WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 10, 147-160. Review Article ISSN 2277– 7105

REVIEW ARTICLE WATER FOR PHARMACEUTICAL USE

***Ramyasree M., Gangadharappa H. V. and Deepak A. M.**

Department of Pharmaceutics (Pharmaceutical Quality Assurance), JSS College of Pharmacy. JSS Academy of Higher Education and Research, Sri Shivarathreeshwara Nagara, Mysore - 570 015, Karnataka, India.

Article Received on
23 March 2018,

Revised on 13 April 2018,
Accepted on 03 May 2018,

DOI: 10.20959/wjpr201810-12252

***Corresponding Author**
Dr. Gangadharappa H. V.
Department of Pharmaceutics (Pharmaceutical Quality Assurance), JSS College of Pharmacy. JSS Academy of Higher Education and Research, Sri Shivarathreeshwara Nagara, Mysore - 570 015, Karnataka, India.

ABSTRACT

Water is necessary for manufacturing, medicinal and clinic reasons, in the formulation and processing of medications and additional well-being merchandises and for clean-up and sanitation reasons. Water is most important and widely used in the pharmaceutical industry as a natural resource ingredients, and solvent in the dispensation, APIs (Active Pharmaceutical Ingredient preparation, and production of medicinal products and intermediates. Regulator of the excellence of water all through the manufacture, storages and delivery processes, as well as bacteriological and organic quality, is a most important concern. This article discusses primarily uses, pharmacopoeia specifications and limits along with production methodologies of different type of water used in pharmaceutical industries. The bacteriological and biochemical analyzing for Water used in medicinal implant, Conductivity analysis launches a tester's capability to conduct electrical energy, which associates to the quantity of suspended salts in sample, water purity effects by high ion count which leads the method complicated. TOC (Total organic compounds) analyzing is used to find whether the carbons present in sample are maintained below the required boundary of Five hundred parts per billion (ppb), bio burden analyzing founds the number of bacteria in a water sample, Microbial test of water includes the estimate of the quantity of possible aerobic bacteria present in present stated quality of water.

KEYWORDS: Consumption H_2O, water for injection, Supply system of water, dissimilar evaluations of water quality.

INTRODUCTION

In pharmaceutical industry water is used as one of the major commodities. Water is generally used as a components, raw material, preparation, diluent in administering and production of medicinal merchandises, APIs and Excipients, and analytic chemicals. It could currently as Excipient, or used for re-formation of commodities, throughout manufacture, throughout synthesis of completed merchandise, or as a washing agents for soaking containers, apparatus and primary packing materials etc. Here are several altered scores of H_2O used in medicinal purpose. Some are defined united states of pharmacopoeia monographs that denote uses, adequate system of formulation, and quality characteristics

The waters can be separated into 2 common classes:

1. Bulk Waters.
2. Packaged Waters.

Bulk Waters: they are characteristically formed on place where they are consumed.

Packed waters: which are formed, packed, and pasteurized to maintain bacteriological quality through packed shelf life.

These are some specified classes of packed waters, different in their certain requests, packing limits, and additional quality characteristics. Special evaluations of water quality are essential dependent on the dissimilar medicinal usages.

Limitation of quality of water, in specific, the biological quality, is a main point and the medicinal manufacturing gives huge source to the growth and preservation of water sanitization methods which shown in Table 01.

Table 01: Characteristics of Impurities in Water.

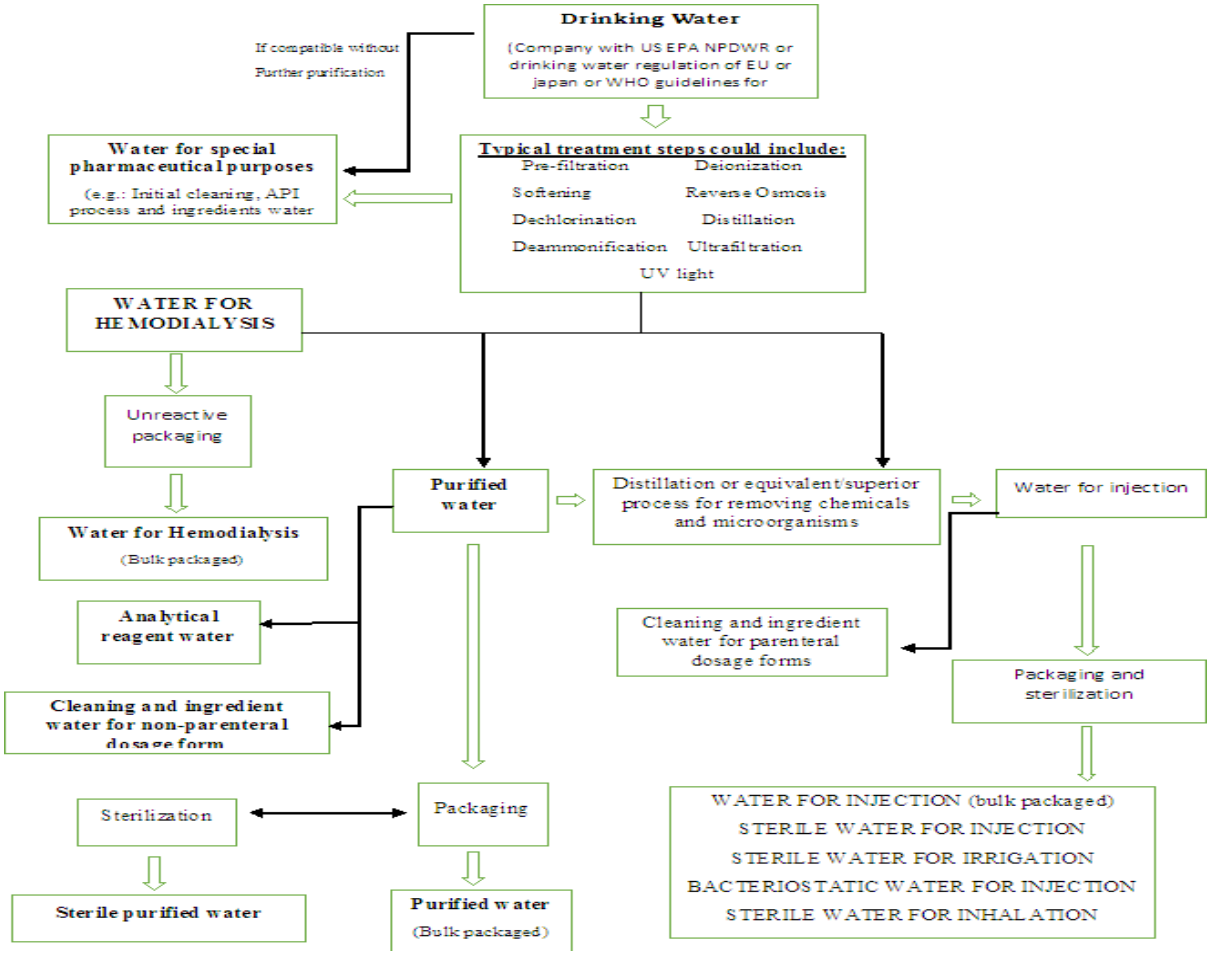
Impurity Types	Characteristics	Types of Tests
Microbiological	Living, organic	Sterility
Microbiological	Dead, organic	BET
Organic	Non ionic	TOC
Inorganic	Ionic	Conductivity
Particulate	Insoluble	Particle count
Dissolved gases	Ionic and non-ionic	Usually benign

Categories of Water

In pharmaceuticals manufacturing company the water is used as most common aqueous vehicle. Figure 01 shows various types of water used in pharmaceutical companies. Water is used in many ways in the formulation of drug product as follows:

- Non-drinking water or Non-portable water
- Portable water
- Filtered water or purified water
- Water for injection (WFI)
- Sterile water for injection
- Bacteriostatic water for injection
- Sterile water for inhalation
- Sterile water for irrigation
- Water for hemodialysis
- Pure steam

Types of water for



1. Non drinking water / Non potable water

Based on the quality it is used in several ways. Non drinking water is raw water which is not treated, such as ground water, grounds wells, lakes and river.

Purpose

- It is used for cleaning factory outer surface
- It is used for washing the vehicles
- It is used in the lawn etc.

2. Portable water

It is consider as portable water (means fit to drink or drinkable), primary drinking water, national drinking water, or EPA drinking water. Drinking water specification is stated (such as United States, Environmental protection Agency national primary drinking water regulation (NPDWR), as cited in 40 CFR part 141), according to the NPDWR or the EU or Japan drinking water regulation, or the World health organization regulation for consumption -water quality this water must comply with the quality attributes. Drinking water may obtained from various source contains public water supply, a private water supply for e.g. a well, or a mixture of both the sources.

Purpose

- It is used for drinking purpose
- It is used to wash the crude drugs and also extraction of crude drugs
- It is used for the preparation of external product.

3. Purified Water

In manufacturing of non-parenteral formulations and further for medicinal purposes like washing apparatus, non-parenteral product-contact components purified water is used as excipient. Purified water should be free from bacterial contamination and recontamination. It is essential to meet the supplies for carbon-based and ionic chemical purity. Drinking water is the source for purified water.

Purpose

- Used in the manufacture of non-parenteral formulation/preparation.
- For washing of specified apparatus's used in manufacturing of non-parenteral preparation.

- For the manufacturing of certain bulk chemicals.
- For the preparation of microbiology laboratories media.

4. Water for injection (WFI)

Water for injection is a water that's meant for the motive in the production of drugs for parenteral organization who's solvent in water (Water for injection in bulk), or water is used for preparations of parenteral administration (heat- sterilized WFI), or water that is used to dilute or dissolve components.

Purpose

- It is used in the preparation of parenteral products / preparation.
- It is used for washing the components of parenteral product contact.
- Use as excipient in manufacturing of potentials
- Used in equipment cleaning like cleaning the surfaces of non-sterile chemicals.

5. Sterile water for Injection

This water has been packed and purified, sterilized. This water is for the treating of sterilized products intended to be used intravenously. Furthermore, it is used for additional uses in bulk Water for injection or distilled water is showed but approach to authorize water system is not applied or only a moderately minor amount is required. Sterilized WFI is generally packing in single-dose containers that are usually less than 1 L in size.

Purpose

- Used for spontaneous preparation compounding
- Used as a sterilized diluents for parenteral products

6. Bacteriostatic water for Injection

It is water for injection, packaged and extracted antiseptic, to which has been more desirable one or more compatible antimicrobial preservative. In parenteral products, multi-dose products that require repeated content material withdrawals bacteriostatic water is used as diluent. It is packed in single dose or more than one-dose containers, not more than 30ml.

Purpose

- In parenteral preparation it is used as diluent

7. Sterile water for Inhalation

It is Water for Injection that's packaged and extracted antiseptic which is used in inhalators and in inhalation solution components. It consists of a much low stringent requirement for microbial endotoxins than sterile WFI, and as a consequence is not fit for parenteral usages.

Purpose

- Used in formulation of inhalators
- Preparation of inhalant solutions

8. Sterile water for Irrigations

This water has been packed and condensed sterile. It is generally used when sterile water is required, however when the appliance does now not have particulate matter requisites. Sterile water for irrigation is most commonly packaged in container which might be typically better than 1 L in size.

Purpose

- To wash and humidify physique tissue
- In urologic process for health practitioner.

Example

- Clinical irrigation resolution (splash resolution)
- Urologic irrigation solution
- Glycine solution
- Sorbitol solution

9. Water for Hemodialysis

It is used for hemodialysis applications, mainly the dilution of hemodialysis concentrate solutions. Drinking water is the source for the preparation of water for hemodialysis which is approved by E.U, U.S, JAPAN, EPA and WHO. The hemodialysis water has to reduce the microbiological and chemical components it has been further purified and it is produced and used on site. This water is not intended for injection because it does not contain antimicrobial agents. The chemical requirements specified in the monograph as well as an additional bacterial endotoxin the water for hemodialysis must meet all the specifications.

Purpose

- It is used for diluting concentration solution of hemodialysis.

10. Pure steam

It's often used for steam sterilization porous inserts and equipment and in different strategies, reminiscent of washing, the place condensate would instantly contact legitimate articles, containers for these articles, system surfaces that might in turn contact these articles, or materials which can be utilized in examining such articles. A pure steam is ready for suitably pretreatment used for purified water or WFI, vaporized with a suitable mist removing, and dispensed below stress.

Purpose

- To get rid of co-deposited illness residues.
- For air humidification in accomplished industrial environments
- It's Used for steam sterilization of gear and porous hundreds
- It is used to clean the places where condensate immediately is available in contact with legit articles, product contact containers, and surfaces.

Sometime also used water miscible solvent in parenteral. Mainly to improve drug solubility, it's essential to say that additionally function stabilizers for these medications that degrade by way of hydrolysis. Water miscible solvent ought to be chosen with grade handle it ought to now not be aggravating, poisonous or sensitizing and it have to no longer exert on the components of the formula. Solvents which are miscible with water are dioxolanes, dimethylacetamide, burylenes glycol, polyethylene glycol 400 and 600' propylene glycol. Glycerin ethyl alcohol and so on. Several grades of water used in pharmaceuticals and preparation techniques are given in Table 02.

Table 02: uses and preparation techniques of various grades of water.

Grades of water	Uses	Preparation of techniques
Non potable water	Used to clean outer surfaces of the factory Used in garden Washing vehicles etc...	Obtained from natural sources.
Potable water	As drinking water Washing and extraction of the crude drugs Preparation of product to externally use etc.	Obtained from natural sources.
Purified water (PW)	For the production of non-parenteral preparation	Deionization

	Used to clean some equipment's used in non-parenteral production preparation To clean non-parenteral product contact component For all types of tests and assay In preparation of some bulk chemicals Used in preparation of media in microbiology laboratories	Distillation Ion-exchange Reverse osmosis Filtration etc.…
Highly purified water (HPW)	HPW is intended for use in the preparation of products where water of high biological quality is needed, except where WFI is required	Deionization Reverse osmosis Ultrafiltration etc.
Water for injection (WFI)	For the production of parenteral preparation For cleaning of parenteral product contact component	Distillation Reverse osmosis Membrane process
Sterile WFI (SWFI)	For extemporaneous preparation compounding As a sterilize diluents for the parenteral products	By distillation of WFI
Bacteriostatic WFI (BWFI)	Used as a diluents in the preparation of parenteral product	By using SWFI
Sterile water for inhalations	Preparation of use in inhalators Preparation of inhalant solution	By using SWFI
Sterile water for irrigations	To bath and moisten body tissue Performing urologic procedure for surgeon	From water for injection
Water for hemodialysis	For the dilution of hemodialysis of concentrate solution	From safe drinking water

Specifications of various grades of water

United State Pharmacopoeia has specified the stipulations and explanations of the numerous ratings of water appropriate for medicinal use. It categorizes medicinal water as (i) potable water (ii) purified water, used for the production of oral formulations and other formulations, and (iii) water for injection (WFI) and (iv) sterile water for injection used for injectable, parenteral and intravenous fluids. United State Pharmacopoeia also stipulates that cleansed water and WFI must adhere to the EPA's (Environmental Protection Agency's) Part l4l, National Interim Primary Drinking Water Regulations. Table 03 presents the principal specification for various grades of water.

Table 03: specification of waters as per United State Pharmacopoeia.

S. No	Parameter	Potable water	Purified water	Water for injection	Sterile water for injection
1.	Appearance	Clear, colorless and no visible particles	Clear, colorless and no visible particles	Clear, colorless	Clear, colorless
2.	Odor	Odorless	Odorless	Odorless	Odorless
3.	P^H	6.5-8.5	5.0-7.0	5.0-7.0	5.0-7.0
4.	Chloride	NMT 250 ppm	0 ppm	0 ppm	0 ppm

5.	Aluminum	0.2 mg/L	0 mg/L	0 mg/L	0 mg/L
6.	Arsenic	0.01 mg/L	0 mg/L	0 mg/L	0 mg/L
7.	Fluoride	1.5 mg/L	0 mg/L	0 mg/L	0 mg/L
8.	Boron	0.3 mg/L	0.3 mg/L	0 mg/L	0 mg/L
9.	Sulfate	NMT 300 ppm	0 ppm	0 ppm	0 ppm
10.	Total hardness	NMT 500 ppm	0 ppm	0 ppm	0 ppm
11.	Microbial count	500 cfu/ml	100 cfu/ml	10 cfu/100 ml	10 cfu/ml
12.	Acidity or alkalinity	-	NMT 0.1 ml of 0.01 M NaOH	NMT0.l ml of 0.01M NaOH	NMT0.l ml of 0.01M NaOH
13.	Ammonia	0.5 ppm	0.2 ppm	0 ppm	0. ppm
14.	Heavy metal	0.5 ppm	0.1 ppm	0 ppm	0.1 ppm
15.	Conductivity	NMT 0.3 µs	NMT 0.1 µs	NMT 0.1 µs	NMT 0.05 µs

Maximum allowable concentrations of toxic substances according to the international standard are given in table 04.

Table 4: Maximum allowable concentration of toxic substances.

Toxic substance	Maximum allowable concentration (mg/L)
Lead (Pb)	0.05
Selenium (Se)	0.01
Arsenic (As)	0.05
Chromium (Cr)	0.05
Cyanide (CN)	0.2
Cadmium (Cd)	0.01
Barium (Ba)	1.0

Quality Control of Pharmaceutical Water system

The aquatic examination is of central substance to confirm the merchandise's disinfection in the pharmaceutical quality control. Once the water has been obtained for pharmaceutical use, it essential be collected and circulated to the points of use; there is no point in making quality water without it is properly deposited and circulated. This phase is central substance to minimalize likely pollution of the water and the propagation of bacteria Systems necessity to be sealed with incessant recirculation and necessity to take a sanitization system.

Storage of samples for microbiological evaluation

The time between sample assortment and evaluation will have to, regularly, not go above six hours, and Twenty four hours is regarded. It is expected that the illustrations are right away positioned in a lightproof isolated container including dissolving ice or ice- packages with water to ensure fast refrigeration. If ice is just not on hand, the transport period should no longer above two hours. It is primary that samples will have to be discarded. When water that

includes or may just incorporate even traces of chlorine is sampled, if it isn't, microbes may be killed during transit and an inaccurate effect might be received. The bottles where the samples are positioned should for that reason contain sodium thiosulfate to neutralize any chlorine reward.

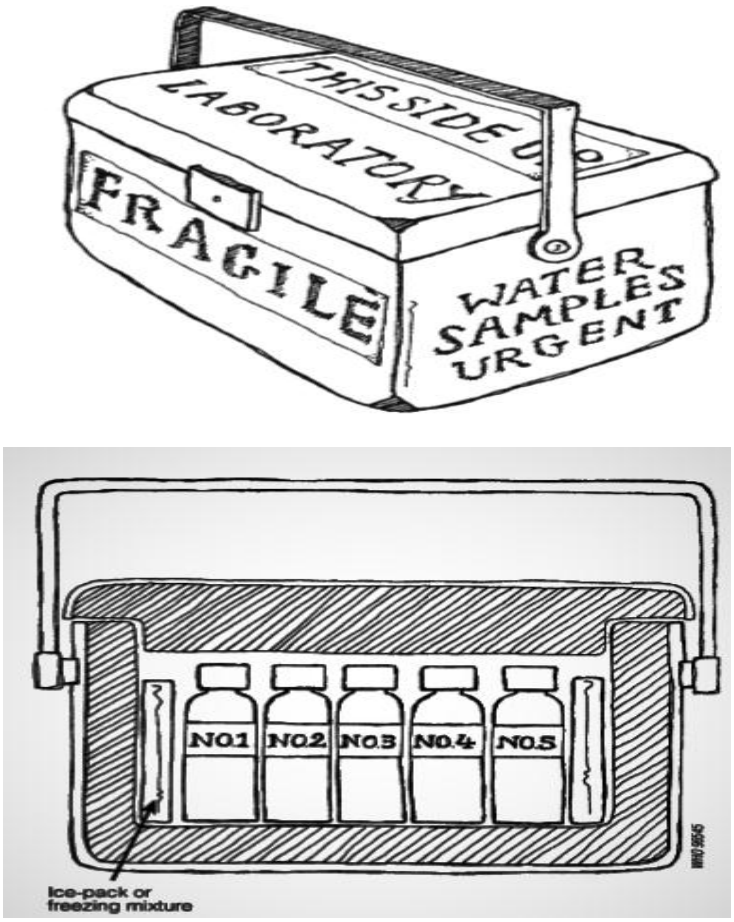


Fig. 02: transportation box for samples for microbiological analysis.

Testing water for pharmaceutical use

1. Total organic carbon (TOC)
2. Conductivity
3. Bacterial endotoxins testing (BET)
4. Sterility
5. Microbial enumeration
6. Particulates
7. Antimicrobial agents
8. pH
9. Calcium, carbon dioxide, and sulfates,

1. Total organic carbon (TOC)

It has been applied for inspection for healthy molecules provided from basis of water, from sanitization and delivery process supplies, and from biofilm establishing within the approach.

2. Conductivity

Conductivity is done to measure the ion- enabled electron run throughout the water. Water particles disassociated into ions as perform of pH and temperature and influence in an expected conductivity. Conductivity will also be concerned via the presence of carbon dioxide and dissolved inorganic solids, reminiscent of chloride, nitrate, sulfate, phosphate anions, sodium, magnesium, calcium, iron, and aluminum cations.

3. Bacterial endotoxins testing (BET)

It's also called as pyrogen checking out, it's an experiment that makes use of limulus Amebocyte lysate, a substance developed from the horseshoe crab blood (limulus Polyphemus), and its used to identify the microbial endotoxin is located in the phone wall of gram negative microorganism and factors a fever in mammalian species.

4. Sterility

Sterility checking out is completed on the water to manipulate the absence or presence of attainable microorganism on innovations or parts thereof.

5. Microbial enumeration

Microbial enumeration trying out enables measureable enumeration of mesophilic microorganism and fungi that may grow underneath cardio stipulations. These trails are intended ordinarily to manipulate whether the water conforms to a centered specification for microbiological exceptional.

6. **Particulates**

Particulates checking out is of unique main issue in injections and parenteral infusion containing of extraneous cellular undissolved particles, rather than gas bubbles, accidentally present within the options. Water detailed for use in injectable products requires this checking out to make certain the supply water will not be adding particulate subject into the final product that would be offered intravenously.

7. Antimicrobial agents

Antimicrobial agent's examination proves the efficiency of antimicrobial safety. Antimicrobial preservers are poisonous resources introduced to non- hygienic dose forms to preserve them from bacteriological development or from microbes that are presented unintentionally for the period of or following to the industrial procedure. Within the circumstance of germ-free objects packed in a couple of dose dosage ampules, antimicrobial preservers are delivered to prevent the development of micrograms that could be offered from many times retreating character dosages.

8. pH

pH checking out is used to calculate the hydrogen ion gift within the water by way of terrible log of exercise.

9. Calcium, carbon dioxide, and sulfates

Calcium, carbon dioxide, and sulfates are the qualitative examinations used to verify the quantity substance reward within the water.

Cleaning schedule for water storage tanks

Cleaning of various water storage tanks should be done as per frequency indicated below:

- Raw water storage tank: clean raw water storing container once in 6 months.
- Treated water storage tank: clean Treated water storing container once in a month.
- Purified water storage tank: clean purified water storage tank once in a month.
- Chemical storage tank: clean chemical storing container once in a month.

Annexure for tank cleaning schedule- yearly

Equipment Name

Equipment Code

Name of the Tanks	Schedule	JAN	FEB	MAR	APIRL	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Raw water storage tank	H												
Treated water storage tank	M												

Chemical storage tank	M												

H→ Half yearly

M→ Monthly

CONCLUSION

In the pharmaceutical companies, different grades of water are used for different purposes. So it is essential to know all the grades of pharmaceutical water, its preparation, specifications and uses to follow the guidelines for the maintenance of quality attributes. Water handling schemes should be activated inside regulatory rules for medicinal manufacturing services by performing various quality checks for physicochemical and microbiological impurities.

REFERENCE

1. United States Pharmacopeia 35, General Chapter <1231>, United States Pharmacopoeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, MD, 2012.
2. European Pharmacopoeia Edition 7 (EDQM.226. avenue de Colmar BP 907, F-67029 Strasbourg, France, 2011.
3. The International Pharmacopoeia. Geneva, World Health Organization; http://www.who.int/medicines/publications/pharmacopoeia/over view/en/index.html.
4. WHO Guidelines for drinking-water quality, 3rd edition. Geneva, World Health Organization, 2008. http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html.
5. WHO guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937); http://www.who.int/medicines/publications/pharmprep/TRS_937.pdf#page=119.
6. Guide to inspections of high purity water systems. Maryland, US Food and Drug Administration, 1993. http://www.fda.gov/ICECI/InspectionGuides.
7. Mehta G, Prabhu SM, Kantawala D. Industrial wastewater treatment-The Indian experience. J. Indian. Assoc. Environ. Management, 1995; 22: 276-287.
8. Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT., Pharmaceuticals, hormones and other organic wastewater contaminants in U.S. Environ. Sci. Technol, 2002; 36: 1202-l211.
9. http://www.pharmaguideline.com/2012/09/pharmaceutical-water.html.

10. http://www.pharmatutor.org/articles/quality-of-water-for-pharmaceutical-use-an-overview.
11. http://www.pharmtech.com/understanding-usp-water-pharmaceutical-use.
12. USFDA. Guide to inspections of high purity water systems, 1993.
13. Genetelli EJ, Heukelekian H, Hunter JV. A rational approach to design for a complex chemical waste. Proceedings of the 5th Texas Water Pollution Association, Industrial Water and Waste Conference, 1965; 372-396.
14. A. Schieving, "Understanding USP <1231> Water for Pharmaceutical Use", 2017. www.pharmTech.com/understanding-usp-water-pharmaceutical-use.
15. USP, USP<1231> Water for Pharmaceutical Purposes (Rockville, MD, March 8, 2017.