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Standard Guide for Biomedical Grade Water [1]

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1. Scope

1.1 This guide is intended to describe the physical and chemical characteristics of water to be used whenever critical purity is essential to the use intended in clinical, pharmaceutical, biophysical, biomedical, chemical, physical research applications, or a combination of these. This guide is not intended for use in preparing water for injectables. Generally, the appropriate use of this guide may include experiments involving tissue culture, chromatography, mass spectroscopy, or analysis where molecular quantities of impurities may be important.

1.2 *This standard does not purport to address all of the safety problems, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*

D 1125 Test Methods for Electrical Conductivity and Resistivity of Water [2]

D 1129 Terminology Relating to Water [2]

D 1426 Test Methods for Ammonia Nitrogen in Water [2]

D 1428 Test Methods for Sodium and Potassium in Water and Water-Formed Deposits by Flame Photometry [3]

D 3919 Practice for Measuring Trace Elements in Water by Graphite Furnace Atomic Absorption Spectrophotometry [2]

D 3973 Test Method for Low Molecular Weight Halogenated Hydrocarbons in Water [4]

D 4453 Practice for Handling of Ultra-Pure Water Samples [2]

D 4517 Test Method for Low-Level Total Silica in High Purity Water by Flameless Atomic Absorption Spectroscopy [4]

D 4779 Test Method for Total, Organic, and Inorganic Carbon in High Purity Water by Ultraviolet (UV), or Persulfate Oxidation, or Both, and Infrared Detection [4]

F 1094 Test Methods for Microbiological Monitoring of Water Used for Processing Electron and Microelectronic Devices by Direct-Pressure Tap Sampling Valve and by the Pre-Sterilized Plastic Bag Method [5]

3. Terminology

3.1 *Definitions*—For definitions of terms used in this guide, refer to Terminology D 1129.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *endotoxins*—substances or by-products usually produced by gram negative micro-organisms which give a positive test for endotoxin in accordance with 8.24.

3.2.2 *heterotropic bacterial counts/1000 mL*—total number of viable micro-organisms present in the 1000-mL sample, excluding anaerobic and microaerophilic bacteria.

3.2.3 *total organic carbon*—carbon measured after inorganic carbon response has been eliminated by one of the prescribed ASTM methods.

3.2.4 *water*—water prepared in accordance with this guide.

4. Significance and Use

4.1 The purity of water is only relative and is usually defined by the limits of impurities found in the water as well as by the methods used to prepare and handle the water. Appendix X1 describes a method of preparation of moderate volumes of water with the highest purity practical using available equipment and techniques.

4.2 The method of preparation of water described in Appendix X1 is designed to remove organic, inorganic, volatile, particulate, and biological impurities to provide water that should meet the concentration limits in Table 1. These are suggested limits, since the actual maxima of the individual impurities will depend upon the required end use of the water. The limits in the guide in most cases are dictated not by the desired maximum concentration of the impurities, but by the methods of analysis. More restrictive limits may be required by mutual consent of the parties concerned, provided a suitable test method is agreed upon.

4.3 The guide for the storage of high purity water is very important because impurities are added to the water in proportion to the solubility, area of contact, and time of contact between the water and the materials of containment. It is

[1] This guide is under the jurisdiction of ASTM Committee D-19 on Water and is the direct responsibility of Subcommittee D19.02 on General Specifications, Technical Resources, and Statistical Methods.

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[2] *Annual Book of ASTM Standards*, Vol 11.01.

[3] *Discontinued 1990*—See 1989 *Annual Book of ASTM Standards*, Vol 11.01.

[4] *Annual Book of ASTM Standards*, Vol 11.02.

[5] *Annual Book of ASTM Standards*, Vol 10.04.

TABLE 1 Suggested Maximum Analyte Concentrations

Analyte	Maximum Concentration, µg/L
Arsenic	0.1
Cadmium	0.1
Chromium	1.0
Cobalt	1.0
Copper	1.0
Fluoride	1.0
Iron	1.0
Lead	1.0
Nickel	0.1
Potassium	2.0
Silica (total)	5.0
Sodium	0.5
Titanium	1.0
Zinc	0.5
Acetate	3.0
Ammonia	1.0
Chloride	1.0
Chloroform	5.0
Formate	2.0
Nitrate	1.0
Phosphate	1.0
Phthalates	0.1
Sulfide	1.0
Sulfate	1.0
Total organic carbon (TOC)	20.0
Volatile chlorinated hydrocarbon	5.0
Endotoxins (Endotoxin Unit)	<0.03 EU/mL
Heterotropic bacterial counts	<10/1000 mL
Electrical resistivity, [A] min, MΩ-cm at 25°C:	
–measured at the production point not in contact with air	10.0
–measured from storage or distribution system in contact with air	1.0

[A]Electrical resistivity can be expressed in microsiemens per centimetre conductivity at 25°C. The conductivity is reciprocal of the resistivity, $\frac{1}{R}$.

important to minimize the contact time of storage and to realize that the containment materials will determine the type of contaminants. Particular emphasis must be placed upon possible contamination from the atmosphere above the water which may add biological as well as gaseous and particulate impurities.

4.4 The distribution systems present a large area of contact between the water and the pipe or tubing and, therefore, must be of a very pure insoluble substance. Organic impurities, such as plasticizers, micro-organisms and their by-products, etc., are often more important considerations than inorganic impurities. Because plastic materials may vary from batch to batch, it is desirable to include limits of specific impurities as part of any installation specification.

4.5 The distribution outlets or faucets must be of non-contaminating design and materials. Particular care must be given to the valve seat and joint construction. The outlet must be protected from biological contamination particularly when the use is only occasional. Ultraviolet (UV), chemical, or heat sterilization should be considered.

5. Reagents

5.1 *Purity of Reagents*—Reagent grade chemicals shall be used in all tests. Unless otherwise indicated, it is intended that all reagents shall conform to the specifications of the Committee on Analytical Reagents of the American Chemical Society, where such specifications are available. [6] Other grades may be used, provided it is first ascertained that the reagent is of sufficiently high purity to permit its use without lessening the accuracy of the determination.

5.2 *Purity of Water*— Unless indicated otherwise, references to water shall be understood to mean water as defined in this guide.

6. Sampling

6.1 The test methods specified in Section 8 assume that great care and skill will be employed in obtaining the water samples to be tested. It is assumed that the operators will prevent container and airborne contamination to the best of their ability, making note of possible sources of contamination due to the sampling procedure. It is recommended that the samples be handled in accordance with Practice D 4453.

6.2 Extreme care must be exercised in handling samples when making analyses. Experimental laboratory-ware should be made of PFA- or TFE-fluorocarbon, and less desirably from quartz or borosilicate glass, to minimize the contamination of the water. Borosilicate glassware may leach ions at picogram-per-litre levels. The major contaminants from borosilicate glass are sodium (Na), potassium (K), boron (B), and silica (SiO_2). No detectable ions leach out of PFA- or TFE-fluorocarbon that has been properly cleaned.

6.2.1 Containers should be cleaned with HNO_3 (1 + 4) or HCl (1 + 4), or both, by filling the container and allowing it to stand for a minimum of 1 h.

6.2.2 The containers should be rinsed with three container volumes of a sampled water and then allowed to stand for 24 h with the same sampled water.

6.2.3 The containers should be rinsed again twice with the sampled water before filling.

6.2.4 The containers should be filled by flushing at least five volumes of the sampled water into the vessel before sealing. The seal must be of a non-contaminating material.

6.2.5 Storage of the sample may be required for the detection of metals, in which case 1 mL of redistilled HNO_3(1 + 99) or HCl (1 + 99) should be added per litre to reduce the pH and to preserve solubility of the metals within the sample.

6.2.6 The water sample should remain in storage a minimal length of time since some impurities have a tendency to adhere to the container surface. Endotoxins may become irreversibly stuck to glass walls, as will certain insoluble colloids.

7. Recommendations for Purity

7.1 Recommendations for purity of water should conform to the properties and chemical limits given in Table 1; however the suggested maximum limits and the actual impurities considered, or both, may be modified by the user based upon the intended use of the water.

[6] "Reagent Chemicals, American Chemical Society Specifications," Am. Chemical Soc., Washington, DC. For suggestions on the testing of reagents not listed by the American Chemical Society, see "Analar Standards for Laboratory Chemicals," BDH Ltd., Poole, Dorset, U.K., and the "United States Pharmacopeia."

7.2 The precision of detection will depend on the purity of the reagents used, equipment employed, experience of the lab personnel, the sampling technique, and cleanliness of the working area.

7.3 A suggested guide of producing, storing, and distributing water for critical purity applications is described in the Appendix. Other procedures may be employed provided the product water meets the limits in Table 1 as modified by the specific requirements of the use.

8. Test Methods

8.1 *Arsenic*—Graphite Furnace AAS, [7] Practice D 3919.
8.2 *Cadmium*—Graphite Furnace AAS, [7] Practice D 3919.
8.3 *Chromium*—Graphite Furnace AAS, [7] Practice D 3919.
8.4 *Cobalt*—Graphite Furnace AAS, [7] Practice D 3919.
8.5 *Copper*—Graphite Furnace AAS, [7] Practice D 3919.
8.6 *Fluoride*. [8]
8.7 *Iron*—Graphite Furnace AAS, [7] Practice D 3919.
8.8 *Lead*—Graphite Furnace AAS, [7] Practice D 3919.
8.9 *Nickel*—Graphite Furnace AAS, [7] Practice D 3919.
8.10 *Potassium*—Flame photometry. [9]
8.11 *Silica*—Test Method D 4517.
8.12 *Sodium*—Flame photometry. [9]
8.13 *Titanium*—Graphite Furnace AAS, [7] Practice D 3919.
8.14 *Zinc*—Graphite Furnace AAS, [7] Practice D 3919.
8.15 *Acetate*. [8]
8.16 *Ammonia Nitrogen*— Test Method D 1426 (Test Method C).
8.17 *Chloride*. [8]
8.18 *Chloroform*—Test Method D 3973.
8.19 *Electrical Resistivity*—Test Methods D 1125.
8.20 *Formate*. [8]
8.21 *Nitrate*. [8]
8.22 *Phosphate*. [8]
8.23 *Phthalates*—Gas chromatography, electron capture detector. [10]
8.24 *Endotoxins—Limulus Amebocyte* Lysate Test. [11]
8.25 *Sulfide*—No specific method is recommended.
8.26 *Sulfate*. [8]
8.27 *Heterotropic Bacterial Count*—Test Methods F 1094.
8.28 *Total Organic Carbon (TOC)*—Test Method D 4779.
8.29 *Volatile Chlorinated Hydrocarbons*—Test Method D 3973.

9. Keywords

9.1 biomedical; clinical; pharmaceutical; research

[7] See *The Guide to Techniques and Applications of Atomic Spectroscopy*, Perkin-Elmer Corporation, Norwalk, CT.

[8] A draft test method for trace anions and cations in high-purity water by ion-chromatography procedure is currently under development by Subcommittee D19.11.02.02.

[9] An acceptable flame photometry method is given in the 1982 version of Test Methods D 1428.

[10] See "USP Current Edition Phthalate Gas Chromatography—Electron Capture Detector," *EPA Method 606, Federal Register*, Vol 44, No. 233, Dec. 3, 1979.

[11] U. S. Pharmacopeia, Current Edition, The United States Pharmacopeial Convention, Inc.

APPENDIXES

(Nonmandatory Information)

X1. SUMMARY OF METHODS OF PREPARATION

X1.1 The method of preparation of the biomedical grade water affects the limits of impurities. It is recommended that it be prepared, distributed, and stored by two distinct systems, as follows:

X1.1.1 *Laboratory System*—In the laboratory system, the purification of tap water shall be accomplished by either double-distillation or by deionization, adsorption, reverse osmosis, ultrafiltration, or membrane filtration, or a combination thereof, followed by distillation and suitable storage.

X1.1.1.1 The double-distillation method of purifying water utilizes the distillation apparatus, which produces water of minimum resistivity of 1.0 MΩ-cm at 25°C, followed by a properly designed distillation apparatus manufactured from a non-contaminating material such as fluorocarbons, quartz, pure tin, titanium or, in many situations, borosilicate glass, which will upgrade the water to meet the requirements.

X1.1.1.2 The adsorption, reverse osmosis, deionization, filtration apparatus step, followed by use of distillation apparatus, which must be manufactured from a non-contaminating material, will upgrade the water to meet the requirements.

X1.1.2 *Central Building System*—In the central building system, where large volumes of biomedical grade water are produced daily, the system shall be of a special design to produce, store, and distribute high purity water. The system shall include the components described in this appendix used to prepare laboratory quantities of biomedical grade water except that the capacity of the system will be larger, which in most cases will mandate the use of metal stills rather than those fabricated of quartz or glass.

X1.2 The systems mentioned above shall be fabricated from materials that shall not contaminate water with undesirable substances. Undesirable materials include copper improperly coated with tin, tin containing lead, stainless steels of all types, aluminum, monel, soft glass, PVC, polypropylene, and many other plastic and metallic materials. Suitable materials include pure tin, titanium, TFE-fluorocarbon, PFA-fluorocarbon, platinum, tantalum, quartz, and if traces of silica are not a problem, borosilicate glass.

X2. SUMMARY OF METHOD OF STORAGE

X2.1 The storage tanks of the ultrapure water grade systems shall be constructed from materials that do not add impurities to high purity water. The maintenance of purity and sterility of the storage system shall be accomplished by one or a combination of these procedures: air filtration, inert gas blanketing, or UV sterilization technique. It must be recognized that the mere fact that the water is stored will reduce its purity despite attempts to prevent contamination; therefore, storage should be avoided or kept at a minimum.

X3. SUMMARY OF METHOD OF DISTRIBUTION

X3.1 The distribution systems used to transfer the high purity water to the individual laboratories shall be of special design to minimize contamination. Gravity feed is the preferred method, since pumps generally add contaminants to the water. If circulating systems are employed, the pumps must be of non-contaminating design. The piping materials, fittings, faucets, and joints must be of non-contaminating materials and design. Outlets should be protected by UV or other means to prevent "back contamination" by airborne biological impurities.