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WATER QUALITY ANALYSIS IN PHARMACEUTICAL INDUSTRY ACCORDING TO THE REQUIREMENTS OF EUROPEAN PHARMACOPOEIA

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ABSTRACT

Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, active pharmaceutical ingredients (APIs) and intermediates and analytical reagents. In this manuscript, we examined purified water from our system 2, and which supplies the water for the purpose of solid oral forms, with following parameters: appearance, conductivity, oxidisable substances, nitrates and heavy metals. All parameters and acceptable limits are according to European Pharmacopoeia.

KEYWORDS: Purified water, Pharmaceutical industry, European Pharmacopoeia.

INTRODUCTION

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriate quality. It is necessary to validate the water production process to ensure the water generated, stored and distributed is not beyond the designed capacity and meets its specifications (Biotechnology., 1998).

Water sources and treated water should be monitored regularly for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results, trend analysis and any actions taken should be maintained. Pharmacopoeial requirements or guidance for water for pharmaceutical use (WPU) are described in national, regional and international pharmacopoeias and limits for various impurities or classes of impurities are either specified or recommended. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias. Similarly, requirements or guidance are given in pharmacopoeias on the microbiological quality of water.

There are several typs of water: drinking water, bulk purified water (BPW) bulk highly purified water (BHPW), bulk water for injections (BWFI) and other grades of water.

Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product. Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes desalinization, softening, removal of specific ions, particle reduction and antimicrobial treatment. Drinking-water quality is covered by the World Health Organization (WHO) drinking-water guidelines, standards from the International Organization for Standardization (ISO) and other regional and national agencies (ISPE Baseline Guide Volume 4., 2001).

Bulk purified water (BPW) should be prepared from a drinking-water source as a minimum-quality feed-water. It should meet the relevant pharmacopoeial specifications for chemical and microbiological purity with appropriate action and alert limits. It should also be protected from recontamination and microbial proliferation. BPW may be prepared by a combination of reverse osmosis (RO) RO/electro-deionization (EDI) and vapour compression (VC) (US Food and Drug Administration. Guide., 2009).

Bulk highly purified water (BHPW) should be prepared from drinkingwater as a minimum-quality feed-water. BHPW is a unique specification for water found only in the European Pharmacopoeia. This grade of water must meet the same quality standard as water for injections (WFI), including the limit for endotoxins, but the water-treatment process used may be different. Current production methods include, for example, double-pass RO coupled with other suitable techniques such as

ultrafiltration and deionization (US Food and Drug Administration. Guide., 2009).

Bulk water for injections (BWFI) should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feedwater. BWFI is not sterile water and is not a final dosage form. It is an intermediate bulk product and suitable to be used as an ingredient during formulation. BWFI is the highest quality of pharmacopoeial WPU. BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxin) with appropriate action and alert limits. BWFI should also be protected from recontamination and microbial proliferation (US Food and Drug Administration. Guide., 2009).

When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within the company quality system, then we have other grades of water. As a minimum it must meet the pharmacopoeial requirements (ISPE Good practice guide., 2007).

EXPERIMENTAL

We examined purified water from our production system 2. Testing period was from february to november 2016. Five point sampling were tested with following physical and chemical parameters: appearance, conductivity, oxidisable substances, nitrates and heavy metals. All parameters and acceptable limits are according to European Pharmacopoeia (European Pharmacopoeia., 2017). All chemicals used are analytical purity and from Merck.

Appearance

Appearance is a visual exam. Purified water is clear and colourless liquid.

Conductivity

The current I (in amperes) flowing in a conductor is directly proportional to the applied electromotive force E (in volts) and inversely proportional to the resistance R (in ohms) of the conductor:

$$I = \frac{E}{R}$$

The conductivity (formerly called specific conductance) of a solution (κ) is, by definition, the reciprocal of resistivity (ρ). Resistivity is defined as the quotient of the electric field and the density of the current. The resistance R (in Ω) of a conductor of cross-section S (in cm^2) and length L (in cm) is given by the expression:

$$R = \rho \frac{L}{S}$$

thus: $$R = \frac{1}{\kappa} \times \frac{L}{S}$$

or $$\kappa = \frac{1}{R} \times \frac{L}{S}$$

L/S corresponds to the ideal cell constant.

The unit of conductivity in the International System is the siemens per metre ($S \cdot m^{-1}$). In practice, the electrical conductivity of a solution is expressed in siemens per centimetre ($S \cdot cm^{-1}$) or in microsiemens per centimetre ($\mu S \cdot cm^{-1}$). According to European Pharmacopoeia, acceptable criteria is max. 4.3 $\mu S \cdot cm^{-1}$.

Oxidisable substances

To 100 mL add 10 mL of dilute sulfuric acid R and 0.1 mL of 0.02 M potassium permanganate and boil for 5 min. The solution remains faintly pink.

Nitrates

Place 5 mL in a test-tube immersed in iced water, add 0.4 mL of a 100 g/L solution of potassium chloride R, 0.1 mL of diphenylamine solution R (This solution contains 1g/L solution of diphenylamine R in sulfuric acid) and, dropwise with shaking, 5 mL of nitrogen-free sulfuric acid R (To 100 mL of water R add a few milligrams of potassium permanganate R and of barium hydroxide R). Transfer the tube to a water-bath at 50°C. After 15 min, any blue colour in the solution is not more intense than that in a reference solution prepared at the same time in the same manner using a mixture of 4.5 mL of nitrate-free water R and 0.5 mL of nitrate standard solution (2 ppm NO_3) R. This solution is prepared immediately before use- dilute nitrate standard solution (10 ppm NO_3) to 5 times its volume with water R. Acceptable limit is maximum 0.2 ppm.

Heavy metals

To 200 mL add 0.15 mL of 0.1 M nitric acid and heat in a glass evaporating dish on a water-bath until the volume is reduced to 20 mL. 12 mL of the concentrated solution complies with test A. Prepare the reference solution using 10 mL of lead standard solution (1 ppm Pb) R and adding 0.075 mL of 0.1 M nitric acid. Prepare the blank solution adding 0.075 mL of 0.1 M nitric acid. Acceptable limit is maximum 0.1 ppm.

RESULTS AND DISCUSSION

Five point sampling from january to november 2016 are presented in Table 1.

Table 1: Review the test results for five point sampling from february to november 2016.

		Appearance	Conductivity	Oxidisable substances	Nitrates	Heavy metals
February	1	pass	0.90	pass	<0.2	<0.1
	2	pass	0.90	pass	<0.2	<0.1
	3	pass	0.90	pass	<0.2	<0.1
	4	pass	0.90	pass	<0.2	<0.1
	5	pass	0.90	pass	<0.2	<0.1
March	1	pass	0.90	pass	<0.2	<0.1
	2	pass	0.90	pass	<0.2	<0.1
	3	pass	0.90	pass	<0.2	<0.1
	4	pass	0.90	pass	<0.2	<0.1
	5	pass	0.90	pass	<0.2	<0.1
April	1	pass	0.90	pass	<0.2	<0.1
	2	pass	0.90	pass	<0.2	<0.1
	3	pass	0.90	pass	<0.2	<0.1
	4	pass	0.90	pass	<0.2	<0.1
	5	pass	0.90	pass	<0.2	<0.1
May	1	pass	0.92	pass	<0.2	<0.1
	2	pass	0.92	pass	<0.2	<0.1
	3	pass	0.92	pass	<0.2	<0.1
	4	pass	0.92	pass	<0.2	<0.1
	5	pass	0.92	pass	<0.2	<0.1
June	1	pass	0.88	pass	<0.2	<0.1
	2	pass	0.88	pass	<0.2	<0.1
	3	pass	0.88	pass	<0.2	<0.1
	4	pass	0.88	pass	<0.2	<0.1
	5	pass	0.88	pass	<0.2	<0.1
July	1	pass	0.87	pass	<0.2	<0.1
	2	pass	0.87	pass	<0.2	<0.1
	3	pass	0.87	pass	<0.2	<0.1
	4	pass	0.87	pass	<0.2	<0.1
	5	pass	0.87	pass	<0.2	<0.1
August	1	pass	0.92	pass	<0.2	<0.1
	2	pass	0.92	pass	<0.2	<0.1
	3	pass	0.92	pass	<0.2	<0.1
	4	pass	0.92	pass	<0.2	<0.1
	5	pass	0.92	pass	<0.2	<0.1
September	1	pass	0.87	pass	<0.2	<0.1
	2	pass	0.87	pass	<0.2	<0.1
	3	pass	0.87	pass	<0.2	<0.1
	4	pass	0.69	pass	<0.2	<0.1
	5	pass	0.69	pass	<0.2	<0.1
October	1	pass	0.88	pass	<0.2	<0.1
	2	pass	0.88	pass	<0.2	<0.1
	3	pass	0.88	pass	<0.2	<0.1
	4	pass	0.88	pass	<0.2	<0.1
	5	pass	0.71	pass	<0.2	<0.1
November	1	pass	0.90	pass	<0.2	<0.1
	2	pass	0.90	pass	<0.2	<0.1
	3	pass	0.90	pass	<0.2	<0.1
	4	pass	0.90	pass	<0.2	<0.1
	5	pass	0.90	pass	<0.2	<0.1

Based on the results in Table 1, we can see that all the parameters are in acceptance levels. In real cheking time there are lot of points for determination quality. We are presented only one target point from system 2, with five subclauses. For the ten months monitoring (february-november 2016.), all appearance are clear and colourless. Conductivity, in range from 0.87 to 0.92 $\mu S \cdot cm^{-1}$. All of them are below acceptable limit max. 4.3 $\mu S \cdot cm^{-1}$. Also,

results for oxidisable substances, nitrates and heavy metals are below acceptable limits.

CONCLUSIONS

All requirements for pharmaceutical industry are clearly defined. Water sources and treated water should be monitored for chemical, microbiological and endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. All precautions are taken to protect the system, the product and the end user, patient.

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