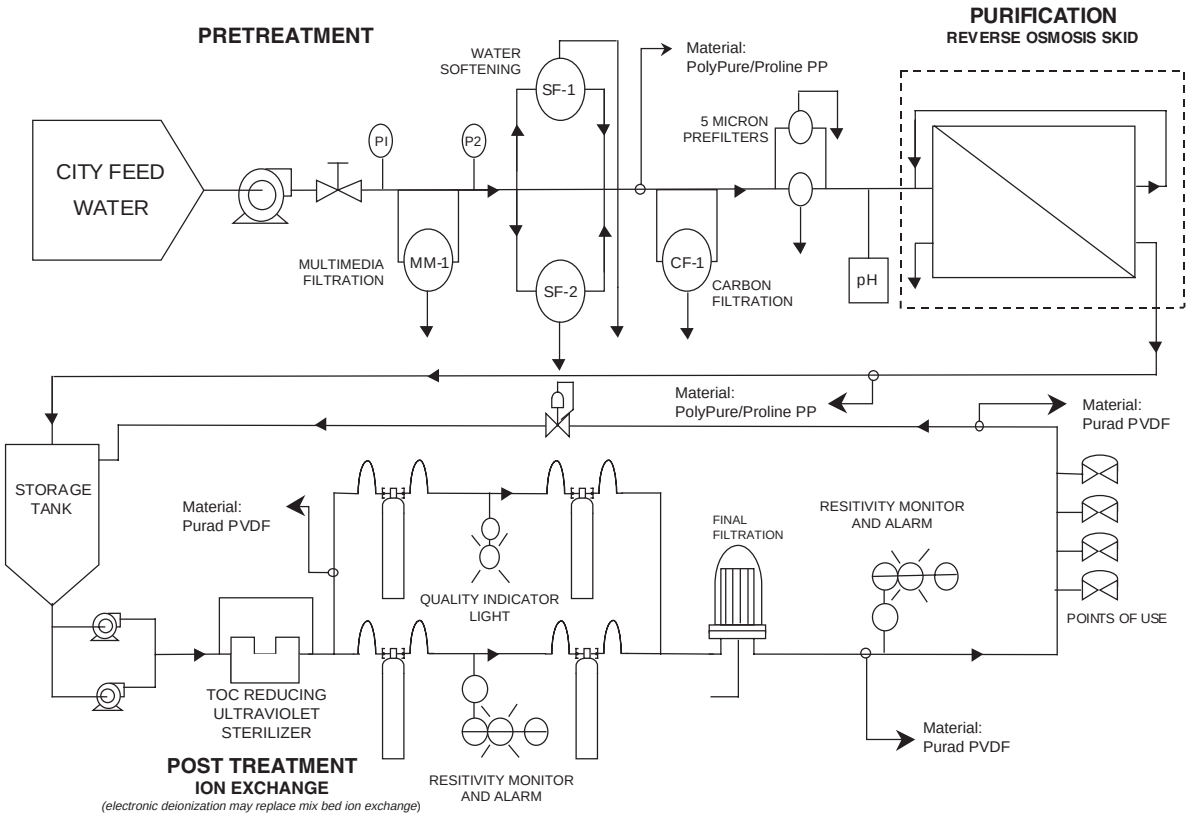

FIGURE 2.A SAMPLE PROCESS PIPING P&ID

2.3.2 Process Design: Pretreatment

The function of pretreatment is the reduction of suspended solids as evidenced by Silt Density Index (SDI). The presence of suspended solids will typically impair carbon absorption efficiency and RO output capacity. Therefore, pretreatment is a vital component in the overall process. Several pretreatment options and methods are availble:

- Media Filtration (i.e. multi-media, manganese green sand or sand filters)
- Water Softeners (usually duplex)
- Carbon Filtration
- RO Prefilter Cartridges

Media Filtration

Surface feedwater with greater than 10-15 SDI requires pretreatment filtration (multi -media) not only to protect the RO unit from fouling, but also the carbon and water softeners. Very difficult waters may be treated with coagulants such as Alum, PAC (poly aluminum chlorate), or polyelectrolytes.

Water Softening

Feedwater with a hardness that exceeds 50 % of the TDS or 35 ppm of CaCO3 require softening. Softening should also be considered if continuous Deionization (CDI or EDI) will be used or if the RO reject is to be reutilized (in Cooling Tower make-up, etc). Softening may be used to remove iron providing it does not comprise more than 15 % of the hardness of the feed water. Softening can also provide some RO membrane fouling protection via a colloidal stabilization process called shielding.

Carbon Filtration

Carbon is used to remove chlorine ahead of the RO and also to reduce incoming organics (TOC). The carbon filter is often unfairly considered the source of microbial problems in water systems. Based on experience, pretreatment microbiological activity is not a problem. The RO unit will reject sodium ions up to 99% efficiency so bacteria are thoroughly and efficiently sent to waste. Therefore, bacteria do not pass through RO membranes. Some will protest that an RO can become biofouled.

Biofouled TFC RO membranes are a symptom of poor RO design or insufficient pretreatment filtration resulting in fouling of the RO membranes. The fouled RO membranes provide a food source that quickly slimes over (instant biofilm). The RO often fouls on surface feedwater due to excessively high conversions (RO product vs reject ratio) or reject water recirculation to conserve water, both of which are a function of proper RO design per application. In lieu of carbon pretreatment, a bisulfite addition is sometimes utilized to neutralize chlorine. Bacteria can metabolize the bisulfite itself, that plus the lack of an additional filtration step, can also result in biofouling. Bisulfite additions in place of carbon filtration may also results in excess TOC in the product water. High TOC levels can result in product water bacteria.

Therefore, the use of carbon in pretreatment is preferred. Carbon pretreatment effectively removes chlorine molecules and does not contribute to TOC build up. Carbon beds do not require steam or hot water sanitization, as it does not enhance performance.

Carbon in pretreatment is found as Granular Activated Carbon (GAC). GAC uses surface area to absorb (trap) impurities. GAC is an effective filtration method and can have a surface area of 1000 – 1200 square meters per gram. This is equal to 100 football fields laid out side by side per pound of GAC

GAC types are distinguished by raw materials and pore size distribution. Other properties include Iodine, carbon tetrachloride activity, surface area, pore volume, moisture content, particle size distribution, mean particle size, and soluble ash content. The Table 2.3 lists the most common GAC Types and their properties.

Coconut Shell - Low ash (5%), low dust, better on low molecular weight Organics due to smaller interstitial pore spaces. High Micropore density, low Macropore density.

Coal based - Bituminous (Steam) Activated Carbon - cheaper, may be dirtier, higher ash (10%) content, medium dust content. Good physical stability (Abrasion #). High micropore & medium macropore density to remove wider molecular range of organics.

Lignite Based - a low ranked coal. GAC made from lignite has a large pore size. This may result in higher TOC removal capacity, perhaps for large fulvic and humic acids (organics). This higher capacity may be offset by reduced physical integrity and high fines content.

Wood based Carbon – Low Micropore & High Macropore density. Ash content (5%), dust level High.

Acid washed Carbon (low to no ash due to acid washing) Low pH > 2, phosphoric acid washed, may damage older RO membranes if not rinsed properly.

NOTE: Check pH of feedwater and new carbon effluent. High pH (approximate 10) due to ash throw may cause a significant loss of RO membrane ion rejection. This may occur in non-acid washed (high ash) carbon.

Property	Coconut	Coal	Lignite	Wood
Micropore	High	High	Medium	Low
Macropore	Low	Medium	High	High
Hardness	High	High	Low	Medium
Ash (percent)	5	10	20	5
Water Soluble Ash	High	Low	High	Medium
Dust	Low	Medium	High	Medium
Regeneration	Good	Good	Poor	Fair
Density (g/cm3)	0.42	0.48	0.3	0.35
Iodine # (mg/gm)	1100	1000	600	1000

TABLE 2.3 ACTIVE CARBON COMPARISON *Source: Henry G. Nowicki; Water Technology; March 1997*

Coconut shell carbon is recommended for chloramine removal due to the propensity of micropores present when compared to coal based carbon. Beware though, Coconut shell carbon may foul more quickly on the macromolecular TOC found in surface water sources. Further, a long path (high column or dual beds in series) is recommended for chloramine removal, due to the slow reaction rate and the formation of carbon oxides from chloramine removal.

In surface waters with chloramines, a safe path may be to use a tall (72 inch straight shell) vessel with coal based GAC. In severe cases, coal based GAC may be used in the primary bed, followed by a coconut shell carbon for chloramines in a second carbon bed, operated in series.

Other chloramine removal techniques involve chloramine destruction via the addition of sodium hypochlorite and UV dissociation of chloramines utilizing intense levels of high-pressure UV lamp irradiation.

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2.3.3 Process Design: Purification

The function of purification is to remove dissolved impurities. The presence of suspended solids will impair most purification technologies.

The Purification phase of treatment deals with dissolved impurities, primarily salts or ions.* All high purity water systems should employ an RO unit. This is important because the RO membrane provides an impenetrable barrier to all solids, including colloids and microbes found in the city feed. Without this barrier, problems downstream will eventually become overwhelming. This is especially true for microbial related issues.

Reverse Osmosis

A single pass RO unit is typically all that is required in purification for standard DI water systems when the size of the RO unit is less than 40 gpm, and or the city fed is less than 300 ppm salt. Larger RO units (ie. water systems) or saltier feed water may benefit economically from a double pass RO unit, or a secondary ion exchange process, such as CDI/EDI or ion exchange polishers on the RO product, prior to storage.

A pH adjustment system may be advised if the feedwater pH range is outside of 7-9, or the RO is larger than 10 gpm or is a double pass RO system.

**Carbon Filtration and Water Softening could be included in this category, but are typically classified in pretreatment.*

RO units should:

1. Utilize Thin Film Composite (TFC) membranes.
2. Operate at 50% conversion with higher rates allowed if no fouling occurs. Larger RO systems (> 25 gpm) require higher conversions as part of the design basis and require a more refined approach.
3. Media should speed up in the RO unit, not slow down (Membrane Staging).
4. Not be operated continuously.
5. Have a significant run when utilized; not short sporadic usage.
6. Not operate more than 14 hours/day (undersized).
7. Provide better than 97% rejection for ions, organics and silica.
8. Not require membrane sanitization (no oxidant tolerance).
9. Not require more than 2 cleanings/year, ideally none (use effective pretreatment filtration).
10. Reutilize the high quality RO reject, but not back into the high purity water system (cooling towers, etc.)

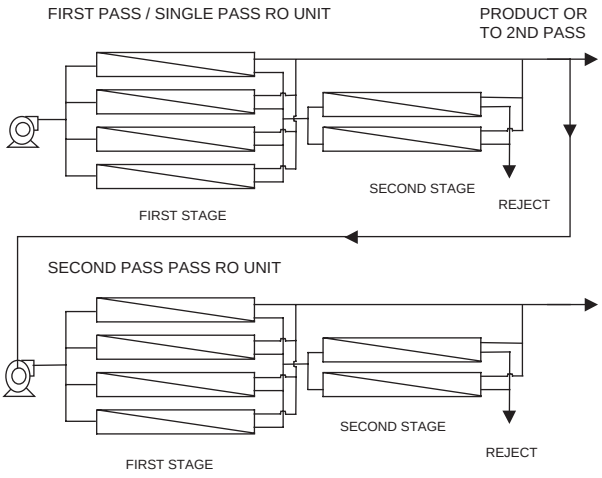

FIGURE 2.B SINGLE / DOUBLE PASS RO UNIT

Warm or Cold Operation

RO units should not require warm water operation to meet quantity levels. The product output of TFC RO membranes are not as temperature dependant as they once were. The water system pumps also dampen out and generally warm the product water more than one would expect. However, a cold water RO may cause a seasonal product water temperature drift if there is a big difference between summer and winter feed temperatures.

Storage Tank Design

Storage tanks less than a thousand gallons are typically molded plastic (polypropylene or polyethylene) with a conical bottom on a non-corrosive stand. Larger tanks are often Fiber Reinforced Plastic (FRP) or powder coated steel for very large tanks above 10,000 gallons. Large tanks should employ a sloped bottom for complete drainage. Specially designed FRP tanks and or lined steel tanks are required for ozonated applications.

Spray balls are not considered useful and promote premature polisher exhaustion due to enhanced carbon dioxide pick up. Consider piping the return water to storage under the water line to reduce carbon dioxide pick up.

Overflows are desired as a safety feature to help prevent tank collapse and tank bursting.

2.3.4 Process Design: Post Treatment

The purpose of post treatment is to polish intermediate quality stored water to specification on demand, remove system generated impurities, and provides emergency back- up protection.

Post Treatment design typically involves pumps, mixed beds, and an UV unit followed by final filtration. This standard Post Treatment configuration is responsible for much of the problems associated with purified water systems due to potentially high microbiological activity in the product water. The primary problems with the 'standard' approach are a lack of TOC control and the improper use of regenerated ion exchange media. The product water TOC in this approach generally ranges from 20 – 200 ppb, typically above 50 ppb. TOC at these levels provide a nurturing microbiological environment resulting in frequent ion exchange replacements. Re-generated media, in turn, may result in much of the microbial activity. The result is a continuous fluctuating bioburden despite routine decontamination. The following alternatives are offered:

Distribution Velocity

Too much emphasis has been placed upon velocity of water in distribution to control microbial activity. There is evidence excessive velocity and turbulence increases product water microbial counts. A certain level of biofilm will always exist within a water system's piping. This is unavoidable. The biofilm will reach equilibrium based upon the nutrition level (i.e. TOC levels) in the water system. Excessive turbulence tends to cause a shearing action and flush bacteria from the biofilm into the product water. The remaining biofilm will reproduce to its equilibrium and the cycle will repeat with excessive velocities. Biofilm will affix to pipe walls at low velocities but not shed continuously into the product stream. Product water velocity of 3-5 ft/sec is always considered ideal, but in certain cases lower velocities may be considered better than higher. (See page 46 for further discussion on system velocities)

TOC Ultraviolet Destruction Unit

A more prudent, and now more common approach is to use a TOC UV Unit, *ahead of mixed bed polishers*, to provide continuous TOC reduction. Low TOC product water is excellent protection against microbial proliferation, and combined with defenses to prevent loop inoculation, provides an effective microbiological control strategy . A TOC UV Unit sized for 2X the size of a standard 254 nm ultraviolet (bug) lamp will provide adequate TOC control, especially if carbon is used in the pretreatment. Be certain to employ light traps as the short wave, high energy 185 nm TOC destruct unit will attack polypropylene and PVDF pipe.

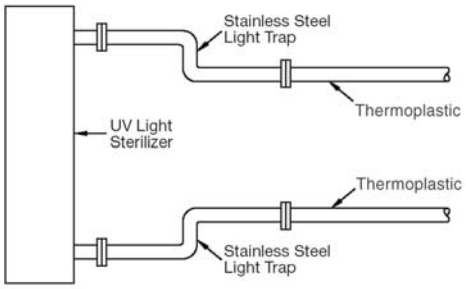

FIGURE 2.C UV LIGHT TRAP DESIGN

Ion Exchange Media

The use of regenerated ion exchange media is often associated with high bioburden loading from recycled, regenerated resins. Monitor the microbiological quality of incoming regenerated ion exchange resins to evaluate vendor Ion Exchange Quality Control. Virgin, Low TOC ion exchange resin will not support microbiological activity, but must be utilized in an efficient manner due to the high expense. It is recommended to consult expert UPW design consultants or OEM manufacturers for designs of efficiency, utilizing virgin resins.

Final Filtration

Final filters should not be relied upon to solely meet product water quality. These filters serve as final protective measures to prevent ion exchange media from getting downstream in the event of a failure in the polishers. Final filters should run for years with no detectable pressure drop. Pressure drops across the final filter housings for any reason is an indication of a processing problem up stream.

SECTION 2.3 PROCESS DESIGN ACKNOWLEDGMENT

The water system design and data provided in this section was provided to Asahi/America and its customers from Arion Water of Hyannis Massachusetts. The design is provided to assist in the concept of designing a reliable and low maintenance water system based on combining proper design with sensible materials of construction.

Asahi/America thanks Arion Water for their assistance and efforts to building this application design guide.

2.4 Materials of Construction

Many polymeric materials are used in the design of a USP Purified Water System. In the pretreatment section, the material of choice has been polyvinyl chloride (PVC) or chlorinated polyvinyl chloride (CPVC). They are very cost effective with easy installation and maintenance. In recent years the use of PVC has started to decline in favor of Polypropylene. Polypropylene offers thermal welding techniques similar to the purification and post treatment sections and offers enhanced purity properties. Thermal welding eliminates solvent cement in the system, which is a major contributor to TOC. Many PW systems are exceptionally served by the use of PP throughout the entire system.

System Description	Recommended Material	Product Name	Maximum Temperature
Pretreatment	Pigmented PP Natural PP	Proline PolyPure	195°F
Post Treatment	Natural PP HP PVDF	PolyPure Purad	195°F
Distribution Loop	Natural PP HP PVDF	PolyPure Purad	250°F

TABLE 2.4 MATERIALS OF CONTRUSTION BY APPLICATION
**See Section 7 for discussion on SIP parameters*

In post treatment (which is the material immediately after the reverse osmosis unit) PP or PVDF should be utilized due to its superior purity compared to other materials. The requirements for water quality and system cleaning techniques are the determining factor for which material should be utilized. Polypropylene is a clean and smooth material that can operate up to 195°F. PVDF offers superior purity and surface finish over polypropylene and can withstand most chemicals used in cleaning as well as ozone sanitization. For exact recommendations on operating conditions, contact Asahi/America's Engineering Department for assistance.

2.4.1 MATERIAL PURITY

High performance thermoplastics, much like high grades of stainless steel, should be manufactured, packaged and installed in clean environments. Only pure resins and materials should be specified for PW and WFI applications. Materials which use excessive additives, stabilizers or un-pure joining techniques should be avoided as they are potential water contamination sources. Using components made of PVC should be discouraged for anything after the initial pretreatment filtration. PVC contains an enormous amount of processing agents and solvent cement joining techniques add TOC to the system.

It is equally important only to accept systems specifically manufactured and engineered for high purity applications. PP and PVDF systems are manufactured with a variety of resins and manufacturing techniques. Not all systems are the same. Many production techniques are suited for industrial applications but are detrimental to system purity. At a minimum, all valves, fittings and piping should be produced in a clean environment and packaged to protect product cleanliness. Pipe should be capped and bagged immediately after production. Furthermore, all fittings and valves should be rinsed with DI water before individual packaging.

The evaluation and selection of materials will have a direct impact on system quality. A complete review of available materials and joining methods is recommended. Section Eight contains detailed product specifications and Asahi/America's Engineering Design Guide is and excellent source of information for design and installation requirements.

Finally, a comparison between thermoplastic and stainless systems is found in Section Four and more detailed information on thermoplastic system properties is contained in Section Six of this guide.

Section Three
Alternate Applications for Thermoplastic Systems

3.0 Scope

The applications in this section are those which are normally constructed with stainless steel but the use of thermoplastics should be considered as a cost effective substitute. Table 3.1 provides a quick reference of various pharmaceutical and biotech processes in which thermoplastics may be considered. A brief description of these applications (with the exception of Purified Water which is dealt with in Section Two) can be found in the balance of Section Three.

The intent of the process diagrams and corresponding discussions is to highlight areas in which thermoplastics should be considered. Many process related issues such as corrosion, pitting and metal ion contamination are effectively resolved with thermoplastics systems. The application discussion provides a specific summary of features and benefits of thermoplastic utilization. Although the discussion is by no mean all-inclusive, it should serve as a guide for initial consultation. Asahi/America's experienced staff is available for further clarification or discussion pertinent to your application.

3.1 Water for Injection (WFI)

Although normally constructed with stainless steel, the use of thermoplastics should be considered as a cost effective substitute in Water for Injection (WFI) applications.

3.1.1 Overview

WFI is also commonly used in pharmaceutical and biopharmaceutical applications similar to the ones listed for Purified Water. WFI systems are considered the most critical water system and generally receive the highest degree of regulatory scrutiny. High quality WFI systems are often considered an excellent indication of a total quality facility.

WFI is most commonly prepared by distillation. The stills are either multi-effect or vapor compression. Materials of construction for the stills are generally 316L stainless steel. USP-25 now recognizes WFI can be produced without distillation by means of Reverse Osmosis and Deionization. However, Japan and Europe still require distallation for WFI systems.

3.1.2 Design

The most common WFI system design is a single storage tank with a continuous recirculating hot loop (65-80°C.) loop (see Figure 3.A). A specially designed

System Description	Material	Brand	Material Temp. Rating	Ambient Pressure Rating	Application
Purified Water	Natural PP PVDF	PolyPure Purad	20 to 80°C	150 psi	Ambient DI Water
WFI*	316/316L SS PVDF-230	N.A. Purad	- 121-130°C*	- 150/230 psi	Hot Water
Solution Prep	316/316L SS PVDF-230	N.A. Purad	- 121-130°C*	- 150/230 psi	Varies
Fermentation and cell culture media prep	316/316L SS PVDF-230	N.A. Purad	- 121-130°C*	- 150/230 psi	Varies
Clean-in-Place (CIP)	Polypropylene PVDF E-CTFE	Proline Purad Halar	< 95°C < 121°C < 121°C	150 psi 150/230 psi 150 psi	Material selection based upon compatibility with cleaning agents
Pure Air and Gases	Eltex Tube124 HDPE	Air-Pro	20 to 60°C	230 psi	Pure Air and Gases

Table 3.1 Material Selection Guide by System Application
These recommendations are provided as a guideline to the usage of thermoplastic piping in pharmaceutical and biotech applications. Specific design considerations apply to each system. Consult Asahi/America's technical department for more information.
*See Section 7 for exact SIP parameters

cooled point of use or a separate ambient loop are sometimes employed. The other type is the batched tank with a recirculating hot loop. This is almost exclusively used when QA release is required for actual preparation of injectable compounds.

3.1.3 Materials of Construction

Traditionally WFI systems have been constructed using 316L stainless steel. The semiconductor industry has demonstrated that PVDF is actually a better material of construction in terms of both cost and vulnerability to contamination. Please refer to Section Seven and consult Asahi/America for exact conditions under which Purad PVDF systems may be steam sterilized for WFI applications.

3.1.4 System Design

The following is a design option for a typical Water for Injection system utilizing distillation. A WFI System generates water, which meets USP 25 standards and is used in various operations to produce pharmaceutical and biopharmaceutical products. The system consists of a multi-effect or vapor compression still, a storage tank and a hot distribution loop.

Purified Water is fed to the still and by the process of evaporation, impurities are removed. The vapors are condensed by a heat exchanger and the water flows by gravity to the storage tank. The water is maintained at approximately 65º to 80º C. and is pumped through the distribution loop and back to the tank. There are hot and cooled Points of Use. Materials of construction historically have been 316L stainless steel but Purad PVDF can be substituted in many areas of the system, providing improved purity.

Utilities

Feed Water	Purified Water
Plant Steam	70 to 110 psig.
Clean Steam	45 to 75 psig. (optional)
Instrument Air	(80 psig. minimum)

Cooling Water or Chilled Glycol

Feed Water Package (typical)

This package is a 50 gallon tank with a level control and a vent filter. A 2 HP sanitary pump feeds the still.

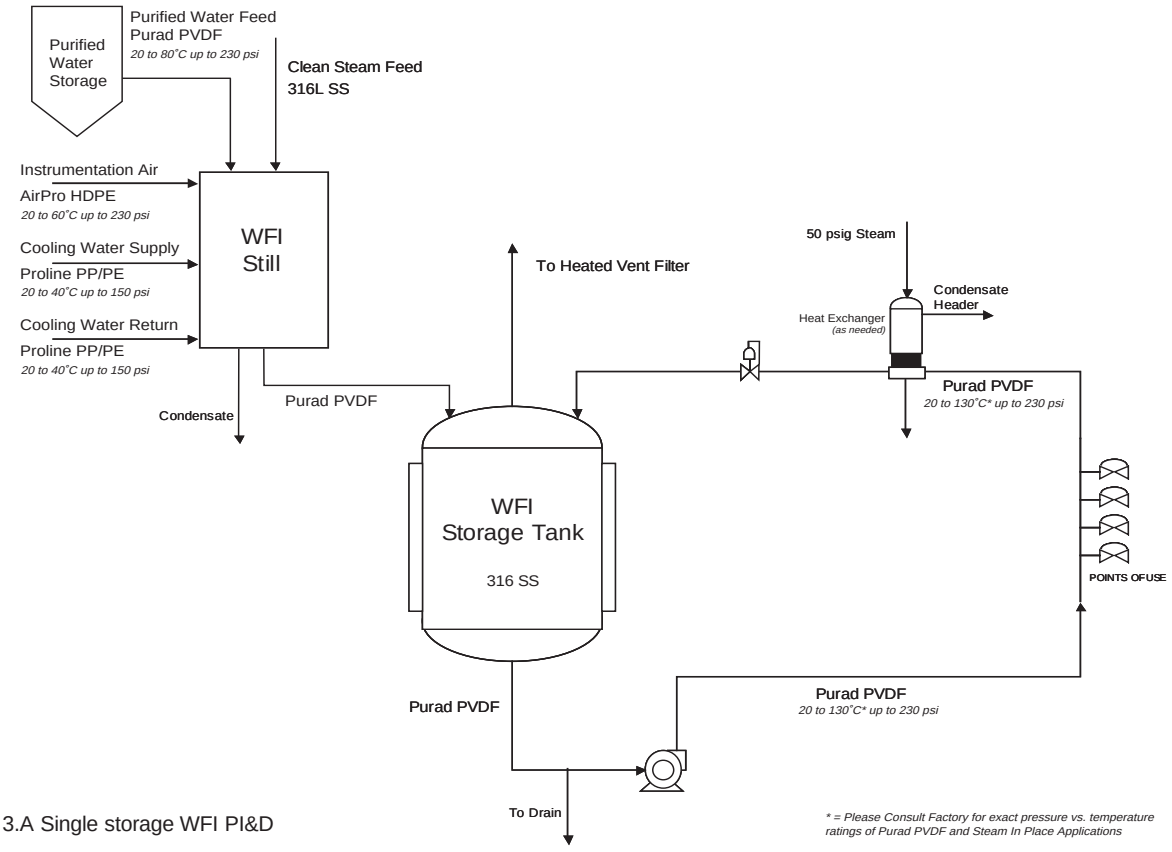

FIGURE 3.A Single storage WFI PI&D

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Still Description
For a typical 4 effect unit, the first effect is heated by plant steam and subsequent effects are heated by the product steam from the previous shell and tube heat exchangers (effects). Only the first effect utilizes a double tube sheet design. The material of construction is 316L stainless steel.

Condenser
The condenser is a shell and tube heat exchanger located on the top of the still. Cold feed water and additional cooling water is used for condensation. Pure steam enters from the evaporator heat exchangers (except the first effect). The top of the condenser is vented with a sterile cartridge filter. The pure distillate drains out of the bottom through temperature and resistivity sensors, a diverter valve and finally to the storage tank.

Preheaters
Warm feedwater from the condenser enters the heater on the last effect. This helps to cool the hot overflow from the last column. The water then goes to the previous effect and the process is repeated until it reaches the first effect where it is fed into the column as hot feed water.

Controls
The still system is controlled by a PLC. The panel board contains the various alarm functions. A chart recorder provides the temperature and quality information for the distillate. If the distillate is out of specification, it will be diverted to drain. A clock recorder indicates the duration of the still operation.

The temperature and pressure in the distribution loop are monitored and alarmed. Also monitored are the level in the storage tank and resistivity at the still and loop return.

Storage Tank
This is a 316L stainless steel insulated vessel. It is fitted with level control, temperature element, rupture disc, spray ball, jacketed 0.2 micron vent filter and SIP connections.

Distribution Loop
The WFI is distributed by single or dual sanitary pumps. Points of use are cooled by heat exchangers or may be used hot. All points of use are fitted with sanitary diaphragm valves. A back pressure regulating valve maintains loop pressure. A heat exchanger downstream of the pump is used to maintain the temperature of the water in the loop return by means of a temperature controller. A TOC meter is installed at the beginning of the loop. It measures both conductivity and Total Organic Carbon.

It is important to mention at this point that when utilizing a PVDF piping system for WFI, certain design requirements, such as thermal stress calculations and related expansion of the piping must be taken into consideration during the design process. For more information on thermoplastic pipe system design, please refer to Asahi/America's Engineering Design Guide.

3.2 Solution and Buffer Preparation

This section describes a design for preparing various solutions in a fermentation or cell culture facility.

3.2.1 Overview

There are many requirements for preparing various solutions in both pharmaceutical and biopharmaceutical operations. Solutions are typically used in such operations as chromatography, filtration or other purification steps. If sterilization is required, Purad PVDF may be utilized. Many solutions are prepared with salts or corrosive chemicals, therefore a thermoplastic material is superior to stainless steel. A typical solution preparation design is shown in Figure 3.B but it should be noted that these designs may vary considerably since every application is different.

3.2.2 Materials of Construction

Many solutions and buffers are required in a typical cell culture or fermentation operation. They are used in purification steps particularly in column chromatography. The use of stainless steel frequently causes problems when salts or acids are used in the formulation. For this reason the use of Purad PVDF provides an excellent substitute. Its high temperature capabilities allow for both sanitization and sterilization if required.

3.2.3 System Description

Figure 3.B shows a typical solution preparation system. It consists of a batching tank followed by a sterile product filter. The tank has provisions for adding high purity water and solids. It is fitted with a sterile vent filter, agitator, sample port, pH and conductivity probes, jacket cooling water or glycol. Transfer of final buffer is most often accomplished by pressurizing the tank with sterile air.

After the batching tank has been cleaned, sanitized and inspected, the required amount of high purity water is added. With agitation, the chemicals are charged in either solid or liquid form through the additional port on the top of the tank. pH is adjusted as necessary. The solution is agitated for one hour and cooled to 5° C. After integrity testing the sterilizing filter, the batch is filtered into another tank by pressurizing the tank with compressed air. Equipment is rinsed with a predetermined amount of high purity water and added to the batch. The buffer process is now complete.

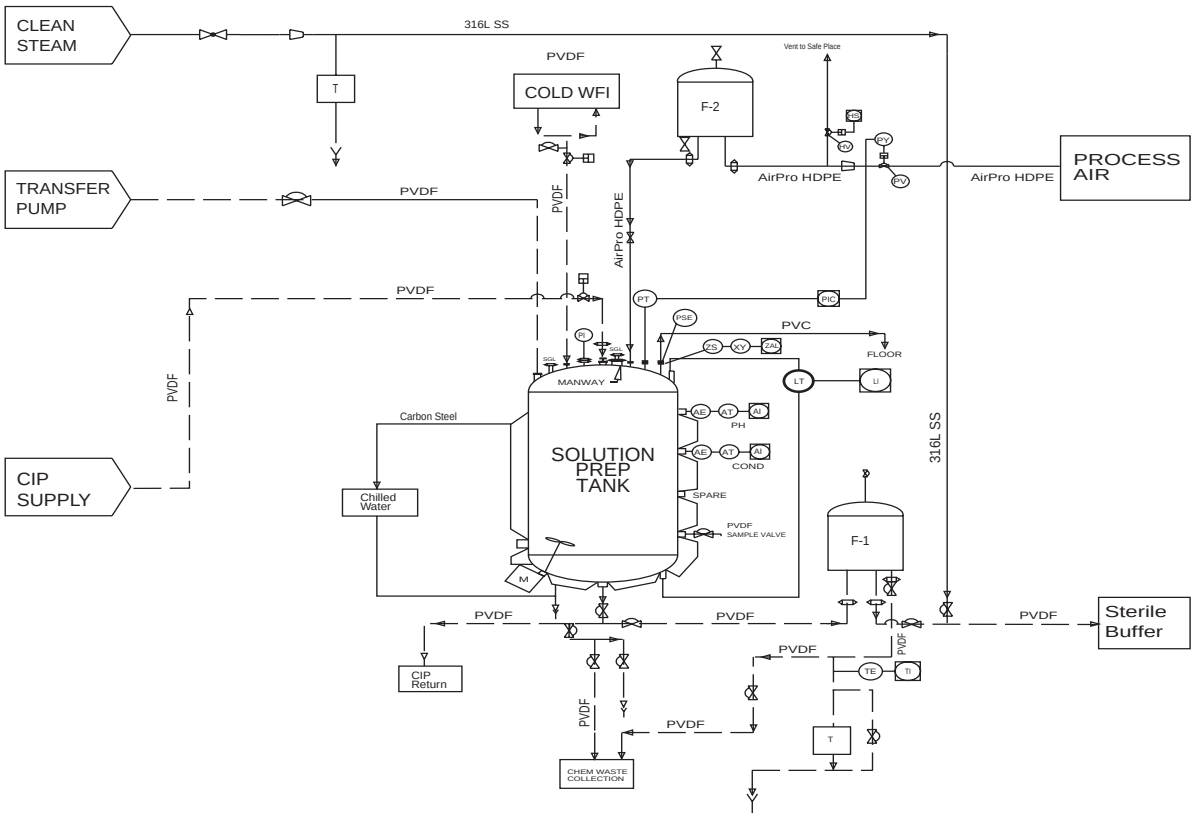

FIGURE 3.B SOLUTION PREP DESIGN

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3.3 Fermentation and Cell Culture Media Preparation

This section describes a design for preparing medium for a fermentation or cell culture facility.

3.3.1 Overview and Material Recommendation

Media is usually prepared and then either filtered or steam sterilized. This media may be used for initial batching or an in-process feed. If the media is filter sterilized, both PolyPure and Purad PVDF can be used. For steam sterilization, Purad is a more appropriate material. Media is often prepared in stainless steel equipment and may be contaminated with trace metal ions. To avoid this problem, Purad PVDF is an excellent substitute. The high temperature properties of Purad PVDF allow for steam sterilization in the same fashion as 316L stainless steel. Considerations to thermal expansion of PVDF must be accounted for in the design.

3.3.2 Equipment

Figure 3.C shows a typical design for media preparation. The equipment is similar to that used by buffer preparation. The tank is outfitted the same way and is supplied with the same utilities. The only major difference in the setup is that either 2 or 3 final filters are used to ensure sterility.

3.3.3 System Description

A media prep procedure may be as follows:
After the batching tank has been cleaned, sanitized and inspected, the required amount of high purity water is added. With agitation, the chemicals in either solid or liquid form are charged through the additional port on the top of the tank. pH is adjusted as necessary. The media is agitated for one hour and cooled to 5° C. After integrity testing the sterilizing filters, the batch is filtered into another tank by pressurizing with compressed air. Equipment is rinsed with a predetermined amount of USP high purity water and added to the batch. The media is now ready for use.

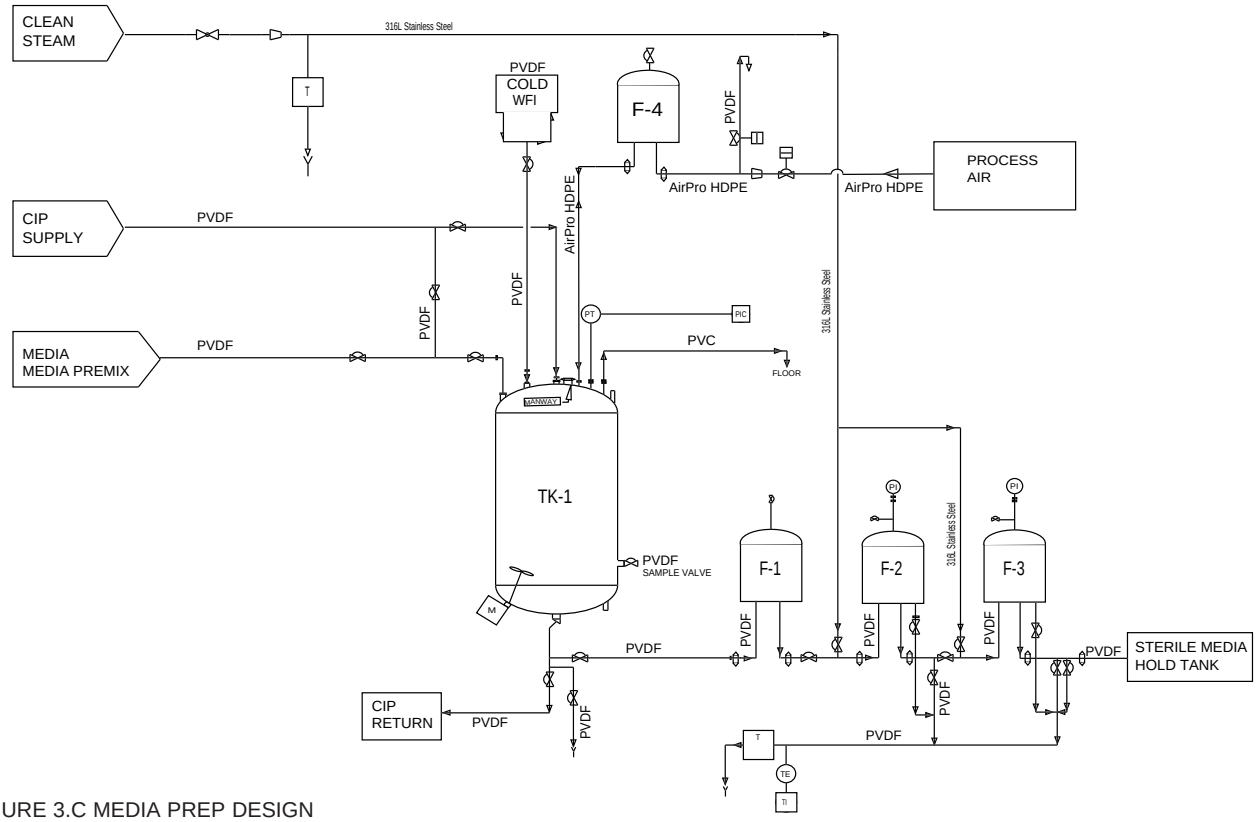

FIGURE 3.C MEDIA PREP DESIGN

Section 3

3.4 Clean-in-Place Systems

3.4.1 Overview

Clean-in-Place (CIP) Systems are commonly used in pharmaceutical and biopharmaceutical facilities. Figure 3.D shows a typical two tank CIP system. Similar designs are found with single and three tank variations.

3.4.2 Materials

Although CIP systems are frequently constructed with either 304 or 316 stainless steel, the use of PVDF or polypropylene (pigmented or unpigmented) can be a viable alternate. Advantages include: reduced installation costs, corrosion resistance, less insulation needs (for hot systems), reduced or eliminated borescoping requirements and no passivation.

Thermoplastic materials will out perform metal systems exposed to caustics, acids or chlorinated medias. However, no one single plastic material is ideal for all media. It is important to consult Asahi/America's engineering department for a specific recommendation.

Polypropylene is ideal for high pH medias and in some cases strong acids. Polypropylene is not recommended for chlorinated service or extremely high acid concentrations.

PVDF is ideal for aggressive acids and many chlorinated services. However, it is not recommended for high pH levels.

E-CTFE, known as Halar®, is an excellent plastic for a broad range of aggressive chemicals. In particular, E-CTFE is excellent in Sodium Hypochlorite applications.

For all systems, factors such as thermal expansion and UV exposure must be considered.

3.4.3 System Description

A CIP system is a packaged unit of integrated components.

- Controlled Rinsing: Controlled temperature rinsing which involves partial cleaning without the usage of chemicals.

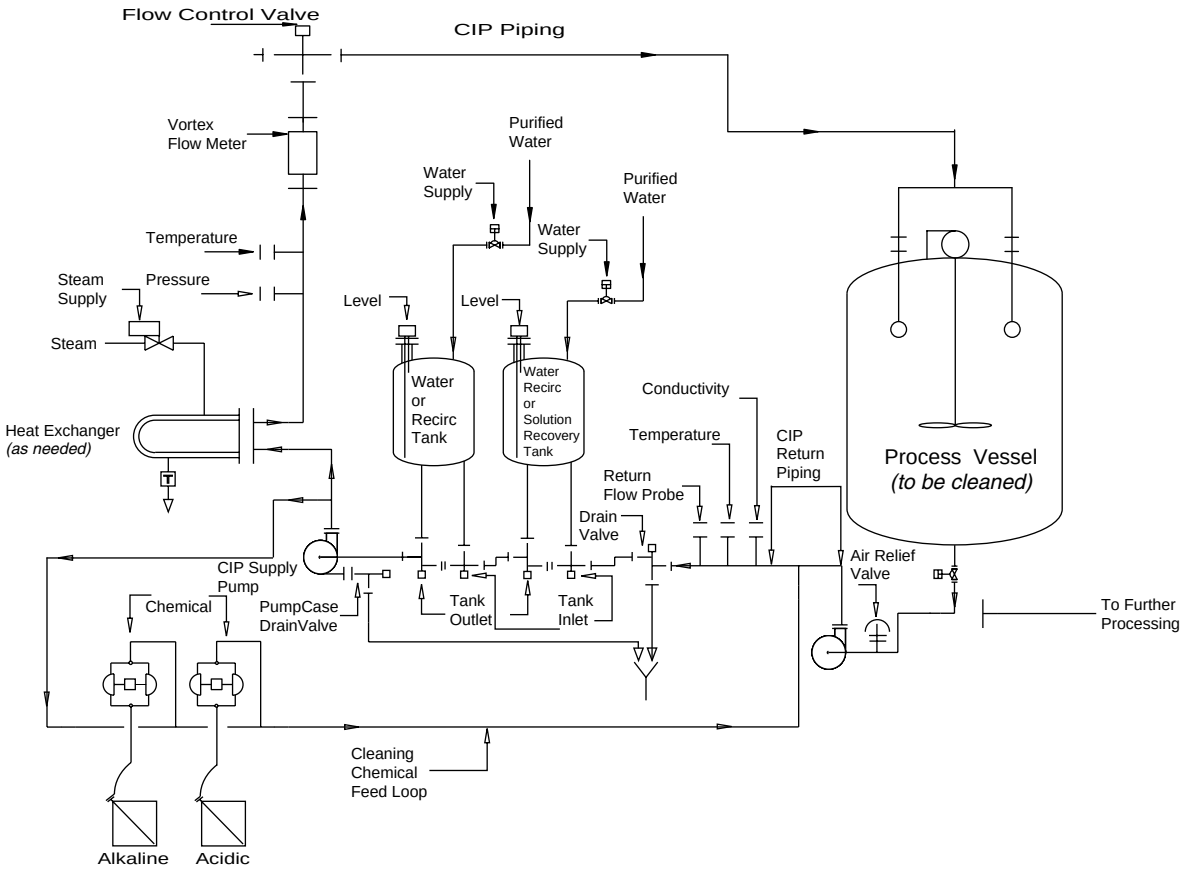

FIGURE 3.D TWO TANK CIP SYSTEM *(Note: Either Proline PP or Purad PVDF can be used as piping material depending upon cleaning agent used. Proline PP is excellent for most caustic agents)*

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- Controlled temperature washing automatically controls the system's exposure to the cleaning agents and rinses to insure consistent results. By controlling volume and pressure, sufficient turbulence is created to insure optimum cleaning conditions.

- Controlled chemical concentrations results in effective cleaning. Consistent and repeatable chemical dosage is essential from maximum effectiveness

- Final rinsing is usually performed with high purity water. It may be sent to drain or used as the first stage rinse of the next cycle.

CIP systems are used in many industries and now have become a standard for pharmaceutical and biopharmaceutical applications.

3.5 Pure Air and Gases

This section describes a design for the generation and distribution of compressed air and gasses in a fermentation or cell culture facility.

3.5.1 Overview

See Figure 3.E for a typical compressed air system. The Air-Pro Compressed Air Piping System is a cost effective alternative to carbon steel, stainless steel and copper. It is a safe and reliable system with many of the advantages of thermoplastic construction. These include:

- Convenient light weight
- Faster/lower installation cost
- More flexible installation
- Minimal system pressure drop over the life of the system
- Corrosion resistance- will never corrode, flake or pit.

The material is a special grade of high density polyethylene (HDPE) resin specifically approved for compressed air systems. HDPE may also be used for special gasses such as nitrogen, oxygen, carbon dioxide and others that are used in both chemical and biopharmaceutical processes. The gas is usually supplied in cylinders or

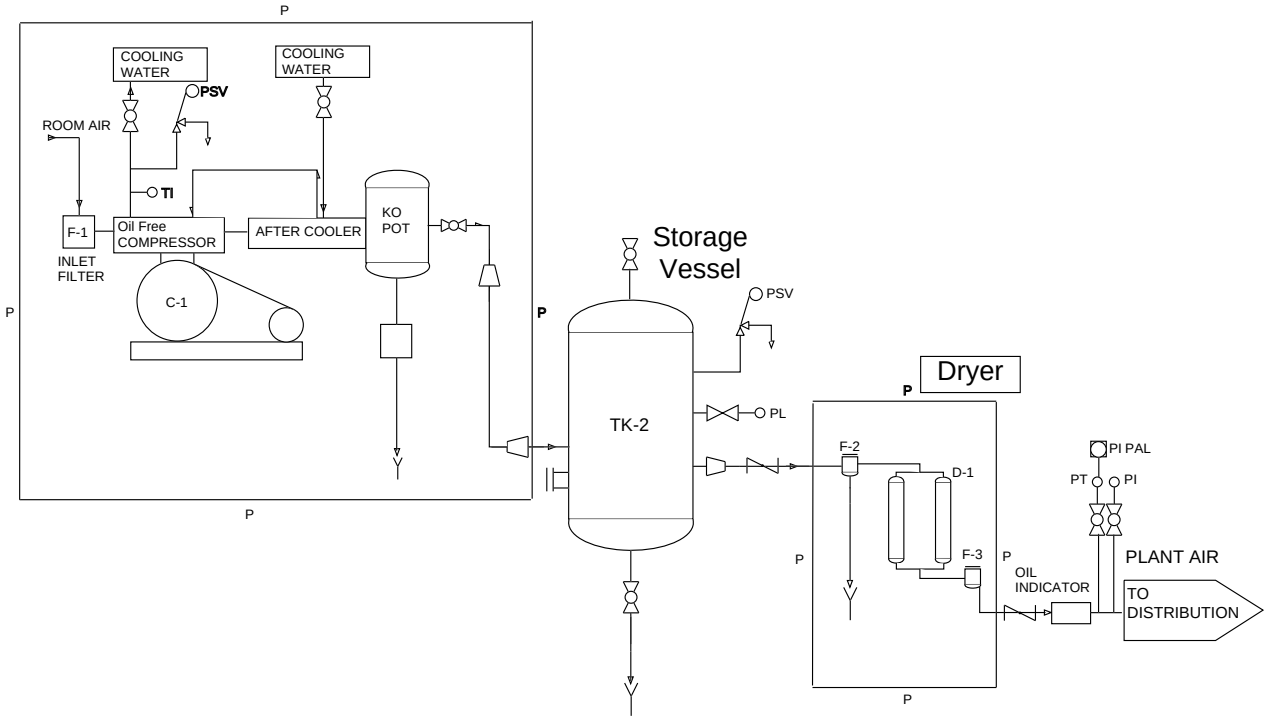

FIGURE 3.E COMPRESSED AIR SYSTEM

tanks

3.5.2 Applications

The following Systems are usually found in both pharmaceutical and biopharmaceutical facilities:

- Compressed Air
- Process
- Instrument
- Breathing
- Nitrogen
- Carbon Dioxide
- Oxygen

Both process air and nitrogen are used for transfer of fluids. Carbon dioxide is used in fermentation or cell culture for pH control. Oxygen and compressed air are used in fermentation and cell culture to supply dissolved oxygen.

Although stainless steel with compression fittings are used, it is neither required nor cost effective. All of these systems may be constructed of thermoplastics. The piping systems should be readily cleanable from the outside. Support spacing is an important design consideration.

3.5.3 Gasses

Bulk storage of gasses using multiple cylinders or a single large storage tank is the preferred method. A segregated access controlled area should be located outdoors adjacent to the building. A contract with a local provider assures that there is always an adequate supply.

3.5.4 Compressed Air

Oil free compressors are required. The system contains the following components:

- Inlet filter
- One or two compressors
- After cooler
- Storage Tank
- Air dryer (refrigerated or desiccant type - depending on dryness required)
- Final 0.2 micron filter

To assure required sterility at points of use, a final 0.2 micron filter is usually recommended. A single compressed air system should be sized to provide instrument air as well as emergency breathing air if required.

Consult the Asahi/America Piping Design Guide for the proper design and layout of a compressed air piping system.

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Section Four
Material Comparisons

4.0 Scope

This section is intended to point out the technical differences between stainless steel and thermoplastic piping systems. While plastic will never fully replace stainless steel, in many applications it is a far superior choice in terms of ease of installation, operational cost reductions, and long term performance.

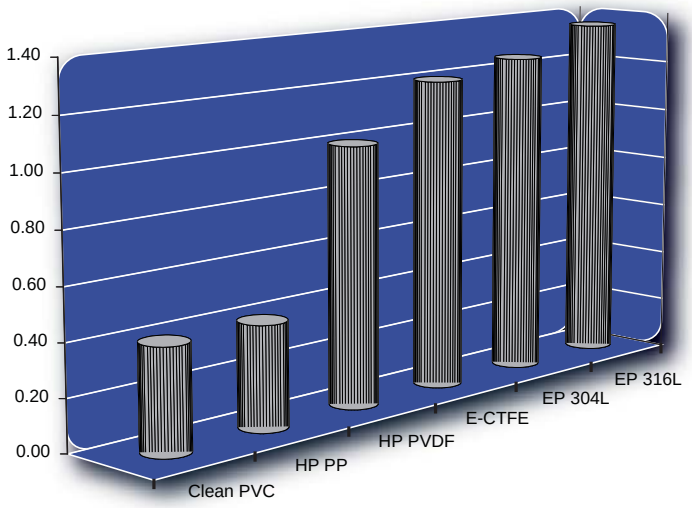

FIGURE 4.A Estimated Installed Cost Comparison of different materials of construction whereas PVDF = 1.0

4.1 Dimensional Comparison

One common issue that needs to be better communicated by polymer piping manufacturers to users is the dimensional difference between SDR thermoplastic piping and stainless steel tubing. The two terms here that need to be stressed are pipe and tube.

While a 316 stainless tube is rigid and looks like a pipe, it is generally provided in tube dimensions, therefore it is referred to as tubing.

4.1.1 Pipe to Tube Dimensional Comparison

Pipe dimensions are larger than tube dimensions. For example a 1 ½" tube is roughly the equivalent of 1 ¼" (40mm) pipe. Therefore if a system is designed based on tube dimensions and thermoplastic pipe is to be used, select a nominal pipe OD one size smaller than the tube for equivalence. A basic rule of thumb is a nominal pipe size is equal to one tube dimension size larger. Table 4.1 compares the dimensions of stainless steel tube to thermoplastic piping.

Another important factor is the connection and use of sanitary style ends and clamps. While these are now readily available in PVDF and Polypropylene, they are again not the same dimensions. For example, a 1 ¼" (40mm) pipe with a sanitary end will need a 1 ½" Sanitary clamp and will directly connect to 1 ½" stainless steel sanitary end. Table 4.2 is a chart depicting the comparison for ease of selection.

Stainless Tube			Purad PVDF, SDR21				PolyPure and Proline PP, SDR11			
OD		ID	OD			ID	OD			ID
Nominal inch	Actual inch	Actual inch	Nominal inch	Actual inch		Actual inch	Nominal inch	Actual inch		Actual inch
½	0.5	0.37								
¾	0.75	0.62	½	20	0.79	0.64	½	20	0.79	0.59
1	1	0.87	¾	25	0.98	0.83	¾	25	0.98	0.77
1 ¼			1	32	1.26	1.07	1	32	1.26	1.02
1 ½	1.5	1.37	1 ¼	40	1.57	1.39	1 ¼	40	1.57	1.3
2	2	1.87	1 ½	50	1.97	1.74	1 ½	50	1.97	1.61
2 ½	2.5	2.37	2	63	2.48	2.24	2	63	2.48	2.02
3	3	2.87	2 ½	75	2.95	2.66	2 ½	75	2.95	2.41

TABLE 4.1 Tube vs Pipe Dimensional Comparison

Thermoplastic Pipe Size		Clamp Size
Nominal	Actual	(Nominal Tube)
½"	20mm	½" / ¾"
¾"	25mm	1"
1"	32mm	1 ½"
1 ¼"	40mm	1 ½"
1 ½"	50mm	2"
2"	63mm	2 ½"

Table 4.2 Sanitary Clamp Size Selection

4.2 Surface Finish Comparison

It is believed that the electropolished pipe is the smoothest pipe available. Table 4.3 compares internal surface finish between PURAD PVDF, 316 electropolished (EP) and 316 mechanically polished (MP). The data is based on manufacturer's published data and not test results. From the chart it can be seen that comparable PVDF systems provide a smoother surface finish as compared to stainless steel. The Purad System is over 8% smoother than standard EP stainless steel and 30% smoother than most MP stainless steel.

Material	RA Result
Purad PVDF (20mm - 90mm)	7.8 µ" max
EP 316L Stainless Steel	15-25 µ" average
MP 316L Stainless Steel	20-30 µ" average

Table 4.3 Surface Finish Comparison PVDF and 316L Stainless

Purad PVDF surfaces are continuously monitored during production. In addition to production control, the Quality Control department conducts separate inspections of surface finish and other quality measures of each lot of production.

Studies conducted by G. Husted of MicroTechno Research, Inc have compared the bioadhesion properties of high performance thermoplastics (PVDF and E-CTFE) with that of high grades of EP and MP 316L stainless steel. Test samples were continuously rinsed at a velocity of 3 feet per second with E-1 quality UPW stream.

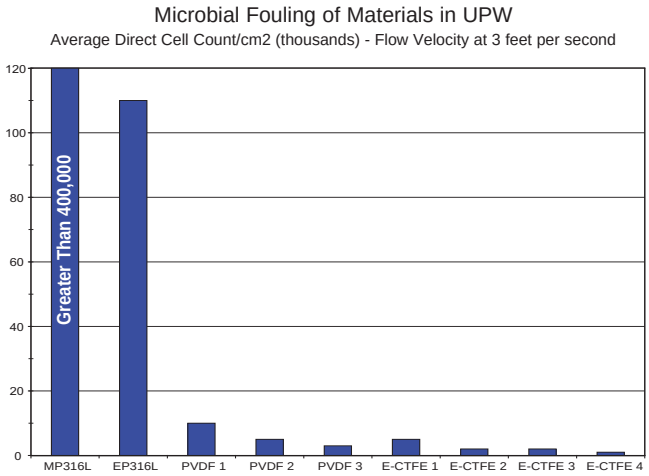

Table 4.4 Bio-adhesion Comparison between MP 316L, EP 316L, PVDF and E-CTFE Materials

> At weekly intervals 3 randomly selected discs of each test material [were] removed from the sampler, rinsed with a jet of double filtered UPW to remove non-firmly associated cells, stained with acridine orange, then viewed with epifluorescent illumination at 1,2400X."

The samples were examined and had their biocolonization levels directly counted. The results of which are shown on Table 4.4

From these tests, it is evident high performance thermoplastics are more resistant to bioadhesion than high grades of stainless steels.

In addition Purad PVDF, Proline PP and PolyPure surface finishes are continuously monitored during production. The roughness data is kept on record by production lot number. The data from this testing showing the Ra values for each production lot can be made available upon request.

4.3 Leachout Performance

While the surface profile is an important factor in terms of reducing bioadhesion, the leachout from a pipe system is more important to a systems overall purity level. A piping system is the transporter of water to the point of use. Its material of construction and joining method directly impacts the ability to maintain strict levels of purity. While the piping cannot positively influence water quality it can have a dramatic negative effect on water quality.

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It is well known; stainless steel piping systems leach higher rates of metal ions than thermoplastic systems. Table 4.5 provides a comparison of detectable ions and trace metals in high purity water systems with materials of construction of PVDF and 316L SS. Water samples were drawn from similar points and analyzed for contamination levels. As should be expected, metal ion contamination levels in the PVDF systems are dramatically lower than those of the stainless steel systems. (Also refer to Chart Figure 1.1 in Section One). The higher rates of contamination of stainless steel systems contribute to elevated conductivity levels, high TOC levels and increased rates of microbial activity by providing bacteria a nutrition rich environment.

As with stainless steel, thermoplastics are not all the same. Differences exist within each material type as well as between material type. A PVC system, even if made clean, leaches high amounts of TOC into a system due to the organic matter found in all solvent cements. Other sources of contamination can be introduced from the manufacturing method. This is true for all thermoplastic materials including high performance types such as PP and PVDF. Unless pipe is made in a cleanroom environment, it is likely to incorporate contaminates from the surrounding production environment. These contaminants may later leach into the water system.

Dynamic Leachout Comaprison of HP PVDF vs 316L SS

Element	PVDF-1	PVDF-2	316L-1	316L-2
Al	< DL	0.006	< DL	0.007
Ba	< DL	< DL	< DL	0.14
B	< DL	< DL	5.6	1.7
Ca	< DL	< DL	< DL	1.1
Cr	< DL	0.004	0.03	0.023
Co	< DL	< DL	0.03	0.033
Cu	< DL	< DL	0.007	0.011
Fe	< DL	< DL	< DL	0.02
Mg	< DL	< DL	0.002	0.36
Mn	< DL	< DL	0.019	0.041
Mo	< DL	< DL	< DL	0.022
Ni	< DL	< DL	0.44	0.24
K	< DL	< DL	< DL	0.5
Si	< DL	< DL	22	< DL
Na	0.015	0.04	0.16	5.4
Sr	< DL	< DL	< DL	0.038
W	< DL	< DL	0.24	0.15
Zn	< DL	< DL	0.023	< DL

DL = Detection Limit

Table 4.5 Actual purity comparison of four sample points in systems with piping materials in HP PVDF and 316L SS. Measurement type is Ion Chromotography.

When evaluating the merits of a particular material, review the production and packaging specification of various manufacturers. Systems well suited for PW applications are easily identified by dedicated cleanroom production and protective packaging. Systems such as these will best prevent introduction of contaminates alien to material composition.

4.4 System Assembly

Orbital welding is the most common method of joining high grades of stainless steel in pharmaceutical and biotech water systems. Used primarily for 300-series stainless steel, properly conducted orbital welding provides reliable, beadless welds. Standard procedures for orbital welding requires weld inspection coupons at the beginning of every shift and change of material lot or operator. This requirement is necessary due to the intrinsic variances in material composition of stainless steel. ASTM A270 specifies the allowed variances of composition including iron, carbon, chromium, nickel and molybdenum. This normally occurring variance translates into slightly different welding characteristics. Which in turn, explains why welding inspection coupons are continuously justified.

The iron content of austenitic stainless steels increases during the orbital welding process. This in turn disturbs the chromium/iron balance at the product surface. Systems become more susceptible to corrosion when this balance is disturbed. Passivation is required to restore the corrosion resistance properties of austenitic stainless steels.

ASTM A380-99 *Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems* specifies how nitric acid, or other similar agents, is used to restore the desired equilibrium between chromium and iron. By requiring passivation, stainless steel systems must be pitched and installed to allow complete drainage. This is the main reason, as well as those systems requiring Clean In Place (CIP) or Steam In Place (SIP), beadless and pitched systems are required. Systems not requiring passivation or CIP (i.e. high performance thermoplastics) do not require beadless welding and pitched installation.

Thermoplastics offer simplified welding techniques and installation. Both PVDF and PP are melt-processable polymers. Systems are joined by a variety of thermal-fusion welding techniques. As mentioned, PVDF and PP resins are extremely pure and immensely consistent from lot to lot. This purity and consistency allows for dependable welding parameters, which translate into repeatable and reliable welding techniques. Stainless steel welding concerns such as sulfur concentration, chromium depletion, condition of tungsten electrodes are not issues for thermoplastics. The result is simplified welding and installation practices with thermoplastic systems.

One of the most common high-purity welding methods for high performance thermoplastics such as PVDF and PP is a non-contact method known as Infrared (IR) Fusion. IR Fusion is accomplished by bringing the pipe components into close proximity with a heating element. Direct contact with the heater is avoided in order to minimize the risk of material contamination. IR Fusion provides superior weld results in terms of purity, reliability and speed of installation. This is evident by the semiconductor industries overwhelming preference for this method of joining, even when compared to various beadless systems.
(Please refer to Section Seven for greater details on IR Fusion and other available joining techniques.)

Many pharmaceutical engineers shy away form IR Fusion because of the presence of an internal bead. It is incorrectly assumed the bead presents an area for microbial proliferation. If this were the case, semiconductor water systems would have continuous problems with microbial levels. This is simply untrue as evident by actual installations. For example, one leading semiconductor manufacturer has warning levels of 2.5cfu/100ml and action limits of 5cfu/100ml for their UPW distributed in IR fused PVDF piping (1). These levels are well below the cGMP action levels of 10cfu/100ml for WFI and 10,000cfu/ml for PW!

Furthermore, leading process engineers have acknowledged the fact not all PW systems require pitched installations with drainage capabilities. "[T]he intent of a fully drainable system [in the context current Good Manufacturing Processes for Large Volume Parenterals (21CFR Part 212)] was to facilitate the draining of condensate after a system had been steam sterilized. The complete drain ability of ambient or chemically sanitized piping systems that do not have the ability to be steamed is not required. Nor is it reasonable for many water treatment operations, many of which do not have the ability to be steamed, to be required to be drained completely free of water" (2).

1. Lee, Ron; Patterson, Michael, Ph.D.; and Painter, John; "Semicondutors: The Efffect of Velocity on High-Purity Systems Rinse Up and Requalification"; Ultrapure Water Journal; March 2002; pg 41.
2. Collentro, Andrew; "Pharmaceuticals: Practical Microbial Control Techniques for Pharmaceutical Water Purification Systems"; Ultrapure Water Journel; March 2002; pg 56.

4.5 Rouging

Rouging is a ubiquitous and perhaps a misunderstood phenomenon that unfortunately is associated with the pharmaceutical industry. Rouge is an unacceptable visible evidence of water contamination by 316L stainless steel with corrosion by-products, primarily heavy metals. Regardless of cause, rouging is a serious issue, which must be dealt with in every stainless sanitary system.

The reason rouge is not well explained lies in part with the ephemeral nature of the effect and its unusual association primarily with the pharmaceutical and dairy industries. A review of the literature also reveals little study of the matter. There is a lot of contradiction on the causes and treatment. Metallurgists hold a part of the puzzle, but they do not have experience with hot WFI systems. Pharmaceutical engineers hold another key, but they may not have corrosion expertise. Passivation engineers have their take on the rouging problem, but are not very helpful in preventing rouge, only treating it.

It is interesting to note the following two facts:

- Nitric acid passivates stainless steel, but does not dissolve ferrous or ferric oxides; therefore it does not remove rouge.
- Acid cleaning removes rouge but does not passivate 316L stainless steel.

Stainless systems inherently require two timely and costly operations not required in thermoplastic systems.

Nobody can convincingly explain the causes or methods to prevent rouge in a stainless system. Having been said, water is truly the universal solvent. Therefore, stainless steel corrodes in high purity water. The metals content or rate of stainless steel corrosion can be determined by direct ICP/MS analysis of high purity water for metals. Experience has documented lower levels of metal ionic contamination is found in ambient

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temperature systems than comparable high temperature systems. In other words, stainless systems corrode and rouge quicker in high temperature operation. High temperature systems may be effective in controlling microbial activity but contribute to the overall degradation of water quality.

The metal content in these water systems is evidence of rouge and its contamination of the water. The heavy metal contamination by-product of rouge includes: Fe, Al, Ba, Cr, Cu, Co, Mn, Ni, Mo, W, Zn. For every corrosion source point, often exhibited by a hard discoloration of the pipe surface, there can be a deposition including in extreme cases, visible particles carried in the water. Rouge may be a self-catalyzing reaction that will reoccur some time after treatment.

The surface area of 316L stainless steel in contact with UPW should be minimized to avoid rouge and its contamination affects. When compared to hot or steam cleaned systems, ambient systems reduce the speed in which rouging spreads its harmful effects. USP25 guidelines now allow WFI quality water to be achieved through RO operation instead of traditional distillation. cGMPs also suggest 65°C is just as effective as 80°C in controlling microbial activity. Under these guidelines, why consider water distribution through expensive and corrosion susceptible stainless steel? High performance thermoplastics such as PP and PVDF can quickly become the obvious answer to rouge and its ubiquitous and unacceptable industry wide contamination issue.

4.4.1 Avoiding Rouge

Stainless steel can not be completely avoided in high purity water systems. In fact, stainless steel may be the preferred material for certain applications. However, the best method to avoid rouging is to limit the usage of stainless steel.

Stills- Stills can be a source of rouge and are often badly corroded when examined. Do not worry about rouge from main boilers; it will not carry over in the steam. The condenser and all wetted surfaces thereafter should be 316L stainless steel or Thermoplastic where applicable.

Pumps – All pump impellers and wetted surfaces should be 316L stainless steel, if not coated with high performance thermoplastic. Erosion due to pump cavitation will exacerbate rouging episodes.

Storage tanks- Use lined storage tanks for ambient temperature storage. Some stainless steel can be accommodated, and a stainless storage tank alone may be acceptable.

Piping – Ideally, piping material should be thermoplastic. Thermoplastic pipe, valves, fittings and measurement device will not rouge or corrode. In applications absolutely requiring stainless steel, 316L should be specified.

4.6 Bioadhesion Comparison & Control

The control of bacteria as a contaminant in product water should be the primary concern in the design and utilization of high purity water systems for Life Sciences applications. It is only recently that scientists have begun conceptualizing and treating bacteria not as discreet units, but as highly diverse, protected, complex communities, known as biofilm.

Understanding the formation, properties and behavior of the biofilm is required to effectively deal with bacteria in Life Sciences' water systems. This understanding assists designers and operators in attacking the core issues rather than the symptoms of bacteria laden water systems.

Biofilm Definitions

- A thin layer of bacteria and organic matter that occurs under the viscous boundary layer, at the interface between the bulk water phase and solid system components such as piping, filters and resins. An immobilized cell thin-film bioreactor.[1]

- A complex and highly diversified community of viable and nonviable microorganisms, their associated glycocalyx, adsorbable organics, and entrained particles.[2]

Bacteria cells are present, to some degree, in all distribution piping systems and adhere to essentially all wetted surfaces. Furthermore, "(b)iofilms form expected densities after 2 weeks on all wetted surfaces, regardless of flow velocity."[3] The presence of biofilms in high purity water piping, to some degree, is unavoidable. Once understood, the issue then becomes how to best minimize and limit biofilm and it adverse effects.

4.6.1 Methods of Controlling Biofilm

Heat
Heat has been proven to be an effective means of controlling overall system biocolonization levels. Hot systems are typically operated at 80ºC. Purad PVDF systems can easily handle systems designed to operate and sanitize at this temperature.

Recently, ISPE's Baseline Guide, Volume IV, "Water and Stream Systems", Jan 02, has recognized 65ºC as an equally effective temperature as 80ºC. PolyPure and Proline PP Systems can and should be considered under these circumstances.

In either case, PVDF and PP are excellent thermal insulators. Hot piping systems (up to 80ºC+) constructed of PVDF and PP do not require external insulation for maintaining critical, hot temperatures or for protection from injury resulting from burns.

However, those who use heat sanitization for ambient temperature systems such as carbon beds, RO membranes, distribution loops, etc. should be aware that heat sanitization does not remove biofilm, regardless of material of construction. In such systems, failure to remove a biofilm may lead to its re-colonization and growth even faster than with bare pipe. The old biofilm serves as an excellent capture and attachment site with nutrients at hand.

In addition, hot stainless steel water Life Sciences applications have become less attractive due to safety, cost and quality considerations (i.e. rouging – *Please refer to Section 4.5 for discussion on rouging*) and the move towards in-line mixing and the preponderance of ambient temperature applications. In addition, most points of use must be cooled prior to supply. This can add to sanitation concerns for improperly operated systems.

Velocity
Powell's work showed the average velocity to remove biofilm from electropolished pipe is 12 ft/sec. This is two times (2X) the average maximum velocity of water in distribution piping which results in an unacceptable pressure drop. The minimum thickness of the laminar sub layer for cold water is about 0.1 – 0.2 mm.[8] Even mature biofilm with films 5 µm thick would require 5 layers to begin to protrude into the turbulent flow at 8.6 ft/sec. As such, high velocity of water in distribution has been shown to have little or no effect in the control of microbiology and biofilm formation.[3, 6] In fact, excessive flow velocities may actually accelerate biofilm growth.[3]

The primary source of planktonic (free-floating) Microorganisms in the bulk phase of the high purity water is detachment of cells from the interfacial biofilm.[2, 4] As biofilm shearing adds to the overall nutrient levels of water systems, the sheared cells are quickly replaced with new levels of biofilm feeding in the relatively nutritious environment. This in turn leads to new layers of biofilm shearing into the flow stream. A troublesome cycle is now possible.

Limiting their growth in the high purity environment may best control biofilms and system bacteria levels. In high purity environments, cell proliferation in the biofilm is severely inhibited by a combination of colonization or inoculation prevention and nutrient deprivation.

Inoculation Prevention
Preventing inoculation of a piping system is a function of the water system design, not the distribution piping design. The water system design must limit and prevent both viable and nonviable organisms from proceeding downstream. It is a function of filtration with RO being one of the more effective means. This prevents seeding of a potential biofilm by colonizing bacteria and perhaps more importantly prevents live and dead organisms from providing a nutrient source to downstream biofilms.

Nutrient Deprivation
In extreme nutrient deficient environments, bacteria will not attach to surfaces. If they do not attach, they cannot form biofilm. – Costerton[7]

TOC control is essential to preventing biofilm proliferation. Water systems should not operate with TOC over 5ppb. Ideally the systems should run at < 0.5 ppb or 500 ppt TOC. This is a far tighter control of TOC than the 500 ppb allowed by regulation in Life Sciences water systems. Water systems with more than 50 ppb TOC are decidedly nutrient rich, and bacteria problems can be expected.

Multiple nutrient restrictions (phosphorous, nitrogen, potassium) appear to limit growth.[4] Water systems should target detectable elements at no more than 10 ppt. Borone should be the exception, which, if required, must be dealt with separately.[8] Standard designed RO/DI water systems are capable of routinely and continuously providing water of this quality. As shown on chart 1.A on page two of this guide, thermoplastic piping systems typically operate at extremely lower rates of ion contamination than 316L systems, thus, avoiding contribution to nutrition level required for the proliferation of biofilm and bacteria laden systems. This is the basis of biofilm control in the semiconductor industry where routine decontaminations and sanitation cycles

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are avoided, as the procedures themselves are considered a source of contamination. Additionally, it requires downtime that is neither available nor appreciated. Although semiconductor water requirements are different than those required for Life Sciences, high quality water with controlled biocolonization and endotoxin levels are issues for both industries.

Materials of Construction
Thermoplastics are the preferred choice for the materials utilized in UPW systems and distribution piping where water quality is the primary concern.

The product water from Life Science water systems utilizing 316L piping, always demonstrate a distinct metal ion signature, mirroring the composition of the 316L distribution piping. Trace metals for 64 elements as measured by ICP/MS are typically negative for high purity thermoplastic water systems to parts per trillion (ppt) levels.[8]

It is clear that 316L stainless steel supports the attachment and apparently promotes the growth of biofilm when compared side by side with thermoplastics in a series of tests. Gray states that stainless steel was generally concluded to allow more extensive biofilm growth than plastics.[9, 6] Husted found consistently lower microbial cell densities and biofouling, per unit area, are noted for thermoplastics when compared to stainless steel.[9] (*See Section 4.2 for more details).*

Surface finish alone does not appear to explain the disparity between 316L stainless steel and Thermoplastic piping systems. The average wall smoothness for Polypropylene is not as good as mechanical finished 316L stainless steel, yet experience indicates bacteria counts in the bulk water phase for Polypropylene is very similar to other thermoplastics reported in the data. This may indicate the biofouling is reduced for Polypropylene despite a rougher average pipe wall finish. Further investigation is ongoing.

As mentioned above, one possible explanation may be the metals in 316L provide a source of scarce limiting nutrients that are definitely not present in either PVDF or PP thermoplastic piping systems. However, thermoplastics such as PVC should be avoided for the solvents required for system joining contribute to contamination concerns and system TOC levels. The fact that PVDF may be employed at 65°C to 80°C and can be steam sanitized could make it an attractive option to replace stainless steel in hot WFI applications and is being utilized more frequently.

There is no correlation between the presence of biofilm and the water quality delivered to Points of Use.[7] By inhibiting biofilm growth, the scant biofilm that may be present is left virtually irreversibly attached to the substrate (pipe surface) in the laminar sub layer where it is unable to be sloughed into the bulk flow. This allows the Semiconductor Industry to achieve total bacteria counts (dead and alive) of less than 10 cells/liter.

4.6.2 Conclusion
In conclusion, thermoplastic piping systems should be specified for exceptionally high quality water systems for the following reasons:

- 316L systems have been shown to be more susceptible than PVDF to excessive biofilm formation.
- Hot water systems, if desired, are compatible with thermoplastic systems and do not experience accelerated corrosion as with stainless systems.
- High performance thermoplastics do not contribute to the nutrition (ion contamination) levels of water systems.

The key to controlling microbiology in high purity water systems is maintaining exceptionally high water quality. Operating higher quality systems than mandated by USP specifications should not be expensive. The use of very low TOC water (< 10 ppb TOC recommended) and thermoplastic distribution piping is conducive to control microbiology via nutrient deprivation.

The Semiconductor/Thermoplastic approach to higher water quality is proven effective and reliable and results in considerable cost savings in:

- Cost of Installation and Maintenance
- No boriscoping, passivation or de-rouging requirements
- No hot water utilities infrastructure and operational costs

The Semiconductor Industry routinely operates ambient DI water systems with less than one cfu/ liter microbiology levels without routine sanitizations being required. The effective and proven practices of biofilm control in this industry, of which thermoplastic piping systems is a major factor, should be considered as applicable and a cGMP for Life Sciences. Regardless of industry, low bacteria counts and high quality water systems are absolutely required.

Section 4.6 Bibliography

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5. "Battling Biofilm"; Scientific American; 7/2001

6. Gray, G.; "Recirculation Velocities in WFI Distribution Systems"; Pharmaceutical Engineering; Volume 17, #6, Nov/Dec 1997

7. Riedewald, F.; "Biofilms in Pharmaceutical Waters"; Pharmaceutical Engineering; Volume 17, #6, Nov/Dec 1997

8. With the exception of very low levels of boron, which can often be detected in high purity water systems regardless of design. Boron is typically the first ion to breakthrough a water system.

9. Husted, G.; " Evaluation of HALAR ECTFE for Surface Properties and Biofilm Formation in Ultrapure Water Service"; Micro Techno Research; Hinesburg, VT, printed by Ausimont, USA (July 11, 1996)

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Section Five
Validation Plan and Sample Validation Protocals

5.0 Generic Validation Plan

Prior to writing and building a validation plan, the essence of validation must be understood. The accepted definition of validation by the FDA is:

Documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Note the underlined words. The documented evidence is prepared with the following industry protocols:

Installation Qualification (IQ)
Documented verification that the equipment or system has been installed according to plans and specifications. All the pertinent information is assembled with this document.

The IQ should be written at the conception of a project and followed throughout the installation. In many cases it is written as an after thought to comply with regulations. Asahi/America provides the guideline for the IQ to make the document useful to a project.

Operational Qualification (OQ)
Verification that the system operates according to the design drawings and specifications. Failure modes and alarms are confirmed.

Process Qualification (PQ)
Confirmation that the system will produce the product or material as intended. Various operating configurations may require simulation. Analytical procedures must also be validated and the final test results complete the validation report.

The final document is a summary report which discusses the validation and determines that all acceptance criteria have been met.

It is extremely important to properly plan the validation of the system that is being installed. The plan becomes the basis of the entire activity and establishes the following components:

1. Scope
2. Facility or Process Description
3. Systems and Equipment to be Validated
4. Responsibilities:
   - Protocol Preparation
   - Protocol Execution
5. Acceptance Criteria
6. Protoc0l Format
7. Reference Procedures:
   - Standard Operating Procedures (SOP)
   - Material Receiving Procedures
   - Inspection Procedures
   - Calibration Procedures
8. Validation Schedule
9. Manpower Requirements
10. Change Control Procedures
11. Re-Validation Requirements
12. Appendices
    - Room Classification and Pressurization Drawings
    - Personnel and Material Flow Diagram
    - Process Flow Charts
    - Discussion

Not all of the above items may be needed for a system which is part of an overall facility project. The two most important documents in the plan and the subsequent protocols are a system description and a detailed process and instrumentation drawing. These should be prepared as soon as the design has been established.

Section Six
Materials and Systems Overview

6.0 Materials Introduction

This section is devoted to the discussion of thermoplastics and their properties as they pertain to pharmaceutical applications. References to polypropylene and PVDF are valid for Proline PP, PolyPure PP and Purad PVDF systems as offered by Asahi/America. Discussions of PVC and CPVC are relevant to our broad line of valving products, as well as a general guide for piping systems constructed of these materials

PVDF (Polyvinylidene Fluoride)
This high molecular weight fluorocarbon has superior abrasion resistance, dielectric properties and mechanical strength. These characteristics are maintained over a temperature range of -40 °F (-40 °C) to 284 °F (140 °C). In piping systems, PVDF is best suited for systems operating from 14 °F (-10 °C) to 250 °F (121 °C). PVDF is highly resistant to wet or dry chlorine, bromine and other halogens, most strong acids, aliphatics, aromatics, alcohols and chlorinated solvents. Because of its extremely low amounts of extractables, PVDF is widely used in the transport of ultra pure water for the semiconductor and pharmaceutical industries.

Asahi/America offers the Purad PVDF System for high purity applications. Purad is ideal for Pure Water and Water for Injection service. It is available in sizes 20mm to 315mm (1/2" to 12") with a wide assortment of fittings, valves and flowmeters.

E-CTFE (Ethylene Tetrafluoroethylene)
E-CTFE fluoropolymer is commonly known by its trade name HALAR®. E-CTFE is essential a 1:1 alternating copolymer of ethylene and CTFE (chlorotrifluoroethylene). It contains about 80% CTFE, one of the most chemically resistant building blocks that can be used to make a polymer. However, CTFE homopolymers are difficult to fabricate, extrude or mold. By the copolymerization with ethylene, E-CTFE displays much of the chemical resistance of CTFE with the ease of processing. It provides excellent chemical resistance, handling applications that almost all other materials can not. In particular, E-CTFE demonstrates effective handling of fuming acids and chlorinated bases.

HALAR is a registered trademark of Solvay Polymers

It is the best material for handling high concentrations of sodium hypochlorite. Additionally, E-CTFE has good electrical properties, and a broad-use temperature range from cryogenic to 300°F (150° C). E-CTFE is a tough material with excellent impact strength over its broad-use temperature range. E-CTFE also maintains useful properties on exposure to cobalt 60 radiation at dosages of 200 megarands. It is one of the best fluoropolymers for abrasion resistance.

Ultra Proline Halar Systems is Asahi/America's E-CTFE Piping System. Ultra Proline Systems are available in sizes between 32mm and 110mm (1" and 4") with a basic assortment of fittings and diaphragm valves. Ultra Proline Systems should be considered for aggressive CIP applications such as high concentrations of sodium hypochlorite, which have traditionally been difficult for other materials to handle.

Thermoplastic Application Range

Material	Max. Operating Temperature	Ranges of Application
PVDF	284 °F / 140 °C	piping: - Cold and hot UPW distribution - Polishing system -Cleanroom loop system - Hook up system - Reclaim system - Drain / waste system - CIP Chemical distribution
E-CTFE	300 °F / 150 °C	semifinished products: - Lining of UPW storage tanks - Lining of chemical storage tanks - Tank construction - Apparatus - Machined components
PolyPure Proline PP	204 °F / 95 °C	piping: -Cold and hot UPW distribution - Reclaim system - Drain / waste system - Reclaim system - CIP Chemical Distribution - Ventilation systems (Duct)
PVC	140 °F / 60 °C	piping: -Cold UPW feedwater - Drain / waste system - Limited Reclaim system - Ventilation systems (Duct)
CPVC	195 °F / 90 °C	piping: -Cold and hot UPW feedwater - Limited Reclaim system - Drain / waste system - Hot Acid Waste - Ventilation systems (Duct)

PP (Polypropylene)
A member of the polyolefin family, PP is one of the lightest plastics known. It possesses excellent chemical resistance to many acids, alkalies and organic solvents. PP is one of the best materials to use for systems exposed to varying pH levels as many plastics do not handle both acids and bases as well. It is not recommended for use with hydrocarbons and aromatics. PP is excellent for the transport of caustic cleaning agents often used in CIP applications. PP has also been extensively used in UPW applications because of its cost effectiveness and good purity performance when compared to PVDF. Its upper temperature limit is 204 °F (95°C).

Asahi/America offers two polypropylene piping systems: PolyPure and Proline. PolyPure is a natural PP produced primarily for Pure Water applications. Its packaging and production environment has been selected to ensure pure quality for UPW systems and is available from 20mm to 110mm (1/2" to 4")

Proline PP is a pigmented PP with a large and versatile application range. Sizes from 20mm to 1400mm (1/2" to 54") are available in a variety of pressure ratings for UPW, Chemical or Vent Systems.

PVC (Polyvinyl Chloride)
Asahi/America uses an unplasticized PVC polymer in all its PVC valves and flowmeters. This material has excellent chemical resistance, strength, rigidity, and modulus of elasticity. It resists attack by most acids and strong alkalies, as well as gasoline, kerosene, aliphatic alcohols and hydrocarbons, and salt solutions. Aromatic, chlorinated organic compounds, and lacquer solvents do affect PVC chemical properties. Its low cost and overall balance of properties make PVC the material best suited to the widest number of corrosive applications. Its temperature limit is 140 °F/60 °C. PVC is joined using a solvent cement process.

Asahi/America has pioneered the application usage of PVC Valves in the United States. Our valve product offering is one of the largest available. Depending on valve type, sizes from 1/2" to 24" are readily available from stock. Please consult our experienced valve department to learn more.

CPVC (Chlorinated Polyvinyl Chloride)
The properties of CPVC and its advantages are very similar to those of PVC; however, its working temperature range is higher (195°F/90°C) than that of PVC. It should be specified in some instances where hot corrosive liquids are being handled and an extra margin of safety is required. CPVC is joined using a solvent cement process.

CPVC valves are available primarily as ball or diaphragm type with sizes 1/2" through 12" commonly stocked. As with our PVC offering, our valve department in available to assist with sizing and selecting the appropriate product for your application.

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6.1 Purad PVDF

6.1.1 Materials

Purad PVDF pipe, valves and fittings are manufactured of natural Polyvinylidene Fluoride resin. PVDF is part of the fluorocarbon family with an alternating fluoride and hydrogen atom. These resins are partially crystalline, high molecular weight polymers of vinylidene fluoride. Purad is 100% PVDF with absolutely no antioxidants, antistatic agents, colorants, fillers, flame retardants, heat stabilizers, lubricants, plasticizers, preservatives, processing aids, UV stabilizers or any other additives. Purad is also resistant to the effects of gamma radiation and has V-O rating according to UL-94 vertical flame test.

Purad PVDF has been qualified for its inherent purity through extensive testing performed by internationally recognized independent laboratories. The outstanding performance of Purad material with respect to extreme conditions is well documented and available upon request. It is well suited to handle such aggressive media as ultrapure water and ultrapure, electronic grade acids. Just as importantly, it conforms to FDA regulations as outlined in Title 21, Chapter 1, Part 177-2510 for contact with food, of Code of Federal Regulations and is suitable for the safe application of products for continuous contact with food stuffs. PVDF corresponds also to the criteria of the 3A Sanitary Standards for multiple use plastic materials used as product contact surfaces for dairy equipment serial No. 2000.

Due to its material properties, surface finish, purity, mechanical strength and ease of installation, PVDF has become the flagship piping product of Asahi/America and high purity water and chemical applications.

The surface of PVDF components prevents the proliferation of microorganisms, similar to the surface of glass. This conclusion is the result of a study carried out be Solvay at the Centre d'Enseignement et de Recherches des Industries Alimentaires et Chimigues, CERIA in Brussels, analysis no. 284.321 dated the 14th of May 1974.

PURAD PVDF PHYSICAL CHARACTERISTICS

Property Test	Standard	Unit	PVDF
Specific gravity	ISO 1183	g/cm^3	1.77
Water absorption	DIN 53495	%	< 0.04
Permissible service temperature	-	°C	-40 to +140
Tensile strength at yield	ISO 527	MPa	50
Elongation at yield	ISO 527	%	9
Tensile strength at break	ISO 527	MPa	46
Elongation at break	ISO 527	%	80
Impact strength	ISO 179	kJ/m^2	124
Notch impact strength	ISO 179	kJ/m^2	11
Ball ind. hardness Rockwell	ISO 2039-1	MPa	80
Flexural strength	ISO 178	MPa	80
Modulus of elasticity	ISO 527	MPa	2000
Vicat softening temp VST/B/50	ISO 306	°C	140
Heat deflection temp	HDT/B ISO 75	°C	145
Coef. of linear therm. Expansion	DIN 53752	$K^{-1} \times 10^{-4}$	1.2
Thermal conductivity at 20 °C	DIN 52612	W/(mxK)	0.13
Volume resistivity	VDE 0303	OHM cm	$> 10^{13}$
Surface resistivity	VDE 0303	OHM	$> 10^{12}$
Dielectric constant at 1MHz	DIN 53483	-	7.25
Dielectric strength	VDE 0303	kV/mm	22
Physiological non-toxic	EEC 90/128	-	Yes
FDA	CFR 21.1177-2510	-	Yes
Friction coefficient	DIN 53375	-	0.34
Flammability	UL94	-	V-0
UV stabilization	-	-	Yes*

*PVDF is not suitable for direct connection to UV-Sterilizers. UV light traps can be installed to eliminate the problem.

6.1.2 System Overview

The Purad high purity PVDF Pipe System is designed specifically for use in ultra pure water application. Every valve, fitting and pipe is designed, produced and packaged for high purity applications. No other system in the world was designed from the ground up with this intention.

Purad is produced with the premiere PVDF resin of the market. It is the only product to exclusively utilize Solvay's high purity Solef resin for all pipe, fittings, valves and flow meters. Single resin source ensures component compatibility and produces reliable, repeatable weld quality. Utilizing a single resin source also simplifies validation protocol.

Solvay's Solef 1000-0001 Series Resin is 100% pure PVDF with absolutely no additives or processing agents. Designed and produced exclusively for high purity applications, Solef resin provides superior performance and reliability.

Purad is available in sizes ½" through 12". All components are produced in a class 1000 or 100 cleanroom. Dedicated extrusion and molding equipment eliminates cross contamination threats. Continuous quality control measures are in place to ensure the Purad product meets our stringent qualifications.

Purad Pipe is immediately packaged after production in a class 100 cleanroom. They are sealed on each end with a PE film and PE cap. The pipe is then sleeved in the PE and heat sealed on each end. Pipes are shipped in rigid PE tubes which are non-particle generating and resistant to moisture and impacts.

Valves and fittings are cleaned after secondary machining in a 6 basin automated hot UPW bath system (UPW quality: TOC <10 ppb, conductivity >18 MΩ, Temperature >70°C). After drying with hot clean-air (class 100) and 100% quality inspection, the valves are assemblied and all fittings and valves are double bagged under a cleanroom class 100 environment.

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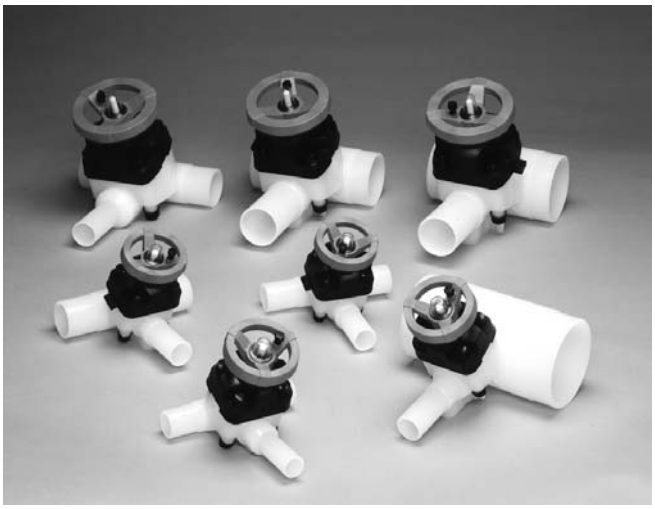

The Purad PVDF system offers zero deadleg valves in over 35 size configurations from 20mm x 20mm to 110mm x 63mm (½" x ½" to 4"x 2"). Specialty fittings such as instrument fittings allow for the proper installation of gauges and sample valves, completely eliminating dead zones in a pipe system. Newly introduced needle valves now provide an excellent method for drawing off low volume samples.

System assembly can be conducted utilizing two approved high purity methods. Beadless smooth surface fusion is available from ½" to 2". Non contact IR fusion is available from ½" to 10". Both methods offer considerable purity advantages over conventional methods. For less critical applications, contact butt fusion and socket fusion are available. Please consult the installation section of this manual and Asahi/America's Engineering Design Guide for further information on joining techniques.

6.1.3 Surface Finish

Purad PVDF is produced with extremely smooth surface finishes. Depending on size, finish quality tolerances are held as tight as 7.5 µm Ra for both pipe and fittings. The excellent surface finish helps resist biofilm and biocolonization. The smooth surface on our high purity components are achieved by application of specially designed and designated manufacturing equipment and tooling. Special materials and surface finishes of tools used for injection moulding and extrusion have a significant influence upon the surface quality of the finished product.

The surface quality is constantly monitored during production of all high purity components. The surface roughness (Ra-values) and micropores are measured to ensure system compliance. These tests are performed on a statistical basis and provide an excellent indication of the quality of the manufacturing process. Additionally, independent labs and interferential microscopy are used to measure quality in accordance with SEMATECH 9201055 B (SEM).

6.1.4 Purad Pressure Rating

As with all thermoplastic materials, Purad's pressure rating is derated as the operating temperature is increased. Purad has two available system ratings depending on the Standard Dimensional Ratio (SDR). SDR21 is rated for PN16/230psi services and SDR33 has a PN10/150psi rating. To determine the rating based on a system's operating temperature use the table below.

Temperature °F	Temperature °C	Correction Factor
68	20	1.00
80	27	0.95
90	32	0.87
100	38	0.80
120	49	0.68
140	60	0.58
160	71	0.49
180	82	0.42
200	93	0.36
240	115	0.25
280	138	0.18

Table 6.1: Purad PVDF Pressure Rating Table.
Multiply the Correction Factor times the nominal pipe rating.
Example: SDR21 Pipe (230psi) at 120 °F, 230psi x 0.68 = 156.4 psi

6.1.4 Purad: The Pure Advantage

While many companies offer PVDF piping, only Asahi/America offers the **Total System Approach**. The Purad System is more than components, it is a highly engineered system providing the greatest level of purity, reliability and safety.

Purad systems consist of many individual advantages when combined provide the most reliable and complete system on the market. Some of the advantages include:

- One resin supplier for all components
- One color for all products
- Largest size range 20mm - 315mm (½" – 12")
- Vortex Flow meters from 16mm - 225mm (¼" – 9")
- More pressure rating options per size
- Sweep 90 elbows instead of sharp radius
- All products class 100 or 1000 clean room produced
- Each fitting and valve hot DI washed for over 1 hour
- Pipe Packaging includes HDPE outer tube; non-particle generating
- Fittings in tear-proof double bags

The Total Systems Approach provides Purad Systems with the Pure Advantage in high purity flow distribution.

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6.2 HALAR® E-CTFE

6.1.1 Materials

HALAR resin, produced by Solvay Polymers is a copolymer of Ethylene and chlorotrifluorethylene. Halar offers superior chemical resistance, electrical properties, and extremely low permeability. Halar has a temperature range of –105 °F to 300 °F.

Severe stress tests have proven that it is not subject to chemically induced stress cracking from strong acids and bases, solvents and chlorine. In particular E-CTFE can with stand high concentrations of Sodium Hypochlorite and Hydrogen Peroxide, out performing most available plastic and alloy materials. It is only affected by hot amines and molten alkali metals.

HALAR is produced in a variety finished and semifinished forms. As a semifinished product, Halar is commonly used as tank liners, sheet material or rod stock. Asahi/America's HALAR systems is martketed as Ultra Proline E-CTFE is the only molded and extruded HALAR piping system for pressure applications.

6.2.2 System Overview

Ultra Proline is available in dimensions between 32mm – 110mm (1" – 4"). Larger sizes can be accommodated on special request. Fittings are produced as butt fusion style suitable for contact butt fusion and IR non-contact butt fusion. Halar piping systems can be specified as high purity or general grade depending on application requirement.

High purity Ultra Proline Pipe, as with Purad PVDF, is immediately packaged after production in a class 100 cleanroom. Pipe ends are sealed with PE film and PE cap. The pipe is then sleeved in the PE and heat sealed on each end. Pipes are shipped in rigid PE tubes which are non-particle generating and resistant to moisture and impacts.

Valves and fittings are cleaned after secondary machining in a 6 basin automated hot UPW bath system (UPW quality: TOC <10 ppb, conductivity >18 MΩ, Temperature >70°C). After drying with hot clean-air (class 100) and 100% inspection, the valves are assembled and all fittings and valves are double packaged under a class 100 cleanroom environment.

6.1.3 Surface Finish

Ultra Proline is produced with surface finishes smoother than that of PVDF. Depending on size, finish quality is better than 7.8 µm Ra for both pipe and fittings. The excellent surface finish helps resist biofilm.

HALAR E-CTFE PHYSICAL CHARACTERISTICS

Property Test	Standard	Unit	E-CTFE
Specific gravity	ISO 1183	g/cm^3	1.68
Water absorption	DIN 53495	%	< 0.1
Permissible service temperature	-	°C	-76 to +150
Tensile strength at yield	ISO 527	MPa	30
Elongation at yield	ISO 527	%	5
Tensile strength at break	ISO 527	MPa	54
Elongation at break	ISO 527	%	250
Impact strength	ISO 179	kJ/m^2	no break
Notch impact strength	ISO 179	kJ/m^2	no break
Ball ind. hardness Rockwell	ISO 2039-1	MPa	R 90
Flexural strength	ISO 178	MPa	47
Modulus of elasticity	ISO 527	MPa	1690
Vicat softening temp VST/B/50	ISO 306	°C	--
Heat deflection temp	HDT/B ISO 75	°C	90
Coef. of linear therm. Expansion	DIN 53752	$K^{-1} \times 10^{-4}$	0.8
Thermal conductivity at 20 °C	DIN 52612	W/(mxK)	0.15
Volume resistivity	VDE 0303	OHM cm	$> 10^{16}$
Surface resistivity	VDE 0303	OHM	$> 10^{14}$
Dielectric constant at 1MHz	DIN 53483	-	2.6
Dielectric strength	VDE 0303	kV/mm	30-35
Physiological non-toxic	EEC 90/128	-	Yes
FDA	CFR 21.1177-2510	-	in prep.
Friction coefficient	DIN 53375	-	0.19
Flammability	UL94	-	V-0
UV stabilization	-	-	Yes

Components are produced by application of special design and designated manufacturing equipment and tooling. Special material and finish of tools used for injection molding and extrusion have a significant influence upon the surface quality of the finished product.

The surface quality is constantly monitored during production of all high purity components. The surface roughness (Ra-values) and micropores are measured to ensure system compliance. These tests are performed on a statistical basis and provide an excellent indication of the quality of the manufacturing process. Additionally, independent labs and interferential microscopy are used to measure quality in accordance with SEMATECH 9201055 B (SEM).

6.2.4 Ultra Proline Pressure Rating

As with all thermoplastic materials, Ultra Proline pressure rating is derated as the operating temperature is increased. All Halar components are produced as a SDR21 system. Halar systems differ from most thermoplastics in that its pressure rating varies according to OD while maintaining the same SDR. Care should be taken when specifying Halar systems to ensure all system components are suitable for the application pressure requirements.

6.2.4 Ultra Proline Advantages

Asahi/America and Agru are uniquely able to provide Halar piping systems offering the following advantages:

- One of the smoothest Surface Finish of any thermoplastic material
- Extremely low levels of leachables
- More cost effective than PFA Pipe
- Superior Chemical Resistance
- Reliable Joining Techniques

Table 6.3 Halar Pressure System Pressure Rating

Temperature [°C]/[°F]	Operation period [years]	PN 10 / ISO S-10 / SDR 21 Permissible system working pressure 1) bar/psi		
		OD 20mm-32mm OD 1/2" - 1"	OD 40mm-50mm OD 1 1/4" - 1 1/2"	OD 63mm-160mm OD 2" - 6"
20/68	1	20.2/287.3	15.9/226.1	12.6/179.2
	10	18.7/265.9	14.7/209.0	11.6/164.9
	25	17.7/251.7	13.9/197.7	11.0/156.4
	50	17.2/244.6	13.5/192.0	10.7/152.1
60/140	1	13.1/186.3	10.3/146.5	8.2/112.3
	10	11.1/157.8	8.7/123.7	6.9/98.1
	25	10.6/150.7	8.3/118.0	6.6/93.8
	50	10.1/143.6	7.9/112.3	6.3/89.6
70/158	1	9.1/129.4	7.1/100.9	5.6/79.6
	10	8.4/119.4	6.6/93.8	5.2/73.9
	25	8.1/115.2	6.3/89.6	5.0/71.1
	50	7.9/112.3	6.2/88.1	4.9/69.6
80/176	1	6.7/95.2	5.3/75.3	4.2/59.7
	10	6.4/91.0	5.1/72.5	4.0/56.8
	25	6.2/88.1	4.9/69.6	3.9/55.4
	50	6.1/86.7	4.8/68.2	3.8/54.0
90/203	1	4.9/69.6	3.9/55.4	3.1/44.0
	10	4.9/69.6	3.9/55.4	3.1/44.0
	25	4.9/69.6	3.9/55.4	3.1/44.0
	50	4.9/69.6	3.9/55.4	3.1/44.0

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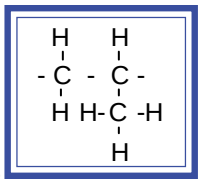
6.3 PolyPure Natural Polypropylene

6.3.1 Materials

PolyPure is a natural, random copolymer polypropylene offering superior mechanical properties over homopolymer materials. PolyPure's flexural modulus is more than 30% lower than homopolymer pipe, making it more flexible in bending applications. Lower crystallinity in the joints also makes PolyPure more reliable.



PolyPure is a pure polypropylene, offering low extractables and excellent surface finish. PolyPure production is conducted on Agru's state-of-the-art extrusion and injection molding equipment. Pipe is capped and sealed immediately after production. Fittings and valves are cleanroom produced, DI rinsed after secondary machining and individually packaged. This production standards helps maintain the purity of the system.

The PolyPure system is a viable, cost-effective alternative to stainless steel and PVDF Pure Water systems. Superior resin and production techniques are employed to maximize the effectiveness of the PolyPure system. In addition, PolyPure conforms to the FDA, CFR, Title 21 (2001) 177.1520 for contact with food stuff.

6.3.2 System Overview

PolyPure is available in sizes 20mm - 110mm (½" –4") with a wide variety of fittings, valves, flow meters and joining techniques.

Produced on dedicated equipment, PolyPure components are packaged to protect its purity and quality. Pipe ends are immediately sealed with PE film and PE Caps. Pipe are then packaged in full length PE bags (quantity dependent) for further protection.

Valves and fittings are cleaned after secondary machining in an automated hot UPW bath system (UPW quality: TOC <10 ppb, conductivity >18 MΩ, Temperature >70°C). After drying with hot clean-air (class 100) and 100% inspection, the valves are assembled and all fittings and valves are double packaged under a cleanroom class 100 environment.

The prefrered methods of system joining are butt or IR fusion. Butt and IR fusion methods provides superior weld mechanical properties exceeding the mechanical properties of socket fusion. IR Fusion provides the additional purity benefit of reduced risk of heater element cross-contamination. If desired, socket fusion is available for sizes 20mm - 63mm (½" - 2").

POLYPURE PHYSICAL CHARACTERISTICS

Property Test	Standard	Unit	PP-R
Specific gravity	ISO 1183	g/cm^3	0.9
Water absorption	DIN 53495	%	(-) < 0.01
Permissible service temperature	-	°C	-5 to +95
Tensile strength at yield	ISO 527	MPa	25
Elongation at yield	ISO 527	%	(-) 12
Tensile strength at break	ISO 527	MPa	40
Elongation at break	ISO 527	%	800
Impact strength	ISO 179	kJ/m^2	no break
Notch impact strength	ISO 179	kJ/m^2	25
Ball ind. hardness Rockwell	ISO 2039-1	MPa	45
Flexural strength	ISO 178	MPa	20
Modulus of elasticity	ISO 527	MPa	(-) 700
Vicat softening temp VST/B/50	ISO 306	°C	65
Heat deflection temp	HDT/B ISO 75	°C	(68) 75
Coef. of linear therm. Expansion	DIN 53752	$K^{-1} \times 10^{-4}$	1.5
Thermal conductivity at 20 °C	DIN 52612	W/(mxK)	0.24
Volume resistivity	VDE 0303	OHM cm	$> 10^{16}$
Surface resistivity	VDE 0303	OHM	$> 10^{13}$
Dielectric constant at 1MHz	DIN 53483	-	2.33
Dielectric strength	VDE 0303	kV/mm	(75) 70
Physiological non-toxic	EEC 90/128	-	Yes
FDA	CFR 21.1177-2510	-	Yes
Friction coefficient	DIN 53375	-	0.3
Flammability	UL94	-	HB
UV stabilization	-	-	No

6.3.3 PolyPure Pressure Ratings

As with all thermoplastic materials, PolyPure's pressure rating is derated as the operating temperature is increased. To determine the rating based on a system's operating temperature use the table below. PolyPure is an SDR 11 piping system rated at 150 psi at 68 °F in all dimensions.

Temperature °F	Temperature °C	Correction Factor
73	22.7	1.0
100	37.7	0.6
140	60.0	0.4
180	82.2	0.3
200	93.3	0.1

Table 6.2 PolyPure Pressure Rating Correction Chart
Multiply the Correction Factor times the nominal pipe rating.
Example: SDR11 Pipe (150psi) at 140 °F, 230psi x 0.60 = 90 psi

6.3.4 PolyPure System Advantages:

PolyPure Systems offer many advantages. The choice of resin, production methods and packaging specifications combine to provide the highest quality polypropylene system. Additional advantages include:

- Purity of Material, random copolymer PP resin offers lower extractables compared to homopolymer PP and high purity PVC system.
- Random copolymer polypropylene offers superior mechanical properties.
- Clean room production insures the purest piping system available
- Available in multiple joining techniques, Butt fusion, Socket Fusion and IR Fusion.
- All joints are made using heat fusion, providing reliability and maintaining purity. No messy cements which increase TOC levels.

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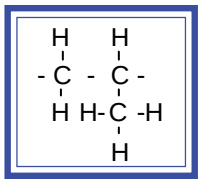
6.4 Proline Pigmented Polypropylene

6.4.1 Materials



Proline systems are pigmented polypropylene and are manufactured from random copolymer resin. Copolymer materials offer superior mechanical properties over homopolymer materials. Proline's flexural modulus is more than 30% lower than homopolymer pipe, making it more flexible in bending applications. Lower crystallinity in the joints also makes Proline systems more reliable.

Proline systems have an extremely large application range. Equally suited for UPW transport, caustic CIP distribution or aggressive vent systems, Proline provides maximum system flexibility.

6.4.2 System Overview

Proline is readily available in sizes 20mm to 630mm (1/2" through 24") and can be supplied in sizes up to 1400mm (54"). The wide size range is supported by a full line of molded fittings and valves up to 400mm (20").

Proline systems are supplied as SDR11 or SDR33 with respected pressure ratings of 150psi and 45psi. Additional ratings are available upon request.

High Purity Proline pipe is immediately packaged after production and is sealed on each end with a PE film and PE cap. The pipe is then sleeved in the PE and heat sealed on each end. Pipes are shipped in rigid PE tubes which are non-particle generating and resistant to moisture and impacts.

High purity grades of Proline valves and fittings are cleaned after secondary machining in an automated hot UPW bath system (UPW quality: TOC <10 ppb, conductivity >18 MΩ, Temperature >70°C). After drying with hot clean-air (class 100) and 100% inspection, the valves are assembled and all fittings and valves are double packaged under a cleanroom class 100 environment.

Proline systems are joined by a variety if methods. For PW, IR is commonly specified. Butt and socket fusion are available options. For vent systems, butt fusion or slip coupling welding can be utilized depending upon system size.

PROLINE PHYSICAL CHARACTERISTICS

Property Test	Standard	Unit	PP-R
Specific gravity	ISO 1183	g/cm^3	0.9
Water absorption	DIN 53495	%	(-) < 0.01
Permissible service temperature	-	°C	-5 to +95
Tensile strength at yield	ISO 527	MPa	25
Elongation at yield	ISO 527	%	(-) 12
Tensile strength at break	ISO 527	MPa	40
Elongation at break	ISO 527	%	800
Impact strength	ISO 179	kJ/m^2	no break
Notch impact strength	ISO 179	kJ/m^2	25
Ball ind. hardness Rockwell	ISO 2039-1	MPa	45
Flexural strength	ISO 178	MPa	20
Modulus of elasticity	ISO 527	MPa	(-) 700
Vicat softening temp VST/B/50	ISO 306	°C	65
Heat deflection temp	HDT/B ISO 75	°C	(68) 75
Coef. of linear therm. Expansion	DIN 53752	$K^{-1} \times 10^{-4}$	1.5
Thermal conductivity at 20 °C	DIN 52612	W/(mxK)	0.24
Volume resistivity	VDE 0303	OHM cm	$> 10^{16}$
Surface resistivity	VDE 0303	OHM	$> 10^{13}$
Dielectric constant at 1MHz	DIN 53483	-	2.33
Dielectric strength	VDE 0303	kV/mm	(75) 70
Physiological non-toxic	EEC 90/128	-	Yes
FDA	CFR 21.1177-2510	-	Yes
Friction coefficient	DIN 53375	-	0.3
Flammability	UL94	-	HB
UV stabilization	-	-	Limited

6.4.3 Proline Pressure Ratings

As with all thermoplastic materials, PolyPure's pressure rating is derated as the operating temperature is increased. To determine the rating based on a system's operating temperature use the table below. PolyPure is an SDR 11 piping system rated at 150 psi at 68 °F in all dimensions.

Temperature °F	Temperature °C	Correction Factor
73	22.7	1.0
100	37.7	0.6
140	60.0	0.4
180	82.2	0.3
200	93.3	0.1

Table 6.3 Proline Pressure Rating Correction Chart
Multiply the Correction Factor times the nominal pipe rating.
Example: SDR11 Pipe (150psi) at 140 °F, 230psi x 0.60 = 90 psi

6.4.4 Proline System Advantages:

Proline Systems offer many advantages such as:

- Largest assortment of molded polypropylene components and fittings.
- Available size range of 20mm to 1400mm (1/2" to 54")
- Flexible application range.
- Available in multiple joining techniques, Butt fusion, Socket Fusion and IR Fusion.
- All joints are made using heat fusion, providing reliability and maintaining purity. No messy cements which increase TOC levels.

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Section Seven
Piping Design
High Purity Water Systems

7.0 Introduction

A pure water system comprised of PVDF or Natural Polypropylene is similar to that of most chemical feed systems. The critical difference in a pure system is to design it as a continuous recirculating loop with minimized dead legs and maintain extremely low TOC levels in order to inhibit microbial growth.

Systems should also be sized to have turbulent flow as a part of the strategy of inhibiting bacteria growth. PVDF and PP systems are ideally suited for pure water as they have extremely smooth inner surfaces which reduce particle generation and inhibit sites for bacteria to adhere to and proliferate. In addition, PVDF and PP systems have low extractables, thus not contaminating the water being transported.

In designing a thermoplastic water system, the following items need to be considered:

- Material of Construction
- Operating Parameters
- System Sizing
- Thermal Expansion/Hanging Methods
- Instrumentation and Controls
- Sanitization Methods
- Welding Method
- Dead Leg Reduction and End-Point Configuration

7.1 Materials of Construction

The Purad High Purity PVDF Piping System is the premier system for Pure Water applications. PVDF has been used in Pure Water Systems for over fifteen years. Purad combines excellent surface finish with extremely low extractables to provide the highest quality piping material. In addition to purity attributes, Purad also has a wide variety components and welding methods well suited for HP applications. Purad is a crystalline material that can withstand high pressures. However, all PVDF is more brittle than PP and requires special planning and handling during installation. These requirements are now commonplace on the market and are accepted as standard operating methods. For the strictest applications, requiring low bacteria counts and virtually undetectable levels of metal ions, Purad PVDF is recommended for the service.

For less stringent water quality applications, PolyPure Natural Polypropylene is an excellent alternative. PolyPure offers excellent surface smoothness, as well as, low extractable levels as compared to stainless steel. PolyPure systems are thermally fused together, eliminating the use of glues, which will continue to leach into a water system for extended periods of time. Polypropylene is an extremely weldable material, making fusion joints that are simple and reliable.

Operating Parameters

Because thermoplastic systems have varying ratings at different temperatures it is important to design a system around all the parameters it will be subjected to. The following operating parameters should be verified:

- Continuous operating Temperature
- Continuous operating Pressure
- Flow rates

Knowledge of the above parameters is required in order to determine the suitability of thermoplastics for your application. Compare the actual conditions to the allowable ratings of the material being selected for the job. It is important to predict elevated temperatures, as thermoplastics have reduced pressure ratings at higher temperature. Valves should be verified in terms of temperature and pressure separately from a piping system, as certain styles and brands of valves have lower ratings than that of the pipe system.

After verifying the standard operating conditions, it is necessary to examine other operations that might effect the piping. The following is a sample of items to consider, prior to specifying a material:

- Will there be spikes in temperature or pressure?
- Is there a cleaning or sanitization operation that the piping will be exposed to?
- If yes, what is the cleaning agent?
- What temperature will cleaning be conducted at?
- Will the system be exposed to Sunlight or employ other sources of UV radiation?

Each of the above questions should be answered and the desired material should be checked for suitability based on the above factors as well as any others that might be special to the system in question.

7.2 System Sizing

It is well known that high purity water systems are designed to operate in a continuously flowing loop to prevent stagnant water in the system. Stagnant water propagates the growth of bacteria and biofilm. The rate of microbial growth is dependent on numerous factors including the initial quality of the water. However, after an initial lag phase, exponential growth is likely to begin within 12 to 24 hours.

Continuous flow is therefore recommended for all areas of PW and WFI distribution. General guidelines have traditionally suggested flow velocities between 3 to 5 ft/second.

However, a more sensible approach with high performance thermoplastics may be to review the Reynolds Number of the system to insure the flow is turbulent. Use of the Reynolds Number may reduce wasteful over sizing of pumps, excessive pressure drops, and unnecessarily high velocities.

Determination of Reynolds' Number
Once the diameter sizes have been selected for a given piping system, the next step is to determine whether the flow through the pipes is laminar or turbulent. The only accepted way of determining this characteristic through analytic means is by calculating the Reynolds' Number. The Reynolds' Number is a dimensionless ratio developed by Osborn Reynolds, which relates inertial forces to viscous forces.

To determine type of flow from Reynolds' Number value, use:

$$N_{re} = (D_e v\rho) / (\mu g)$$

Where:

N_{re} = Reynolds' Number (dimensionless)
D_e = equivalent diameter (ft = inside diameter fully-filled circular pipe)
v = velocity (ft/s)
ρ = fluid density (lb/ft3)
μ = relative viscosity (lb x sec/ft2)

Laminar flow:	N_{re} < 2100
Transition region:	N_{re} 2100 to 3000
Turbulent flow:	N_{re} > 3000

In addition to this approach recent tests results compared the effectiveness of 0.5 and 1.0ft/sec velocities in rinsing contaminated UPW into specification[1]. UPW samples were exposed to prolonged stagnation (over 8 hours) allowing prolific microbial growth. High-purity, IR Fused, PVDF systems rinsed into specification from greater than 90 cfu/100ml to under 2.5 cfu/100ml in 30 minutes with 1.0 ft/sec. This clearly suggests maintaining system velocities at 1.0 ft/sec may be sufficient and can effectively limit microbial activity associated with stagnant water.

Sizing Laterals
A Purified Water system may be made of a main loop and branches known as Laterals. It is important in design to not dead end laterals and ensure that there is always flow movement in the main and the lateral. Systems are designed with different loop configurations to accommodate the needs of production. However, all laterals must be designed for continuous flow and should feed back unused water into a return line.

1. Lee, Ron; Patterson, Michael, Ph.D.; and Painter, John; "Semicondutors: The Effect of Velocity on High-Purity Systems Rinse Up and Requalification"; Ultrapure Water Journal; March 2002; pg 41.

7.3 Thermal Expansion

Purad and PolyPure systems designed for ambient or Cold DI water that are inside at a constant temperature building generally do not need to compensate for thermal expansion. However, thermal expansion is an important factor that should be at least reviewed on each and every installation design.

Hot systems, normally operating at temperatures of 65 °C to 120 °C, require a more complex design. Purad PVDF systems can be used in many hot water applications and applications where the temperature is cyclical, it just requires analysis of the thermal expansion effects and proper design to compensate for those effects.

Polypropylene and PVDF will grow significantly with the introduction of heat. For example polypropylene will grow close to 1 inch for every 10 ºF of temperature increase over 100 feet of straight pipe. The growth of pipe can be properly compensated for utilizing expansion loops, offsets or changes in direction. Figure 7.A depicts one recommended methods of expansion design. Using the loops, offsets or changes in direction is ideal since they

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are homogenous with the pipe system. Other devices such as pistons or bellows can also be used, but are not recommended for PW or WFI applications as they rely on mechanical features and connections that could leak over time and are not compatible with sanitary design.

Offset

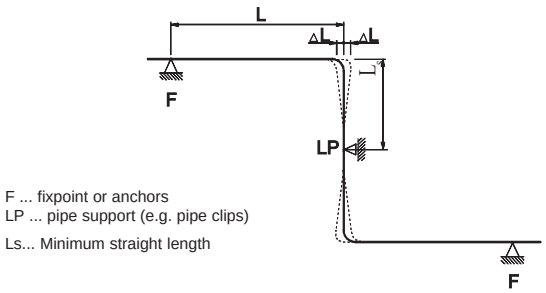

Figure 7.A An Example of one Thermal Expansion Design Options

For a thorough review of thermal expansion and proper design, consult Section C of the Asahi/America Engineering Design Guide.

Hot DI systems also reduce the rigidity of thermoplastic piping systems, which in turn decreases the support spacing between pipe hangers. In smaller dimensions it is recommended to use continuous support made of some type channel or split plastic pipe.

The use of hangers as guides and anchors becomes important. As the design procedures in Section C of the Engineering Design Guide indicate, certain hangers should be used as guides to allow the pipe to move back and forth in-line, while other hangers shall be anchoring locations used to direct the expansion into the compensating device. The anchors and hangers should be designed to withstand the end load generated by the Thermal Expansion. Figure 7.B an example of an anchor type fitting with a fixing pipe clamp available from Asahi/America, Inc.

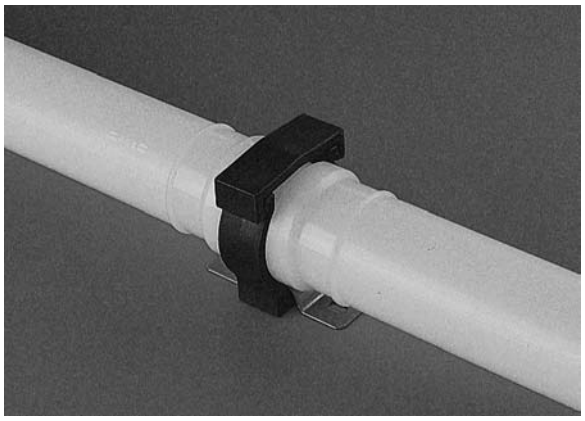

Figure 7.B Fixed Anchor Design

7.4 Instrumentation and Controls

In the proper design of an Ultra Pure Water system it is important to monitor the quality of the water, temperature, pressure and the flow rate.

The following chart outlines recommended instruments and sample points along with their location in the Process.

Instrumentation Type and Location

Process Step	Measurement Type	Readout Location
Feed Water	PVC Vortex Flow Meter	Line Mount
	Totalizer	Wall Mount
Pretreatment	PVC/PP Vortex Flow Meter	Line Mount
	Supply Water Temperature	Line Mount
	Media Filter Pressure Gauges	Line Mount
Purification	RO Low Feed Pressure	Alarm at RO Panel
	RO Product Totalizer	RO Panel
	PP/PVDF Product Vortex Flow Meter	RO Panel
	RO Reject Flow Meter/Total	RO Panel
	RO Reject Recirculation	RO Panel
	RO Percent Ion Rejection	RO Panel
Post Treatment	Mix Bed Polish Resitivity	Polisher Panel
	Point of Distribution Resitivity	Polisher Panel
Distribution Loop	PP/PVDF Supply Vortex Flow Meter	Line / PLC
	PP/PVDF Return Vortex Flow Meter	Line / PLC

All devices should be picked on the following criteria

- Accuracy of Indication
- Repeatability
- As unobtrusive to the process as possible
- Cleanliness
- Devices in contact with the Water should be thermoplastic.
- Ease of use
- Operating parameters: Temperature, Pressure, media compatibility.

In regards to monitoring flow, it is important to use devices that do not rely on moving parts to determine the flow rate. Ideally, all thermoplastic construction should exactly match that of the pipe. An ideal Flow measurement device is the Vortex Meter. A Vortex Meter from Asahi/America will provide accurate, repeatable flow without the use of any moving parts. The features translate into the benefit of clean operating design and long lifetime. With no moving parts, no particles will be generated and there are no parts to wear out. In addition, Vortex meters are simple to install and wire up. With all thermoplastic components the device is unobtrusive to the process and provides years of reliable, clean operation.

Vortex meters operate on the vortex principal. A bluff in the flow body cause a slight pressure drop behind it as the flow passes by. The water turns inward into the pressure differential causing the formation of small eddies or whirl pools. The vortices as they are called alternate from one side to the other in direct proportion to the flow. The frequency is calculated to flow and is transmitted as a 4-20mA signal or a digital pulse depending on customer preference.

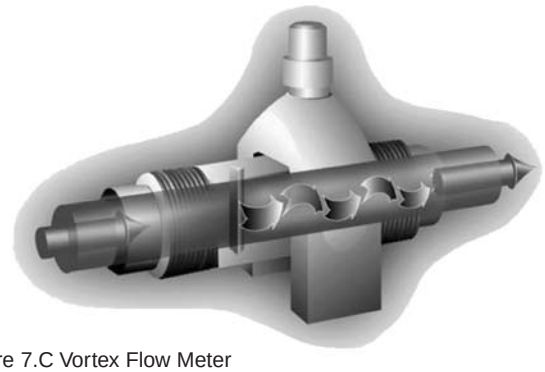

Figure 7.C Vortex Flow Meter

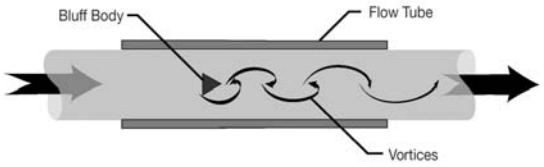

Figure 7.D Vortex Priniciple

7.5 Welding Method

Asahi/America offers several choices for joining Purad PVDF and PolyPure natural Polypropylene. The choice of a particular method should be based on the following concerns:

- Purity of the system
- Installation location
- Size range
- System complexity.

While the welding method is instrumental in the purity of a water system, the choice of a welding method is not the final factor. The environment that welding takes place under maybe more important than the actual welding method. Asahi/America recommends the welding method be based on the type of installation, rather than the desire to have the most advanced equipment on site.

PVDF can be installed using, butt fusion, IR fusion, socket fusion and beadless HPF fusion. All methods are proven in DI water systems, and each has its own advantages. E-CTFE is available as butt or IR fusion and Polypropylene is weldable using socket, butt or IR fusion.

7.5.1 Socket Fusion

Socket fusion is a simple method for basic, low-cost systems. In small diameters, 20mm to 40mm (½" – 1¼"), socket fusion can be done quite easily with a hand held welding plate and a few inserts. With just a limited amount of practice an installer can make reliable joints. For larger dimensions, up to a maximum of 110mm (4"), bench style socket fusion equipment is available for keeping joints properly aligned.

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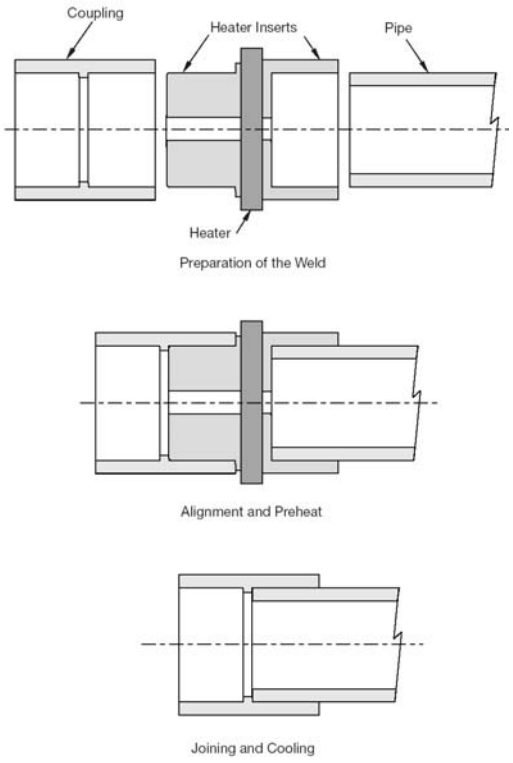

Figure 7.E Steps of Socket Fusion

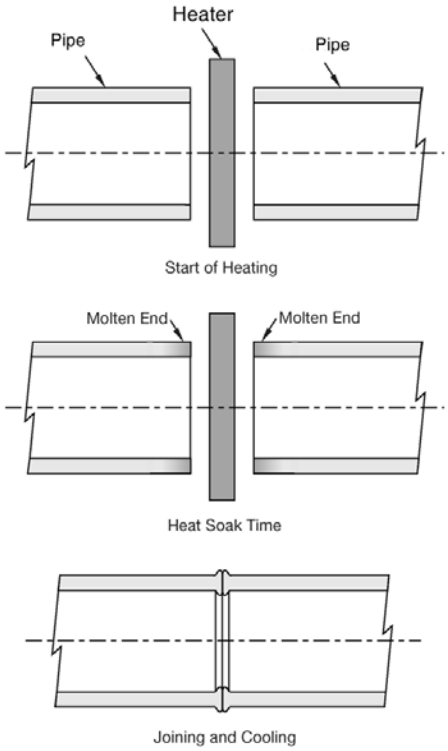

Figure 7.F Steps of IR Non-Contact Fusion

7.5.3 IR Fusion

For systems that have larger dimensions above 110mm (4”), butt and IR fusion make a logical choice. Both systems are available for welding all dimensions from 20mm to 250mm (½” to 10”). IR fusion has several advantages; during the welding process the material is not in contact with the heat source, thus eliminating a possible source of contamination. In the course of an IR weld there is no force against the heating element like in butt fusion, therefore the weld beads are smaller when making an IR weld. In a flowing system an IR bead will flush cleaner, due to its round, smoother shape as compared to a butt weld.

IR fusion is neat, clean and reliable. Current day welding equipment is computer controlled making each weld identical and making the inspection processes more reliable. IR fusion equipment also allows for complete traceability of each weld, by each operator.
IR fusion is suited for clean room environments and bench top type welding. Equipment is highly sophisticated and is not generally recommended for making field or location welds.

7.5.3 Butt Fusion

Butt fusion is similar to IR fusion, however the components to be welded are in contact with the heat source. Butt fusion is the parent of IR fusion and still maintains its one advantage; it can be done in a variety of environments. Wind or a strong breeze can make IR welding troublesome, for these cases butt fusion is preferred. Additionally, field or in-place welds should be performed with butt fusion. A variety of different types of butt fusion equipment are available, making location welds possible, where an IR would not be.

7.5.4 HPF Fusion

HPF Fusion is a welding method that combines a smooth internal seam with practical portability. It is available in ½” – 2” PVDF. The method is simple in use. Pipe is simply inserted into a coupling and locked into place using a clamp. The tool is set for each weld using a bar code scanner to set the parameters. As the coupling is electrified the heat joins the pipe and coupling together. Inside the pipe an internal balloon is used to maintain the shape of the pipe. The weld can also be accomplished without an internal balloon. In this case the heat is stopped prior to reaching the internal pipe diameter. In

both cases the pipe is completely bead free on the inside, but when welded without the balloon a small seam is present. This seam however is smaller than a gap that would be present between any joint containing a gasket such as union or sanitary clamp connection.

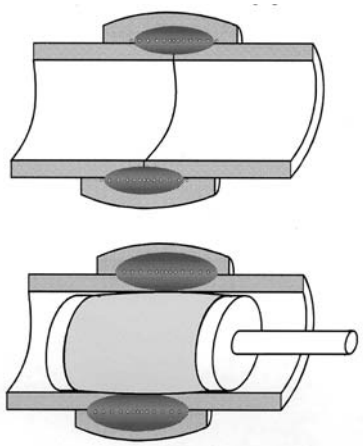

Figure 7.G HPF Fusion without and with internal support balloon

7.6 Sanitization Methods

Many different methods for the sanitizing of a distribution pipe system can be incorporated. If heat or hot water are to be used, the main area of concern is thermal expansion and the temperature/pressure ratings. If a chemical sanitization method is to be used, the chemical compatibility of the piping material needs to be verified with the pipe manufacturer.

7.6.1 UV Exposure

All plastics react differently to UV exposure. In addition to the external exposure of UV lights, it also common for UV sterilizing lamps to be used to control bacteria levels in a water system. These lamps, give off high intensity light to breakup living bacteria in a water. Depending on the wave length of the lamp, trace amounts of Ozone can be generated from these lamps. The combination of the intense UV and Ozone can create stress cracking in piping components directly in contact with the light source. To avoid a possible problem it is recommended to build a light trap from SS components. The use of SS diaphragm valves or a couple changes in direction will eliminate the concern altogether. Below is a graphic representation of an efficient light trap.

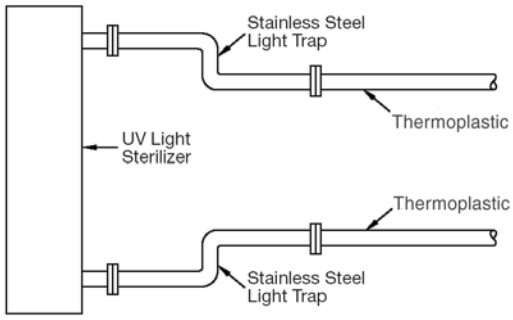

Figure 7.H UV Light Trap Design

7.6.2 Steam Sterilization

Steam In Place (SIP) is considered by many to be the most reliable method of ensuring sterility and maintaining microbial control. For effective steam sterilization, the steam must be saturated, that is, it must be at a temperature and pressure that falls along the liquid/gas interface on a phase diagram. SIP must be conducted at 121°C (250°F) at the coldest point in the system. Terminal sterilization or “Overkill” is generally achieved after 15 to 20 minute exposure to saturated steam. Longer durations are not necessary and should be curtailed in PVDF

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systems. A heat penetration study documenting sufficient temperature is maintained throughout the piping system is critical to validation.

Steam sterilized Purad PVDF systems offer several advantages over those constructed of stainless steel. Purad PVDF's extremely low thermal conductance factor of 1.32 Btu-in/hr ft^2 minimizes heat loss. Heat penetration throughout a system is more easily ensured without the need for pipe insulation. Purad PVDF can safely transport hot media without risk of serious injury to those who may come in contact with it. Additionally, the hot temperatures do not contribute to accelerated corrosion as is the case in with stainless steels. Clean steam is highly corrosive to stainless steels. High grades, such as 316L, are not immune to its corrosive effects. The corrosion can contribute to degradation of the system's overall water quality. Purad PVDF, on the other hand, can handle SIP without corrosion and without restorative passivation requirements. This is an important factor to consider when selecting system material of construction and determining operating and maintenance costs.

Recommended SIP Parameters for Purad PVDF*

Temperature	121-130 °C
Gauge Pressure	15-25 psig
Duration	15-20 minutes
Frequency	As Needed

**Values based on SDR21 Pipe and Fittings. Valves and other components should also be checked for suitability. SIP necessitates expansion calculations and compensation.*

7.6.3 Ozone Sterilization

Ozone is currently under utilized in Life Science water applications. Ozone is an extremely effective method of sanitation. Bacteria are easily destroyed at low concentration levels and with limited exposure. Ozone concentrations of 0.2 to 0.5ppm and at contact times as little as 10 minutes are recommended for water sterilization. Ozone can be destroyed downstream of point of injection by UV sterilization lights.

Ozone is a strong oxidant. As such, material compatibility issues need to be considered. Extended exposure may deteriorate gasket materials and some piping materials. Purad PVDF is fully resistant to Ozone as used for sanitation control. High concentrations of Ozone are harmful to all PP . However, effective levels may be introduced into Proline and PolyPure systems. Weekly CIP with Ozone at 0.2-0.5ppm in Proline and PolyPure lines at periods 30 minutes or shorter is perfectly acceptable. However, care should be taken with use of Ozone in PP systems. Please consult our Engineering Department for exact application guidelines concerning the use of Ozone.

7.7 Hanging

Polymer piping systems act differently than metal piping systems and varying hanger styles are required. The three uses of hangers are as a support, a guide and/or an anchor. The hanger itself may be used to accomplish two of these goals, but all three uses need to be considered when laying out the hanger configuration. The designer of a system should specify the exact hanger and location and not leave this up to the installer.

Support spacing for thermoplastic piping systems differs greatly as compared to metallic piping. It generally requires more supports, and the introduction of higher temps will further increase that support spacing requirement. For support space requirements by

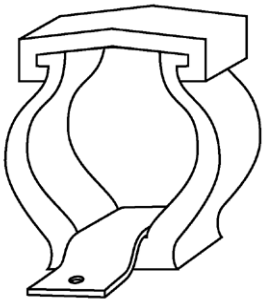

Figure 7.I Recommended Pipe Hanger Design

Hangers that evenly grip 360 degrees around the pipe are preferred. Clamps, such as U-bolts, can tighten down on the pipe providing a pin point load on the pipe that can lead to eventual damage. Thermoplastic clamps are recommended when installing a thermoplastic pipe system. Above is a detail of a recommended clamp. If a metal clamp is to be utilized, a rubber gasket material should be placed between the pipe and the clamp as a cushion to protect the pipe. Clamps should be checked for sharp or jagged edges that could scrape or penetrate the pipe.

For thorough hanging design recommendations, refer to Asahi/America's Engineering and Design Guide.

7.7 Dead Leg Reduction and End Point Configuration

The term dead leg refers to a stagnant zone of water in the distribution system. Dead legs are often found in the branch of a tee that is closed off with a valve. This is especially true in cases where the branch reduces from the main.

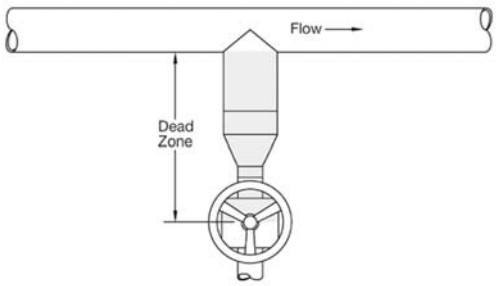

Figure 7.J Improper Dead Leg Design

Accepted cGMP design is to keep all dead legs to a maximum of 6 internal pipe diameters in length. The turbulent flow in the main trunk line will create significant amount of movement to keep the leg moving and prevent bacteria from proliferating. However, the Purad system allows designers to avoid dead legs altogether with the advent of T-Diaphragm valves and Zero dead leg fittings. T-valves take the place of a tee, reducer and diaphragm

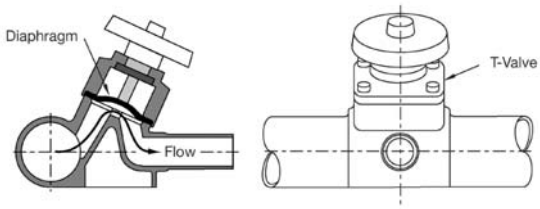

Figure 7.K Molded T-Valve with significantly reduced dead-leg

valve, by combining all three into one component. T-Valves reduce the quantity of welds in a system as well. By using a T-Valve, branch lines can be shut off at any time without creating a dead leg and turned back on without an extensive flush procedure.

Dead legs in a system can be found in more than just branch lines. Often times the introduction of a gauge, measurement device, and/or sampling valve can create a dead leg. Standard plastic fittings require the use of Tees and reducers to accommodate the addition of these components into the system. This is often called the "Christmas Tree" effect, as many reducers can end up stacked on top of each other to reduce down to the required thread size

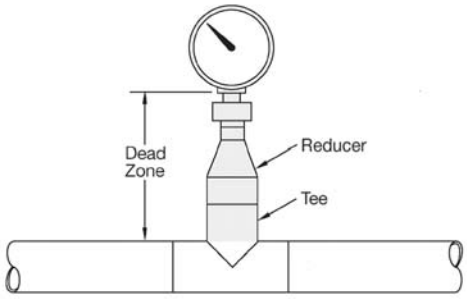

Figure 7. L Dead leg to improper instrument installation

Since these tee configurations are narrow in diameter they create a dead leg in the branch where microorganism growth can be initiated. The use of instrumentation fittings eliminate dead legs while being a safe adapter for gauges or sample valves. Instrumentation fittings are available in multiple configurations and can accommodate more than one instrument per fitting.

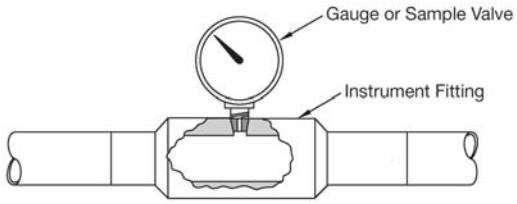

Figure 7.M Proper instrument installation

The insert of a resistivity probe can also be a possible source for dead legs. Since most probe manufacturers recommend that fluid flows directly at the probe, they are often situated in the leg of a tee and the tee acts as a 90° elbow. Since almost all probes are supplied as a ¾" or 1 ½" sanitary adapter, there is the necessity to weld reducers onto the tee leg to accommodate the sensor. A simple fitting, the probe adapter, conveniently eliminates the needs for reducers and shortens the leg of the tee, see figure 7N. Probe adapters are available in all sizes

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and pressure ratings. Pressure gauges can also be installed utilizing sanitary adapters. Sample valves can also be built into the same fitting to reduce space and the amount of fittings used. Multiple configurations are available.

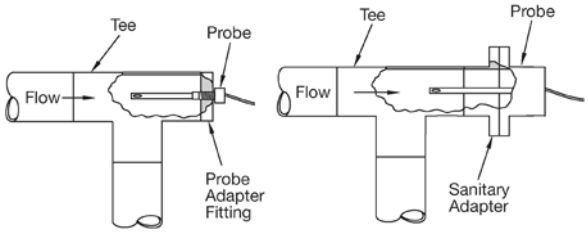

Figure 7.N Instrument probe installation

Connecting a new thermoplastic system to existing or new equipment is often a concern. New Purad and PolyPure systems are fully equipped with sanitary adapter that make transition seamless and hassle free. Please refer to Section Four for further details concerning sanitary adapter sizing and selection. Finally, most purified water systems feed a sink or wet station. The need for zero dead leg use points is required. There are many ways of accommodating the need, from recirculating faucets to simple flow through T-Valves. Recirculation faucets offer reduced stagnant zones of flow, but increase plumbing complexity. T-Valves are highly recommended as the cleanliest component for a use point configuration. Multiple end connections are available to adapt to existing tubing or final connections.

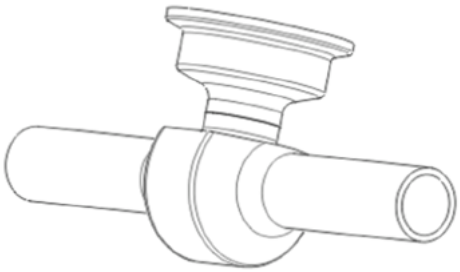

Figure 7.O Sample sanitary instrumentation adapter

End Point Configurations

Very often, the quality of product water is maintained throughout the distribution system, but cannot be utilized without contamination. Gooseneck faucets, dead ended drops, needle valves and ball valves are often improperly utilized as Point of Use fittings. The microbiological integrity of a Water System should be measured at a minimum of at least three places:

1) Point of Distribution - the quality of product water the system is capable of making.
2) Return from Distribution – The quality of water after transport in the piping system.
3) Point of Use – The quality of water delivered by the end point configuration.

All three points are rarely identical with the most important, Point of Use, typically the lowest quality of the three.

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