

Water for Injection

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union, Japan, or with the World Health Organization's Guidelines for Drinking Water Quality. It contains no added substance.

NOTE—Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Water for Injection sterile and, thereafter, protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and, thereafter, protect it from microbial contamination. The tests for *Total organic carbon* and *Water conductivity* apply to Water for Injection produced on site for use in manufacturing. Water for Injection packaged in bulk for commercial use elsewhere meets the requirement of the test for *Bacterial endotoxins* as indicated below and the requirements of all the tests under *Sterile Purified Water*, except *Labeling*.

USP Reference standards (11)—*USP 1,4-Benzoquinone RS*. *USP Endotoxin RS*. *USP Sucrose RS*.

Bacterial endotoxins (85)—It contains less than 0.25 USP Endotoxin Unit per mL.

Total organic carbon (643): meets the requirements.

Water conductivity (645): meets the requirements.

Bacteriostatic Water for Injection

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Bacteriostatic Water for Injection is prepared from Water for Injection that is sterilized and suitably packaged, containing one or more suitable antimicrobial agents.

NOTE—Use Bacteriostatic Water for Injection with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Packaging and storage—Preserve in single-dose or multiple-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass, of not larger than 30-mL size.

Labeling—Label it to indicate the name(s) and proportion(s) of the added antimicrobial agent(s). Label it also to include the statement "NOT FOR USE IN NEWBORNS" in boldface capital letters on the label immediately under the official name, printed in a contrasting color,

preferably red. Alternatively, the statement may be placed prominently elsewhere on the label if the statement is enclosed within a box.

Sterility (71): meets the requirements.

USP Reference standards (11)—*USP Endotoxin RS*.

Antimicrobial agent(s)—It meets the requirements under *Antimicrobial Effectiveness Testing* (51), and meets the labeled claim for content of the antimicrobial agent(s), as determined by the method set forth under *Antimicrobial Agents—Content* (341).

Bacterial endotoxins (85)—It contains less than 0.5 USP Endotoxin Unit per mL.

Particulate matter (788): meets the requirements.

pH (791): between 4.5 and 7.0, in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.

Calcium—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Sterile Water for Inhalation

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Sterile Water for Inhalation is prepared from Water for Injection that is sterilized and suitably packaged. It contains no antimicrobial agents, except where used in humidifiers or other similar devices and where liable to contamination over a period of time, or other added substances.

NOTE—Do not use Sterile Water for Inhalation for parenteral administration or for other sterile compendial dosage forms.

Packaging and storage—Preserve in glass or plastic containers. Glass containers are preferably of Type I or Type II glass.

Labeling—Label it to indicate that it is for inhalation therapy only and that it is not for parenteral administration.

USP Reference standards (11)—*USP Endotoxin RS*.

Bacterial endotoxins (85)—It contains less than 0.5 USP Endotoxin Unit per mL.

Sterility (71): meets the requirements.

pH (791): between 4.5 and 7.5, in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.

Ammonia—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

Calcium—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Chloride—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)) containing 10 µg of chloride (0.5 mg per L), viewed downward over a dark surface with light entering the tubes from the sides.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Inhalation in containers having a fill volume of less than 50 mL, add 0.4 mL of Δ 0.02 M_{▲USP30} potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of Δ 0.02 M_{▲USP30} potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Sterile Water for Injection

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Sterile Water for Injection is prepared from Water for Injection that is sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage—Preserve in single-dose glass or plastic containers, of not larger than 1-L size. Glass containers are preferably of Type I or Type II glass.

Labeling—Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute.

USP Reference standards (11)—*USP Endotoxin RS*.

Bacterial endotoxins (85)—It contains less than 0.25 USP Endotoxin Unit per mL.

Sterility (71): meets the requirements.

pH (791): between 5.0 and 7.0 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.

Particulate matter (788): meets the requirements.

Ammonia—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

Calcium—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Chloride—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)) containing 10 µg of chloride (0.5 mg per L), viewed downward over a dark surface with light entering the tubes from the sides.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers having a fill volume of less than 50 mL, add 0.4 mL of Δ 0.02 M_{▲USP30} potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of Δ 0.02 M_{▲USP30} potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Sterile Water for Irrigation

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Sterile Water for Irrigation is prepared from Water for Injection that is sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage—Preserve in single-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass. The container may contain a volume of more than 1 L, and may be designed to empty rapidly.

Labeling—Label it to indicate that no antimicrobial or other substance has been added. The designations “For irrigation only” and “Not for injection” appear prominently on the label.

USP Reference standards (11)—*USP Endotoxin RS*.

Bacterial endotoxins (85): not more than 0.25 Endotoxin Unit per mL.

Sterility (71): meets the requirements.

pH (791): between 5.0 and 7.0 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.

Ammonia—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

Calcium—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Chloride—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity*

Water (see *Reagents* under *Containers* (661)) containing 10 µg of chloride (0.5 mg per L), viewed downward over a dark surface with light entering the tubes from the sides.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Irrigation in containers having a fill volume of less than 50 mL, add 0.4 mL of $^{A}0.02 M_{USP30}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of $^{A}0.02 M_{USP30}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Purified Water

H₂O 18.02

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Purified Water is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union, Japan, or with the World Health Organization's Guidelines for Drinking Water Quality. It contains no added substance.

NOTE—Purified Water is intended for use as an ingredient of official preparations and in tests and assays unless otherwise specified (see *Water in Ingredients and Processes* and in *Tests and Assays* under *General Notices and Requirements*). Where used for sterile dosage forms, other than for parenteral administration, process the article to meet the requirements under *Sterility Tests* (71), or first render the Purified Water sterile and thereafter protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection. The tests for *Total organic carbon* and *Conductivity* apply to Purified Water produced on site for use as an ingredient of official preparations and in tests and assays. Purified Water packaged in bulk for commercial use elsewhere meets the requirements of all of the tests under *Sterile Purified Water*, except *Labeling* and *Sterility* (71).

USP Reference standards (11)—*USP 1,4-Benzoquinone RS*. *USP Sucrose RS*.

Total organic carbon (643): meets the requirements.

Water conductivity (645): meets the requirements.

Sterile Purified Water

H₂O 18.02

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Sterile Purified Water is Purified Water sterilized and suitably packaged. It contains no antimicrobial agent.

NOTE—Do not use Sterile Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.

Packaging and storage—Preserve in suitable, tight containers.

Labeling—Label it to indicate the method of preparation and that it is not for parenteral administration.

Sterility (71): meets the requirements.

pH (791): between 5.0 and 7.0 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.

Ammonia—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* (661)), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

Calcium—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Chloride—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of a solution of sodium chloride in *High-Purity Water* (see *Reagents* under *Containers* (661)), containing 825 µg of sodium chloride per L (10 µg of Cl in 20 mL), viewed downward over a dark surface with light entering the tubes from the sides.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Purified Water in containers having a fill volume of less than 50 mL, add 0.4 mL of $^{A}0.02 M_{USP30}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of $^{A}0.02 M_{USP30}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Water for Hemodialysis

NOTE—See *Water for Health Applications* (1230) for guidelines on microbial and chemical testing.

» Water for Hemodialysis is water that complies with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations and that has been subjected to further treatment, using a suitable process, to reduce chemical and microbiological components. It is produced and used onsite under the direction of qualified personnel. It contains no added antimicrobials and is not intended for injection.

Packaging and storage—Preserve in unreactive storage containers that are designed to prevent bacterial entry. Store at room temperature.

USP Reference standards (11)—*USP Endotoxin RS*.

Microbial limits (61)—The total viable count does not exceed 100 cfu per mL.

Bacterial endotoxins (85)—It contains less than 2 USP Endotoxin Units per mL.

Water conductivity (645): meets the requirements.

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2N sulfuric acid, and heat to boiling. Add 0.2 mL of Δ 0.02 M Δ ^{USP30} potassium permanganate, and boil for 5 minutes. The pink color does not completely disappear; or alternatively follow the test method for *Total Organic Carbon* (643).

Pure Steam

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* (1231).

» Pure Steam is water that has been heated above 100° and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or Japan, or with WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of noncondensable gases are to be determined by the Pure Steam application.

NOTE—Pure Steam is intended for use where the steam or its condensate comes in contact with the article or the preparation. Pure Steam quality is difficult to assess in its vapor state; therefore the attributes of its condensate are used to test its quality. The process used to create and collect the condensate for analysis must not adversely impact these quality attributes.

USP Reference standards (11)—*USP 1,4-Benzoquinone RS*. *USP Endotoxin RS*. *USP Sucrose RS*.

Bacterial endotoxins (85)—The condensate contains less than 0.25 USP Endotoxin Unit per mL (when used in the production of parenterals).

Total organic carbon (643): the condensate meets the requirement.

Water conductivity (645): the condensate meets the requirement.

Wheat Bran

» Wheat Bran is the outer fraction of the cereal grain, comprising the pericarp, seed coat (testa), nucellar tissue, and aleurone layer, and is derived from *Triticum aestivum* Linné, *T. compactum* Host, *T. durum* Desf., and other common einkorn and emmer wheat cultivars. It is obtained by the milling and processing of the whole wheat grain meeting U.S. Standards for Number 1 wheat (7 CFR 810.2201). It contains not less than 36.0 percent of dietary fiber.

Packaging and storage—Preserve in well-closed containers, secured against insect attack (see *Preservation under Vegetable and Animal Substances* in the *General Notices*).

Identification—When examined microscopically, the following components of Wheat Bran are visible. Fragments of aleurone and nucellar layers (about 60% of the components) and fragments of seed coat and pericarp (about 40%). Aleurone and nucellar tissues composed of a usually single layer of thick-walled, isodiametric, translucent cells having conspicuous protoplasm and a single, inconspicuous layer of thick-walled, nearly transparent cells. Inconspicuous seed coat, consisting of two layers of thin-walled cells crossing at roughly right angles to each other. Pericarp composed of an inconspicuous endocarp layer of elongated, thick-walled tube cells; a cross layer with cells longer than wide, arranged side-by-side in rows, having thick, highly pitted side and end walls; and epicarp and hypoderm layers with cells longer than wide, arranged alternately in rows and having thick, highly pitted side and end walls. Epicarp and hypoderm cells larger than and crossing at right angles to the cells of the cross layer. A few trichomes also present, with lumens narrower than the thickness of their cell walls and originating from isodiametric-polygonal epicarp cells. If micronized, the original structures are mostly destroyed.

Microbial limits (61)—The total aerobic microbial count does not exceed 10,000 cfu per g, and it meets the requirements of the test for the absence of *Salmonella* species and *Escherichia coli*.

Water, Method III, Procedure for Articles of Botanical Origin, (921)—It loses not more than 12% of its weight.

Total ash (561): not more than 8%.

Heavy metals, Method II (231): 0.004%.

Absence of peroxidase activity—Transfer about 1 g of Wheat Bran to a test tube, and add 50 mL of water. Add, in the order specified, 2 mL of 5.68 mM erythorbic acid, 3 mL of 0.69 mM dichloroindophenol, and 0.1 mL of 1.2% hydrogen peroxide, each freshly prepared. Stopper the test tube tightly, and shake until the sample is dissolved. Place into a water bath at 38° for 5 minutes: no color change is observed, indicating the absence of peroxidase activity.

Limit of fat—Transfer about 2 g of Wheat Bran, previously dried in a vacuum oven at 100° for 5 hours and accurately weighed, to an extraction thimble, and mix with an equivalent quantity of dry, clean sand. Place a fat-free cotton or glass wool plug on top of the thimble. Place the thimble in a continuous-extraction apparatus provided with a tared collection flask. Pour about 75 mL of solvent hexane through the sample into the collection flask. Extract at a condensation rate of 5 to 6 drops per second for 4 hours, then at a rate of 2 to 3 drops per second for the next 16 hours. Detach the collection flask, carefully evaporate the solvent, and dry the collection flask and its contents in a drying oven at 100° for 30 minutes to constant weight. Calculate the percentage of the extract (crude fat) in the portion of Wheat Bran taken: not more than 6% is found.

Limit of insect infestation—Prepare a smooth slurry by transferring about 50 g of Wheat Bran to a 1 L beaker and adding 500 mL of 1.5N hydrochloric acid. Add 50 mL of light mineral oil, and