UTILITY SERVICES AND SERVICE FACILITIES

UTILITY SERVICES:

- All utilities that could affect product quality should be qualified and appropriately monitored and action should be taken when these utility limits are exceeded.
- UTILITY SERVICES include
  1. HEATING, VENTILATION AND AIR CONDITIONING
  2. PLUMBING
  3. DRAINAGE SYSTEMS
  4. GAS SYSTEMS
  5. SANITATION
  6. WATER FOR PHARMACEUTICAL USE.
  7. PESTICIDES etc...
- Services used by a factory include compressed gases, water, vacuum, electricity and room air conditioning.

1. HVAC has been covered in other seminar.

2. PLUMBING:
   - Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.
   - The pipes and fittings must be of quality good enough to withstand the pressure and heat conditions.
   - Metals are often included in pharmaceutical facility waste water permitting criteria but are not commonly a discharge issue. Compatibility of the materials of construction with the characteristics of the waste water must be considered during the design of the facility. For example: Copper plumbing should not be used in drain line for acidic
waste water because it might fail from corrosion but also may result in waste water discharge above copper concentration limits.

- The pipes should be colour coded according to the material it carries.

<table>
<thead>
<tr>
<th>Colour</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey</td>
<td>Raw water</td>
</tr>
<tr>
<td>Orange</td>
<td>Distilled Water</td>
</tr>
<tr>
<td>Green</td>
<td>Cooling water</td>
</tr>
<tr>
<td>Insulated</td>
<td>Steam</td>
</tr>
<tr>
<td>White</td>
<td>Air</td>
</tr>
</tbody>
</table>

3. DRAINAGE SYSTEMS:
They remove effluent from spaces, systems, or process.
- Drains shall be of adequate size and, where, connected directly to sewer, shall be provided with an air break or other mechanical device to prevent back-siphoning.
- They should be easy to clean. And they must be cleaned at a proper interval. They must be well closed and air tight.
- For biological waste, it should be treated in a proper manner before disposal to not to harm the environment.
- Dissolved oxygen content in waste to be disposed in lake or river must be within limits.

Sanitary waste system
A separate sanitary waste drainage and vent system is provided to convey waste from toilets, lavatories, non-process service sinks and floor drains. Sanitary drainage is connected to the site sanitary sewer system generally without treatment. Any other materials or product that may present a hazard or environmental problem in the sewer system must be conveyed by a separate waste and vent system.

Laboratory waste system:
A separate laboratory waste drainage and vent system is often provided in cases where acids or caustics used in laboratory processes must be sampled
and potentially neutralized before disposal into the sanitary waste system. A batch or continuous neutralization system may be utilized.

**Process Waste System**

A separate process waste drainage and vent system is often provided in cases where products used in the manufacturing process must either be contained separately or treated before disposal into the sanitary waste system. If they are contained, they are usually removed by tanker truck and disposed of offsite.

Because the drainage may be potentially hazardous and certainly possess a potential contamination and environmental threat, the piping distribution system must either be protected (double wall piping system) or provided in a location that is easily monitored (i.e., exposed service corridors).

**Hazardous Material Waste and Retention**

Separate hazardous waste drainage and vent systems are provided in cases where hazardous materials such as solvents, toxins, radioactives, high concentrations, etc. must be contained. Generally these systems are limited in distribution and highly contained. They can either be local such as “in-lab” safety containers or larger as in the case of a solvent spill retention system in a dispensing area. These systems must maintain isolation of the hazardous material for other drainage systems.

**Storm Drainage System**

A separate storm drainage system is provided to drain rainwater from all roof and area drains. This system is generally not combined with any other drainage system. All precautions must be taken to ensure that contaminated fluids cannot flow into the storm drainage system. In case of potentially hazardous material spills, valving is generally provided in the drainage system to isolate the drainage area.

**4. GAS SYSTEMS**

Many types of gases are utilized in the manufacturing process. The most prevalent of these include compressed air use in process and controls, breathing air for hazardous environments, nitrogen, vacuum, vacuum cleaning,
natural gas, propane, and other process systems. All gases used in manufacturing and processing operations, including the sterilization process, should be sterile filtered at points of use to meet the requirements of the specific area. Gases to be used in sterilizers after the sterilization OR used at the filling line or microbiological testing area must also be sterile filtered.

**Compressed Air**

In general compressed air should be supplied by an “oil-free” type compressor and must be free of oil and oil vapor unless vented directly to a non-controlled environment area. It should also be dehumidified to prevent condensation of water vapor (generally to around -40°F dewpoint). Centrally distributed compressed air is generally provided at 100 to 125 psig and reduced as required.

**Breathing Air**

Breathing air is generally provided for use to personnel working in hazardous environments. It can be provided centrally through a breathing air distribution system or at the local level with “backpack” type breathing air units worn by each person. Personal units are more cumbersome but less expensive than central units. Air must be purified to meet OSHA Grade D breathing air requirements. System reliability must be provided in the design with redundancy or storage to provide for “escape time” in case of equipment failure.

**Nitrogen**

Nitrogen is an inert gas generally utilized in the pharmaceutical laboratory and manufacturing environments primarily for the purging of electrical equipment in volatile or explosive environments. Cryogenic uses are limited in the pharmaceutical manufacturing industry. Nitrogen, however, can be provided locally utilizing small individual bottles or generators. In the central system, nitrogen may be distributed at 100 to 125 psig with pressure regulation as required. Laboratory nitrogen is generally provided at lower pressures (40 to 90 psig).
Vacuum
Vacuum is utilized throughout pharmaceutical laboratory and manufacturing facilities. A great deal of vacuum is utilized in the encapsulation and tablet compression areas. Vacuum is generally generated at between 20 and 25 inches Hg and provided at between 15 and 20 inches Hg at the inlet.

Vacuum Cleaning
Vacuum cleaning is utilized throughout the pharmaceutical manufacturing environment for dry particulate and powder pickup. Individual units are more cumbersome, require stricter cleaning regimens between uses, can be a source of cross contamination, but are less expensive than central units. Vacuum cleaning is generally generated at between 5 and 10 inches Hg and provided at about 2 inches Hg at the inlet. This reduced pressure range compared to the vacuum system described above may be more conducive to some processes.

Natural Gas and Propane
Natural gas and propane are sometimes required in the pharmaceutical laboratory environment for such processes as maintaining solvent oxidization and heating hot water and steam. Gas is generally distributed to laboratory outlets at 5 to 10 inches wg.

5. SANITATION IN THE MANUFACTURING PREMISES

- The manufacturing premises shall be maintained clean and in orderly manner, free from accumulated waste, dust, debris, etc;
- Eating, chewing, smoking or any unhygienic practices shall not be permitted in manufacturing area;
- The manufacturing area shall not be used for general thoroughfare for personnel or storage for storage of materials, except for material being processed;
- Routine sanitation programme shall be drawn up and observed which shall be properly recorded and which shall indicate:
  - Specific areas to be cleaned and cleaning intervals;
Cleaning procedure to be followed, including equipment and materials to be used for cleaning;
- Personnel assigned to and responsible for cleaning operations.
- Records of compliance in respect of sanitation shall be maintained for inspection.

Objectives of sanitation are:
- Removal of dirt and other waste material;
- Minimize the risk of cross contamination between different products in the same area;
- Reduce the number of micro-organisms in work area;
- Control pests so that these do not affect the quality of materials tp be used in the manufacture of drugs.

Sanitation in the manufacturing premises doesn’t obviate necessity of sanitation in other areas. However, sanitation in manufacturing areas is more important than other areas because of risk of contamination is more in these areas, protection from outside environment too is necessary. For protection of premises from outside environment, some important measures are:
- Effectively seal manufacturing plant from outside environment by :-
  - Avoiding multiple entry/ exit positions,
  - Installing ‘air curtain’ at each main entrance,
  - Providing air-lock at each entry point.
- Install insectocutors at effective positions like main entrances, entrances to manufacturing areas including packaging section, inside manufacturing areas.
- Keep surrounding of the building clean. Maintenance of lawn will keep incidence of dust low.
- Carry out pest control periodically. Services of pest control agency can be availed for this purpose.

**CLEANING AGENTS AND DISINFECTANTS**
Cleaning agents help to remove extraneous materials from surfaces some of the commonly used cleaning agents their chemical nature, concentration in which they are used and their uses are given below:
<table>
<thead>
<tr>
<th>Name of cleaning agent</th>
<th>Active ingredients</th>
<th>Conc.</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teepol</td>
<td>Sodium benzene sulphonate, alcohol, ether sulphate and alcohol ethoxylate</td>
<td>0.1 %</td>
<td>Multipurpose cleaning agent can be used for equipment, floors, glass wares</td>
</tr>
<tr>
<td>Avipol</td>
<td>Liquid detergent of the sodium alkyl sulphate type</td>
<td>1 %</td>
<td>Tanks and vessels in liquid oral manufacturing</td>
</tr>
<tr>
<td>Liquid soap</td>
<td>Soap</td>
<td>As required</td>
<td>Can be used for washing hands, gloves, machine parts</td>
</tr>
<tr>
<td>Vim</td>
<td>Mixture of detergents</td>
<td>As required</td>
<td>Toilets, floors, sinks, etc.</td>
</tr>
</tbody>
</table>

Disinfectants destroy pathogenic and other micro organisms and are used to reduce microbial count in manufacturing area. Commonly used disinfectants their chemical nature and uses are given here under:

<table>
<thead>
<tr>
<th>Name of disinfectant</th>
<th>Active ingredients</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dettol</td>
<td>Chloroxylenol and terpineol</td>
<td>2.5 % solution can be used for hands and spray.</td>
</tr>
<tr>
<td>Savlon</td>
<td>Chlorhexidine gluconate and cetrimide</td>
<td>2.5 % solution can be used for treating all surfaces in aseptic area.</td>
</tr>
<tr>
<td>Farigenol</td>
<td>Dichloro meta xyleneol, terpineol and soap</td>
<td>2% solution can be used for treating all surfaces in aseptic area.</td>
</tr>
<tr>
<td>Formalin</td>
<td>Formaldehyde</td>
<td>A mixture of potassium permanganate and formalin is used for disinfection of sterile areas.</td>
</tr>
</tbody>
</table>

It is advisable to use these disinfectants on a rotation basis with predetermined periodicity. For sterile areas the periodicity of change of disinfectant should be of higher frequency like change on alternate days.
Typical cleaning schedule for tablet manufacturing areas are given below. Similar schedules can be prepared for other manufacturing areas.

<table>
<thead>
<tr>
<th>AREA</th>
<th>FREQUENCY OF CLEANING</th>
<th>METHOD OF CLEANING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floors</td>
<td>Minimum once a day</td>
<td>Vacuum cleaning and damp mop with disinfectant</td>
</tr>
<tr>
<td>Walls</td>
<td>Twice a week</td>
<td>Vacuum cleaning, jet wash and damp mop.</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Weekly</td>
<td>Vacuum cleaning</td>
</tr>
<tr>
<td>Windows</td>
<td>Daily</td>
<td>Vacuum cleaning and dry mop</td>
</tr>
<tr>
<td>Exhaust fans</td>
<td>Weekly</td>
<td>Wet mop with disinfectant</td>
</tr>
<tr>
<td>Light fixture, ducts of air conditioning</td>
<td>Weekly</td>
<td>Vacuum cleaning</td>
</tr>
<tr>
<td>Equipment washing area</td>
<td>Daily</td>
<td>Scrubbing, jet washing and disinfection with disinfectant</td>
</tr>
</tbody>
</table>

Records of sanitation should be maintained. Records can be maintained in the form of log-book. A separate log-book can be maintained for each section. Format of log book is given below:-

**LOG BOOK FOR SANITATION**

Work Area ___________________________

<table>
<thead>
<tr>
<th>Date</th>
<th>Code* no. of SOP for sanitation</th>
<th>Sign of person</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Who executed Job</td>
</tr>
</tbody>
</table>

* SOP for sanitation can be given code numbers
6. WATER FOR PHARMACEUTICAL USE:

INTRODUCTION:

The importance of process water to a pharmaceutical manufacturing facility cannot be overstated. Water is most widely used material in pharmaceutical manufacturing. A greater volume of water is used in cleaning and rinsing processes than in formulation in most facilities. Regardless of the water volume used in actual drug formulation, all pharmaceutical water is subject to cGMPs even when the water does not remain in the finished product.

GOOD MANUFACTURING PRACTICES (GMPs):

Most of the GMP requirements for water derived from broad statements in 21CFR Part211: cGMP for finished pharmaceuticals. These general statements relate to the requirements for water used in production or cleaning processes to not “alter the safety, identity, strength, quality or purity of the drug product.” These statements open all water system unit operations, contact surfaces of equipment and piping, installation, and maintenance to FDA scrutiny. All materials must be proven to be compatible with the product and process, and must not contribute objectionable contaminants.

Additional 21 CFR Part 211 GMP requirements for verification of proper cleaning and sanitization procedures mandate written records and procedures for these steps. All rinse and cleaning water qualities must be proven to be appropriate.

WATER QUALITY REQUIREMENTS:

The types of water defined in the pharmacopoeial monographs such as Purified Water and Water for Injection (WFI) are known as compendial waters. Other quality waters used in manufacturing, not defined by USP or other recognized compendia, are known as non-compendial waters. Non-compendial waters can be used in many applications such as production of many Active Pharmaceutical Ingredients (APIs) and in many cleaning and rinsing steps.

Non-compendial waters are not necessarily lower quality than compendial waters. Non-compendial waters range from water that is required
only to meet the U.S. Environmental Protection Agency (EPA) National Primary Drinking Water Requirements (NPDWR), to water that is specified to exceed the requirements for Water for Injection. Non-compendial water systems are not necessarily less tested, maintained or validated than compendial waters, and they are subject to the same cGMP requirements.

**MONOGRAPH REQUIREMENTS:**

The monographs require that the water purity is proven by conductivity and total organic carbon (TOC).

The conductivity requirement using USP <645> can be met with online testing (Stage 1) or in laboratory testing (Stages 1, 2, or 3). The Stage 1 conductivity test requires measurement of conductivity and water temperature. The conductivity limit varies from 0.6 microsiemens/centimeter (µS/cm) at 0°C to 3.1 µS/cm at 100°C. Intermediate values include 1.3 µS/cm at 25°C and 2.7 µS/cm at 80°C.

The TOC test is a limit response test with a theoretical limit of 500 parts per billion (ppb). The test is designed to accommodate virtually any TOC analyzer that meets the USP suitability requirements. The microbial limits for USP Purified Water (PW) are not defined in the legally binding monograph. The General Information Chapter <1231> Water for Pharmaceutical Purposes states that a maximum of 100 colony forming units per milliliter (mL) may be used as an action level. Some products and processes require an absence of certain objectionable species such as *Pseudomonas aeruginosa* as well as a low total viable plate count.

Water for Injection (WFI) has the same chemical requirements as PW and has a limit of 0.25 endotoxin units per milliliter (EU/mL). The microbial level for WFI also is absent from the monograph but is stated to be a maximum action level of 10 cfu/100 mL.

The USP 28 WFI monograph states “Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.” Several prior volumes of USP limited WFI production to distillation or reverse osmosis.
Distillation currently produces over 99% of USP WFI. Other processes such as a combination of reverse osmosis, deionization, and ultrafiltration have a significant history of production of WFI quality water for rinsing, API production, and other uses. Distillation was the only allowable process for WFI production for decades and became the standard method of production. The revised USP 28 WFI monograph may stimulate an increase in alternative system designs if the alternative designs are evaluated to be as reliable as distillation and more cost effective.

**WATER QUALITY SELECTION:**

![Water Quality Selection Diagram]

The water quality or qualities selected for the pharmaceutical process must be consistent with the final product requirements. The final rinse water must be the same quality as the water used in manufacturing.
Oral products must use a minimum of USP PW for manufacturing and PW is normally used as final rinse water. Since the method of manufacture for PW is not stated by USP, there is little advantage to use of non-compendial water for final rinse water where PW is acceptable.

Parenteral products must use a minimum water quality of USP WFI for manufacturing and WFI is used in most plants for final rinse water. It is acceptable to use “WFI quality” non-compendial water for final rinse in parenteral processes if practical.

The water quality requirements for Active Pharmaceutical Ingredients (API) and Bulk Pharmaceutical Chemicals (BPC) are complex. The minimum water quality permitted in API or BPC manufacturing is water meeting the U.S. Environmental Protection Agency (EPA) National Primary Drinking Water Requirements (NPDWR) or equivalent. APIs use a wide range of waters for manufacturing, initial rinses and final rinses, up to and including WFI.

FDA may expect WFI to be used in certain inhalation products depending upon use. Water quality exceeding USP, PW, or WFI requirements may be required for some products such as intrathecal. A large volume parenteral product may have to be produced with water with endotoxin limits well below WFI limits dependent upon the expected patient weight and the dosage volume. The manufacturer is required to determine the appropriate water quality.
TYPES OF WATER:

A) POTABLE WATER (drinking water) being the source for obtaining various higher qualities of water, adequate pretreatment are essential before it is used. It may be used for synthesis of active ingredients and also used for cleaning of equipments and facilities.

B) PURIFIED WATER monograph identify quality attributes that include ionic and organic contaminants and limits the level of microbiological contaminants. This water is used in preparation of nonparenteral dosage forms.

C) WATER FOR INJECTION (WFI)
   o Monograph includes the same chemical attributes as purified water. Additionally, they include attributes for bacterial Endotoxin and lower level of microbiological contamination.
   o It is used in parenteral products. In bulk, this type of water is also called Pyrogen free water or PFU and if it is sterilized, it is called sterile WFI.
   o WFI must be free from pyrogens, and so should pass the rabbit pyrogen test, or the LAL limit of less than 0.25EU/mL.
   o It is recommended that WFI water systems be tested at predetermined intervals. The inspector should check the frequency of these tests.
   o Storage time for all water must be less than 24 hrs unless stored at 80°C. The GMP guideline of some countries, however, indicates that at or above 70oC is acceptable.

D) SOFTENED WATER, which has its Calcium and Magnesium removed. Such a water can be used e.g. for first washing steps. Certain processes require special well-defined qualities of water.

E) CLEAN STEAM is a form of water that may be used for sterilization purpose and prepared from deionized water.
F) **WATER FOR FINAL RINSE** is used for rinsing equipment after washing. It must be of the same quality as the water used for manufacturing the product.

G) **STERILE WATER FOR INJECTION** water for injection which is sterilized within 12 hours of collection and distributed in sterile containers. It is intended mainly for use as a solvent for injectable preparations such as powders for injection that are distributed dry because of limited stability of their solutions. It should be packaged only in single dose containers of not larger than 1-litre size.

H) **BACTERIOSTATIC WATER FOR INJECTION**

I) **STERILE WATER FOR IRRIGATION**

Now the pharmacopoeia may additionally include monographs for water for specific applications, such as hemodialysis, inhalation, or irrigation. The types of water produced and the steps required are shown in flow chart.

**WATER SYSTEMS: USER REQUIREMENT SPECIFICATIONS AND DESIGN QUALIFICATION:**

It is the designing of water generation and treatment system which consistently supports water quality. Seasonal variations in feed water quality, change of source due to supply issues also affect output water quality. An ideal water system should have robust design which takes care of any such considerations and consistently gives water of desired water quality.

Designing a water system involves identification of needs with respect to end results – qualitative and quantitative. It should also incorporate treatment systems and controls at appropriate stages to ensure consistency in output water quality. Designing starts from conceiving the ideas in a systematic manner. When this conception documented, forms User Requirement Specifications (URS).
**URS**: ISPE (International Society of Pharmaceutical Engineering) defines URS as a description of requirements of conditions, systems and facilities to get the required quality output consistently. URS therefore forms a part of Validation Master Plan.

**URS for water systems:**
URS is driven by:
- a. Input water quality considering seasonal variations
- b. Organic matter
- c. Compliance to pharmaceutical requirements
- d. End usage of water.

URS team should consist of members with specialized knowledge from
- a. System water
- b. Designer of the system
- c. Validation team
- d. QA and
- e. Project management

In generating URS for water system, it is necessary to classify the components and then define the sub components. Each sub component has to be then defined in terms of quantifiable parameters that substantiate end requirements of the user system.

The following can be the broad guideline for classification of components
1. Process control parameters
2. Purification/Treatment requirements
3. Materials of construction for the system
4. Distribution system
5. Sanitization

**1. Process Control Parameters:**
1.1 pH- This is indirect measure of ionic content and hence conductivity. Ideally the measurements are done post RO stage. The contamination with the buffer is likely and hence the location of measuring device should be in a side
stream which is drained. The flow rate also needs control for stable measurements.

1.2 **Conductivity** - It is a valuable tool for measuring total ionic quality of water. USP and BP specify the values which are useful in developing controls. Since measurements are temperature dependent, due care must be taken in URS data. Location of measurement is generally after the final treatment step to verify the acceptable quality prior to delivery to final storage tank. In addition, conductivity meters are often installed in the return piping of distribution loops, downstream of the final point of use.

The conduction of electric current depends on the ions contained (org. comp. dissolved) in water. The purer the water, the lower is the concentration of such ions and, therefore, the lower is conductivity. For low conductivity, the reciprocal applies, high resistivity, as they are different expressions for the same phenomena.

The water conductivity at the purification theoretical limit, that is, when almost all ions have been removed and only H+ and OH- remains, is 0.055 micro Siemens/cm or 18.2 Megohm.cm, at 25º C. This is called ultra pure water.

1.3 **TOC** - Installation of on line TOC instrumentation need careful evaluation for cost reasons. However the measurement provides useful control for biofilms. USP describes instrument precision, system suitability, test methodology and calibration procedure. This is useful for URS documentation. Location of measurement is generally after the final treatment step to verify the acceptable quality prior to delivery to final storage tank. In addition, TOC meters are also installed. Feed water TOC monitoring helps to detect seasonal quality changes that could impact pretreatment or membrane fouling.

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon.

Analytical technologies utilized to measure TOC share the objective of completely oxidizing the organic molecules in an aliquot of sample water to
carbon dioxide (CO2), measuring the resultant CO2 levels, and expressing this response as carbon concentration. All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO2 and bicarbonate, and the CO2 generated from the oxidation of organic molecules in the sample.

The water used for the preparation of solution must have a TOC level below 0.25mg/L.

1.4 Microbial Load- Measurements of certain strains helps to ideally judge the robustness of the system. In spite of TOC meters it is widely accepted that microbial determination is critical and TOC cannot substitute for these measurements.

**Method:** The common methods for microbial total count are Most Probable Number Test (not reliable for low numbers), Spread or Pour Plate (can only test only 1 or 10mL respectively; not reliable for low counts) or membrane filtration, which is preferred.

**Media:** There are various types of test media that can be used.

**Incubation time and temperature:** Preferably 32°C or lower (higher temperatures than this inhibit aquatic microflora) and up to 5 days (sub-lethally damaged organisms may not revive quickly).

**Objectionable and indicator organisms:** Any organism, which can grow in the final product, or can cause physical and chemical changes to the product, or is pathogenic, is unacceptable in purified water. Indicator organisms, such as *Escherichia coli* or *pseudomonas auriginosa* or *coliforms*, point to faecal contamination. They “indicate” possible contamination by other pathogenic organisms.

The manufacturer must set specifications for total count and absence of objectionable and indicator organisms.

1.5 BET(Bacterial Endotoxin Test)- BP and USP define limits for purified water and WFI which serve as useful guide. Like microbial measurements, BET measurement is also an important tool for controls.
**PYROGEN AND ENDOTOXINS**
- Any compound injected into mammals which gives rise to fever is a “Pyrogen”
- Endotoxin are pyrogenic, come from Gram negative bacterial cell wall fragments
- Detect Endotoxin using a test for lipopolysaccharides (LPS)
  - Rabbit test detects pyrogen
  - LAL test detects Endotoxin
- Ultrafiltration, distillation, & RO may remove pyrogen

**1.6 Hardness**
Hardness of water is due to the presence of calcium and magnesium salts. The concentration of these salts makes water “hard” or “soft”. Hardness is expressed as mg/l or ppm of Calcium Carbonate (CaCO₃).

<table>
<thead>
<tr>
<th>Water hardness classification</th>
<th>mg/L or ppm as CaCO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft</td>
<td>0-60</td>
</tr>
<tr>
<td>Moderate</td>
<td>61-120</td>
</tr>
<tr>
<td>Hard</td>
<td>121-180</td>
</tr>
<tr>
<td>Very Hard</td>
<td>&gt; 180</td>
</tr>
</tbody>
</table>

Very hard water has the potential for forming scale in equipment, especially if evaporation occurs, for example, in boilers.
Hard water must be softened before further treatment, since the calcium and magnesium salts can interfere with other purification processes. Removal is usually by water softeners that exchange the calcium and magnesium for sodium. Sodium salts are more soluble than calcium and magnesium salts, which can precipitate to form scale, or which can chelate drug products. Sodium is later removed in the de-ionizer or reverse osmosis units.

**2. Purification/Treatment requirements:**
Raw water used for generation of purified water or WFI comes from varied sources like supply from municipal storages, bore well and river water etc..
CONSIDERATION IN SELECTING WATER TREATMENT METHODS

- Water quality specified
- Yield or efficiency required
- Nature and quantity of contaminants
- Reliability and robustness of equipment
- Availability of water treatment equipments
- Operation cost.

2.1 Pretreatment- This involves sand filters for preliminary filtration. Further pretreatment depends upon feed water quality which is source specific. Chlorination is done to control bacterial growth. However, it is necessary to remove the traces of chlorine to avoid damage to system membranes like RO. Charcoal bed is to be provided to remove the excess chlorine. Pretreatment equipment typically is implemented to control scale, fouling, and oxidation of final treatment equipment.

Scale Control:
Scale or precipitation occurs when the solubility of sparingly soluble salts is exceeded in the concentrate streams of RO and distillation units.

The most common form of scale control is the use of water softeners. Water softeners utilize cation exchange resin in the sodium form to remove divalent cations such as calcium, magnesium, barium, and strontium.

The most common forms of scale in reverse osmosis units and stills are calcium carbonate, calcium sulfate, calcium fluoride, barium sulfate, strontium sulfate, and silica. Softeners cannot control silica scale but can prevent formation of the other forms of scale through the removal of calcium, magnesium, barium, and strontium from the feed water in exchange for sodium. Sodium salts are highly soluble.

Softener construction varies broadly. Vessel construction is typically plastic lined, reinforced fiberglass (FRP), lined carbon steel, or stainless steel. Piping materials are typically PVC, copper, or stainless steel. Multi-port valve units are used as well as individual valves.

- Hard water is made water soften by removal of Ca and Mg salts.
- Using zeolite exchange column-Ca & Mg exchanged for Na & Na is removed by deionizer or RO
- Improves performance of RO
- Does Not Remove, Exchange only
- It is sanitizable but can grow bacteria.

**Anti-scalant/anti-foulant chemicals** can also be used to control scale and fouling in RO units. These chemicals also have anti-foulant properties and can be very useful in minimizing particulate fouling. The anti-foulant properties limit deposition of inorganic and organic particulates and colloids. The capital cost of anti-scalant systems is generally significantly less than the capital cost of water softeners.

Under application of the chemical may result in significant scaling of the RO or distillation equipment, and over application may lead to significant membrane fouling requiring frequent cleaning.

**Adjustment of feed water pH** can also be utilized to minimize scale in RO systems. Lowering of the pH increases the solubility of most sparingly soluble salts. Lowering of pH converts some bicarbonate to carbon dioxide that is not removed by RO. The system design must address this carbon dioxide or an alternate scale control method must be implemented.
**Fouling Control:**
Fouling is a mechanical coating of membranes rather than a chemical precipitation such as scale. Fouling occurs from common feed water contaminants such as silt, dissolved organics, colloids, heavy metals, and Microorganisms.

Silt, colloids, and other types of particulate are generally controlled through different methods of filtration. Large particulate or suspended solids are typically minimized through pretreatment steps such as multi-media filtration, disposable cartridge filtration, nanofiltration, and ultrafiltration, or through a clarification or flocculation process.

**1. Multimedia Filtration:**
The most common particulate fouling control is use of a multi-media filter as the first component of the pharmaceutical water system. Multi-media filters are pressure filters generally employing three active layers of media filtration in a pressure vessel utilized in a downward service flow. The active layers vary but are most commonly anthracite followed by a layer of sand with a final filtration layer of fine garnet. Multi-media filters can generally filter down to the 7–10 micron range, although not on an absolute basis.

Multi-media filters are sized as a function of the pretreatment requirement and the feed water quality. Multi-media filters are generally sized larger to provide better filtration ahead of reverse osmosis systems than ahead of either distillation units or demineralizers.

**2. Disposable Cartridge Filters/Bag Filters:**
The most common alternative to multi-media filtration is an inexpensive disposable cartridge filter or bag filter. These filters reduce the capital cost and reduce the generation of wastewater, but generally increase operating cost.

Disposable cartridge filters and bag filters can filter just as effectively as multi-media filters or better as a function of the disposable filter micron rating. In cases of high flow and high suspended solids, multi-media filters are generally the better choice since they are typically automatically backwashed and necessitate very little labor.

**3. Carbon filters(Organic scavangers):**
When organic fouling reduction is included, it is generally an organic scavenger, activated carbon filtration, or ultrafiltration.
Organic scavengers utilize specially selected anion resins in a pressure vessel configuration very similar to water softeners. The anion resin selected has the ability to remove a wide variety of dissolved organics from feed water and have the ability to have the organics eluted from the resin during a regeneration process.

Activated carbon has been used in several applications for organic reduction as well as dechlorination. The reduction of organics varies greatly with time in service, carbon type, application, and feed water properties. The reduction of organics through use of activated carbon may range from only a few percent to as high as perhaps 80%. It is difficult to predict the effectiveness of organic reduction with activated carbon without pilot testing.

Microbial fouling is an issue in membrane systems. Microbial fouling can be effectively controlled through the presence of residual chlorine in the feed water to many processes. Some of the processes such as multimedia filters, disposable cartridge filters, and softeners generally tolerate levels of chlorine that are high enough to control microbial growth and low enough to avoid significant media oxidation.

Other processes such as some RO, ultrafiltration, or microfiltration processes frequently incorporate membranes or media that are not chlorine tolerant. Microbial fouling control methods in these cases often include the use of ultraviolet light upstream of the process in order to moderate the microbial

Ultraviolet (UV) light has been utilized for decades to control microorganism growth in water systems. The UV light spectrum includes several wavelengths that are effective in minimizing the replication of microorganisms in the water stream. UV units typically incorporate UV lamps housed inside of quartz sleeves that allow penetration of UV light into the water stream that surrounds the quartz sleeves.

The microbial control of UV units is based upon UV radiation penetration of the cell wall of the microorganisms. UV light is absorbed by DNA, RNA, and enzyme modules. The absorption of UV energy inhibits the ability of the microorganisms to replicate.
Oxidation Control:

Another critical part of pretreatment systems is the implementation of a process to remove feed water disinfectants from the process stream. Most municipal feed waters utilize chlorine or chloramines for bacterial control. Many private supply systems utilize injection of chlorine for the same microbial control purpose. The chlorine or chloramines are damaging to many pretreatment and final treatment components. Ammonia can be a byproduct of dechloramination and the system must be designed to remove the ammonia or USP conductivity limits may not be met.

Distillation units and RO units that include the widely used thin film composite membranes are subject to extreme damage from chlorine compounds. Most distillation units are only rated up to 0.02 ppm free chlorine. The reality is that chlorine should be at non-detectable levels ahead of all distillation and thin film composite RO systems for the most reliable operation.

Dechlorination or dechloramination is accomplished in most pharmaceutical systems through implementation of activated carbon, injection of sodium sulfite compounds, or through the use of UV light.

A) Carbon Filtration Or Sodium sulphite

![Diagram of a filtration system]

Water is kept circulating
- Activated carbon beds to remove some organic compounds, chlorine that is generally present as an antimicrobial agent and other particles.
- Removal of chlorine is recommended because further treatment steps such as deionization, reverse osmosis, and distillation are affected by its presence.
- Carbon beds provide a nutrient-rich environment for microbial growth and absence of antimicrobial agent makes the water susceptible to contamination.
- So periodic sanitization to control the microbial levels and replacement of carbon that no longer remains organic compounds.

OR

- Sodium Bisulphate does not facilitate the microbial growth as does an AC filter and less costly then AC.
- Dechlorination reactions

  \[
  \text{NaHSO}_3 + \text{CL}_2 + \text{H}_2\text{O} \rightarrow \text{NaHSO}_4 + 2 \text{HCL}
  \]

- When bisulphite is injected into the process stream, it is oxidized to sulphate, and it also reduces free chlorine to the chloride ion. The by-products, sulphate and chloride, are removed or reduced by a de-ionizer or an RO system.
- The by-products, sulphate and chloride, are removed or reduced by a de-ionizer or an RO system.
- Note that bisulphite does not remove organic contaminants, whereas AC does remove organic contaminants.

B) UV Light:

- Extremely high intensity levels are required for quantitative reduction of free or combined chlorine. The range of UV light energy can vary from 10 times the energy required for microbial control to as high as 150 times the energy required for germicidal control.
- The greatest advantage of UV dechlorination is that no microbial risk exists, The massive doses of UV light applied are lethal to feed water microbes. The capital cost is generally higher than sodium sulfite injection but lower than or equal to thermally sanitized activated carbon
• The principal disadvantage of UV light dechlorination is that attainment of chlorine levels below the limit of detection is quite difficult without using significant UV light energy levels. The effectiveness of UV dechlorination is a direct function of the feed water disinfectant level and the UV energy level applied. Significant increases in feed water disinfectant level such as those encountered when coliform microorganisms are detected in municipal feed water may present a challenge to UV light dechlorination. Sodium sulfite injection can be used as a supplemental dechlorination method when peak chlorine levels are encountered.

Prefiltration:
- Water is polished through a 5 micron filter
- Multiple Prefilters with different micron ratings in series can length filter life
- Final micron size determined by RO membrane requirements
- Removal of Suspended particles and Microorganisms

**ADVANTAGES:**
1. Removes all particles > pore size,
2. Minimal maintenance,
3. Sterilizable

**DISADVANTAGES:**
1. Expensive,
2. Non-regenerable does not remove Endotoxin &
3. Dissolved inorganic

2.2 Final Treatment (Purification systems):
   a. Deionization
   b. Reverse osmosis(RO)
   c. Ultrafiltration
   d. Distillation
   e. Electrodeionization

A) DEIONIZATION
The deionization process is performed using ion exchange porous globular resins.
- Removes ions & ionized organic comp.
- The performance of the deionizer is monitored by conductivity measurement.
- The resin is periodically recharged to remove accumulated ions with strong acids and bases.

**ADVANTAGES:**
1. Simple installation,
2. Low investment,
3. Regenerable

**DISADVANTAGES:**
1. Promote bacterial growth
2. High operation cost
3. Do not remove organic material or Microorganism

**B) REVERSE OSMOSIS**
- Removal of ions, organics comp., Endotoxin, dissolved inorganic and Microorganisms.
- Physical separation of impurities through semipermeable membrane.
- The most economical way of removing variety of contaminants in a water system.
ADVANTAGES
1. Minimal maintenance
2. Can eliminate ion exchange
3. Good control of operation parameters
4. More effective microbial control than ion exchange

DISADVANTAGES
1. Membrane may be subjected to encrusting & clogging
2. Consumption of heat and electricity
3. Low flow rates
4. Can support bacterial growth
5. Permeate will concentrate CO2 from feed water

USES
1. Purifies water that meets pharmacopoeia specifications
2. Feeding of distillation units – prevents scaling and ensures quality WFI
3. Water for final rinse
4. Water for injection only permitted by local regulations

C) ULTRAFILTRATION
- Same principle of RO but lower pressure and more permeable membranes
- Pore size of membrane is 10 to 200 0A.
- UF membrane is a thin polymeric material either polysulfone or polyacrylonitrile with an anisotropic pore structure.
- But cannot remove ions, gases and low molecular weight organic matter
- Can produce water that meets the microbial & bacterial end toxins of WFI &/or water for final rinse for parenteral mfg
Its main features are:

1. Removal of organic contaminants such as Endotoxin
2. Operation at 80°C possible
3. Sterilization at 121°C possible

**ADVANTAGES**

1. Effective removal (>99%) of all organic molecules having a molecular weight above the NMWL. Very effective removal of pyrogen and virus, as well as particles.
2. No risk of incrustation.
3. Low consumption of water and electricity.
4. Low maintenance; well documented/accepted procedures

**DISADVANTAGES**

Almost no removal of ions, gases and low molecular weight organic matter (UF membranes provided with a narrower mesh have a cut-off of 1.000 dalton)

**D) DISTILLATION**

- Classic method for producing WFI
- **Principle:** - phase change, mechanical separation & in some designs, centrifugal separation
- Water evaporated & steamed is condensed into WFI. A portion of feed water is discharge with concentrated contaminants

**ADVANTAGES**

1. Remove all types of contaminants medium investment
2. Easy to operate

**DISADVANTAGES**

1. Water quality is not controlled
2. High operation cost regular maintenance

**E) ELECTRODEIONIZATION**

Deionizes water by means of applied electrical current removal of dissolved inorganic compound

**ADVANTAGES**

1. No chemical regeneration,
2. Low operating cost,
3. Sanitizable

**DISADVANTAGES**
Needs RO or DI pretreatment relatively high capital cost

**3. Materials for Construction:**
- Primary source of contamination. It should be compatible with the processes adopted for sanitization, cleaning and passivation.
- Materials for construction should be resistant to the chemicals or additives and temperatures used in sanitization. Turbulent flow and elevated velocities accelerate wear and tear.
- Stainless steel of suitable grade is the material recommended. Electro polishing provides resistance against corrosion and limits bacterial growth. Materials should be selected to avoid shedding, extractability and microbial activity.

**4. Distribution system:**

**4.1 Storage Tank-**
- Ability to withstand full vacuum is desirable so that ozonisation or steam penetration can be effective.
- In hot water circulation system, return flow is through spray nozzle which ensures permanent rinsing of the internal surface and keeps it hot.
- Storage tanks are to be fitted with hydrophobic vent filter to reduce bioburden and particles. Inert blanket over the tank head space is a must to avoid absorption of CO₂ and thus its effect on conductivity.
- In WFI storage tanks, 0.2 microns hydrophobic vent filter is recommended. The filters should be capable of withstanding sterilization.

**1] Continuous Hot Storage:**

The continuous hot system is self-sanitizing and microbial problems are virtually always external to the sanitary system. A continuous hot system is generally considered to be the most conservative and lowest risk storage
system design. Use point heat exchangers for cooling or cooled sub-loops are commonly employed where hot water is not suitable for manufacturing.

2] Ozonated Storage:

An excellent alternative to continuous hot storage with cooled water for usage is continuously ozonated storage as shown below. The continuous application of ozone ensures low microbial counts in storage and the stored ozonated water can be used to periodically sanitize the distribution system. Ozone can destroy most (i.e., those not embedded in biofilm) microorganisms in seconds of contact time, is easily removed from manufacturing water with UV light, and has been successfully documented in many installations. Microorganisms embedded in biofilm necessitate significantly longer ozone contact time for destruction.

The residual ozone in water from storage is removed with inline UV units downstream of the distribution pump. These UV units use approximately three times the energy, per gallon processed, as UV units sized for microbial control. Continuous addition of ozone to stored water will cause an increase in conductivity. The increase may cause the conductivity to rise above the USP conductivity limit during lengthy periods of low or no water usage. This issue is eliminated or minimized through repurification of some of the stored water, use of appropriately low applied ozone levels.

Since ozone is an extremely strong oxidizing agent, material compatibility must be addressed in system design. Most ozonated systems use components constructed of 316L or 316 stainless steel. PVDF piping, fittings, and valves are also very compatible with ozone.

3] Ambient Storage:

Many systems utilize ambient temperature water storage without continuous or intermittent ozone. These systems rely on periodic hot water sanitization (80 to 121°C) or chemical sanitization. Properly designed sanitary 316 stainless steel systems with daily hot sanitization are commonly used with great success in both WFI and PW applications. Many systems operate successfully with hot sanitization less frequently than daily, but the microbial risk increases.
4.2 Distribution Loop-
This is the most important part of the water system since incidences of stagnation and dead legs cause failures due to microbial growth. URS should cover-

- Whether hot(65°C-80°C), ambient(18-28°C) or cold(4-10°C) loop is required
- Piping slope to avoid stagnation
- Drain points
- Pump design to deliver turbulent flow to retard the development of biofilm
- Velocity of water flow
- Usage points in distribution loop and minimum dead legs
- Sanitization methods
- User points
- Sampling points

4.3 Heat Exchangers-
These are provided to reduce the temperature of output water. It also conserves energy by exchanging heat from outlet water to inlet water. The possibility of mix-up at the inter phase should be avoided by providing proper material and design to the exchanger.

5. Sanitization:

5.1 HEAT

- Heat is the preferred disinfection method because it is safe, inexpensive, and effective and leaves no residues.
- The most reliable method and disinfection by products.
- Time and temp. of the heat disinfection cycle: >60c for purified water for 1 hr. and > 70c for WFI for 1 hr. in continuous circulation

5.2 OZONE

- It is highly unstable, and is one of the strongest oxidizing agents. It leaves no residue. However, because it is highly reactive, O3 must be stripped
from the water before the water is used to manufacture pharmaceuticals. Otherwise it will quickly degrade the actives.

- The use of Ozone in storage and distribution systems is growing because of its relatively low capital and operating costs, compared to hot water generation and storage.

5.3 UV LIGHT (254 nm UV light use)

- UV light is bactericidal, but water can attenuate the radiation quickly. The design and maintenance of the system is important. The units do not “sterilize” water as is sometimes claimed; at best the manufacturer can expect about a 3 log reduction of bacteria for properly installed and maintained equipment.
- Some organisms have efficient UV repair mechanisms, and so sub-lethally damaged organisms can grow again if they pass through the unit too quickly. They can then colonise the water treatment system downstream of the UV light unit, causing considerable problems.

5.4 CHLORINATION

This is an effective pre-treatment for control of microbial load in fed water. It is also given if there is intermediate storage.

5.5 DISINFECTION – OTHER CHEMICALS

- XO₂-the peroxygen family of hydrogen peroxide, peracetic acid and perxitane.- good disinfectant
- Halogen – strong and good disinfectants, but leaves residues that have corrosive effect.
- Formaldehyde- good effect but has a toxic vapour at low levels and persistent residues so system becomes re-contaminated – therefore not used widespread.
VALIDATION OF WATER SYSTEM:

Major components

Installation Qualification (IQ)  Operational Qualification (OQ)  Performance Qualification (OP)  Validation maintenance

Validation is a program for assuring that the product is acceptable by systematically verifying the installation, operation, and performance of the water treatment and distribution process.

A) MAJOR COMPONENTS

1. Installation Qualification (IQ)
   IQ verifying and documents that the system has been properly installed. Operating procedures, instrument calibration, and preliminary operating range should be established prior to implementation of the test protocol.

2. Operational Qualification (OQ)
   OQ tests and documents that the system functions properly and ensure that the control sequences for equipment function in the correct order.

3. Performance Qualification (OP)
   PQ generates data to characterize the ability of the system to repeatability produce, hold and distribute water over an extended period of time.

4. Validation Maintenance
   Validation of water systems is an ongoing activity that the system continuously produces water which meets the quality standards.

B) VALIDATION FOR WATER SYSTEMS CONSISTS OF THREE PHASES
   Phase 1:  2 – 4 weeks
   Phase 2:  4 weeks
   Phase 3:  1 year
1. **Phase 1 – Investigational Phase (2 – 4 Weeks)**
   - IQ and OQ
   - Develop operational parameters
   - cleaning and sanitization procedures and frequencies
   - Sample daily at each point of use
   - End of Phase I, develop SOPs for the water system

2. **Phase 2 (Verifying Control), (4 Weeks)**
   - Demonstrate the system is in control
   - Same sampling as in phase 1

3. **Phase 3 – Verifying Long-Term Control (1 Year)**
   - PQ
   - Demonstrate the system in control over a long period of time
   - Weekly sampling

**C) INSPECTION**

When commencing an inspection, start with the use of water – the inspection approach will be different according to the products being made. Options may include:

1. **Sterile products**: Production of WFI is the most challenging. Check pyrogen and Endotoxin requirements for the water.
2. **Non-sterile products**: Check if there are any special requirements for the pharmaceutical products, such as aluminium limit test for dialysis products.
3. **Liquid products**: These are more susceptible to microbiological contamination so more stringent bacterial limits may be appropriate.
4. **Solid dose products**: e.g. tablets and capsules may use water as part of the granulation step.
5. **Water** is also used for washing and rinsing equipment. It is necessary to have specifications for these types of water.
6. Check specifications and trends, especially the requirements for pyrogen or endotoxins for sterile manufacturing, and microbial limits. Microbial limits are always a problem. Only a few of the pharmacopoeia recommend
microbial limits but the pharmaceutical manufacturer should be setting its own limits and frequency of monitoring.

**D) CHECK FOR**

1. Check for weld quality. Electropolished internal **welds** smooth internal surface which helps in reducing bacterial colonization.
2. Hygienic **couplings** - no threaded fittings in the water flow which can become contaminated. Example on next slide.
3. "**Passivation**" records. Whenever equipment in contact with water is repaired or changed, passivation should be considered, especially for systems producing water of very high purity. Passivation is the removal of free iron from the surface of the steel. This is performed by immersing the steel in an oxidant, such as nitric acid or citric acid solution. Since the top layer of iron is removed, passivation diminishes surface discoloration. While passivation does not affect the thickness or effectiveness of the passive layer, it is useful in producing a clean surface for a further treatment. WFI systems may need to be periodically re-passivated.
4. No direct connections to **drains or sewers**, and that non-return valves and back-flow preventers are working or have been properly checked. **Tundish** is the engineering term for an air break to a fixed funnel, to prevent bacteria from a drain or sewer growing into the water treatment plant.
5. **Check pipes and pumps:** There are hygienic couplings (Ladish® or Tri-Clover ® clamps), welded pipes and hygienic pumps. Note also hygienic sampling points.
6. Assess physical **condition** of equipment. Look for stains and leaks that could indicate problems.
7. Check to make sure **heat exchangers** are double tube or double shell. If not, there should be continuous pressure monitoring to ensure the heating or cooling liquid does not contaminate the pure water through any pinholes. For single plate heat exchangers, the pressure of the heating or cooling liquid must be LOWER than the purified water at all times. An exception may be where the liquid is of a higher purity than the water being produced.
8. Note from the heat exchanger example above that even high grade stainless steel, such as 318SS, can be subject to pit corrosion!

9. Check maintenance of the entire system by examining the **maintenance procedure and records**. For example, check the “O” rings of connections and the maintenance of the pump seals. The pump on the left shows good connections and a good standard of engineering.

10. The one on the right shows a threaded **coupling**, called a **milk coupling** or sanitary coupling. Threaded couplings and couplings in general should be avoided whenever possible.

11. Where welding is impossible, hygienic couplings should be used or milk (sanitary) coupling, which are acceptable since the threaded fitting is not part of the fluid pathway, and so should not contaminate the water.

12. The inspector must be satisfied that hidden seals and “O” rings have actually been removed, examined and/or replaced during maintenance.

13. Check **air filters** which should be hydrophobic (otherwise, they can be blocked by a film of water condensate) and should be able to be sanitized. Those on WFI plants should be able to be sterilized and integrity-tested.

14. Check **replacement frequency**, which the pharmaceutical manufacturer should determine with assistance from the filter supplier.

15. Check **burst discs** because if they have ruptured without being noted the storage system can become contaminated.

16. **By-pass valves and by-pass lines** are often used for maintenance procedures. In critical situations there may be, for example, two pumps in parallel, in case one breaks down. Additionally, engineers like to be able to replace a pump or a filter without dismantling large sections of the system. However, valves in bypass lines can leak, be left open, or be contaminated, and so they are undesirable. A “blanking” piece is often better during operation of the system, so that there is no physical connection.
17. **Activated carbon bed sanitization** – these can become overgrown with bacteria quite quickly. Check sanitization frequency to ensure the AC remains uncontaminated.

18. **Calibration of temperature**-compensated conductivity meters is often overlooked or not done properly.

19. Influence of plastic pipe adhesive on **Total Organic Carbon (TOC) compliance** - some adhesives will leach into the water and these can be volatile.

20. **Non-condensable gases in pure steam** – for example nitrogen and oxygen. They affect the apparent pressure of sterilization processes, lowering their effectiveness.

21. **Polypropylene welding inspection**. If polypropylene pipe is used and welded, has the manufacturer checked for pin holes?

22. **Retrospective validation of WFI system**. Many water plants are 10 – 20 years old and may not have been properly validated. Can they be properly retrospectively validated?

23. **Rouging of WFI Systems**. The high temperatures of these storage and distribution systems seem to lead to a build-up of a deposit known as rouge. Check to see if the manufacturer carries out a periodic physical check for this effect, and what steps are taken to remove the rouge. Sometimes re-passivation is effective.

24. **Spray ball efficacy**. This is not easy to determine and must be assessable. If the spray ball is jammed it will not work properly, but because it cannot be seen it is not easy to check. There are non-rotating or fixed spray balls or sprays cones which may be better in small systems.

25. **UV light** – monitoring performance and lamp life. The lethal radiant energy from UV lights drops off quickly, so many have to be replaced approximately every 6 months. Does the manufacturer have an hour meter and is the lamp replaced according to the supplier’s recommendations? Can the intensity of the light be measured?

26. **Validating ozone dosage** is difficult. It may be possible for the manufacturer to get the supplier’s validation studies showing worst case lethal effects.
27. **Water softener** sodium chloride specifications. Like any ancillary material, the salt, acids and alkalis used as consumables in water treatment plant should have purchase specifications. Note: testing is not required unless for trouble shooting purposes.

28. Check the drawings to see if valves are marked as “**Normally Open**” or “**Normally closed**”, and then physically check the valve position. It is surprising sometimes those valves are not returned to the correct operating position; for example, after de-ionizer regeneration.

**BIOFILMS:**

Biofilms are a collection of microorganisms surrounded by the slime they secrete, attached to either an inert or living surface. Biofilms exist wherever surfaces contact water. When microbial levels are not controlled in a water supply system, they will eventually form biofilms.

Slime (glycocalyx) enhances the bacterial cell ability to adhere to the surface. The slime layer helps adhere other bacterial cells and nutrients which float past and also acts as a protective layer, which resists chemical disinfectant penetration.

**Biofilm Development Factors:**

- **Surface material** has no or little effect.
- **Surface area** is one of the primary factor. RO membranes, DI resins, storage tanks, cartridge filters and joints in pipe fittings etc all provide surfaces suitable for m.o. growth.
- **Dead leg** is an area in a piping system where water can become stagnant and where water is not exchanged during flushing. Modern piping design limits the length of any dead end pipe to 6 times the pipes diameter. This is known as the six-diameter rule.
- **Smoothness**- smoother surfaces delay the initial build up of attached bacteria, but does not affect the total amount of biofilm after several days.
- **Flow velocity** High flow will not prevent the bacteria attachment nor completely remove the existing films but it will limit the thickness of the film.
• **Nutrients** limiting will limit the growth of bacteria.

• **Detecting and Counting:**
  - Routine monitoring of bacterial levels is an essential part.
  - The most common way to enumerate bacteria in water is PLATE COUNT.
  - But a low plate count doesn’t mean that bacteria are less because more than 99% of bacteria in the water systems are attached to the pipe surfaces which cannot be counted by plate count method.
  - If recent flushing has not disrupted the integrity of mature film, it may not slough off the cells in the water.
  - As biofilms grow, single cells or rafts of cells are sloughed off during flushing. This resulted in random ‘particle showers’ of bacteria, which can explain day-to-day fluctuations and occasional high bacteria count results.

• **Biofilm Recovery (Regrowth):** it is common to observe a rapid regrowth of biofilm immediately following sanitization. Incomplete removal of the biofilm will allow it to quickly return to its equilibrium state, causing rebound in total plate counts following sanitization.

**What we can do?**

- Use of biocide
- Purify water
- Flush
- Minimize crevices and avoid dead legs
- Sanitize
- Take expert advise
7. SERVICE FACILITIES:

Medical services, canteen facilities, washing and toilet facilities, protective clothing, change rooms, educational programmes and training, and safety programmes will be covered in the personal facilities.

FIRE PROTECTION SYSTEMS:

Pharmaceutical manufacturing facilities are typically provided with automatic fire suppression and protection system throughout.

Sprinkler Systems

**Wet Sprinkler System:** A sprinkler system with automatic sprinkler heads attached to a piping system containing water and connected to a water supply, so that water discharges immediately from sprinkler heads that are opened directly by heat from a fire.

**Dry Pipe Sprinkler System:** A sprinkler system using automatic sprinklers attached to a piping system containing air or nitrogen under pressure which, when released during the opening of the sprinkler heads, permits the water pressure to open a “dry pipe valve.” The water then flows into the piping system and out of the opened sprinkler heads.

**Preaction Sprinkler System:** A sprinkler system using automatic sprinklers attached to a piping system containing air that may or may not be under pressure, with a supplemental detection system (smoke, heat, or flame detectors) installed in the same areas as the sprinklers. Actuation of the detection system opens a valve that permits water to flow into the sprinkler piping system and to be discharged from any sprinkler heads that may be open. Preaction systems can operate by one of the following three basic means:

- Systems that admit water to the sprinkler piping upon operation of detection devices (single interlock).
- Systems that admit water to the sprinkler piping upon operation of detection devices or automatic sprinklers (non-interlock).
• Systems that admit water to sprinkler piping upon operation of both detection devices and automatic sprinklers (double interlock).

**Deluge Sprinkler System:** A sprinkler system using open sprinkler heads attached to a piping system connected to a water supply through a valve that is opened by the operation of a detection system (smoke, heat, flame detectors, etc.) installed in the same areas as the sprinklers. When the valve opens, water flows into the piping system and discharges from all attached sprinkler heads.

**Antifreeze Sprinkler System:** A wet pipe sprinkler system using automatic sprinkler heads attached to a piping system containing an antifreeze solution and connected to a water supply. The antifreeze solution is discharged, followed by water, immediately upon operation of sprinkler heads opened directly by heat from a fire

**Deluge Foam-Water Sprinkler and Foam-Water Spray Systems**

**Foam-Water Sprinkler System:** A special system of piping connected to a source of foam concentrate and a water supply, and equipped with appropriate discharge devices for extinguishing agent discharge and for distribution over the area to be protected. The piping system is connected to the water supply through a control valve that is usually actuated by operation of automatic detection equipment (smoke, heat, flame detectors, etc.) installed in the same areas as the sprinklers. When this valve opens, water flows into the piping system and foam concentrate is injected into the water; the resulting foam solution discharging through the discharge devices generates and distributes foam. Upon exhaustion of the foam concentrate supply, water discharge will follow the foam and continue until the system is shut off manually.

**Foam-Water Spray System:** A special system of piping connected to a source of foam concentrate and to a water supply and equipped with foam-water spray nozzles for extinguishing agent discharge (foam or water sequentially in that order or in reverse order) and for distribution over the area to be protected. System operation arrangements parallel those for foam-water
sprinkler systems as described previously.

**Closed-Head Foam-Water Sprinkler System**: A sprinkler system with standard automatic sprinklers attached to a piping system containing air, water, or foam solution up to the closed-head sprinklers, that discharges foam or water directly onto the fire after the operation of a sprinkler(s). This system can also be a dry-pipe or preaction type system.

**General Design Requirements**

The building will typically be provided with one or a combination of systems to provide automatic fire suppression and protection throughout the building. Suppressing agents other than those mentioned above (such as CO₂, Dry Chemical, Foam and Halon alternatives) can be used to address specific hazards, and would not be used as a suppression agent throughout.

In general the **first choice for automatic fire suppression is a wet-pipe sprinkler** system. This most common type of system provides the quickest actuating, most reliable, and least expensive type of suppression for most applications.

In areas which are susceptible to water damage or where contamination is a concern, the **use of preaction sprinkler systems** are appropriate. These space may include, computer rooms, high voltage electric rooms, telecommunications rooms, sterile areas, containment areas, and other GMP spaces. At a minimum, a single interlock preaction system can be provided. Where the accidental or unnecessary discharge of water is a concern, a double-interlock preaction system can be provided.

**Dry-pipe valve systems** are appropriate for use in unheated spaces such as remote detached buildings, warehouses, outside loading docks, combustible concealed spaces, parking garages, etc.

**Antifreeze sprinkler systems** are also appropriate for unheated spaces but are typically limited for applications requiring twenty sprinkler heads or less, such as small loading dock areas or a vestibule. Caution must be taken with the application of these systems to support local water company requirements regarding to cross-connection control (backflow prevention) due to the
addition of the antifreeze to the sprinkler system.

**Control and monitoring:**
Water flow detection and alarms are typically provided for each floor, zone, or specific hazard space and are monitored by the building fire alarm system. Each floor or zone is equipped with electrically supervised water supply control valves that are also monitored by the building fire alarm system. Other items such as fire detection and loss of air pressure are monitored for preaction, dry and deluge type systems.

**Portable Fire Extinguishers**
Portable fire extinguishers are provided to suit the type of hazard and are provided in accordance with locally adopted building codes and NFPA 10 “Portable Fire Extinguishers.” Extinguishers are typically the dry chemical multi-purpose ABC type, but can be water, CO$_2$ or other substance depending on the occupancy and hazard involved.
References:

1. Good Design Practices for GMP pharmaceutical Facilities by Signore and Jacob
2. www.who.org
3. www.fda.gov
4. Encyclopaedia of pharmaceutical technology vol-16 water for pharmaceutical use 293-306
5. Types of water and its applications in oral and parenteral dosage forms; pharma times vol.36; December 2004
6. WHO GMP: water for pharmaceutical use (WPU)
7. Water system design and planning-ppt.
9. ftp://ftp.who.int/medicines/GMP/gmptraining/m09.ppt
11. Manufacturing Strategy Concepts (PDF) Massachusetts Institute of Technology Sloan School of Management
12. GMPs for Pharmaceuticals by James Swardbrick.
13. How to practice GMP by P. P. Sharma,