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23 July 2024

Reference: Chinese Pharmacopeial Chapter <0261> Water for Pharmaceutical Purposes

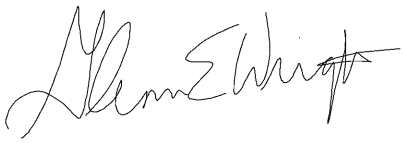
Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the Chinese Pharmacopeia on Chapter <0261> Water for Pharmaceutical Purposes. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important Chapter.

PDA is a non-profit international professional association with over 10,000 individual members, including scientists, industry professionals, and consultants who have an interest in pharmaceuticals, biologics, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,



Glenn E. Wright
President and CEO

cc. Josh Eaton, PDA; Carrie Horton, PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

PDA Comments to Chinese Pharmacopoeia Guidance: 0261 Water for Pharmaceutical Purposes

General Comments about the Guidance		
Comment	**Proposed Change**	**Rationale**
For WFI and Sterile WFI: There is no analysis requirement for Aluminum.	For WFI and Sterile WFI: add Aluminum test with a note of "where it is labeled as intended for use in the manufacture of peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions".	Proposed changes will account for additional testing necessary to support hemodialysis applications (WFI and Sterile WFI).
Under Appendices 1-2, there are statements that if Conductivity meets requirements, then specific tests are not required. These tests include the following: Acidity or Alkalinity, Heavy Metals, Nitrate, Nitrite, and Ammonia. PDA recommends removing these test requirements along with the clausal statement. If this proposal is not acceptable, refer to the comments below for updates for these sections.	Remove the statements addressing tests not being required if Conductivity meets requirements in Appendices 1-2. Remove the following tests from Appendices 1-2: Acidity or Alkalinity, Heavy Metals, Nitrate, Nitrite, and Ammonia. If this proposal is not acceptable, refer to the comments below for recommended changes on this subject.	If the water meets the conductivity requirements, there is no need to perform a test for acidity or alkalinity, heavy metals, nitrate, nitrite, or ammonia. If any of the other listed tests are not acceptable, the conductivity would not meet requirements. Further, if conductivity does not pass, the water (purified or water for injection) should not be used even if it passes for the subsequent tests of acidity or alkalinity, heavy metals, nitrate, nitrite, and ammonia. This approach will harmonize the recommendations with those found in other current industry and regulatory documents.

Introduction					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
10-11	10 - 11	"The source water used for purified water, water for injection and sterile water for injection is usually drinking water."	PDA proposes to change text to harmonize with the recommendations found in other current industry and regulatory documents.	"The source water used for purified water, water for injection and sterile water for injection is at a **minimum drinking water**."	By updating the wording, the recommendation of this guidance will be more aligned to that found in other current industry and regulatory documents.
15-17	15-16	"The system for water for pharmaceutical purposes should be qualified/validated, systems of daily monitoring, analysis and report should be established, and complete original data should be kept for reference."	PDA suggests changing recommendation of "daily monitoring" to "routine monitoring and breaking the statement into two sentences.	"The system for water for pharmaceutical purposes should be qualified/validated, and **include routine** monitoring and analysis **based on risk assessment**. **Reports** should be established and complete original data should be kept for reference."	By making this language change, it will harmonize recommendations with current industry and regulatory documents and allow companies the flexibility to determine monitoring frequency based on the system and associated risks. By dividing the statement into two sentences, it will clarify the intent for the reader.
18-21	18-21	"Sterilization could be conducted using thermal or chemical processes. The cleaning and disinfection methods used and the removal of cleaning agents and disinfectants after chemical treatments should be qualified/validated."	PDA encourages the use of the term "sanitization" in place of "sterilization". PDA recommends expanding the statement to include other process beyond thermal or chemical processes. Additionally, PDA suggests using the general terminology	**"Sanitization** could be conducted using thermal or chemical processes **or other suitable processes**. Removal of **chemical agents used in the process** should be qualified/validated."	Water systems are sanitized at high temperatures but not designed to support sterilization. By updating the statement to include "or other suitable processes, it will account for other optional processes such as ultra-violet (UV) radiation that can be used for

Introduction					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
			of cleaning agents and focusing on the removal of chemical agents being qualified/validated.		sanitization. Generalizing will focus on the critical elements of focusing on removal of chemical solutions without specifying specific category of solutions.

Drinking Water					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
25-27	25-27	"Drinking water may be used for washing crude drugs before purification, for preliminarily washing pharmaceutical appliances and may also be used as the solvent for extraction of medicine material crude slices."	PDA recommends expanding the statement and using more general descriptions of the manufacturing process/equipment.	**"**Drinking water may be used **in the early stages of cleaning pharmaceutical manufacturing equipment and product-contact components. Drinking water is also the minimum quality of water that should be used for the preparation of drug substances and other bulk pharmaceutical ingredients. Where compatible with the processes, the contaminant levels allowed in drinking water are generally considered safe for use in preparing official substances**	By updating this statement, it will provide more guidance to the user regarding suitable uses for drinking quality water in the manufacturing process. This update in language also harmonizes the statement with current industry and regulatory documents.

Drinking Water					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
				and other drug substances. A risk assessment may be performed to determine suitability of proposed water sources for specific dosage forms or products."	

Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
48-52	48-52	**"Water for injection** Water for injection is water prepared by distillation of purified water, and its quality should comply with the requirements of the Annex 2 of Water for injection in this General Chapter; or water for injection is prepared through a purification process equivalent to distillation, and its preparation process should meet the requirements of relevant procedures of regulatory authorities, and its quality should meet relevant provisions. It contains no	PDA proposes to update the statement to clarify that drinking water can be used as feed water for the preparation of Water for Injection. Additionally, PDA proposes to clarify the water quality characteristics to assess when determining process equivalency.	**"Water for injection** Water for injection is water prepared by distillation of **Drinking Water** or purified water, and its quality should comply with the requirements of the Annex 2 of Water for injection in this General Chapter; or water for injection is prepared **from Drinking Water or Purified Water** through a purification process equivalent to distillation **in the removal of chemicals, Microorganisms and endotoxins.** Its quality should	The feed water to generate Water for Injection (WFI) is ruled as Drinking Water (suitably pretreated) or Purified Water in most international Pharmacopoeias. Regarding the alternative to Distillation, the updated language provides guidance for assessing equivalent processes.

Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		additives."		meet relevant provisions. It contains no additives.	

Microbial Monitoring					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
75-77	75-77	"Take no less than 1ml purified water or no less than 100ml water for injection, process with the membrane filtration method, culture with R2A agar medium at 30-35℃ for no less than 5 days, and carry out the test as described (1105)."	PDA recommends adding a statement allowing the use of other suitable media for culture.	"Take no less than 1ml purified water or no less than 100ml water for injection, process with the membrane filtration method, culture with R2A agar medium at 30-35℃ for no less than 5 days, and carry out the test as described (1105). **For optimum recovery, other suitable low nutrient media, incubation time and/or temperature may be needed**."	Other types of media can be suitable for culture in addition to R2A. By adding this statement, it will clarify for the reader that they should select the media type most suitable for their specific process. This update also harmonizes the statement with current industry and regulatory documents.
79-82	79-82	"The microbial limit of purified water shall be no more than 100 cfu/ml, and that of water for injection shall be more than 10 cfu/100ml. On the premise of meeting the limit standards, appropriate alert and action limits should be set	PDA recommends adding missing word "no" in the statement "water for injection shall be more than 10cfu/100 ml". PDA also recommends adding clarifying statement and rewording last sentence.	"The microbial limit of purified water shall be no more than 100 cfu/ml, and that of water for injection shall be **no** more than 10 cfu/100ml. On the premise of meeting the limit standards, appropriate alert and action limits should be set to monitor	Adding in missing word will make the statement/intent accurate and align with the wording used for the purified water microbial limit. By adding the proposed statement, it will harmonize the language with current

Microbial Monitoring					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		to monitor adverse trends. Tighter alert and action limits may be imposed as needed for high-risk drug products or aseptic processes."		adverse trends. **For aseptic processing, stricter alert levels may need to be applied.**"	industry and regulatory documents (e.g., European Pharmacopoeia). By removing "high-risk" it will eliminate confusion for the reader and focus on aseptic processing of sterile products.
89-92	89-92	"Suitability test for R2A agar Carry out the method described under growth promotion of soya bean casein digest agar in Growth Promotion of the Counting Media, Pseudomonas aeruginosa and Bacillus subtilis as test strain, complies with the microbiological examination of non-sterile products: microbial enumeration tests <1105>. Complies with the requirements."	PDA proposes to generalize the media reference and expand statement to include use of soya bean casein digest broth.	"Suitability test for **the media used (e.g., R2A or other suitable, validated media) should be carried out per** the method described under growth promotion of soya bean casein digest agar **or soya bean casein digest broth** in Growth Promotion of the Counting Media, Pseudomonas aeruginosa and Bacillus subtilis as test strain, complies with the microbiological examination of non-sterile products: microbial enumeration tests <1105>. Complies with the requirements."	This update in language will harmonize with those found in <1105> and with current industry and regulatory documents. Additionally, the use of a general media reference aligns with the above proposed change for alternate media may needing to be used.

Appendix 1: Purified Water					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
101-103	101-103	"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity meets the requirements, the pH value and heavy metal test will not be conducted."	PDA encourages updating statement to be inclusive of all tests that do no need to be performed if the WFI meets the conductivity requirements.	"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity meets the requirements, the, **acidity or alkalinity,** pH value, **nitrate, nitrite, ammonia** and heavy metal test**s** will not be conducted."	Conductivity test limits were developed such that if you passed the conductivity tests, you would pass the existing compendial chemical tests. Therefore, if the water for injection meets the conductivity requirements, there is no need to perform a test for acidity or alkalinity, nitrate, nitrite, or ammonia. If any of the other listed tests are not acceptable, the conductivity would not meet requirements. By updating the statement, it will clarify this for the reader.
111-114	111-114	"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity is determined to meet the requirements according to the first step of determination method, nitrate, nitrite and ammonia test will not be conducted."	PDA recommends removing this statement and instead update the language in lines 101-103 to include the additional tests.	~~"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity is determined to meet the requirements according to the first step of determination method, nitrate, nitrite and ammonia test will not be conducted."~~	There is no need for a separate statement because if the water meets the conductivity requirements (regardless of which stage of testing), there is no need to perform a test for nitrate, nitrite or ammonia. Therefore, all applicable tests can be stated in the first statement.

Appendix 2: Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
144-147	144-147	"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity is determined to meet the requirements according to the first step of determination method, nitrate, nitrite and ammonia test will not be conducted."	PDA recommends updating the language to align with the approach in the proposed changes in lines 101-103 with regards to conductivity acceptance requirements.	"If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), **and the conductivity meets the requirements**, nitrate, nitrite and ammonia test will not be conducted."	By making this change, the verbiage will be aligned with the verbiage used in lines 101-103 and aligned with the proposed verbiage for lines 111-114.

Appendix 3: Sterile Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
177-213	177-213	**"pH** To 100 ml add 0.3 ml of saturated potassium chloride solution. pH 5.0-7.0 (0631). **Chlorides, sulfates and calcium** Add 50 ml to each of three test tubes, to the first	PDA suggests removing all tests with the exception of oxidizable substances and conductivity.	**Oxidizable substances** Boil 100 ml with 10 ml of dilute sulphuric acid, add 0.10 ml of potassium permanganate (0.02 mol/L) VS and continue to boil for 10 minutes; the pink colour does not	Sterile Water for injection (SWFI) is made from Water for Injection (WFI) and thus should meet all these requirements. The oxidizable substances and conductivity tests will provide assessment

Appendix 3: Sterile Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		tube add 5 drops of nitric acid and 1 ml of silver nitrate TS; to the second tube add 5 ml of barium chloride TS; and to the third tube add 2 ml of ammonium oxalate TS; no opalescence is produced in any one of the tubes. **Nitrate** To 5 ml in a test tube, cooled in an ice bath, add 0.4 ml of 10 % potassium chloride solution and 0.1 ml of 0.1 % diphenylamine solution in sulfuric acid and shake well. Add 5 ml of sulfuric acid dropwise and allow to stand in a water bath at 50°C for 15 minutes. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of potassium nitrate in water to produce a solution containing 1 µg of NO_3 per ml. To 0.3 ml add 4.7 ml of nitrate-free water, repeat the operation using the solution instead of the substance being		disappear completely. **Conductivity** Complies with the test for water conductivity (0681).	for potential impurities that may be introduces due to the SWFI packaging. The other chemical tests are covered either through the WFI test requirements or through the conductivity tests. This update in language will harmonize the recommendations with those found in current industry and regulatory documents.

Appendix 3: Sterile Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		examined) (0.000 006%). **Nitrite** To 10 ml in a Nessler cylinder add 1 ml of sulfanilic amide solution (dissolve 1 g in 100 ml of dilute hydrochloric acid) and 1 ml of 0.1% N-naphthylethylenediamine dihydrochloride solution and shake well. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of sodium nitrite in water to produce a solution containing 1 µg of NO_2 per ml. To 0.2 ml add 9.8 ml of nitrite-free water, repeat the operation using the solution instead of the substance being examined) (0.000 002%). **Ammonia** To 50 ml add 2 ml of alkaline mercuric potassium iodide TS and allow to stand for 15 minutes. Any colour produced is not more intense than that of a reference prepared by mixing 1.0ml of ammonium chloride solution			

Appendix 3: Sterile Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		(dissolve 31.5 mg of ammonium chloride CRS in ammonia-free distilled water to produce 1000 ml) with 48 ml of ammonia-free distilled water and 2 ml of alkaline mercuricpotassium iodide TS (0.000 02%). **Carbon dioxide** Mix 25 ml with 25 ml of calcium hydroxide TS in a 50 ml stoppered cylinder, shake, allow to stand; no opalescence is produced within 1 hour. **Oxidizable substances** Boil 100 ml with 10 ml of dilute sulphuric acid, add 0.10 ml of potassium permanganate (0.02 mol/L) VS and continue to boil for 10 minutes; the pink colour does not disappear completely. **Conductivity** Complies with the test for water conductivity (0681). **Non-volatile substances**			

Appendix 3: Sterile Water for Injection					
Line Numbers-Original	**Line Numbers-Translation**	**Referenced Text**	**Comment**	**Proposed Text**	**Rationale**
		Evaporate 100 ml in an evaporating dish previously dried at 105℃ to constant weight, to dryness on a water bath, and dry at 105℃ to constant weight, the residue is not more than 1 mg. **Heavy metals** To 100 ml add 19 ml of water, evaporate to 20 ml, cool. Add 2 ml of acetate BS (pH 3.5) and a quantity of water to 25 ml. Add 2 ml of thioacetamide TS, mix and allow to stand for 2 minutes. Any colour produced is not more intense than that of the solution prepared in the same manner using 1.0 ml of lead standard solution mixed with 19 ml of water (0.00001%).”			

0261 制药用水

制药用水用于药物生产过程和药物制剂的制备。

本版药典中所指的制药用水，因其使用的范围不同而分为饮用水、纯化水、注射用水和灭菌注射用水。一般应根据各生产工序或使用目的与要求选用适宜的制药用水。药品生产企业应确保制药用水的质量符合预期用途的要求。

纯化水、注射用水和灭菌注射用水的原水通常为饮用水。

制药用水系统的设计、材质选择、制备过程、储存、分配、使用和维护等均应符合药品生产质量管理规范的要求。

制药用水系统应经过确认/验证，并建立日常监控、检测和报告制度，有完善的原始记录备查。

制药用水系统应定期进行清洗与消毒，消毒可以采用热处理或化学处理等方法。采用的清洗与消毒方法，以及化学处理后清洗剂与消毒剂的去除应经过确认/验证。

饮用水 为天然水经净化处理所得，其质量应符合现行中华人民共和国国家标准《生活饮用水卫生标准》。

饮用水可作为药材净制时的漂洗、制药用具的粗洗用水，一般也可以作为饮片的提取溶剂。

纯化水 为饮用水经蒸馏法、离子交换法、反渗透法或其它适宜的方法制备所得，其质量应符合本通则附 1 纯化水的规定。不含任何附加剂。

纯化水中可能存在的元素杂质是药品生产中元素杂质的潜在来源之一，必要时，可参考 ICH 元素杂质指导原则（Q3D）来评估和控制药品中元素杂质。

纯化水在制备、储存和分配过程中，应采取适当的措施确保微生物得到充分控制和监测。采用本通则“微生物监测”项下方法进行微生物监测。具体可参考制药用水微生物监测和控制指导原则（指导原则 9209）。

纯化水可作为配制普通药物制剂用的溶剂，中药注射剂、眼用制剂等无菌制剂所用饮片的提取溶剂，口服、外用制剂配制用溶剂或稀释剂，非无菌制剂用器具的精洗用水，非无菌制剂所用饮片的提取溶剂等。纯化水不得用于注射剂的配制和稀释。

注射用水 为纯化水经蒸馏所得，其质量应符合本通则附 2 注射用水的规定；

或为通过一个等同于蒸馏的纯化工艺制备所得，其制备工艺应符合监管部门有关程序要求，其质量应符合有关规定。不含任何附加剂。

注射用水中可能存在的元素杂质是药品生产中元素杂质的潜在来源之一，必要时，可参考 ICH 元素杂质指导原则（Q3D）来评估和控制药品中元素杂质。

注射用水在制备、储存和分配过程中，应采取适当的措施确保微生物/细菌内毒素得到充分控制和监测。采用本通则“微生物监测”项下方法进行微生物监测。具体可参考制药用水微生物监测和控制指导原则（指导原则 9209）。

注射用水的储存方式和储存期限应经过确认/验证，确保水质符合质量要求。

注射用水可作为配制注射剂、眼用制剂等的溶剂或稀释剂，以及容器的精洗等。

灭菌注射用水 为注射用水按照注射剂生产工艺制备所得，其质量应符合附 3 灭菌注射用水的规定。不含任何附加剂。

主要用于注射用无菌药品粉末的溶剂或注射剂的稀释剂。

灭菌注射用水灌装规格应与临床需要相适应，避免大规格、多次使用造成的污染。

微生物监测 采用下列方法，或经充分验证的等同或更优方法，进行微生物监测。

纯化水取样不少于 1ml，注射用水取样不少于 100ml，经薄膜过滤法处理，采用 R2A 琼脂培养基，30-35℃培养不少于 5 天，依法检查（通则 1105）。可根据监测数据适当调整检验量，以能够监测到微生物数量变化。

纯化水微生物限度标准为不大于 100cfu/ml，注射用水微生物限度标准为不大于 10cfu/100ml。应在满足限度标准的前提下，设置适当的警戒限度和纠偏限度，以监测不良趋势。如用于高风险制剂或无菌工艺，可根据需要设定更严格的警戒限度和纠偏限度。

R2A 琼脂培养基处方及制备：酵母浸出粉 0.5g、蛋白胨 0.5g、酶蛋白水解物 0.5g、葡萄糖 0.5g、可溶性淀粉 0.5g、磷酸氢二钾 0.3g、无水硫酸镁 0.024g、丙酮酸钠 0.3g、琼脂 15g、纯化水 1000ml。除葡萄糖、琼脂外，取上述成分，混合，微温溶解，调节 pH 值使加热后在 25℃的 pH 值为 7.2±0.2 ，加入琼脂，加热溶化后，再加入葡萄糖，摇匀，分装，灭菌。

R2A 琼脂培养基适用性检查试验 照非无菌产品微生物限度检查：微生物计

数法（通则 1105）中“计数培养基适用性检查”的胰酪大豆胨培养基的适用性检查方法进行，试验菌株为铜绿假单胞菌和枯草芽孢杆菌。应符合规定。

附 1：纯化水

性状 本品为无色的澄清液体。

总有机碳 不得过 0.50 mg/L（通则 0682）。

易氧化物 取本品 100ml，加稀硫酸 10ml，煮沸后，加高锰酸钾滴定液（0.02mol/L）0.10ml，再煮沸 10 分钟，粉红色不得完全消失。

以上总有机碳和易氧化物两项可选做一项。

电导率 应符合规定（通则 0681）。

如按制药用水电导率测定法（通则 0681）中注射用水测定法测定电导率，电导率符合规定，则不再进行酸碱度和重金属检查。

酸碱度 取本品 10ml，加甲基红指示液 2 滴，不得显红色；另取 10ml，加溴麝香草酚蓝指示液 5 滴，不得显蓝色。

重金属 取本品 100ml，加水 19ml，蒸发至 20ml，放冷，加醋酸盐缓冲液（pH 3.5）2ml 与水适量使成 25ml，加硫代乙酰胺试液 2ml，摇匀，放置 2 分钟，与标准铅溶液 1.0ml 加水 19ml 用同一方法处理后的颜色比较，不得更深（0.000 01%）。

如按制药用水电导率测定法（通则 0681）中注射用水测定法测定电导率，电导率按判定法第一步判定符合规定，则不再进行硝酸盐、亚硝酸盐和氨检查。

硝酸盐 取本品 5ml 置试管中，于冰浴中冷却，加 10%氯化钾溶液 0.4ml 与 0.1%二苯胺硫酸溶液 0.1ml，摇匀，缓缓滴加硫酸 5ml，摇匀，将试管于 50℃水浴中放置 15 分钟，溶液产生的蓝色与标准硝酸盐溶液［取硝酸钾 0.163g，加水溶解并稀释至 100ml，摇匀，精密量取 1ml，加水稀释成 100ml，再精密量取 10ml，加水稀释成 100ml，摇匀，即得（每 1ml 相当于 1μg NO_3）］0.3ml，加无硝酸盐的水 4.7ml，用同一方法处理后的颜色比较，不得更深（0.000 006%）。

亚硝酸盐 取本品 10ml，置纳氏管中，加对氨基苯磺酰胺的稀盐酸溶液（1→100）1ml 与盐酸萘乙二胺溶液（0.1→100）1ml，产生的粉红色，与标准亚硝酸盐溶液［取亚硝酸钠 0.750g（按干燥品计算），加水溶解，稀释至 100ml，摇匀，精密量取 1ml，加水稀释成 100ml，摇匀，再精密量取 1ml，加水稀释成 50ml，摇匀，即得（每 1ml 相当于 1μg NO_2）］0.2ml，加无亚硝酸盐的水 9.8ml，用同一方法处理后的颜色比较，不得更深（0. 000 002% ）。

氨 取本品 50ml，加碱性碘化汞钾试液 2ml，放置 15 分钟；如显色，与氯化铵溶液（取氯化铵 31.5mg，加无氨水适量使溶解并稀释成 1000ml）1.5ml，加无氨水 48ml 与碱性碘化汞钾试液 2ml 制成的对照液比较，不得更深（0.000 03%）。

微生物监测 按照制药用水（通则 0261）中微生物监测的要求进行。

注：① 本品密闭保存。② 基于风险评估，必要时，可测定本品的不挥发物（可按下述测定方法测定）。

取本品 100ml，置 105℃恒重的蒸发皿中，在水浴上蒸干，并在 105℃干燥至恒重，遗留残渣不得过 1mg。

附 2：注射用水

性状 本品为无色的澄明液体。

总有机碳 不得过 0.50 mg/L（通则 0682）。

电导率 应符合规定（通则 0681）。

如按制药用水电导率测定法（通则 0681）中注射用水测定法测定电导率，电导率按判定法第一步判定符合规定，则不再进行硝酸盐、亚硝酸盐和氨检查。

硝酸盐 取本品 5ml 置试管中，于冰浴中冷却，加 10%氯化钾溶液 0.4ml 与 0.1%二苯胺硫酸溶液 0.1ml，摇匀，缓缓滴加硫酸 5ml，摇匀，将试管于 50℃水浴中放置 15 分钟，溶液产生的蓝色与标准硝酸盐溶液［取硝酸钾 0.163g，加水溶解并稀释至 100ml，摇匀，精密量取 1ml，加水稀释成 100ml，再精密量取 10ml，加水稀释成 100ml，摇匀，即得（每 1ml 相当于 1μgNO_3）］0.3ml，加无硝酸盐的水 4.7ml，用同一方法处理后的颜色比较，不得更深（0.000 006%）。

亚硝酸盐 取本品 10ml，置纳氏管中，加对氨基苯磺酰胺的稀盐酸溶液（1→100）1ml 与盐酸萘乙二胺溶液（0.1→100）1ml，产生的粉红色，与标准亚硝酸盐溶液［取亚硝酸钠 0.750g（按干燥品计算），加水溶解，稀释至 100ml，摇匀，精密量取 1ml，加水稀释成 100ml，摇匀，再精密量取 1ml，加水稀释成 50ml，摇匀，即得（每 1ml 相当于 1μgNO_2）］0.2ml，加无亚硝酸盐的水 9.8ml，用同一方法处理后的颜色比较，不得更深（0. 000 002% ）。

氨 取本品 50ml，加碱性碘化汞钾试液 2ml，放置 15 分钟；如显色，与氯化铵溶液（取氯化铵 31.5mg，加无氨水适量使溶解并稀释成 1000ml）1.0ml，加无氨水 48ml 与碱性碘化汞钾试液 2ml 制成的对照液比较，不得更深（0.000 02%）。

细菌内毒素 取本品，依法检查（通则 1143），每 1ml 中含内毒素的量应小

于 0.25EU。

微生物监测 按照制药用水（通则 0261）中微生物监测的要求进行。

注：① 本品密闭保存。② 基于风险评估，必要时，可测定本品的不挥发物（可按下述测定方法测定）。

取本品 100ml，置 105℃恒重的蒸发皿中，在水浴上蒸干，并在 105℃干燥至恒重，遗留残渣不得过 1mg。

附 3：灭菌注射用水

性状 本品为无色的澄明液体；无臭。

pH 值 取本品 100ml,加饱和氯化钾溶液 0.3ml,依法测定(通则 0631),pH 值应为 5.0～7.0。

氯化物、硫酸盐与钙盐 取本品,分置三支试管中,每管各 50ml,第一管中加硝酸 5 滴与硝酸银试液 1ml,第二管中加氯化钡试液 5ml,第三管中加草酸铵试液 2ml,均不得发生浑浊。

硝酸盐 取本品 5ml 置试管中，于冰浴中冷却，加 10%氯化钾溶液 0.4ml 与 0.1%二苯胺硫酸溶液 0.1ml，摇匀，缓缓滴加硫酸 5ml，摇匀，将试管于 50℃水浴中放置 15 分钟，溶液产生的蓝色与标准硝酸盐溶液［取硝酸钾 0.163g，加水溶解并稀释至 100ml,摇匀,精密量取 1ml,加水稀释成 100ml,再精密量取 10ml，加水稀释成 100ml，摇匀，即得（每 1ml 相当于 1μgNO_3）］0.3ml，加无硝酸盐的水 4.7ml，用同一方法处理后的颜色比较，不得更深（0.000 006%）。

亚硝酸盐 取本品 10ml，置纳氏管中，加对氨基苯磺酰胺的稀盐酸溶液（1→100）1ml 与盐酸萘乙二胺溶液（0.1→100）1ml，产生的粉红色，与标准亚硝酸盐溶液［取亚硝酸钠 0.750g（按干燥品计算），加水溶解，稀释至 100ml，摇匀，精密量取 1ml，加水稀释成 100ml，摇匀，再精密量取 1ml，加水稀释成 50ml，摇匀，即得（每 1ml 相当于 1μgNO_2）］0.2ml，加无亚硝酸盐的水 9.8ml，用同一方法处理后的颜色比较，不得更深（0.000 002%）。

氨 取本品 50ml，加碱性碘化汞钾试液 2ml，放置 15 分钟；如显色，与氯化铵溶液（取氯化铵 31.5mg，加无氨水适量使溶解并稀释成 1000ml）1.0ml，加无氨水 48ml 与碱性碘化汞钾试液 2ml 制成的对照液比较，不得更深（0.000 02%）。

二氧化碳 取本品 25ml，置 50ml 具塞量筒中，加氢氧化钙试液 25ml，密塞振摇，放置，1 小时内不得发生浑浊。

易氧化物 取本品 100ml,加稀硫酸 10ml,煮沸后,加高锰酸钾滴定液(0.02mol/L)0.10ml，再煮沸 10 分钟，粉红色不得完全消失。

电导率 应符合规定（通则 0681）。

不挥发物 取本品 100ml，置 105℃恒重的蒸发皿中，在水浴上蒸干，并在 105℃干燥至恒重，遗留残渣不得过 1mg。

重金属 取本品 100ml，加水 19ml，蒸发至 20ml，放冷，加醋酸盐缓冲液（pH 3.5）2ml 与水适量使成 25ml，加硫代乙酰胺试液 2ml，摇匀，放置 2 分钟，与标准铅溶液 1.0ml 加水 19ml 用同一方法处理后的颜色比较,不得更深(0.000 01%)。

细菌内毒素 取本品，依法检查（通则 1143），每 1ml 中含内毒素的量应小于 0.25EU。

其他 应符合注射剂（通则 0102）项下有关的各项规定。

注：①本品为溶剂、冲洗剂。②本品密闭保存。

起草单位：北京市药品检验研究院、中国食品药品检定研究院、中国医药设备工程协会

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0261 Water for Pharmaceutical Purposes

Water for pharmaceutical purposes is used in the production process and the preparation of medicines in pharmaceutical industry.

In this edition of the Pharmacopoeia of the People's Republic of China, water for pharmaceutical purposes includes drinking water, purified water, water for injection and sterile water for injection according to the purposes for which it is to be used.

Water for pharmaceutical purposes should be suitably selected according to manufacturing processes or usage purposes and requirements. The quality of water for pharmaceutical purposes should comply with the requirements of expected usage.

The source water used for purified water, water for injection and sterile water for injection is usually drinking water.

The design, material selection, preparation process, storage, distribution, use and maintenance of the system for water for pharmaceutical purposes shall comply with the requirements of the Good Manufacturing Practice.

The system for water for pharmaceutical purposes should be qualified/validated, systems of daily monitoring, analysis and repoport should be established, and complete original data should be kept for reference.

The system for water preparation should be cleaned and sterilized periodically. Sterilization could be conducted using thermal or chemical processes.

The cleaning and disinfection methods used and the removal of cleaning agents and disinfectants after chemical treatments should be qualified/validated.

Drinking water Drinking water is prepared by purification of natural water and its quality should comply with the current National Standard of the People's Republic of China (“Hygienic Standard of Living Drinking Water”).

Drinking water may be used for washing crude drugs before purification, for preliminarily washing pharmaceutical appliances and may also be used as the solvent for extraction of medicine material crude slices.

Purified water Purified water is prepared from drinking water by distillation, ion exchange, reverse osmosis or by means of any other appropriate methods. Its quality should comply with the requirements of the Annex 1 of Purified water in this General Chapter. It contains no additives.

Elemental impurities that may be present in purified water are one of the potential sources of elemental impurities in pharmaceutical manufacturing and, where necessary, can be assessed and controlled in pharmaceutical products by reference to ICH Guideline for Elemental Impurities (Q3D).

Purified water is prepared, stored and distributed with appropriate measures to ensure adequate microbial control and monitoring. Microbial monitoring is performed with the method under “Microbial monitoring” in this General Chapter. For details, please refer to the Guidelines for Microbiological Monitoring and Control of Water for Pharmaceutical Purposes (Guideline 9209).

Purified water may be used as the solvent for preparation of ordinary pharmaceutical

preparations, or as the solvent for extraction of medicine material crude slices for preparation of sterile preparations such as injections or eye drops of traditional Chinese drugs, or as the solvent or diluent for preparation of oral preparations or preparations for external use, or as the water for precisely washing appliances for nonsterile preparations, or as the solvent for extraction of medicine material crude slices for nonsterile preparations. Purified water should not be used for preparation of injections or as their diluent.

Water for injection Water for injection is water prepared by distillation of purified water, and its quality should comply with the requirements of the Annex 2 of Water for injection in this General Chapter; or water for injection is prepared through a purification process equivalent to distillation, and its preparation process should meet the requirements of relevant procedures of regulatory authorities, and its quality should meet relevant provisions. It contains no additives.

Elemental impurities that may be present in water for injection are one of the potential sources of elemental impurities in pharmaceutical manufacturing and, where necessary, can be assessed and controlled in pharmaceutical products by reference to ICH Guideline for Elemental Impurities (Q3D).

Water for injection is prepared, stored and distributed with appropriate measures to ensure adequate microorganism/bacterial endotoxin control and monitoring. Microbial monitoring is performed with the method under “Microbial monitoring” in this General Chapter. For details, please refer to the Guidelines for Microbiological Monitoring and Control of Water for Pharmaceutical Purposes (Guideline 9209).

The storage condition and shelf life of water for injection should be qualified/validated to ensure that the water quality meets the quality requirements. Water for injection is used as the solvent or diluent for preparation of injections, ophthalmic preparations, etc., and as the water for fine washing of containers.

Sterile water for injection Sterile water for injection is prepared from water for injection according to technological conditions under which injections are prepared, and its quality should comply with the requirements of Annex 3 of Sterile water for injection in this General Chapter. It contains no additives.

It is mainly used as the solvent for sterile powders for injection or as dilute for injections.

The specification of filling for Sterile water for injection should meet the clinical requirements. Contamination due to large volume or multi-use must be avoided.

Microbial monitoring Microbial monitoring is performed with the following method, or a fully validated equivalent or superior method.

Take no less than 1ml purified water or no less than 100ml water for injection, process with the membrane filtration method, culture with R2A agar medium at 30-35℃ for no less than 5 days, and carry out the test as described (1105). The test quantity may be adjusted appropriately based on monitoring data to enable detection of changes in the number of microorganisms.

The microbial limit of purified water shall be no more than 100 cfu/ml, and that of water for injection shall be more than 10 cfu/100ml. On the premise of meeting the limit standards, appropriate alert and action limits should be set to monitor adverse trends. Tighter alert and action limits may be imposed as needed for high-risk drug products or aseptic processes.

Prescription and preparation of R2A agar: yeast extract 0.5g, protease peptone 0.5g, casein hydrolysate 0.5g, glucose 0.5g, starch 0.5g, dipotassium hydrogen phosphate 0.3g, magnesium

sulfate, anhydrous 0.024g, sodium pyruvate 0.3g, agar 15g, purified water 1000ml. Mix the above ingredients in water except for glucose and agar, warming slightly until the substances are dissolved. Adjust the pH so that after heating it is 7.2 ± 0.2 at 25℃. Add agar, heat until melted and then add glucose, shake thoroughly, dispense and sterilize.

Suitability test for R2A agar Carry out the method described under growth promotion of soya bean casein digest agar in Growth Promotion of the Counting Media, Pseudomonas aeruginosa and Bacillus subtilis as test strain, complies with the microbiological examination of non-sterile products: microbial enumeration tests <1105>. Complies with the requirements.

Appendix 1: Purified water

Description A clear, colourless liquid, odourless.

Total organic carbon Not more than 0.50 mg per L <0682>.

Oxidizable substances Boil 100 ml with 10 ml of dilute sulphuric acid, add 0.10 ml of potassium permanganate (0.02 mol/L) VS and continue to boil for 10 minutes; the pink colour does not disappear completely.

Total organic carbon and Oxidizable substances may be used alternatively.

Conductivity Complies with the test for water conductivity (0681).

If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity meets the requirements, the pH value and heavy metal test will not be conducted.

Acidity or alkalinity To 10 ml add 2 drops of methyl red IS, no red colour is produced. To another 10 ml add 5 drops of bromothymol blue IS, no blue colour is produced.

Heavy metals To 100 ml add 19 ml of water, evaporate to 20 ml, cool. Add 2 ml of acetate BS (pH 3.5) and a quantity of water to 25 ml. Add 2 ml of thioacetamide TS, mix and allow to stand for 2 minutes. Any colour produced is not more intense than that of the solution prepared in the same manner using 1. 0 ml of lead standard solution mixed with 19 ml of water (0.00001%).

If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity is determined to meet the requirements according to the first step of determination method, nitrate, nitrite and ammonia test will not be conducted.

Nitrate To 5 ml in a test tube, cooled in an ice bath, add 0.4 ml of 10 % potassium chloride solution and 0.1 ml of 0.1 % diphenylamine solution in sulfuric acid and shake well. Add 5 ml of sulfuric acid dropwise and allow to stand in a water bath at 50℃ for 15 minutes. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of potassium nitrate in water to produce a solution containing 1 µg of NO_3 per ml. To 0.3 ml add 4.7 ml of nitrate-free water, repeat the operation using the solution instead of the substance being examined) (0.000 006%).

Nitrite To 10 ml in a Nessler cylinder add 1 ml of sulfanilic amide solution (dissolve 1 g in 100 ml of dilute hydrochloric acid) and 1 ml of 0.1% N-naphthylethylenediamine dihydrochloride solution and shake well. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of sodium nitrite in water to produce a solution containing 1 µg of NO_2 per ml. To 0.2 ml add 9.8 ml of nitrite-free water, repeat the operation using the solution

instead of the substance being examined) (0.000 002%).

Ammonia To 50 ml add 2 ml of alkaline mercuric potassium iodide TS and allow to stand for 15 minutes. Any colour produced is not more intense than that of a reference prepared by mixing 1.5 ml of ammonium chloride solution (dissolve 31.5 mg of ammonium chloride CRS in ammonia-free distilled water to produce 1000 ml) with 48 ml of ammonia-free distilled water and 2 ml of alkaline mercuricpotassium iodide TS (0.00003%).

Microbial monitoring Carry out in accordance with the requirements of microbial monitoring in Water for pharmaceutical purposes (0261).

Note: ① Preserve in well closed containers. ② Based on risk assessment, if necessary, the non-volatile substances of this product can be measured (which can be determined with the following method).

Evaporate 100 ml in an evaporating dish previously dried at 105℃ to constant weight, to dryness on a water bath, and dry at 105℃ to constant weight, the residue is not more than 1 mg.

Appendix 2: Water for injection

Description A clear, colourless liquid; odourless.

Total organic carbon Not more than 0.50 mg per L (0682).

Conductivity Complies with the test for water conductivity (0681).

If the conductivity is determined according to the procedure for water for injection in the Determination of Conductivity of Water for Pharmaceutical Use (0681), and the conductivity is determined to meet the requirements according to the first step of determination method, nitrate, nitrite and ammonia test will not be conducted.

Nitrate To 5 ml in a test tube, cooled in an ice bath, add 0.4 ml of 10 % potassium chloride solution and 0.1 ml of 0.1 % diphenylamine solution in sulfuric acid and shake well. Add 5 ml of sulfuric acid dropwise and allow to stand in a water bath at 50℃ for 15 minutes. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of potassium nitrate in water to produce a solution containing 1 μg of NO_3 per ml. To 0.3 ml add 4.7 ml of nitrate-free water, repeat the operation using the solution instead of the substance being examined) (0.000 006%).

Nitrite To 10 ml in a Nessler cylinder add 1 ml of sulfanilic amide solution (dissolve 1 g in 100 ml of dilute hydrochloric acid) and 1 ml of 0.1% N-naphthylethylenediamine dihydrochloride solution and shake well. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of sodium nitrite in water to produce a solution containing 1 μg of NO_2 per ml. To 0.2 ml add 9.8 ml of nitrite-free water, repeat the operation using the solution instead of the substance being examined) (0.000 002%).

Ammonia To 50 ml add 2 ml of alkaline mercuric potassium iodide TS and allow to stand for 15 minutes. Any colour produced is not more intense than that of a reference prepared by mixing 1.0ml of ammonium chloride solution (dissolve 31.5 mg of ammonium chloride CRS in ammonia-free distilled water to produce 1000 ml) with 48 ml of ammonia-free distilled water and 2 ml of alkaline mercuricpotassium iodide TS (0.00002%).

Bacterial endotoxins Carry on the test for bacterial endotoxins (1143): less than 0.25 EU per ml.

Microbial monitoring Carry out in accordance with the requirements of microbial monitoring

in Water for pharmaceutical purposes (0261).

Note: ① Preserve in well closed containers. ② Based on risk assessment, if necessary, the non-volatile substances of this product can be measured (which can be determined with the following method).

Evaporate 100 ml in an evaporating dish previously dried at 105℃ to constant weight, to dryness on a water bath, and dry at 105℃ to constant weight, the residue is not more than 1 mg.

Appendix 3: Sterile water for injection

Description A clear, colourless liquid; odourless.

pH To 100 ml add 0.3 ml of saturated potassium chloride solution. pH 5.0-7.0 (0631).

Chlorides, sulfates and calcium Add 50 ml to each of three test tubes, to the first tube add 5 drops of nitric acid and 1 ml of silver nitrate TS; to the second tube add 5 ml of barium chloride TS; and to the third tube add 2 ml of ammonium oxalate TS; no opalescence is produced in any one of the tubes.

Nitrate To 5 ml in a test tube, cooled in an ice bath, add 0.4 ml of 10 % potassium chloride solution and 0.1 ml of 0.1 % diphenylamine solution in sulfuric acid and shake well. Add 5 ml of sulfuric acid dropwise and allow to stand in a water bath at 50℃ for 15 minutes. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of potassium nitrate in water to produce a solution containing 1 μg of NO_3 per ml. To 0.3 ml add 4.7 ml of nitrate-free water, repeat the operation using the solution instead of the substance being examined) (0.000 006%).

Nitrite To 10 ml in a Nessler cylinder add 1 ml of sulfanilic amide solution (dissolve 1 g in 100 ml of dilute hydrochloric acid) and 1 ml of 0.1% N-naphthylethylenediamine dihydrochloride solution and shake well. Any colour produced is not more intense than that of the reference solution (Dissolve a quantity of sodium nitrite in water to produce a solution containing 1 μg of NO2 per ml. To 0.2 ml add 9.8 ml of nitrite-free water, repeat the operation using the solution instead of the substance being examined) (0.000 002%).

Ammonia To 50 ml add 2 ml of alkaline mercuric potassium iodide TS and allow to stand for 15 minutes. Any colour produced is not more intense than that of a reference prepared by mixing 1.0ml of ammonium chloride solution (dissolve 31.5 mg of ammonium chloride CRS in ammonia-free distilled water to produce 1000 ml) with 48 ml of ammonia-free distilled water and 2 ml of alkaline mercuricpotassium iodide TS (0.000 02%).

Carbon dioxide Mix 25 ml with 25 ml of calcium hydroxide TS in a 50 ml stoppered cylinder, shake, allow to stand; no opalescence is produced within 1 hour.

Oxidizable substances Boil 100 ml with 10 ml of dilute sulphuric acid, add 0.10 ml of potassium permanganate (0.02 mol/L) VS and continue to boil for 10 minutes; the pink colour does not disappear completely.

Conductivity Complies with the test for water conductivity (0681).

Non-volatile substances Evaporate 100 ml in an evaporating dish previously dried at 105℃ to constant weight, to dryness on a water bath, and dry at 105℃ to constant weight, the residue is not more than 1 mg.

Heavy metals To 100 ml add 19 ml of water, evaporate to 20 ml, cool. Add 2 ml of acetate BS (pH 3.5) and a quantity of water to 25 ml. Add 2 ml of thioacetamide TS, mix and allow to

stand for 2 minutes. Any colour produced is not more intense than that of the solution prepared in the same manner using 1.0 ml of lead standard solution mixed with 19 ml of water (0.00001%).

Bacterial endotoxins Carry on the test for bacterial endotoxins (1143): less than 0.25 EU per ml.

Other requirements Complies with the general requirements for injections (0102).

Note: ① This product is a solvent and rinsing agent. ② Preserve in well closed containers.

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