PHARMA SCIENCE MONITOR
AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

WATER QUALITY FOR PHARMACEUTICAL USE: A REVIEW

Amit V. Patel[*1], Dipen A. Trambadiya[1], Lalji Baldania[2]

[1]Research Scholar, School of Pharmacy, RK University, Kasturbadham, Rajkot, Gujarat
[2]Assistant Professor, Anand College of Pharmacy, Anand, Gujarat.

ABSTRACT

Water is a chemical substance with the chemical formula H_2O. Water is a liquid at standard condition for temperature and pressure, but it often co-exists on earth with its solid state and gaseous state. In pharmaceutical industry different type of water is used depend on different type of formulation manufactured. Water quality play important role in pharmaceutical industry, water quality should be measure by various parameter of water and also various devices are available for testing of water. Water quality is determined by standard guidelines. We also include water quality standard and many purification techniques for purification water and different chemical and microbiological tests of water. It also includes property of sterile water for injection and validation protocol and life cycle of water.

Keywords: Water quality, Pharmaceutical water, Microbiological test for water, Water quality standard, Validation protocol of water.

INTRODUCTION

Water is a chemical substance with the chemical formula H_2O. Water molecule contains one oxygen and two hydrogen atoms connected by covalent bonds. Water is a liquid at standard condition for temperature and pressure, but it often co-exists on earth with its solid state (ice) and gaseous state (water vapour and steam). Water also exists in a liquid crystal state near hydrophile surfaces. Under nomenclature used to namechemical compounds dihydrogen monoxide is the scientific name for water, though it is almost never used.[1,2]

TYPES OF WATER [3, 4, 5]

Hard Water

This is saturated with calcium, iron, magnesium, and many other inorganic minerals. All water in lakes, rivers, on the ground, in deep wells, is classified as hard water.

Boiled Water

Boiling helps remove some of the germs, but concentrates the inorganic minerals. Other germs are carried into a fertile element for rapid and lusty propagation of germs and viruses already in the body.

Raw Water

This has not been boiled. Raw water may be hard (as calcium hardened water) or soft as rain water. It contains millions of germs and viruses. Some of these viruses and bacteria may adversely affect the thyroid gland, the liver and other vital body organs.

Rain Water

This has been condensed from the clouds. The first drop is distilled water. But when it falls as rain, it picks up germs, dust, smoke, minerals, strontium 90, lead and many other atmospheric chemicals.

Snow Water

This is frozen rain. Freezing does not eliminate any germs. All snowflakes have hardened mineral deposits. Melt the cleanest snow and you will find it saturated with dirt, inorganic minerals, germs and viruses.

Filtered Water

This water has passed through a fine strainer, called a filter. Some calcium and other solid substances are kept in the filter; there is no filter made which can prevent germs from passing through its fine meshes.

Soft Water

This water is soft in comparison with water which is harder. It may contain many trace minerals and chemicals, viruses and bacteria. It is not to be confused with "softened water." Soft water may be classified as water which is harder than distilled water.

Brackish Water

Brackish water contains between 1 and 2.5% sodium chloride**,** either from natural sources around otherwise fresh water or by dilution of seawater.

Seawater

Seawater typically contains about 3.5% sodium chloride. Seawater is normally more corrosive than fresh water because of the higher conductivity and the penetrating power of the chloride ion through surface films on a metal.

Distilled or Demineralized Water

The total mineral content of water can be removed by either distillation or mixed-bed ion exchange. In the first case, purity is described qualitatively in some cases (e.g., triple-distilled water), but is best expressed, for both distilled and demineralized water, steam condensate water.

Water condensed from industrial steam is called steam condensate. It approaches distilled water in purity, except for contamination (as by DO or carbon dioxide) and the effect of deliberate additives (e.g., neutralizing or filming amines).

Potable Water

Potable water is fresh water that is sanitized with oxidizing biocides such as chlorine or ozone to kill bacteria and make it safe for drinking purposes. For example, chlorinate will be not more than 250 ppm chloride ion in the United States or 400 ppm on an international basis.

Waste Water

Waste water is any water that is discarded after use. Sanitary waste from private or industrial applications is contaminated with fecal matter, soaps, detergents, etc., but is quite readily handled from a corrosion standpoint.

Spring Water

It is obtained from underground formation and flow naturally to the surface of the earth. It is collected at the spring or through a bore hole tapping the underground formation finding the spring.

Purified Water

It contains ionic and organic contaminant and limits the level of microbiological contaminants. This water is used in preparation of nanoparentral dosage forms.

Softened Water

It is obtained by removing calcium and magnesium salts. It is used for first washing step in pharmaceutical industries.

Water For Injection

It contains bacterial endotoxins and lower level of microbiological contamination. It is used in parenteral products. It is called as pyrogen free water (PFU).

Bacteriostatic Water For Injection

It is a sterile, nonpyrogenic preparation of water for injection containing 0.9% (9 mg/mL) of benzyl alcohol added as a bacteriostatic preservative. The bacteriostatic water can be used in diluting drugs that can subsequently be administered by intravenous, intramuscular, or subcutaneous injection.

Sterile Water For Injection

It is a sterile, nonpyrogenic preparation of water for injection which contains no bacteriostatic, antimicrobial agent or added buffer and is supplied only in single-dose containers to dilute or dissolve drugs for injection.

PARAMETERS FOR WATER [6]

Acidity

Acidity of water is its quantitative capacity to react with a strong base to a designated pH. Acidity is a measure of an aggregate property of water and can be interpreted in terms of specific substances only when the chemical composition of the sample is known.

Alkalinity

The Alkalinity or the buffering capacity of a stream refers to how well it can neutralize acidic pollution and resist changes in pH. Alkalinity measures the amount of alkaline compounds in the water, such as carbonates, bicarbonates and hydroxides.

Conductivity

Conductivity is a measure of how well water can pass an electrical current. It is an indirect measure of the presence of inorganic dissolved solids such as chloride, nitrate, sulfate, phosphate, sodium, magnesium, calcium, iron and aluminum. The presence of these substances increases the conductivity of a body of water. Organic substances like oil, alcohol, and sugar do not conduct electricity very well, and thus have a low conductivity in water.

Dissolved Oxygen

The amount of Dissolved Oxygen (DO) in water is expressed as a concentration. A concentration is the amount of in weight of a particular substance per a given volume of liquid. The DO concentration in a stream is the mass of the oxygen gas present, in milligrams per liter of water. Milligrams per liter (mg/L) can also be expressed as parts per million (ppm). The samples are forced through a filter and incubated at a specific

temperature for a certain amount of time. The resulting colonies that form during incubation are counted and recorded as the number of colony producing units per 100 mL of water (1991, Stream keeper's Field Guide: Watershed Inventory and Stream Monitoring Methods) .

Hardness

Hardness is frequently used as an assessment of the quality of water supplies. The hardness of a water is governed by the content of calcium and magnesium salts (temporary hardness), largely combined with bicarbonate and carbonate and with sulfates, chlorides, and other anions of mineral acids (permanent hardness).

TABLE 1: HARDNESS OF WATER

Water hardness classification	mg/L OR PPM as caco3
SOFT	0-60
Moderate	61-120
Hard	121-180
Very hard	>180

Metals

The effects of metals in water and wastewater range from beneficial through troublesome to dangerously toxic. Some metals are essential; others may adversely affect water consumers, wastewater treatment systems, and receiving waters. Some metals may be either beneficial or toxic, depending on concentration.

Temperature

Water Temperature is a controlling factor for aquatic life. it controls the rate of metabolic activities, reproductive activities and therefore, life cycles. If stream temperatures increase, decrease or fluctuate too widely, metabolic activities may speed up, slow down, malfunction, or stop altogether. Temperature affects the concentration of dissolved oxygen in a water body. Oxygen is more easily dissolved in cold water.

Turbidity

Turbidity is a measure of the cloudiness of water. Cloudiness is caused by suspended solids (mainly soil particles) and plankton (microscopic plants and animals) that are suspended in the water column. Moderately low levels of turbidity may indicate a healthy, well-functioning ecosystem, with moderate amounts of plankton present to fuel

the fuel the food chain. However, higher levels of turbidity pose several problems for stream systems. Turbidity blocks out the light needed by submerged aquatic vegetation.

WATER QUALITY SPECIFICATIONS [7, 8, 9, 10]

Reagent grade water (RGW) is defined as water suitable for use in a specified procedure such that it does not interfere with the specificity, accuracy, and precision of the procedure. In addition, the water quality must meet the specifications established for the application. This definition applies to any high purity water application.

National Committee for Clinical Laboratory Standards (NCCLS), and American Society for Testing and Materials (ASTM) have established RGW specifications for uses ranging from general laboratory to specific clinical laboratory applications.

General laboratory applications include glassware washing and rinsing, chemical reagent and buffer solution preparation, making blanks and standards for calibrating analytical instrumentation, culture media, etc. Clinical laboratory applications include procedures in bacteriology, immunology, hematology, histology, etc. The NCCLS reagent grade water specifications are shown in (Table 2), and the ASTM reagent grade water specifications are shown in Table 3.

TABLE 2: WATER QUALITY SPECIFICATION

Parameter	Type 1	Type 2	Type 3
Bacteria, max.(CFU/ml)	10	1000	NS
PH ,units	NS	NS	5-8
Resistivity, min.(megohm)	10	1.0	0.1
Silica ,max.(mg/l)	0.05	0.1	1.0
Particles	0.22 micron filtration	NS	NS
Organics	Carbon filtration	NS	NS

TABLE 3: REAGENT GRADE WATER BY ASTM

	Type I	TYPE II	Type III	Type IV
Electrical conductivity *us/cm at 298 K (25°C)*	0.056	1.0	0.25	5.0
Electrical resistivity *megohm-cm at29K(25° C)*	18.0	1.0	4.0	0.2
pH *at 298 K (25°C)*	NA	NA	NA	5.0-8.0
Total organic carbon, *ug/L* 50	50	200	no limit	no limit
Sodium, max, *ug/L*	1	5	10	50
Chlorides, max, *ug/L*	1	5	10	50
Total silica, max, *ug/L*	3	3	500	no limit

NCCLS, Type I water systems must include granular activated carbon treatment for organics and chlorine removal, mixed-bed deionization to meet resistivity and silica specifications, and 0.2 micron post-filtration for bacteria and particle control. Type II water can generally be produced by distillation, deionization, or reverse osmosis with polishing deionization or electrode ionization (EDI). Reverse osmosis technology is capable of providing Type III reagent grade water depending on the feed water quality and the design and operation of the reverse osmosis system.

REAGENT GRADE WATER BY ASTM: [7]

Reagent grade water is defined by ASTM as water that has greater than 1 megohm-cm resistivity. Standard specification for reagent water covers requirements for water suitable for use in methods of chemical analysis and physical testing. Four grades are specified. The method of preparation of the various grades of reagent water determines the limits of impurities and shall be as follows.

The American Society For Testing And Materials (ASTM)

The ASTM establishes specifications for Types I, II, III, and IV reagent grade water (D1193-99e1) as shown in Table 2. In addition, the water quality is further classified as Type A, Type B, or Type C depending on the applicable bacteriological and endotoxins quality. Type I water is the highest quality and is generally used for the most critical applications – trace element analysis, HPLC, reagent preparation, etc.

The ASTM further specifies that:

Type I

Water is produced by mixed-bed deionization with suitable pretreatment (distillation or other equal process that can produce water with a maximum conductivity of 20 uS/cm) and post filtration with 0.2 micron membrane filters. Type I water quality cannot be maintained in storage and must be produced on demand at the point of use. Resistivity can only be measured using inline resistivity monitoring equipment.10

Type II

Reagent grade water is produced by distillation with suitable pretreatment (reverse osmosis or deionization) and, depending on the design of the storage tank, is generally sterile and endotoxins free. This grade of water is suitable for preparing culture media, microbiology, bacteriology, etc. Care must be taken in the design of the storage tank and the distribution system to prevent bacterial contamination.

Type III

Reagent grade water is produced by distillation, deionization, reverse osmosis, electrode ionization, or a combination of these technologies, followed by post-filtration with a 0.45 micron membrane filter. This grade of water is generally suitable for preparing various reagents, qualitative analysis, etc. Design of storage tanks and distribution systems is critical to prevent contamination.

Type IV

Reagent grade water is produced by any of the primary treatment methods (distillation, deionization, electro dialysis, or reverse osmosis) or a combination of these methods. This water quality is generally used for glassware washing, cooling applications, etc.

WATER QUALITY STANDARDS [11]

The Water Quality Standards as set by Union Health Ministry and followed by APHED are:-

TABLE 4: WATER QUALITY STANDARD

TABLE 4A: PHYSICAL STANDARD

PHYSICAL STANDARDS			
Sr No.	Characteristics	Acceptable*	Cause for Rejection*
1	Turbidity (units on J.T.U. scale)	2.5	10
2	Colour (units on platinum-cobalt scale)	5.0	25
3	Taste and odour	Unobjectionable	Unobjectionable

TABLE 4B: CHEMICAL STANDARD

CHEMICAL STANDARD			
Sl No.	Characteristics	Acceptable*	Cause for Rejection*
1	pH	7.0-8.5	6.5-9.2
2	Total dissolved solids (mg/l)	500	1500
3	Total hardness (as $CaCo_3$) (mg/l)	200	600
4	Chlorides (as Cl) (mg/l)	200	1000
5	Sulphates (as So_4) (mg/l)	200	400
6	Fluorides (as F) (mg/l)	1.0	1.5
7	Nitrates (as No_3) (mg/l)	45	45
8	Calcium (as Ca) (mg/l)	75	200
9	Magnesium (as Mg) (mg/l)	>30 (If there are 250 mg/l of sulphates, Mg content can be increased to a maximum of 125 mg/l with the reduction of sulphates at the rate of 1 unit per every 2.5 units of sulphates)	150
10	Iron (as Fe) (mg/l)	0.1	1.0
11	Manganese (as Mn) (mg/l)	0.05	0.5
12	Copper (as Cu) (mg/l)	0.05	1.5
13	Zinc (as Zn) (mg/l)	5.0	15.0
14	Phenolic compounds (as phenol) (mg/l)	0.001	0.002
15	Anionic detergents (as MBAS) (mg/l)	0.2	1.0
16	Mineral oil (mg/l)	0.01	0.3
17	Arsenic (as As) (mg/l)	0.05	0.05
18	Cadmium (as Cd) (mg/l)	0.01	0.01
19	Chromium (as hexavalent Cr) (mg/l)	0.05	0.05
20	Cynides (as CN) (mg/l)	0.05	0.05
21	Lead (as Pb) (mg/l)	0.1	0.1
22	Selenium (as Se) (mg/l)	0.01	0.01
23	Mercury (total as Hg) (mg/l)	0.001	0.001
24	Polynuclear aromatic hydrocarbons (PAH) (µg/l)	0.2	0.2
25	Gross alpha activity (pCi/l)	3	3
26	Gross beta activity (pCi/l)	30	30

TABLE 4C: BIOLOGICAL STANDARD

BACTERIOLOGICAL STANDARDS
1) Water entering the distribution system in piped supply chrorinated or otherwise disinfected shall satisfy the following crieria: Coliform count in any sample of 100 ml should be zero. A sample of the water entering the distribution system that does not conform to this standard calls for an immediate investigation into both the efficacy of the purification process and the method of sampling.
2) Water in the distribution system shall satisfy these three criteria 1. E.Coli count in 100 ml of any sample should be zero. 2. Coliform organisms not more than 10 per 100 ml shall be present in any sample. 3. Coliform organisms should not be detectable in 100 ml of any two consecutive samples or more than 50 percent of the samples collected for the year.
3) In individual or small community supplies E.Coli count should be zero in any sample of 100 ml and coliform organisms should not be more than 3 per 100 ml. If coliforms exceed 3 per 100 ml, the supply should be disinfected.
VIROLOGICAL STANDARDS
0.5 mg/l of free residual chlorine for one hour is sufficient to inactivate virus, even in water that was originally polluted. This free chlorine residual is to be insisted in all disinfected supplies in areas suspected of endemicity of infectious hepatities to inactivate virus and also bacteria. 0.2 mg/l of free residual chlorine for half an hour should be insisted for other areas.

TESTS USED FOR DETECTION OF VARIOUS COMPOUNDS IN WATER

TABLE 5: TESTS USED FOR DETECTION OF VARIOUS COMPOUNDS IN WATER

Compounds	TESTS
Chlorine Detection	O-Tolidine Testmethyl Orange Test
Chlorine Dioxide	Iodometric Titrations,O-Tolidine Reagent
Chloride	Argentimetric Titration With Mohrindication,Mercurimetric Titration,Spectrophotometric Chloride Determinations
Phenolic Compounds	Liquid Chromatographic Determination Gas Chromatographic Determination Nonchromatographic Techniques
Detergent	Gas Chromatography High-Performance Liquid Chromatography Supercritical Fluid Chromatography
Nitrogen	Kjeldahl Digestion Ultraviolet Oxidation

	Persulfate Oxidation
Cynide	Flow Injection Method
Oil	Sorptive Extraction Techniques Membrane Extraction Techniques
Sulfate	Photometric Detecter,Multiple Reaction Monitoring
Metals(Cd,Mn,Cr,etc)	electrothermal atomic absorption method (**ETAAS**), Graphite furnace atomic absorption spectrometry (GFAAS)

WATER PURIFICATION TECHNIQUES [12]

Various techniques are used for purification of water. Many techniques are used for purification water in industry. Some of them are as below.

A. Distillation:-

Distillation is probably the oldest method of water purification. Water is first heated to the boiling point. The water vapor rises to a condenser where cooling water lowers temperature so the vapor is condensed, collected and stored.

Many contaminants remain behind in the boiling vessel. However, the process has several

Limitations:

Inorganic contaminants are able to migrate along the thin water film that forms on the inner walls of the still. This explains why ions can be found in the distillate, whose resistivity is therefore usually between 0.5 and 1 MΩ•cm at 25 °C.

Organics with boiling points lower than 100 °C will automatically be transferred to the distillate, and even organics with a boiling point superior to 100 °C can dissolve in the water vapor and also pass into the distillate.

Distillation is a slow process that requires storage of water for long periods. Distillation requires large amounts of energy and water, and therefore is expensive to operate. In addition, a still requires regular cleaning of the boiling pot with HCl, a brush and sand paper to remove the contaminants accumulated during the process. (Figure-1)

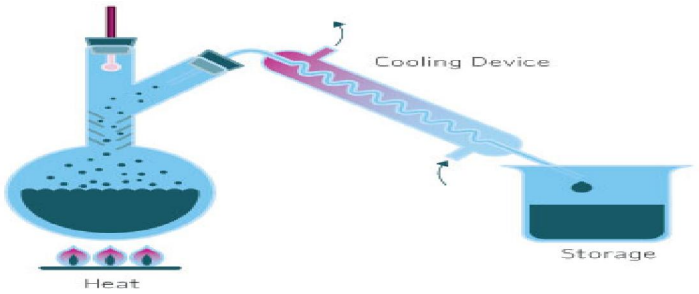

Figure 1
Distillation Technique

Benefits:

1. Removes a broad range of contaminants and therefore useful as a first purification step.
2. Reusable.

Limitations:

1. Contaminants are carried to some extent into the condensate.
2. Requires careful maintenance to ensure purity.
3. Consumes large amounts of tap water (for cooling) and electrical energy (for heating).
4. Not environment-friendly.

B. Ion Exchange:

The ion-exchange process percolates water through spherical, porous bead resin materials (ion-exchange resins). Ions in the water are exchanged for other ions fixed to the beads. The two most common ion-exchange methods are softening and deionization. Softening is used primarily as a pretreatment method to reduce water hardness prior to reverse osmosis (RO) processing. The softeners contain beads that exchange two sodium ions for every calcium or magnesium ion removed from "softened" water.

Deionization (DI) beads exchange either hydrogen ions for cations, or hydroxyl ions for anions. The cation-exchange resins, which are made of polystyrene chains cross-linked by divinylbenzene with covalently bound sulfonic acid groups, will exchange a hydrogen ion for any cations they encounter (e.g., Na^{+}, Ca^{++}, Al^{+++}). Similarly, the anion-exchange resins, which are made of polystyrene polymer chains with covalently bound quaternary ammonium groups, will exchange a hydroxyl for any anions (e.g., Cl^{-}, NO^{3-}, and SO^{4-}). The hydrogen ion from the cation-exchanger unites with the hydroxyl ion of the anion exchanger to form pure water.

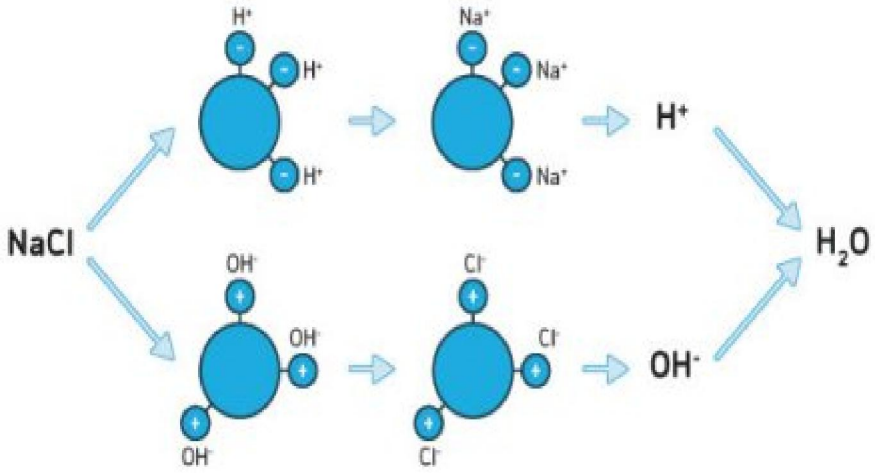

Figure 2
Ion Exchange Technique

Benefits:

1. Removes dissolved inorganic (ions) effectively, allowing resistivity levels above 18.0 MΩ•cm at 25 °C to be reached (corresponding roughly to less than 1 ppb total ionic contamination in water).
2. Regenerable (by acid and bases in "service deionization" or by electrodeionization).
3. Relatively inexpensive initial capital investment.

Limitations:

1. Limited capacity: once all ion binding sites are occupied, ions are no longer retained (except when operating in an electodeionization process).
2. Does not effectively remove organics, particles, pyrogens or bacteria.
3. Chemically regenerated DI beds can generate organics and particles.
4. Single use, "virgin" resins require good pretreated water quality to be economically efficient.

C. Activated Carbon:

Activated carbon is made of organic material porous particulates containing a maze of small pores, which account for the substance's highly developed surface. One gram of activated carbon has a surface of up to 1 000 m^2. Organic molecules dissolved in water may enter the pores and bind to their walls due to van der Waals forces. The adsorption process is controlled by the diameter of the pores in the carbon filter and by the diffusion rate of organic molecules through the pores. The rate of adsorption is a function of

molecular weight and the molecular size of the organics. Activated carbon used in water purification is available in two forms, natural activated carbon and synthetic activated carbon.

Natural activated carbon:- It produced by treating vegetal products such as coconut shells at high temperature. The result of this process is a fine powder made of irregularly shaped grains. Natural activated carbon contains a high concentration of ionic contaminants and is therefore used only as a pretreatment step to remove excess chlorine from tap water by a reduction reaction and, to some extent, to reduce organic contamination.

Synthetic activated carbon:- It is made by the controlled pyrolysis of polystyrene spherical beads. This cleaner material is used for the removal of trace organics of low molecular weight.

Activated carbon is usually used in combination with other treatment processes. The placement of carbon in relation to other components is an important consideration in the design of a water purification system (figure-3).

Figure 3
Activated Carbon Technique

Benefits:

1. Removes dissolved organics and chlorine effectively.
2. Long life due to high binding capacity.

Limitations:

1. Does not efficiently remove ions and particulates.
2. Limited capacity due to a high, but limited, number of binding sites.
3. Can generate carbon fines.

D. Ultrafiltration:

A microporous membrane filter removes particles according to pore size. By contrast, an ultra filtration (UF) membrane functions as a molecular sieve. It separates dissolved molecules on the basis of their size–often reported as the "molecular weight" (both parameters are related, but not always directly)—by passing a solution through an infinitesimally fine filter.

The ultrafilter is a tough, thin, selectively permeable membrane that retains most macromolecules above a certain size (Nominal Molecular Weight Limit, or NMWL) including colloids, microorganisms and pyrogens. Smaller molecules, such as solvents and ionized contaminants, are allowed to pass into the filtrate. Thus, UF provides a retained fraction (retentate) that is rich in large molecules and a filtrate that contains few, if any, of these molecules. Ultrafilters are available in several selective ranges. In all cases, the membranes will retain most, but not necessarily all, molecules above their rated size. In water purification, ultrafilters are routinely used to provide pyrogen-free and nuclease-free water for critical cell culture or molecular biology experimentation. The key point here is the validation process, which ensures that the ultrafilter, when challenged by pyrogens, RNases or DNases at levels far above those likely to occur during regular operation, will be able to reliably deliver water within specification.(figure- 4)

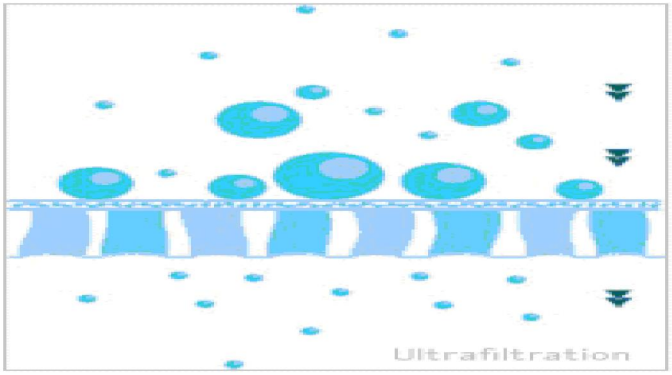

Figure 4
Ultrafiltration Technique

Benefits:

1. Effectively removes most particles, pyrogens, enzymes, microorganisms and colloids above their rated size, retaining them above the ultrafilter surface.
2. Efficient operation throughout their lifetime, unless they are damaged.
3. Their lifetime can be extended by a regular water flush at high speed.

Limitations:

1. Will not remove dissolved inorganics or organic substances.
2. May clog when challenged by an excessive level of high-molecular-weight contaminants.

E. Reverse Osmosis:

Reverse osmosis (RO) is the most economical method of removing 95 % to 99 % of all contaminants. The pore structure of RO membranes is much tighter than that of UF membranes. RO membranes are capable of rejecting practically all particles, bacteria and organics > 200 Dalton molecular weight (including pyrogens) at a rate close to 99 %. Natural osmosis occurs when solutions with two different concentrations are separated by a semi-permeable membrane. Osmotic pressure drives water through the membrane; the water dilutes the more concentrated solution; and the end result is an equilibrium.

In water purification systems, hydraulic pressure is applied to the concentrated solution to counteract the osmotic pressure. Pure water is driven from the concentrated solution at a flow rate proportional to applied pressure and collected downstream of the membrane. Because RO membranes are very restrictive, they yield slow flow rates per surface unit. Storage tanks are required to produce an adequate volume in a reasonable amount of time.

RO also involves an ionic exclusion process. Only solvent (i.e., water molecules) is allowed to pass through the semi-permeable RO membrane, while virtually all ions and dissolved molecules are retained (including salts and organic molecules such as sugars). The semi-permeable membrane rejects salts (ions) by a charge phenomenon action: the greater the charge, the greater the rejection. Therefore, the membrane rejects nearly all (> 99 %) strongly ionized polyvalent ions but only 95 % of the weakly ionized monovalent ions like sodium. Salt rejection increases significantly with applied pressure up to 5 bar.

Different feed water may require different types of RO membranes. Membranes are manufactured from cellulose acetate or thin-film composites of polyamide on a polysulfone substrate.

If the system is properly designed for the feed water conditions and the intended use of the product water, RO is the most economical and efficient methods for purifying tap water. RO is also the optimum pretreatment for reagent-grade water polishing systems. (figure-5)

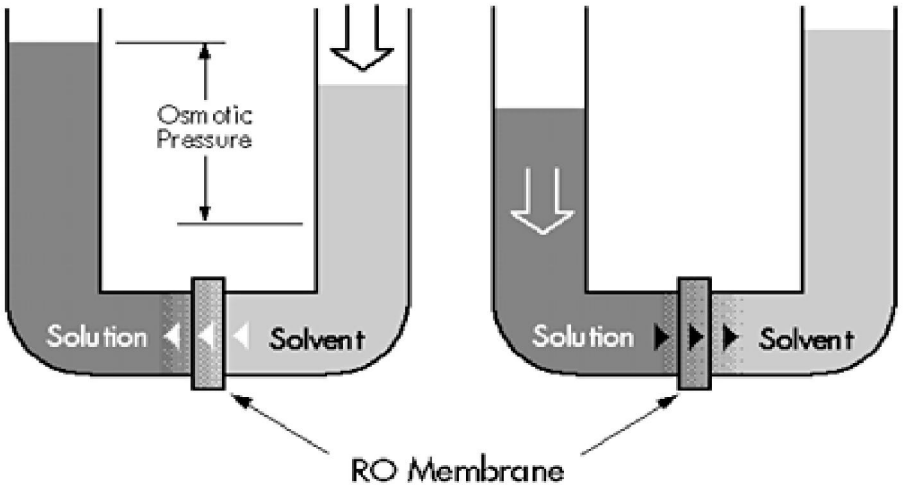

Figure 5
Reverse Osmosis Technique

Benefits:

1. Effectively removes all types of contaminants to some extent (particles, pyrogens, microorganisms, colloids and dissolved inorganics), and is therefore useful as a first purification step.
2. Requires minimal maintenance.
3. Operation parameters (pressure, temperature, flow rate, ionic rejection) are easy to monitor.

Limitations:

1. LImited flow rates per surface unit require either large membrane surfaces or an intermediate storage device to satisfy user demand.

2. Requires good pretreatment to avoid rapid membrane damage by water contaminants: scaling (CaCO3 deposits on the surface), fouling (deposits of organics or colloids on the surface) or piercing (RO membrane cut by hard particulates).

F. Elix Ion Exchange Technique:

This technology is a combination of electrodialysis and ion exchange, resulting in a process which effectively deionizes water, while the ion-exchange resins are continuously regenerated by the electric current in the unit. This electrochemical regeneration replaces the chemical regeneration of conventionalion-exchange systems. The Elix module consists of a number of "cells" sandwiched between two electrodes. Each cell consists of a polypropylene frame onto which are bonded a cation-permeable membrane on one side, and an anion-prmeable membrane on the other. The space in the center of the cell, between the ion-selective membranes, is filled with a thin bed of ion-exchange resins. The cells are separated from one another by a screen separator. The feed water entering the module is split into three parts. A small percentage flows over the electrodes, 65-75 % of the feed passes through the resin beds in the cell, and the remainder passes along the screen separator between the cells.

The ion-exchange resins capture dissolved ions in the feed water at the top of the cell. Electric current applied across the module pulls those ions through the ion-selective membrane towards the electrodes. Cations are pulled through the cation-permeable membrane towards the cathode, and anions through the anion-selective membrane towards the anode. These ions, however, are unable to travel all the way to their respective electrodes since they come to the adjacent ion-selective membrane which is of the opposite charge. This prevents further migrations of ions, which are then forced to concentrate in the space between the cells. This space is known as the "concentrate" channel, and the ions concentrated in this area are flushed out of the system to the drain. (figure-6)

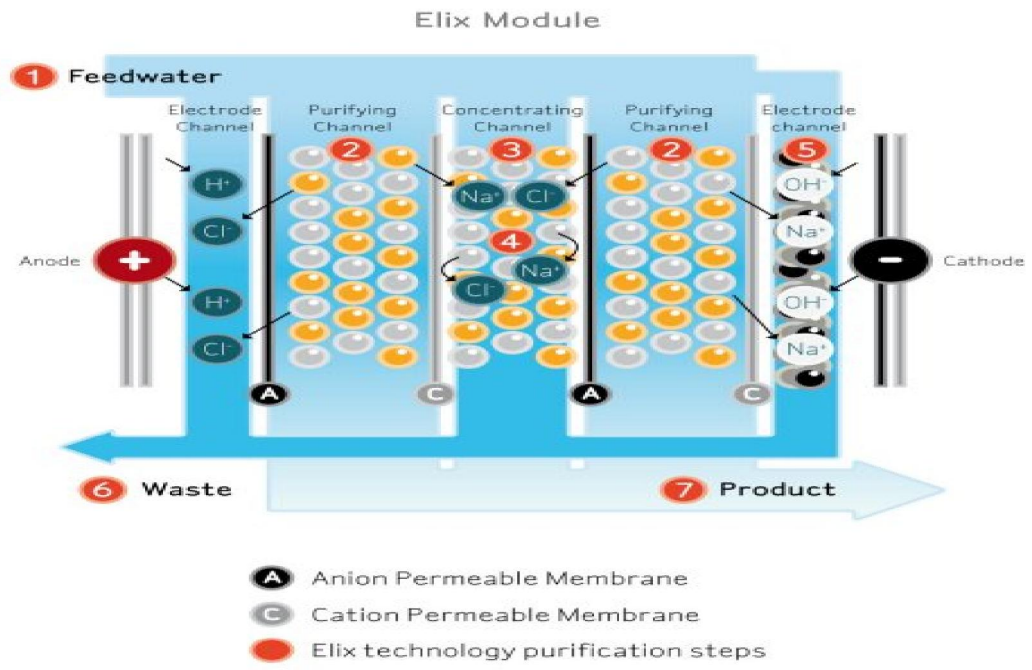

Figure 6
Elix Ion Exchange Technique

Benefits:

1. Removes dissolved inorganics effectively, allowing resistivity above 5 Ω•cm at 25° to be reached (which corresponds to a total ionic contamination level in water of approximately 50 ppb).

2. Environment-friendly

No chemical regeneration

No chemical disposal

No resin disposal

3. Inexpensive to operate.

4. Safe: No heating element.

Limitations:

1. Removes only a limited number of charged organics.

2. Requires feed by good quality water (for instance, reverse osmosis-treated water) for economically efficient operation.

G. Ultraviolet (Uv) Radiation

Ultraviolet radiation has been widely used as a germicidal treatment for water. Mercury low pressure UV lamps generate light at different wavelengths, including 185 and 254 nm. UV lamps with a regular quartz sleeve allow passage of 254 nm light. These lamps are an effective means of sanitizing water. The adsorption of UV light by the DNA in the microbial cells results in the inactivation of the microorganism (figure-7).

Figure 7
Ultraviolet Technique

Benefits:

1. Effective sanitizing treatment.
2. Oxidation of organic compounds (185 nm and 254 nm) to reach water TOC levels below 5 ppb.

Limitations:

1. Photooxidation of organics is a polishing step, able to decrease the TOC level only by a limited value.
2. The CO_2 produced during photooxidation decreases the water's resistivity.
3. UV light will not affect ions, particles or colloids.

MICROBIOLOGICAL TESTS FOR WATER:-

Limulus Amoebocyte Lysate (LAL) Test [13] :-

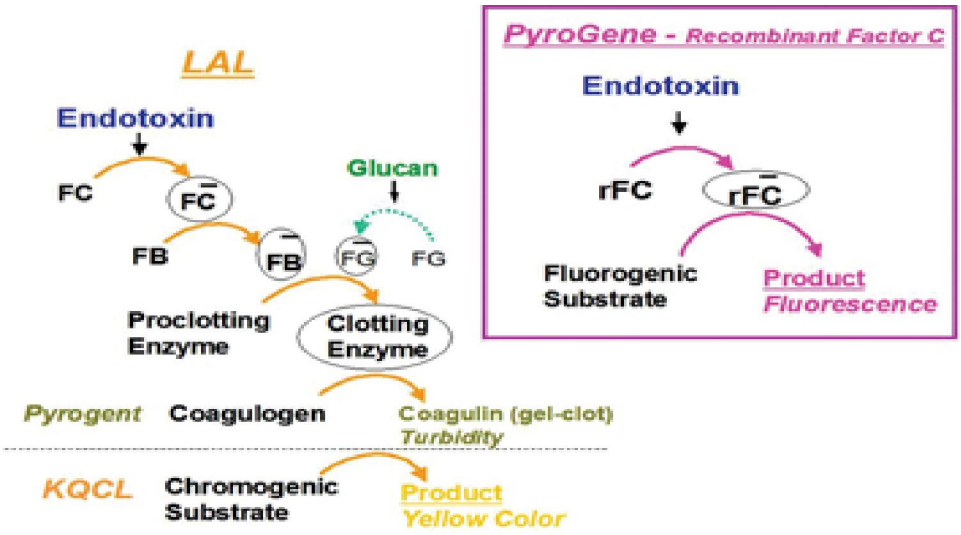

Figure 8
Limulus Amoebocyte Lysate (LAL) Test

The current Limulus Amoebocyte Lysate (LAL) method for endotoxin detection uses an enzymatic coagulation cascade found in the LAL that is activated by endotoxin. A new method for endotoxin detection using recombinant factor C (rFC) has been developed and evaluated. The activation of rFC is determined by the fluorescence generated by the enzymatic cleavage of a peptide-coumarin substrate. Fluorescence is measured after one-hour incubation with endotoxin standards at 37^{o}C. The fluorescence is proportional to the endotoxin concentration and is linear in the 0.01-10 EU/ml range in log scales.

The assay detected no (1, 3)-glucan activity and measured similar potency of endotoxin from Salmonella and Pseudomonas strains as those in LAL assays. Both the LAL assays and the assay gave similar endotoxin concentration results in various samples.

Endotoxin, also known as Lipopolysaccharide, is found in the cell membrane of Gram negative bacteria. Endotoxin can cause excessive inflammation when introduced into a host by inducing cytokine responses in macro-phages. As a result, endotoxin levels in

injection materials are strictly monitored by the pharmaceutical and medical device industries.

The most widely used endotoxin detection methods are the Limulus Amebocyte Lysate (LAL) tests derived from horseshoe crab hemolymph. The LAL tests employ a serine protease catalytic coagulation cascade that can be activated by endotoxin.

Factor C (FC), the first component in the cascade, is a protease zymogen that is activated by endotoxin binding. An alternative pathway, the Factor G (FG) pathway, can be activated by glucan binding. Downstream, these two pathways activate a proclotting enzyme into a clotting enzyme. The kinetic chromogenic LAL assay (KQCL) uses the synthetic peptide-pNA substrate that can be cleaved by the clotting enzyme, resulting in a product that exhibits a yellow color. The kinetic turbidimetric assay uses the native substrate, coagulogen that can be cleaved into coagulin. Coagulin then begins to form a gel-clot, resulting in an increase in turbidity. The densities of the yellow color (OD 405nm) and the turbidity (OD 340nm) are correlated with endotoxin concentration.

The LAL tests are very sensitive and can detect as little as femtograms of endotoxin. However, because of the alternative glucan pathway, endotoxin detections by LAL tests sometimes have false positive results in samples contaminated with glucan, such as biologicals and cellulosic materials (filters). In addition, LAL lot-to-lot variation with respect to endotoxin sensitivity has been reported. Finally, since the limulus hemolymph is the sole supply for LAL, any decrease in the population of horseshoe crabs would pressure commercial production of the LAL assay. Because Factor C only binds to endotoxin, a new endotoxin detection assay using recombinant Factor C (rFC) has been developed by Ding and Ho.

Endotoxin Sensitivity and Detection Range:-

The endotoxin concentration and fluorescence signal have a linear correlation in a log-log scale plot. The endotoxin detection range for a one-hour assay is 0.01-10 EU/ml. This is comparable to KQCL that has a detection range of 0.005-50 EU/ml and to kinetic turbidimetric assay that has a range of 0.01-100 EU/ml. Both KQCL and the kinetic turbidimetric assay are measured kinetically, therefore require continuous absorbance signal recording during the entire reaction time, usually in less than an hour. The endotoxin detection assay, on the other hand, is a simple endpoint assay, which only

takes minutes to record data. Thus, the assay can assay more samples in less time, which can better fit into high throughput applications.

Various water quality tests are available to detect the number and types of microorganisms in waters and assist communities in keeping the microbial content of water supplies at a low level. These tests vary from the more sophisticated tests to the standard procedures that have been used for decades.

A. Gene Probe Tests [14]**:**

Among the most sophisticated tests for water bacteriology are those that employ gene probes. Gene probes are fragments of DNA that seek out and combine with complementary DNA fragments. Often the test is designed to test for the presence of *Escherichia coli* in water. This Gram-negative rod, usually found in the human intestine, is used as an indicator organism. If it is present, then it is likely that the water has been contaminated with human feces. The feces may contain microbial pathogens.

To use a gene probe test for *E. coli* in water, the water is treated to disrupt any bacteria present and release their nucleic acid. Then a specific *E. coli* probe is added to the water. Like a left hand seeking a right hand, the probe searches through all the nucleic acid in the water and unites with the *E. coli* DNA, if present. A radioactive signal indicates that a match has been made. If no radioactivity is emitted, then the gene probe has been unable to locate its matching DNA, and *E. coli* is probably absent from the water.

B. The Membrane Filter Technique:

The membrane filter technique uses a filtration apparatus and a cellulose filter called a membrane filter. A 100-ml sample of water is passed through the filter, and the filter pad is then transferred to a bacteriological growth medium. Bacteria trapped in the filter grow on the medium and form colonies. By counting the colonies, an estimate can be made of the number of bacteria in the original 100-ml sample.

C. The Standard Plate Count:

It is generally impractical to test for all pathogenic organisms, but the total number of bacteria can be calculated. One test is the standard plate count**.** In this test, samples of water are diluted in jars containing 99-ml sterile water, and samples are placed in Petri dishes with nutrient agar or other nutritious medium. After incubation, the colony count

is taken and multiplied by the dilution factor to obtain the total number of bacteria per ml of sample. (Figure-9)

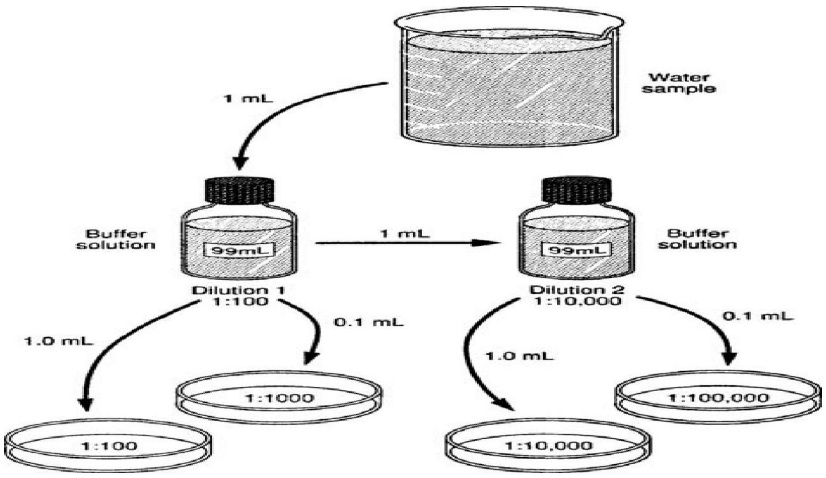

Figure 9
The Standard Plate Count Test

The standard plate count procedure: 1ml water sample is diluted in buffer solution, and various amounts are placed with nutrient medium into petri dishes to encourage bacterial colonies to form. The colony count is multiplied by the dilution factor to yield the total plate count.

Indicator bacteria can be detected to give an estimate of pathogens. The most common indicator organisms in water bacteriology are the coliform bacteria. These are Gram-negative rods normally found in the intestine and typified by Escherichia coli. To test for the presence of coliforms, a standard plate count can be performed, with violet red bile agar used as the growth medium to encourage proliferation of the coliform bacteria.

Specific Microbiological Test For Bacteria [15]

Aeromonas in finished water by membrane filtration using ampicillin-dextrin agar with vancomycin.

Specific Microbiological Test For Protozoans

Cryptosporidium and Giardia in Water by Filtration

Specific Microbiological Test For Viruses And Coliphage

1. Male-specific (F+) and Somatic Coliphage in Water by Two-step Enrichment Procedure

2. Male-specific (F+) and Somatic Coliphage in Water by Single Agar Layer (SAL) Procedure

WATER QUALITY TESTING DEVICE:

A. Six In One Multi-Parameter Water Quality Monitor/Water Quality Meter Pht-027

Figure 10
Six in One Multi-Parameter Water Quality Monitor/Water Quality Meter PHT-027

Specifications:

1. Measuring range: pH: 0.00~14.00 pH, °C: 50°C~70°C (-58°F~158°F)
2. Resolution: pH: 0.01 pH , °C: 0.1°C (0.2°F)
3. Accuracy: pH: ±0.1pH , °C: ±1.0°C

B. Oxidation Reduction Potential Water Testing Equipment (ORP)

Figure 11
Oxidation Reduction Potential (ORP) Water Testing Equipment

Specifications:

1. Range: -1999 to 1999mV

2. Resolution: 1mV

3. Accuracy: ±5 mV

4. Parameter:

Environment: 0 to 50°C, RH 95% max; Dimensions: 175x41x23mm Weight: 72g

C. Dissolved oxygen meter

Figure 12
Dissolved Oxygen Meter

Specification

1. Model Number: SR-980

2. Dissolved Oxygen Range: 0.00~20.00mg/L ppm

3. Resolution: 0.01mg/L

4. Dissolved Oxygen Accuracy: ±0.3mg/L, Saturation of Oxygen: 0.0~200.0%, Accuracy: ±5.00%

5. Temperature range: 0.0~50.0°C (32~122°F)

Temperature Accuracy: ±1^{o}C, ±1.8^{o}F, Temperature Compensation: 0.0~40.0^{o}C

6. Barometric Pressure Correction: 450~850mmHg, 60.0~112.5kPa

D. Total dissolved salt water testing (TDS) meter

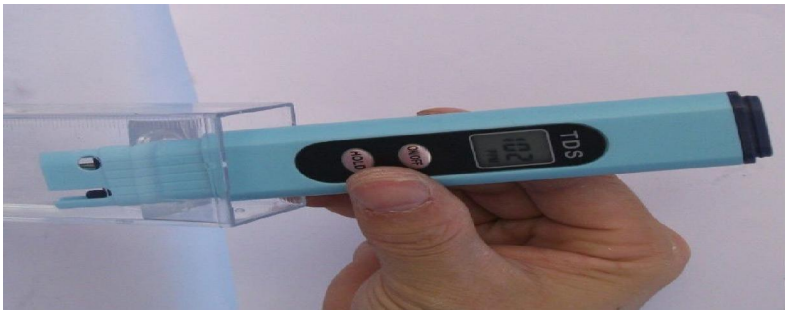

Figure 13
Total Dissolved Salt Water Testing (TDS) Meter

Specifications

1. Range: 0~9990 ppm (mg/L)

2. Accuracy: ±2%F.S

3. Temperature Compensation: Automatic operating Temperature: 0~50°C

4. Power source: 2×1.5 v (button cell) size: 142×25×15mm

STERILE WATER FOR INJECTION [16]

Physical and chemical properties of sterile water for injection

TABLE 6: PHYSICAL AND CHEMICAL PROPERTIES OF STERILE WATER FOR INJECTION

Characteristic	Properties
Color	clear, colorless solution
Odor / Odor Threshold	odorless
Physical State	liquid
pH	5.0 to 7.0
Freezing Point	32 degrees fahrenheit
Boiling Point	212 degrees fahrenheit
Flash Point	not applicable
Evaporation Rate	not applicable
Flammability	nonflammable,noncombustible
Upper Flammable Limit	not applicable
Lower Flammable Limit	not applicable
Vapor Pressure	17.5 mm hg (68 degrees fahrenheit)
Vapor Density	not applicable
Specific Gravity	1.0
Solubility (water)	freely soluble in water
Partition Coefficient	not applicable
Auto-ignition Temperature	not applicable
Percent Volatile	0 percent
Volatile Organic	0 percent

Description

Sterile Water for Injection, USP is a sterile, nonpyrogenic water for injection intended only for dilution purposes. The pH is 5.4 (5.0 to 7.0). The Pharmacy Bulk Package is a sterile dosage form which contains multiple single doses for use only in a pharmacy bulk admixture program.

Sterile Water for Injection, USP contains no bacteriostat, antimicrobial agent or added buffer. Sterile Water for Injection, USP may be classified as a sterile diluent and pharmaceutical vehicle. Sterile Water for Injection, USP is chemically designated H2O.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

Label

NOT FOR DIRECT INFUSION. DO NOT USE FOR NON-AUTOMATED ADMIXTURE PREPARATIONS.

FOR DILUTION ONLY.

Do not heat over 66°C (150°F).This preparation is solute-free and its entry into the circulation undiluted will cause hemolysis.

Contraindication

Absorption of large amounts of Sterile Water for Injection, USP with additives can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, over hydration, congested states or pulmonary edema. The risk of dilution states is inversely proportional to the electrolyte concentrations of administered solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of such solutions.

Warning:

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature

neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Precautions

Do not use unless water is clear, seal is intact and container is undamaged. Aseptic technique is essential with the use of sterile preparations for compounding admixtures. Discard container within 4 hours of entering closure.

Adverse Reactions

Accidental contamination from careless technique may transmit infection. Should any adverse reaction occur, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination, if deemed necessary.

Dosage and Administration

Sterile Water for Injection, USP in the 2000 mL flexible Pharmacy Bulk Package is designed for use with automated compounding devices for preparing intravenous admixtures. Dosages will be in accordance with the recommendation of the prescribing physician.

Sterile Water for Injection, USP is not intended for direct infusion. Admixtures should be made by or under the direction of a pharmacist using strict aseptic technique under a laminar flow hood. Compounded admixtures may be stored under refrigeration for up to 24 hours. Administration of admixtures should be completed within 24 hours after removal from refrigeration.

Recommended Directions for Use of the Pharmacy Bulk Package

Use Aseptic Technique

1. During use, container must be stored, and all manipulations performed, in an appropriate laminar flow hood.
2. Remove cover from outlet port at bottom of container.

3. Insert piercing pin of transfer set and suspend unit in a laminar flow hood. Insertion of a piercing pin into the outlet port should be performed only once in a Pharmacy Bulk Package solution. Once the outlet site has been entered, the withdrawal of container contents should be completed promptly in one continuous operation. Should this not be possible, a maximum time of 4 hours from transfer set pin or implement insertion is permitted to complete fluid transfer operations; i.e., discard container no later than four hours after initial closure puncture.

4. Sequentially dispense aliquots of Sterile Water for Injection, USP into I.V. containers using appropriate transfer set. During fluid transfer operations, the Pharmacy Bulk Package should be maintained under the storage conditions recommended in the labeling.

VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS:

The validation defines the critical process parameters and their operating ranges. A validation program qualifies the design, installation, operation and performance of equipment. It begins when the system is defined and moves through several stages: Qualification of the Design (DQ), Installation (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

A validation plan for a water system typically includes the following steps:

1. Establishing standards for quality attributes and operating parameters.

2. Defining systems and subsystems suitable to produce the desired quality attributes from the available source water.

3. Selecting equipment, controls, and monitoring technologies.

4. Developing an IQ stage consisting of instrument calibration, inspection to verify that the drawings accurately depict the as built configuration of the water system, and, where necessary, special tests to verify that the installation meets the design requirements.

5. Developing an OQ stage consisting tests and inspection to verify that the equipment, system alerts, and controls are operating reliably and that appropriate alert and action levels are established. This phase of qualification may overlap with aspects of the next step.

6. Developing a prospective PQ stage to confirm the appropriateness of critical parameter operating ranges. A concurrent or retrospective PQ is performed to demonstrate system

reproducibility over an appropriate time period. During this phase of validation, Alert and action levels for key quality attributes and operating parameters are verified.

7. Supplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance, including recalibration of instruments. In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program. (Figure 14)

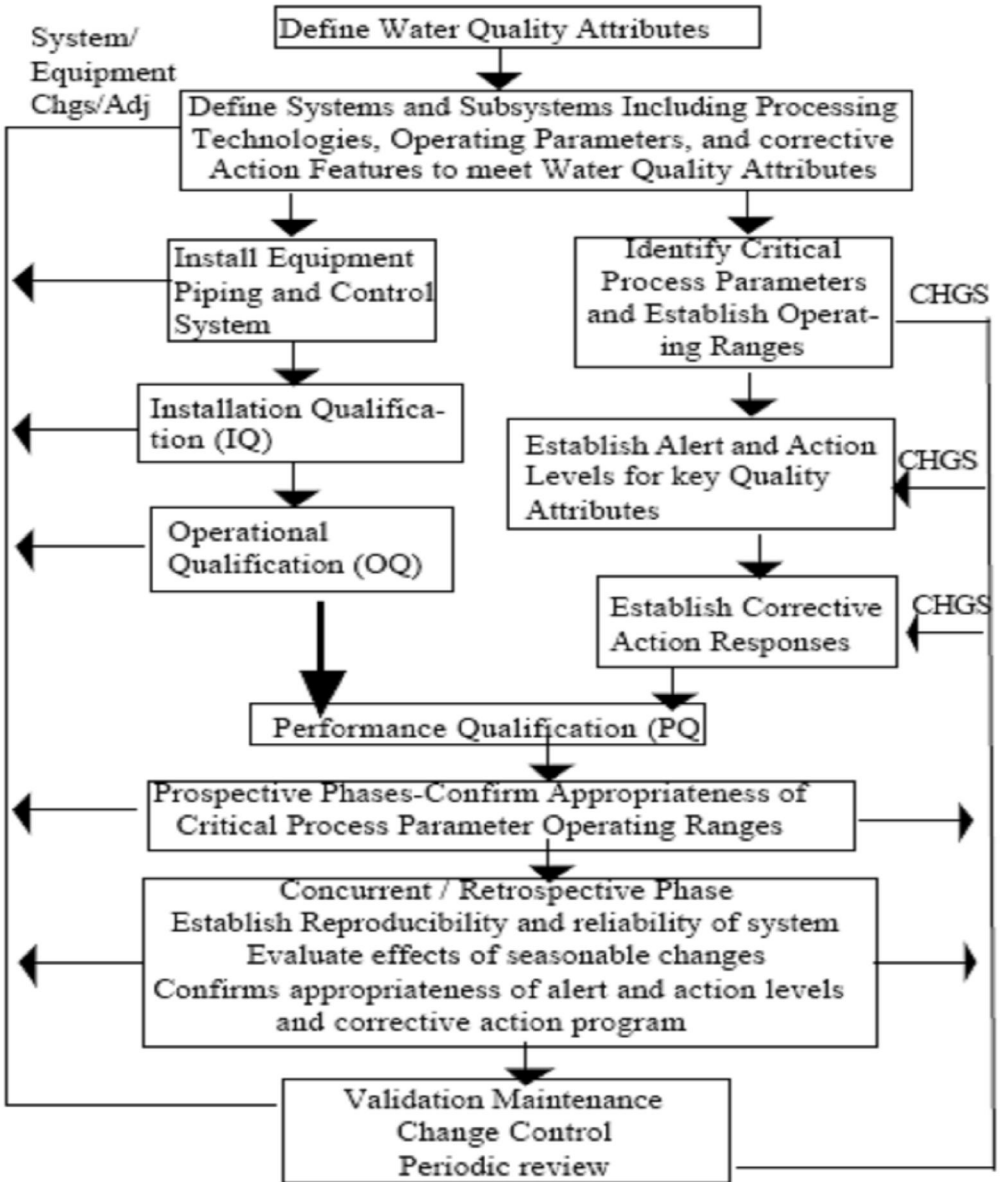

Figure 14
Water system validation life cycle

Validation Sequence:-

A. Design Qualification (Dq) [18, 19]

The design qualification should include the participation of all appropriate groups, such as engineering design, production operation, quality assurance, analytical services etc. The design qualification lists the activities necessary for the consistent production of the stipulated grade of water. It also provides the calibration of critical instruments.

The basic design package should include the following,

1. Flow schematics for the proposed water system showing all of the instrumentation, controls and valves and component should be numbered for reference.
2. A complete description of features and functions of the system.
3. Detail specification for the equipment to be used for water treatment and pretreatment.
4. Detail specification for all other system components such as storage tanks, heat exchangers, pumps, valves and piping components.
5. Detailed specifications for sanitary system controls and description of their operation.
6. Specification for construction techniques to be employed where quality is of critical importance.
7. Procedure for cleaning the system, both after construction and on a routine basis.

B. Installation Qualification (IQ) [19, 20]

IQ provides construction verification in that established specifications have been complied. IQ conforms the "As-Built" drawing and ensures the suitability of the completed system. Make the list of instruments and controls, calibration of these instruments shall be traceable to the national and international standards. Calibrations of instruments can be performed at the end of IQ process and recorded as a part of IQ or at the beginning of the operational qualification.

C. Operational Qualification (OQ) [19, 20, 21]

The system should be carefully clean and all construction derbies removed to minimize any chance of contamination and corrosion. After completion of cleaning, equipment should be started up and carefully checked for the proper operation OQ verifies the capabilities of processing units to perform satisfactorily within operational limits. Consideration of feed water quality of system capacity, temperature control, flow rates are involved in OQ. Focus the critical items and parameters during OQ.

D. Performance Qualification (PQ) [19, 20, 21]

The purpose of PQ is to provide rigorous testing of demonstrate the effectiveness and reproducibility of the total integrated process.

The three phase validation is regulatory expectation.

Phase 1

Test period shall be 2- 4 weeks (14 days minimum) for monitoring the system intensively.

Phase 2

A further test period of 2-4 weeks (30 days) should be spent carrying out further intensive monitoring, while developing all the refined SOP's after the satisfactory completion of phase1.

Phase 3

Phase 3 typically runs for one year after the satisfactory completion of phase 2.

Revalidation

Revalidation should be performed only when there has been a significant change to the system or to the operational parameters. Routine monitoring and inspection will continue under the same condition as those that existed during the original validation. Routine maintenance or replacement of parts should have a specific written procedure, which must be validated at the time of original validation.

Operation, maintenance and control [17, 18, 19, 21]

Operating procedure – Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required.

Monitoring program – Critical quality attributes and operating parameters should be documented and monitored.

Sanitization- Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control.

Preventive maintenance – A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed,

Change control – The mechanical configuration and operating condition must be controlled. Proposed changes should be evaluated for their impact on the whole system.

CONCLUSION

Water has great importance for many purposes regarding manufacturing of different dosage form in pharmaceutical industry. Water used in industry should have some criteria regarding its use, it have all parameter in specified range according to reliable guideline. National Committee for Clinical Laboratory Standards (NCCLS), and American Society for Testing and Materials (ASTM) have established specifications for uses of water ranging from general laboratory to specific clinical laboratory applications. Water should not contain other organic and inorganic compound out of limit of specified range. Water should have criteria as specified in biological standards. Validation of water must be performed and passed as per standard water protocol.

REFERENCES

1. Johnson, D.L., S.H. Ambrose, T.J. Bassett, M.L. Bowen, D.E. Crummey, J.S. Isaacson, D.N. Johnson, P. Lamb, M. Saul, and A.E. Winter-Nelson: Meanings of environmental terms. Journal of Environmental Quality 1997; 26: 581-589.
2. Henniker, J. C: The Depth of the Surface Zone of a Liquid. Reviews of modern physics 1949; 21 (2): 322–341.
3. http://www.herballegacy.com/August_22_2007.html
4. http://corrosion-doctors.org/Corrosion-by-Water/Types-of-water.htm
5. Pharmaceutical Waters 05 (PW05), USP29–NF24. Pharmacopeial Forum: Volume No. 30(5): 3056
6. http://www.dnr.mo.gov/env/esp/waterquality-parameters.htm.
7. American society for testing and materials, ASTM D1193-99e1: Annual book of ASTM standards, American society for testing and materials, Philadelphia. Vol. 11, 2001.
8. Meltzer, Theodore H.: High purity water preparation for the semiconductor, Pharmaceutical, and power industries. Tall oaks publishing, inc. 1993.
9. International society for pharmaceutical engineers, baseline pharmaceutical Engineering Guides for New and Renovated Facilities, water and steam Systems. Vol. 4, 2001.

10. Murphy, Daniel B. and Viateur Rousseau: Foundations of college chemistry. New York: The Ronald Press Company.1969.
11. http://www.dnr.mo.gov/env/esp/waterquality-parameters.htm
12. http://www.millipore.com/lab_water/clw4/tutorial&tabno=5
13. http://en.wikipedia.org/wiki/Limulus_amebocyte_lysate.html
14. http://www.cliffsnotes.com/study_guide/Water-Quality-Tests.topicArticleId524,articleId-8510.html
15. http://www.epa.gov/microbes/online.html
16. http://www.drugs.com/pro/sterile-water-for-injection.html
17. James Swarbrich and James C Boylan: Encyclopedia of Pharmaceutical Technology –Marcel Dekker INC, New York Vol. 16, 293 – 306.
18. Robert A Nash and Alfred H: Wachter, Pharmaceutical Process Validation, A International, Revised and Expanded, Marcel Dekker, Vol. 3, 401 – 422.
19. William V. Collentro: Pharmaceutical Water System Design, Operation and Validation, Vol.21, 271-274.
20. D.A. Sawant: Pharma Pathway,Vol. 2, 2007.
21. Syed Imtiaz Haider: Pharmaceutical Master Validation Plan, A Ultimate Guide to FDA, GMP & GLP Compliance, Vol.1, 2006.
22. Pharmaceutical Engineering Guide, A Guide for new facilities, Water and steam guide, Vol 4, 2000.

For Correspondence:
Amit V. Patel
Email: amitrx18490@gmail.com