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REGULATORY CONSIDERATION ON GOOD MANUFACTURING PRACTICES COMPLIANCE OF WATER FOR PHARMACEUTICAL USE: A REVIEW

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ABSTRACT

The pharmaceutical sector is a water-intensive industry that requires various levels of water purity. To achieve pharmacopeial standards, pharmaceutical water treatment entails the removal of certain pollutants from municipal drinking water. Depending on the mode of administration of various medicinal drugs, different water quality categories are necessary. However, water used in the manufacturing of pharmaceutical goods must be either Purified Water (PW) or Water for Injections (WFI). Both have comparable chemical purity criteria, but differ in the amount of microbiological contamination they tolerate, which is evaluated by colony count and endotoxin level. Water for Pharmaceutical Use (WPU), unlike other commodities and process ingredients, is frequently pulled from a system on demand and is not subject to testing or batch or lot release prior to use. As a result, quality assurance is critical in order to match the on-demand requirement. Furthermore, certain microbiological tests may have incubation periods, causing the results to be delayed in water use. Control of the microbiological quality in Water for pharmaceutical use is of great importance. No less important than avoiding the proliferation in storage and distribution is the avoidance of biological contamination in the water treatment systems. The control over water quality, including microbiological and chemical quality, throughout the treatment and storage process, is therefore an important concern that is in keeping with Good Manufacturing Practices. The study provides an overview of the current water quality standards, as well as restrictions and safety implications. Also discusses GMP requirements and water usage inspections for pharmaceutical drugs.

KEYWORDS: Water for pharmaceutical use, WHO GMP requirements, Quality of water, Inspections.

1. INTRODUCTION

In many pharmaceutical and dwelling science activities, water is a key ingredient. In the processing, formulation and manufacturing of drug products, active pharmaceutical ingredients (APIs) and intermediates, water has been widely used as a raw material, component and solvent. Whether for washing devices, rinse containers or as analytical reagents, water used in the production of pharmaceutical products must meet the quality requirements set out in the pharmacopeia of respective region or World Health organization(WHO). Because of its polarity and hydrogen bonds, water has unique chemical properties.[1] This means that many different compounds can be dissolved, absorbed, absorbed or suspended. These include impurities that may constitute a hazard or which can react with the intended product materials, leading to health risks.

Water quality control throughout the processes of production, storage and distribution, including microbiological and chemical quality, is a key concern. Waters can be utilised in various applications, some with rigorous microbial monitoring and others without microbiological control. The microbiological standard required for a certain bulk water relies on its application. Typically the test procedures take 48 to 72 hours to achieve findings for microbial requirements.[2] Due to the fact that drug waters are generally produced by continuous processes and are soon after generation used in products and production processes, water is expected to have been used well before definite test results are possible. If a compendial specification is failing, the impact and decision to cross/fail all product batches should be examined between the acceptable testing findings of the previous sampling and the acceptable test results of the subsequent sampling. Water used in drug substances or in the preparation of various types of cleaned water must satisfy the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the US Environmental Protection Agency (EPA) or the WHO Drinking Water Regulations in order to ensure compliance with some minimum chemical and microbiological quality standards. Depending on the route of administration of the pharmaceutical products, different levels of water quality are required.[2]

Types of water

The water used for pharmaceutical purposes are of many different grades. In USP monographs, several acceptable methods of preparation are described that specify uses. This water can be split into two types: **-bulk water**, generally produced on the premises in which it is used, and **packaged water**, produced, packaged and sterilised to maintain the microbial quality throughout its shelf life.[3]

1. Non-potable
2. Potable water
3. Purified water
4. Water for injection (WFI)
5. Sterile water for injection (SWFI)
6. Sterile water for inhalation
7. Bacteriostatic water for injection
8. Sterile water for irrigation
9. Water for haemodialysis

1. Drinking water (Potable water)

Potable water is the term for drinking water. Drinking water must meet the quality requirements of the NPDWR, the European Union's drinking water laws, or the WHO Drinking Water Guidelines. It can come from a public water utility, a private water supply (such as a well), or a mix of these sources. The type of treatment required to make the source water suitable for human consumption will be determined by its condition (drinking). Drinking water can be used to clean pharmaceutical production equipment and product-contact components in the early stages. Drinking water is also the minimal standard for the manufacture of official drugs and other bulk medicinal ingredients. Drinking water should be delivered under constant positive pressure in a plumbing system that is devoid of any flaws that could lead to product contamination. Desalinization, softening, ion removal, particle reduction, and antimicrobial treatment are all common treatments. Official drugs and other pharmacological substances are generally regarded safe to use in drinking water.[4]

Production

A raw water source, such as a well, a river, or a reservoir, is used to make drinking water. There are no established procedures for treating raw water in order to generate drinking water from a specific source.

The following are examples of typical processes used at a user plant or by a water supply authority: –

– Desalinization.
– Filtration.
– Softening.
– Disinfection or sanitization (e.g. by sodium hypochlorite (chlorine)injection).
– Iron (ferrous) removal.
– Precipitation.
– Reduction of concentration of specific inorganic and/or organic materials.

Drinking water quality should be checked on a regular basis to account for changes in the environment, seasons, or supplies that may affect the quality of the source water. Drinking water production equipment and systems should be able to be emptied and cleaned.[4,5]

2. Non drinking water/Non potable water

It is utilized in a variety of ways depending on the quality. Ground water, ground wells, lakes, and rivers are examples of non-drinking water that has not been treated.

Purpose

- It's used to clean the factory's exterior.
- It is used to clean automobiles.
- It's utilized in the lawn, among other things.

Production

Obtained from natural sources.

3. Purified water

Purified Water is utilized as an excipient in the manufacture of non-parenteral preparations as well as in other pharmaceutical applications such as the cleaning of equipment and non-parenteral product-contact components. Purified water must meet ionic and organic chemical purity standards, as well as be free of microbiological contamination. Drinking water is used as a source or feed water in the purification process. It should also be safeguarded from microbial multiplication and recontamination.

Production

Ion exchange, reverse osmosis (RO), ultra filtration or electrode ionisation techniques, and distillation are all common methods for purifying water. Microbiological contamination is especially common in ambient temperature systems like ion exchange, RO, and ultra filtration. It's critical to think about microbiological control and sanitization procedures.

- Temperature control in the system via heat exchanger or plant room cooling to prevent microbial development (recommendation value 25 < °C).
- Ultraviolet disinfection is provided.
- Choosing water-treatment components that can be thermally sanitised on a regular basis.

4. Highly purified water

As a minimum-quality feed-water, highly purified water (HPW) should be made from drinking water. Only the European Pharmacopoeia uses the term "highly purified water" to describe water. Although this grade of water must fulfil the same quality standards as water for injections (WFI), including the endotoxin limit, the water-treatment procedure may differ. Double-pass RO, in combination with other relevant processes such as ultrafiltration and deionization, is one of the current manufacturing methods. HPW can be made using a variety of techniques, including RO, ultrafiltration, and deionization. HPW should also be safeguarded from microbial proliferation and recontamination.

Production

Double-pass reverse osmosis with ultrafiltration, or any other qualified purification technology or sequence of techniques, can yield highly purified water (HPW). It's critical to think about microbiological control and sanitization procedures.

- Temperature control in the system via heat exchanger or plant room cooling to prevent microbial development (recommendation value < 25 °C).
- Ultraviolet disinfection is provided.
- Choosing water-treatment components that can be thermally sterilized on a regular basis.
- Chemical sanitization (agents such as ozone, hydrogen peroxide, and/or peracetic acid); – thermal sanitization at temperatures above 65°C.

5. Water for injection

WFI is utilised as an excipient in the production of parenteral and other preparations where endotoxin content must be regulated, as well as in other pharmaceutical applications like

cleaning of certain equipment and parenteral product-contact components. As a minimum-quality feed water, water for injections should be made from drinking water (typically after further treatment) or purified water. WFI is not sterile water, and it is not intended to be used as a final dose form. It's a bulk intermediate product that can be employed as a component in a recipe.

WFI should also be safeguarded from microbial multiplication and recontamination.

Production

The chemical purity of WFI can be controlled, however there are a few issues to consider. The most important challenge is establishing consistent microbiological quality in terms of bacterial and bacterial endotoxin elimination.

Distillation has a long history of dependable performance and can be validated as a unit operation, hence it is the only official method for WFI at the moment.

WFI is obtained in bulk from water or purified water by distillation in an apparatus with neutral glass, quarts, or appropriate metal parts in contact with water, and which is equipped with an effective system to prevent droplet entrainment.

- During production and storage, proper maintenance of the apparatus is required, and necessary measures are made to guarantee that the total viable aerobic count is properly managed and monitored.
- WFI passes a purified water test that includes extra standards for bacterial endotoxins (less than 0.25 IU per ml), conductivity, and total organic carbon.[5]

6. Bacteriostatic water for injection

It is injectable water that has been packaged and extracted antiseptically, and to which one or more appropriate antimicrobial preservatives have been added. Bacteriostatic water is utilised as a diluent in parenteral and multi-dose solutions that require repeated content material withdrawals. It comes in single-dose or multiple-dose containers with a maximum capacity of 30ml.

Purpose

- It is used as a diluent in parenteral preparations.

Applications

- Used in the manufacture of parenteral products as diluents.

Production

- By utilising SWFI.

7. Sterile water for inhalation

It is packaged and extracted antiseptic Water for Injection, which is utilised in inhalators and inhalation solution components. It has a far lower microbial endotoxin requirement than sterile WFI, and as a result, it is not suitable for parenteral use.

Purpose

- Used in the formulation of inhalators
- Inhalant solution preparation.

8. Sterile water for irrigations

This sterile water has been packaged and condensed. It's commonly utilised when sterile water is required yet the device doesn't have particle matter requirements. Sterile irrigation water is often packed in a container that is greater than 1 litre in volume.

Purpose

- To clean and humidify the tissues of the body.
- For health practitioners in the urologic procedure.

Example

- Resolved clinical irrigation (splash resolution)
- Solution for urologic irrigation
- A solution of glycine
- A solution of sorbitol.

9. Water for hemodialysis

It's mostly used in hemodialysis for dilution of hemodialysis concentrate solutions. Drinking water is the only source of hemodialysis water that has been approved by the European Union, the United States, Japan, the Environmental Protection Agency, and the World Health Organization. The microbial and chemical components of haemodialysis water have been reduced, and it is now produced and used on site. Because it lacks antibacterial agents, this

water is not suitable for injection. The water for haemodialysis must meet all of the chemical standards mentioned in the monograph, as well as an extra bacterial endotoxin.

Purpose

- It is used to dilute the haemodialysis concentration solution.[3,4,5]

2. Presence of impurities in water intended for pharmaceutical USE[6]

Water contamination sources

Defects in the piping system can contaminate pure incoming water. Because of this potential, point-of-use sampling, which involves drawing a sample of water after it has passed through the pipe system, is recommended.

Microbial contamination of oral liquid and topical medicinal solutions is still a major issue, and it's mainly the result of using contaminated water. Because of the potential health concerns associated with drinking tainted water, deionized (DI) water systems should be given extra consideration, especially by small, less skilled producers. The USP recommends that water systems used in pharmaceutical manufacturing have "corrective facilities" to reduce pollution. They signify access to the system for sanitization or steam introduction, chlorinators, high-temperature storage, filtration, and so on. During your inspection, inquire about these.

Differences in microbial composition of source water may be caused by seasonal variations in temperature and flora growth. Monitoring should be done on a regular basis to account for these differences.[6]

Table 01: Impurity properties in water.[7]

Types of impurity	Properties	Relevant tests
Microbiological	Living, Organic	Sterility
Particulate	Insoluble	Particle count
Dissolved gases	Ionic and non-ionic	Usually benign
Microbiological	Dead, Organic	BET
Organic	Non ionic	TOC
Inorganic	Ionic	Conductivity

3. Various techniques for water purification[8,9]

- **Reverse osmosis (RO)**

The United States Patent and Trademark Office (USPTO) has proposed specifications for purified water. More selective testing for conductivity and TOC has increased the importance

of these specifications, which is reflected in the quality of water produced. The heart of a treatment system is a two-pass ROsystem capable of removing bacteria. When designing a RO system, there are several variables to consider. The key factors are membrane type and flow rate recovery. Pressure vessels that hold these membranes play an important role in bacterial growth control. A typical function of a two-pass RO would be to reduce ionic impurities, TOC, and microbiological substances to prescribed levels.

- **Electrode ionization (EDI) system**

Water's online conductivity is required by the USP purified water monograph. At stage I testing, conductivity of less than 1.3 microsiemens/cm at 25°C is required. To obtain water of higher quality, with resistivity in the range of 12-15 Mohm, an EDI system is used.

- **Ultrafiltration**

To ensure that the product water quality at the POU (Point Of Use) meets highly purified water specifications, the water is continuously passed through ultrafiltration membranes to remove bacteria and endotoxins from the purified water. Because of its hygienic design and heat tolerance, polyether sulfone hollow fibre membranes are utilised for hot water sanitization.[9]

4. Various grades of water specifications as per IP and USP[10,11]

The Indian Pharmacopeia, the British Pharmacopeia, and the United States Pharmacopeia all include water specifications. Different types of water used in pharmaceutical manufacture should be able to meet these requirements.

Table 02: Water specifications on the basis of different parameters.[11]

S. no.	Parameter	Potable water	Purified water	Water for injection	Sterile water for injection
1.	Appearance	No visible particles and clear & colourless.	Clear and colourless.	Clear and colourless.	Clear and colourless.
2.	pH	6.5-8.5	5.0-7.0	5.0-7.0	5.0-7.0
3.	Odour	Odourless	Odourless	Odourless	Odourless
4.	Boron	0.3 mg/L	-	0 mg/L	0 mg/L
5.	Sulfate	NMT 300 ppm	0 ppm	0 ppm	0 ppm
6.	Acidity or Alkalinity	-	NMT 0.1 ml of 0.01M NaOH	NMT 0.1 ml of 0.01M NaOH	NMT 0.1 ml of 0.01M NaOH

7.	Ammonia	0.5 ppm	0.2 ppm	0 ppm	0 ppm
8.	Chloride	NMT 250 ppm	0 ppm	0 ppm	O ppm
10.	Total Hardness	NMT 500 ppm	0 ppm	0 ppm	0 ppm
11.	Fluoride	1.5 mg/L	0 mg/L	0 mg/L	0 mg/L
12.	Heavy metal	0.5 ppm	0.1 ppm	0 ppm	0.1 ppm
13.	Conductivity	NMT 0.3	NMT 0.1	NMT 0.1	NMT 0.005
14.	Microbial count	500 cfu/ml	100 cfu/ml	10 cfu/100 ml	10 cfu/ml
15.	Microbiological Limits 1.Total bacterial count 2.Total fungal count 3.Escherichia coli 4.Salmonella 5.Pseudomonas aurogenosa		-NMT 100 cfu/ml -NMT 10 cfu/ml -To be absent -Absent -Absent		

Maximum allowable concentrations of toxic substances according to the international standards are given in Table no.3.

Table 03: Maximum allowable concentration of toxic substances.[10]

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

Water must be tested for pharmaceutical use in order to maintain the highest degree of quality. As a result, testing is done based on the properties listed below.[13]

1. Total organic carbon (TOC)
2. pH
3. Conductivity
4. Particulates
5. Bacterial endotoxins testing (BET)
6. Antimicrobial agents
7. Sterility
8. Microbial enumeration
9. Calcium, carbon dioxide, and sulfates.[12]

5. Water quality for pharmaceutical USE[12,13]

Water purification, storage, and distribution system validation and qualification are an important aspect of GMP and are included in the GMP inspection. In the pharmaceutical dossier, the quality of water used at various stages in the synthesis of active pharmaceutical components and pharmaceutical products should be discussed. The grade of water used should be determined by the finished product's composition and planned applications, as well as the stage at which the water is employed**.**

a. In the final formulation, the use of water as an excipient

Water is a typical excipient in pharmaceutical preparations; the minimal quality of water required depending on the product's intended purpose. WFI is necessary for products intended for parentral administration, such as haemofiltration and haemodiafiltration solutions, as well as peritoneal dialysis. WFI is frequently used in the pharmaceutical sector to prepare ophthalmic, sterile nasal or ear, and cutaneous treatments. Table 4 covers the use of water as an excipient in the manufacturing of sterile pharmaceutical products and specifies the water quality for each final formulation while Table 5 discusses the use of water as an excipient in manufacturing of non-sterile medicinal products.

Table 4: Water in sterile medicinal products.[12]

Sl. no	The Sterile Medicinal Product's Name	Water of minimum acceptable quality
1.	Parenteral	WFI
2.	Nasal/Ear Preparations	Purified Water
3.	Irrigation Solutions	WFI
4.	Peritoneal Dialysis Solutions	WFI
5.	Cutaneous Preparations	Purified Water
6.	Ophthalmic	Purified Water
7.	Haemofiltration Solutions Haemodiafiltration Solutions	WFI

Table 5: Non-sterile medicinal products.

The product names of Non-sterile Medicinal	Water of minimum acceptable quality
Nasal/Ear Preparations	Purified water
Cutaneous Preparations	Purified water
Vaccines for non-parentral use	Purified water
Oral Preparations	Purified water
Nebulizer solutions	Purified water

b. Water Used in API and Medicinal product manufacturing[12]

The permissible quality of water will be determined by the stage in the manufacturing process at which it will be employed, the subsequent processing steps, and the nature of the final product.

Table 6: Water used in the production of active substances is listed.

Active substance (AS) type/purpose	Manufacturing step	Minimum acceptable quality of water
No requirement for sterility or apyrogenicity in AS or the finished product in which it will be used.	Synthesis of all intermediates of AS prior to final isolation and purification steps. Final isolation and purification	Potable water
AS is fermentation product or biological and is not a vaccine or ATMP	Fermentation media and cell culture media	Potable Water
AS is intended for manufacture of vaccines. Also applicable to ATMPs and starting materials intended for the manufacturing of ATMPs which are subjected to a sterilisation step (such as viral vectors).	Fermentation media and cell culture media	Purified Water
AS is intended for manufacturing of ATMPs and not subject to a subsequent sterilisation step (such as cell based products).	All steps including fermentation media, cell culture media, initial purification, final isolation and purification.	WFI
AS is in solution, not sterile, and intended for parenteral use.	Any step excluding final isolation and purification.	Purified Water
AS is not in solution, not sterile, and intended for use in a parenteral product.	Final isolation and purification	Purified water
AS is not sterile and intended for the preparation of non-sterile vaccines for non-parenteral use.	Final isolation and purification	Purified Water

Table 7: Water used in the manufacturing of pharmaceuticals but is not included in the final formulation.

Manufacture	Minimum acceptable quality of water
Granulation	Purified Water
Tablet coating	Purified water
Used in formulation prior to non-sterile lyophilisation	Purified Water
Used in formulation prior to sterile lyophilisation	WFI

c. Cleaning and Rinsing of equipment, containers, and closures using water

In general, the final rinse water used for equipment, containers, and closures should be of the same quality as the water used in the last step of API manufacturing or as an excipient in a pharmaceutical product.

Table 8: Water for cleaning and rinsing.[12]

Cleaning/Rinsing of Equipment, Containers, closures.	Product type	Minimum acceptable quality of water
Initial rinse	Intermediate and AS	Potable Water
Final rinse	AS	Use same quality of water as used in the AS manufacture
Initial rinse including CIP* of equipment, containers and closures, if applicable.	Medicinal products – non sterile	Potable water
Final rinse including CIP* of equipment, containers and closures, if applicable.	Medicinal products Non-sterile	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Initial rinse including CIP* of equipment, containers and closures, if applicable.	Sterile products	Purified Water
Final rinse including CIP* of equipment, containers and closures, if applicable.	Sterile non-parenteral products	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Final rinse including CIP* of equipment, containers and closures, if applicable.	Sterile parenteral products	WFI

* CIP = Clean In Place

6. Systems for water Storage and Distribution[14,15]

The storage and distribution system should be viewed as a critical component of the overall system, and it should be designed to work in tandem with the water treatment components.

Contact materials for the WPU system

This section covers the generation, storage, and distribution systems for the PW, WHP, and WFI systems.

The materials that come into contact with WPU, such as pipes, valves and fittings, seals, diaphragms, and instruments, should all meet the following criteria.

- Tolerance to the temperature and chemicals utilised by or in the system is required.
- Leaching. At the range of working temperatures, all materials that come into contact with WPU must be non-leaching. Some materials on approved food processing materials lists may be appropriate.
- Corrosion resistance is a plus. Because PW and WFI are very corrosive materials, the materials chosen must be appropriate, the manner of jointing must be carefully monitored, and all fittings and components must be compatible with the pipework used to avoid system failure and water pollution. WPU systems can use appropriate polymers and stainless steel materials. When using stainless steel, make sure it's at least Grade 316L. After fabrication, the system should be passivated.
- Where sanitary unions are unavoidable, they should be designed in a sanitary or hygienic manner. Controlling the seals utilised and tightening the fittings should be done with appropriate controls.
- Documentary proof. All system components should be well-documented, with original or verified copies of material certificates to back them up.System sanitization and bioburden control

Bioburden Control and System sanitization

Features to prevent the development of microbiological organisms in normal usage, as well as ways for sanitising or sterilising the system after intervention for maintenance or modification, shall be provided for PW, WHP, and WFI water treatment equipment, storage, and distribution systems. The strategies used must be considered during the system's design, and their effectiveness must be demonstrated during the commissioning and qualification processes.

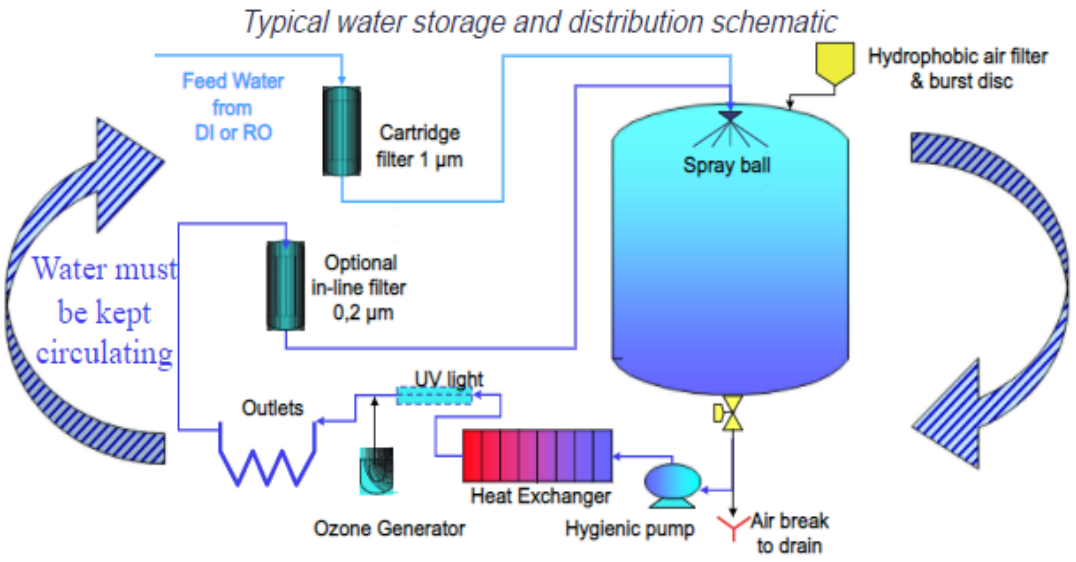

Figure 1: Depicts water Storage and Distribution schematic diagram.[14]

Microbiological contamination is less likely in systems that operate and are maintained at higher temperatures, typically over 65 °C, than in systems that operate and are maintained at lower temperatures. Special measures should be made to prevent the infiltration and growth of microbiological contamination when lower temperatures are required due to the water treatment methods used or the temperature requirements for the water in use.

Requirements for storage vessel

A system's water storage tank provides a number of critical functions. The vessel's design and dimensions must take into account the following factors.

1. Capacity
2. Considerations for Contamination Control

Necessitates for water distribution

A continuously circulating piping loop should be used for the distribution of PW, WHP, and WFI. The spread of contamination within the storage tank and distribution loop must be limited.

Filtration shall not be utilised to control bio-contamination in distribution loops or at take-off user points. Filters like these are likely to mask system pollution.

1. Heat exchangers and temperature regulation
2. Pumps for circulation
3. Techniques for preventing bio-contamination

7. Considerations for operational activities[14]

Water system Startup and Commissioning

Water system validation requires a well-planned, well-defined, successful, and well-documented commissioning process. setting up the system, loop tuning, and documenting all system performance parameters are all part of the commissioning process. if commissioning data is to be used or referred to in the validation work, the quality of the commissioning work and associated data must match the validation plan standards.

Qualification

When a water system has a direct impact on the quality of the water, it must be qualified. The design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) validation conventions should be followed (PQ).

In order to demonstrate consistent and reliable system performance, the following specific requirements for WPU systems should be considered at the PQ stage. To meet the goal of proving the system's reliability and robustness in service over a long length of time, a three-phase strategy should be considered.

Phase 1: During a 2-4 week test period, the system should be closely monitored. During this time, the system should run continuously with no failures or performance variations.
Phase 2: A 2-4 week test phase should be used to conduct more rigorous monitoring while deploying all of the improved SOPs. In general, the sample scheme should be the same as in Phase 1.
Phase 3: Is the third phase, which can last up to a year after Phase 1 ends.

Continous system surveillance

Following Phase 3 of the qualification, the system should be monitored on a regular basis, similar to Phase 3.

A combination of on-line and off-line grab sample monitoring from the system and points of use should be used for monitoring. Water samples obtained at the point of use must be taken in the same manner as the water is utilised in service.

Conductivity, total organic carbons, total viable count, heavy metals, and nitrates should all be determined according to the approved pharmacopoeia standard.

Water system maintenance

WPU systems should be maintained in accordance with a documented, regulated maintenance programme that considers the following factors.:

- Control of approved spares;
- SOPs for specific tasks;
- Review and approval of systems for use upon completion of work;
- Issue of clear maintenance instructions;
- Defined frequency for system elements;
- Record and review problems and faults during maintenance.

Examining the system[15]

WPU systems should be inspected at least once a year. Engineering, quality assurance, operations, and maintenance should all be represented on the review team. Performance, reliability, quality trends, failure events, investigations, and out of specifications (OOS) monitoring findings should all be considered in the assessment**.**

8. Water system inspection[16]

Regulatory inspections of water systems are expected to occur from time to time. Users should consider auditing and self-inspecting their existing water systems on a regular basis. The inspection might be based on this GMP guidance. The items and logical sequence for a WPU system inspection or audit are listed below:

- A plan for sampling and monitoring;
- The monitoring alert and action levels are set;
- Keeping track of findings and assessing trends;
- A review of the most recent yearly system evaluation;
- Examine any system modifications since the last audit and verify the change control procedures in place;
- The monitoring alert and action levels are set;

- Recorded deviations and their inquiry;
- Checking the state and condition of the system as a whole;
- Examine the logs for maintenance, failures, and repairs; and
- Verify the calibration and standardisation of important instruments.

If the gmp are not complied[17]

The Top 5 Quality (CGMP) Problem Areas with the Most Regulatory Action>

1. Investigating and addressing inconsistencies or flaws
2. Microcontrols for sterile and non-sterile environments
3. The programme of stability
4. Design and qualification of the process (validation)
5. Creating and adhering to sound tests and sampling plans

Inspections[16]

Types of cGMP Audits/Inspections Performed by the USFDA:

According to the USFDA's Compliance Programs, the USFDA conducts the following inspections to assess a drug manufacturer's GMP compliance:

1. Pre-approval inspections are the first step in the approval process.
2. Audit Inspections Following Approval
3. Routine cGMP(Surveillance) Inspections in Drug Manufacturing

Companies may receive FDA-483 after an FDA site inspection for non-compliant cGMP conditions with US regulations. The FDA can take the following regulatory (advisory, administrative, or judicial) actions if there is apparent noncompliance with US regulations, although the loss of consumer confidence in the product is frequently the most harmful.

- Warning Letter
- Application Action: e.g. [Recommendation for Denial of Pending Application (NDA,ANDA) Recommendation for Revocation of Approved Application (NDA, ANDA)]
- Recall
- Import Alert/Banning
- Implementation of the Application Integrity Policy
- Seizure/Detention
- Injunction

- Civil Penalty
- Prosecution under the FD&C Act

Form FDA 483 [FDA 483 or 483]

The investigator conducting the investigation (FDA investigator) uses this form with the eponymous number 483 to document his findings (Inspectional Observations). It is handed out at the conclusion of the inspection and should be officially responded to. After submitting Form 483, you should receive a response within 15 working days. A good answer can usually save a company from obtaining an FDA Warning Letter, product approval denial, or regulatory action. However, not every inspection results in the issuance of a Form 483. In most cases, the 483 will not include real regulatory or regulation references.[16,17]

FDA warning letter[18,19]

A Warning Letter is sent out when there are serious findings or if the Form 483 response is deemed unsatisfactory. The District Offices, not the investigator, issue the warning letters after the review by the competent centre. The company is required to respond in a timely manner and to specify how the failure will be fixed and future occurrences avoided. The FDA Web Portal is where most warning letters are posted. Unlike the Form FDA 483, each infringement in the Warning Letter will be accompanied by regulatory/regulation references.[19]

9. CONCLUSION

This article has covered a variety of topics concerning the water system.

Diverse kinds of water are utilised for different purposes in pharmaceutical industries. To follow the standards for the maintenance of quality attributes, it is necessary to be aware of all the grades of pharmaceutical water, as well as their preparation, specifications, and uses. Knowledge of inputs and outputs, excellent engineering techniques and water system design, a good monitoring/control programme, and correct maintenance all contribute to the capacity to deliver safe water consistently and confidently.

Compliance with the specification of pharmaceutical water is not enough, according to FDA Warning Letters issued in recent years. It is envisaged that the treatment method would be validated. This includes proof of the capacity of the process to manufacture pharmaceutical water to specifications. However, if we don't know the quality of the source water, we won't

know the purifying capacity. As a result, changes in the quality of the source (feed) water may result in water that does not meet the specifications after purification. Alternatively, it is unknown up to what quality level of source water pharmaceutical water may be produced that meets the specifications.

As a result, it's critical to understand the contaminants and their concentrations in the source (feed). Most importantly, all of the problems can be avoided if proper manufacturing practises requirements are strictly followed. The keys to delivering the highest quality of water for pharmaceutical use are strict execution and taking significant action against individuals who do not comply.

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