QUALITY CONTROL OF DISTILLED WATER USED FOR RECONSTITUTION OF POWDERS FOR ORAL SUSPENSION IN PHARMACIES ON THE TERRITORY OF BOSNIA AND HERZEGOVINA

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Abstract: In this paper, presented are the results of quality control of distilled water used for the reconstitution of powders for oral suspension usually intended for pediatric population. By reviewing the legislation, there is no clearly defined shelf life and storage instruction for this type of water. The conducted analyses confirmed that some pharmacies on the territory of Bosnia and Herzegovina use technical distilled water (water for accumulators, iron and antifreeze dilution), but also distilled water that does not meet quality requirements prescribed by European Pharmacopoeia. The tested water samples did not have adequately labeled packaging (production time and shelf life). The results showed that out of a total of 10 samples, 2 had conductivity greater than permissible, 3 had an exceeded limit for heavy metals, and 2 of the samples showed the presence of oxidisable substances. Out of all tested samples, only one sample met microbiological criteria for purified water. Based on the results of these analyses, it can be assumed that in many pharmacies around the country, inadequate distilled water is used which could endanger the stability of the pharmaceutical preparation and the safety of the patient. Bearing in mind that antibiotic oral suspensions are prescribed from the age of the infant, and that a large number of children consume these products for a long period due to frequent infections, the question arises as to whether prepared drugs accomplish their purpose and whether pharmacists are sufficiently aware of the importance of the quality of this type of water?

Keywords: water quality control, distilled water, water for reconstitution, water in pharmacy.

1. INTRODUCTION

Distilled water is one of the most frequently used resources in pharmaceutical industry. In the production of pharmaceutical preparations, it is widely used as an excipient, with a different role: solvent, vehiculum, diluent, adjuvant in certain phases of production of variety of pharmaceutical dosed products. It is also used in synthesis processes of active and auxiliary substances, in production of a final product, for reconstitution of powders and granules for oral suspensions (for example oral suspensions for pediatric purposes). It is used as a washing and rinsing agent for dishes, production equipment, primary and secondary packaging [1,2]. Water and water vapor are proved to be very effective in the processes of sterilization of aqueous parenteral preparations, aqueous ophthalmic preparations, accessories, devices and bandage materials. It has been proven that this method of sterilization rapidly destroys microorganisms with minimal harmful effects on material that is sterilized [3].

The wide use of water is explained by its chemical stability in various aggregate states and good biological tolerance, as it is an integral part of the cell and the main component of body fluids. Physico-chemical properties of water such as: low molecular weight, expressed polarity, ability to form hydrogen bonds, high dielectric constant, allow compatibility and dissolution of a large number of substances, but also good resorption after administration of the drug in the form of an aqueous solution. There are many different types of water that are used for pharmaceutical purposes and depending on the type of application, water is of a different quality [1].

The term „water” in pharmacy is commonly used to label drinking water (lat. Aqua Fontana), which is derived from natural sources or by purifying water from natural sources. The quality of drinking
water is not included in the monograph of modern Pharmacopoeia, but must be in accordance with the guidelines laid down by the World Health Organization (WHO) [4] and the standards laid down in national water documents set by the regulatory body [1,5].

Drinking water contains salts of aluminium, calcium, iron, magnesium, potassium, sodium, zinc and manganese. Compounds of arsenic, barium, mercury, cadmium, chromium, lead, selenium, nitrogen (nitrates and nitrites) may be dangerous for human health. If traces of heavy metals and toxic compounds are found in drinking or distilled water which is used for reconstitution of powders for oral suspensions, they may have negative effects on human health, so their presence in drinking water is permanently monitored [6]. Based on experimental and epidemiological studies, the WHO recommended a maximum permissible concentration limit for each substance found in water intended for human consumption (organic and inorganic components, solids, gases, microorganisms). It is the duty of all regulatory bodies to harmonize their national quality control regulations for all of those waters with the WHO guidelines [4].

The greatest risk to human health in drinking water is the presence of microorganisms (bacteria, viruses, fungi, parasites). The influence of microorganisms is most often manifested after consuming water containing pathogenic and/or conditionally pathogenic microorganisms, but also because of contact with surfaces previously treated with microbiologically irregular water. The clinical picture of the disease after the use of microbiologically defective water depends on the type of pathogen, its virulence, the number of microorganisms that enter the body, and the resistance of the human organism. Poisoning is manifested as diarrhea, dysentery, hepatitis, skin and mucous membranes infections.

Microbiological hazards in drinking water are pathogenic microorganisms such as Salmonella spp, Shigella spp, Campylobacter, Escherichia coli, Aspergillus spp, Enterobacter, Proteus spp, Pseudomonas aeruginosa, bacteriophages, spores, enteroviruses, fungi and algae. Pseudomonas aeruginosa, Proteus species and Escherichia coli are the most dangerous for human health. Primary vulnerable populations are children, pregnant women, nursing mothers, old and chronically ill persons and immunocompromised persons [7].

Bacteriological examination of drinking water includes the following analyses:
- determination of the total number of bacteria in 1 mL of water on a non-selective substrate,
- determining the presence of Escherichia coli,
- determination of the presence of thermostable coliform bacteria,
- determining the presence of faecal streptococci,
- determining the presence of the Proteus species,
- determining the presence of Pseudomonas aeruginosa,
- determining the presence of bacteriophage [6].

Aqua purificata/destilata is water obtained by the proper treatment processes of drinking water, such as distillation, ion exchange or reverse osmosis. It is used as excipient in the process of manufacturing of various pharmaceutical dosage forms that do not require apergy and sterility, but must satisfy the corresponding values of physico-chemical and microbiological parameters that confirm its quality, as shown in Table 1 [2, 8].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Clear, colorless and odorless liquid</td>
</tr>
<tr>
<td>Conductivity</td>
<td>≤ 3.6 µS/cm at 10 °C</td>
</tr>
<tr>
<td></td>
<td>≤ 4.3 µS/cm at 20 °C</td>
</tr>
<tr>
<td></td>
<td>≤ 5.1 µS/cm at 25 °C</td>
</tr>
<tr>
<td></td>
<td>≤ 5.4 µS/cm at 30 °C</td>
</tr>
<tr>
<td></td>
<td>≤ 6.5 µS/cm at 40 °C</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 0.1 ppm</td>
</tr>
<tr>
<td>Total organic carbon (TOC) or oxidisable substances</td>
<td>≤ 0.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Absence/100 mL</td>
</tr>
<tr>
<td>Nitrates</td>
<td>≤ 0.2 ppm</td>
</tr>
</tbody>
</table>
In Bosnia and Herzegovina (B&H), specifications that comply with the requirements prescribed by the European Pharmacopoeia (including tests and limits as presented in Table 1) are used for quality control of distilled water.

Literature review showed that there are no published scientific papers on testing the quality of distilled water used in pharmacies for the reconstitution of powders for oral suspensions. We found published papers describing the significance of different water purification systems in the pharmaceutical industry for quality of purified water [9-12]. Also, papers that describe the proper production and storage of distilled water in order to ensure the prescribed microbiological quality have been found [13]. Lately, great importance has been given to the purification of wastewaters, especially wastewater from the pharmaceutical industry. The reason for this is that various organic pollutants, pharmaceutical products and personal hygiene products are disposed of via wastewater into drinking water used as a raw material for obtaining water for pharmaceutical use [14-16].

The aim of this paper was to examine the quality of distilled water (physical and chemical analysis and microbiological quality) used in pharmacies throughout B&H for the reconstitution of powders for oral suspensions.

2. MATERIAL AND METHODS

The water quality test was performed by the procedures and methods prescribed in the European Pharmacopoeia (Ph. Eur. 9.0), and the physical, chemical and microbiological quality of the water was examined [2].

1. **Determination of conductivity** – a conductometer with a precision of 0.1 μS/cm of Hanna Instruments EC214 was used. Measurement was performed at 20 °C.

2. **Determination of heavy metals** – Pharmacopoeia prescribes several methods designated as method A, B, C, D, E, F, G and H, of which the method A was used:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological contamination</td>
<td>≤ 100 CFU/mL</td>
</tr>
<tr>
<td>Coliform bacteria</td>
<td>Absence/100 mL</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Absence/100 mL</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Absence/100 mL</td>
</tr>
</tbody>
</table>

Test solution – 200 mL of distilled water was heated 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 limit test A.

Standard solution – a mixture of 10 mL of standard lead solution (1 ppm Pb), as prescribed in Ph. Eur. 9.0, and 2 mL of test solution was used.

Blank solution – a mixture of 10 mL of water R and 2 mL of test solution was used. A 2 mL of buffer solution pH 3.5 was added, and, after stirring, 1.2 mL of thioacetamide reagent R was added. The solution was tested after 2 minutes.

Procedure - To the test and standard solution, 2 mL of buffer solution pH 3.5 per solution was added. After stirring, 1.2 mL of thioacetamide reagent R per solution was added. The solution was visually examined after 2 minutes.

Sensitivity of the procedure – the standard solution shows a slightly brown color in relation to a blind rehearsal.

Result – the brown color of the test solution should not be more intense than the color of the standard solution.

3. **Presence of oxidisable substances** – represents an alternative method of determining total organic carbon. In 100 mL of purified water, 10 mL of dilute sulfuric acid R and 0.1 mL of 0.02 M potassium permanganate was added and boiled for 5 minutes. The solution should remain faintly pink.

4. **Determination of microbiological purity** – it was performed by filtration through a membrane filter pore size 0.45 μm. The filter paper was seeded on the appropriate nutrient medium and incubated at 30-35 °C for a minimum of 5 days.

- **Coliform bacteria and Escherichia coli** – 100 mL sample water was filtered through a filter, pore size 0.45 μm. The filter was seeded on the Endo agar substrate and incubated at 32.5 °C for at least two days. The absence of an increase in red colored colonies and red colored colonies with metallic glow means the absence of coliform bacteria and E. coli. In the case of an increase in the colonies corresponding to the description, make identification. If there is an increase in other colonies, make identification.
(possible presence of Salmonella, Staphylococcus aureus, Clostridia or Candida albicans).

The analysis was done in the following time periods:

Day 0 (after opening a bottle with distilled water that is within the shelf-life), 5th day, 10th day, 15th day and one month after opening the same bottle with distilled water.

- Pseudomonas aeruginosa – 100 mL of water sample was filtered through a filter, pore size 0.45 μm. The filter was seeded on Cetrimid Agar and incubated at 32.5 °C for at least two days. The absence of an increase in yellow green colonies that are fluorescent under UV light means the absence of Pseudomonas aeruginosa. In the case of an increase in the colonies corresponding to the description, make identification. If there is an increase in other colonies, make identification (possible presence of Salmonella, Staphylococcus aureus, Clostridia or Candida albicans).

The analysis was done in the following time periods:

Day 0 (after opening a bottle with distilled water that is within the shelf-life), 5th day, 10th day, 15th day and one month (30th day) after opening the same bottle with distilled water.

Label types of distilled water used for analysis with labels for shelf life from the manufacturer:

- Sample 1 - Aqua purificata for steam irons, cooling devices and accumulators, (shelf life unlimited);
- Sample 2 - Technical distilled water (shelf life unlimited);
- Samples 3 and 4 - Aqua purificata Ph. Eur. (shelf life 3 months from the date of production);
- Samples 5, 7 and 9 - Aqua purificata Ph. Eur. (shelf life of unopened bottle 2 months, shelf-life after opening 5 days);
- Samples 6 and 8 - Aqua purificata (shelf life of unopened bottle 10 days, shelf-life after opening 5 days);
- Sample 10, no label, sample taken from water purification system in pharmacy (shelf life 1 month).

3. RESULTS AND DISCUSSION

In this paper, the quality of distilled water was examined (physical and chemical analysis and microbiological quality) used in pharmacies throughout B&H for the reconstitution of powders for oral suspensions. Low quality distilled water can lead to degradation of active substances or other components of pharmaceutical preparation which may result in formation of toxic products that can endanger safety of the patient.

After reviewing the government regulations related to water testing and water quality, the European Pharmacopoeia and similar documents, it was concluded that the shelf life and the storing instructions for distilled water were not clearly stated. This means that in each pharmacy the responsibility for the quality of distilled water is in a great extent on pharmacists.

For this study, 10 samples of distilled water from five different manufacturers were purchased in various pharmacies in B&H.

First, visual analyzes were made, where it was concluded that all samples were a clear, colorless, odorless and flavorless liquid. Appearance testing was performed visually – by observing the water sample in transparent tubes, flask bottles or adequate glasses, as defined by Ph. Eur. 9.0 [2].

Then, physico-chemical analyses of quality control of distilled water were carried out which included testing of:

1. Conductivity,
2. pH value,
3. The presence of heavy metals,
4. The presence of oxidisable substances.

Finally, microbiological stability was studied on day 0, then after 5, 10, 15 and 30 days of opening the bottle.

Conductivity

According to the European Pharmacopoeia [2] and American Pharmacopoeia [8], maximum values for conductivity of distilled water at certain temperature points are clearly defined (Table 1). The water conductivity is based on the measurement of the ionic directed flow of electrons through the water. It is an indirect method and represents a measure of the presence of inorganic ions dissolved in water, such as chloride, nitrate, sulphate, phosphate, sodium, magnesium, calcium, iron and aluminium. The presence of these ions increases the water conductivity, and pollution of organic origin decreases the conductivity [4]. To measure the conductivity, all 10 samples were thermostated prior to analysis at a temperature of 20 °C. The results of conductivity testing are shown in Table 2.
Table 2. Conductivity values and pH values of distilled water samples used for reconstitution of powders for oral suspensions

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Sample mark</th>
<th>Conductivity [µS cm(^{-1})] at 20 °C</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sample 1</td>
<td>1.5</td>
<td>5.43</td>
</tr>
<tr>
<td>2.</td>
<td>Sample 2</td>
<td>63.8</td>
<td>6.32</td>
</tr>
<tr>
<td>3.</td>
<td>Sample 3</td>
<td>3.4</td>
<td>5.20</td>
</tr>
<tr>
<td>4.</td>
<td>Sample 4</td>
<td>2.7</td>
<td>5.11</td>
</tr>
<tr>
<td>5.</td>
<td>Sample 5</td>
<td>2.9</td>
<td>5.73</td>
</tr>
<tr>
<td>6.</td>
<td>Sample 6</td>
<td>0.1</td>
<td>5.63</td>
</tr>
<tr>
<td>7.</td>
<td>Sample 7</td>
<td>3.9</td>
<td>5.47</td>
</tr>
<tr>
<td>8.</td>
<td>Sample 8</td>
<td>1.5</td>
<td>5.17</td>
</tr>
<tr>
<td>9.</td>
<td>Sample 9</td>
<td>3.9</td>
<td>5.07</td>
</tr>
<tr>
<td>10.</td>
<td>Sample 10</td>
<td>7.4</td>
<td>5.87</td>
</tr>
</tbody>
</table>

It can be seen from Table 2 that most samples have conductivity less than the prescribed of 4.3 µS cm\(^{-1}\). However, Sample 2 has a much higher value than permitted, and it is assumed that this distilled water is not of adequate quality in terms of ionic composition – it contains a higher amount of water-soluble ions, and is not suitable for use in pharmacy. This specimen is a technical distilled water which is intended as water for iron, batteries, engine coolers and antifreeze dilution, and as such it must not be used for pharmaceutical use.

Measurement of the pH (Table 2) showed that all samples meet the criteria given in Ph. Eur. 9.0 (pH 5 - 7) [2].

**Heavy metals**

For all ten samples, the presence of heavy metals was examined individually. The analysis was performed according to the procedure described in the Material and Methods section. By visual comparison of test solution with a standard solution containing the maximum allowed quantity of heavy metals, it was concluded that Samples 3, 4 and 5 have the brown color of solution more intense than the color of the standard solution (Figure 1). This indicate that Samples 3, 4 and 5 have exceeded the limits of heavy metals prescribed by Pharmacopoeia (max. 0.1 ppm = 0.1µg mL\(^{-1}\)) for distilling water intended for pharmaceutical use (Table 1). The other samples (sample 1, 2, 6, 7, 8, 9 and 10) showed a significantly lower intensity of brown color compared to the standard solution, which means that the amount of heavy metals is less than 0.1 ppm, which is in accordance with the specification prescribed by Ph. Eur. 9.0 [2].

![Figure 1](image-url)  
*Figure 1. Comparison of the test solution (left: 3A, 4A and 5A) and standard solution (right: 3B, 4B and 5B) for samples 3, 4 and 5 having exceeded the limit of heavy metals*
Determination of heavy metals is very important since they can have many negative effects on human health. Distilled water used to reconstitute oral suspensions for pediatric population should be of high quality with minimal content of heavy metals. Heavy metals (mostly mercury, aluminum, cadmium, lead, etc.) in human organism take places of trace elements (zinc, magnesium, calcium, selenium, etc.) found in vital enzymes and amino acids that participate in decisive metabolic processes. Excessive exposure to heavy metals could cause various chronic diseases, systemic exhaustion, damage of nervous and endocrine system, as well as digestive tract. Recent studies have shown the potential role of heavy metals in autism, because of irregular metabolism of heavy metals in autistic children. [17-20]

Due to all of the above facts, and in particular the correlation between the occurrence of autism in children and the presence of heavy metals in their organism, it is of utmost importance to reconstitute oral suspensions with distilled water of high quality, which has very low content of heavy metals (< 0.1 ppm).

Oxidisable substances

Determination of oxidisable substances is an alternative method of determining total organic carbon (TOC). TOC determination is an indirect measure of organic substances present in water for pharmaceutical use. A variety of acceptable methods is available for determining TOC. Various apparatus have in common the objective of completely oxidising the organic molecules in the sample water to produce CO₂ followed by measurement of the amount of CO₂ produced, the result being used to calculate the carbon concentration in water. The apparatus used must discriminate between organic and inorganic carbon. [21] Determination of oxidisable substances is described in detail in the Material and Methods section.

After analyses, most samples (Sample 1, 2, 3, 4, 5, 6, 8, and 9) preserved the pink color of the solution (Figure 2) which originates from potassium permanganate. These results indicate that these samples do not have present oxidisable substances which would cause reduction of potassium permanganate and discoloration of the solution. However, Samples 7 and 10 were completely colorless (Figure 2 and Figure 3), indicating the presence of oxidisable substances. Based on these results, it can be concluded that Samples 7 and 10 are not of satisfactory quality, and cannot be used as such for the reconstitution of oral suspensions, nor as excipients in the production of an active pharmaceutical ingredient (API) or a final product. Oxidisable substances are indirect measure of organic contaminants present in pharmaceutical water. These contaminants may originate from biofilms, germs, from materials and systems during purification and production and can have negative impact on water quality, especially for pharmaceutical use where a high purity water is essential.

Microbiological testing

This test was carried out with new samples of distilled water from 5 manufacturers obtained from the pharmacies in B&H. The microbiological analysis was carried out according to the procedure described in the Material and Methods section, and the obtained results are shown in Table 3.
Samples were taken in five time intervals (0, 5, 10, 15 and 30 days after opening) and tested for the presence of Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and coliform bacteria, and their presence was not proven.

Further, number of alive bacteria in the sample was investigated, and from the obtained results shown in Table 3 it can be concluded that only Sample 2 meets the criteria for the microbiological quality prescribed by the pharmacopoeia (Table 1). All the other samples have a higher number of alive bacteria than allowed by regulation [2]. Samples 3, 4, and 5 contain a worryingly high number of alive bacteria (CFU/mL > 4,000 at 0th point), and such water should not be used to reconstitute powder for oral suspensions. Although the samples did not contain Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and coliform bacteria, number of alive microorganisms found in the examined water for the pharmaceutical use raises the question of the safety of this water for the patients.

### Table 3. Results of microbiological examination of water quality

<table>
<thead>
<tr>
<th>No</th>
<th>Number of alive bacteria [CFU/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 0</td>
</tr>
<tr>
<td>1. sample</td>
<td>200</td>
</tr>
<tr>
<td>2. sample</td>
<td>100</td>
</tr>
<tr>
<td>3. sample</td>
<td>6 400</td>
</tr>
<tr>
<td>4. sample</td>
<td>4 100</td>
</tr>
<tr>
<td>5. sample</td>
<td>10 000</td>
</tr>
</tbody>
</table>

**4. CONCLUSION**

In this paper, quality of water used for reconstitutions of oral suspensions was investigated. Ten samples from five manufacturers were obtained from pharmacies in B&H. All samples had a satisfactory pH value, while only one sample showed higher conductivity than the permitted value – it is a technical distilled water that cannot be used for pharmaceutical purposes. Further tests revealed that 3 samples had exceeded the limits of heavy metals. Considering that heavy metals are the cause of many severe diseases, and that distilled water is used to reconstitute powders for oral suspensions in pediatrics, their presence in distilled water must be lower than 0.1 ppm, as prescribed by Pharmacopoeia. Presence of oxidisable substances was revealed in 2 samples. These are organic contaminants that originate from different sources and can endanger quality of purified water. Finally, the microbiological quality of distilled water from five manufacturers was tested, and it was concluded that only one sample met the requirements prescribed by the pharmacopoeia, i.e. had a lower number of alive bacteria than allowed (100 CFU/mL). Other samples had a number of alive bacteria considerably higher than those allowed, and this distilled water is not recommended for pharmaceutical use. None of the samples had Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and coliform bacteria. Based on the results of this study, it can be concluded that additional studies are necessary. Further study that would include greater number of samples should be conducted to confirm these results.
5. ACKNOWLEDGMENT

The authors thank the Ministry for Scientific and Technological Development, Higher Education and Information Society of Republic of Srpska for supporting these investigations in Project (19/6-020/961-73/18).

6. REFERENCES

ИСПИТИВАЊЕ КВАЛИТЕТА ДЕСТИЛОВАНЕ ВОДЕ КОРИШЋЕНЕ ЗА РЕКОНСТИТУЦИЈУ ПРАШКОВА ЗА ОРАЛНЕ СУСПЕНЗИЈЕ У АПОТЕКАМА НА ТЕРИТОРИЈИ БОСНЕ И ХЕРЦЕГОВИНЕ

Сажетак: У овом раду приказан су резултати испитивања квалитета дестиловане воде која се користи за реконституцију прашкова за оралне суспензије, најчешће намијењених за педијатријску популацију. Прегледом законских прописа, не постоји јасно дефинисан рок употребе и начин чувања ове врсте воде. Спроведене анализе потврдили су да неке апотеке на територији Босне и Херцеговине користе техничку дестиловану воду (вода за акумулаторе, пеглу и разблаживање антифриза), али и дестиловану воду која не задовољава захтјеве за квалитет прописане Европском фармакопејом. Испитивани узорци воде нису имали адекватно означену амбалажу (датум производње и рок употребе). Добијени резултати показују да су, од укупно 10 узора, два имала проводљивост већу од дозвољене, затим, да су три узorca имала прекорачен лимит за тешке метале, а код два узorca доказано је присуство оксидујућих супстанци. Од свих испитиваних узorca, само је један узorак био микробиолошки исправан. На основу резултата ових анализа, може се претпоставити да се у многим апотекама широм Босне и Херцеговине користи неадекватна дестилована вода која може да угрози стабилност фармацевутског препарата и безбједност пацијента. Имајући у виду да се антибиотске оралне суспензије прописују од узраста дојенчета, те да велики број дјеце због честих инфекција конзумира наведене препарате дужи временски период, поставља се питање да ли тако припремљени лијекови остварују своју намјену, те да ли су фармацевти у апотекама довољно свјесни значаја квалитета ове врсте воде?

Кључне ријечи: контрола квалитета воде, дестилована вода, вода за реконституцију, вода у фармацији.

Paper received: 12 December 2018
Paper accepted: 9 April 2019