WHO良好的生产实践(GMP): 制药用水篇

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Annex 3

附件3

WHO Good Manufacturing Practices: water for pharmaceutical use

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1. Introduction介绍

1.1 Scope of the document文件范畴

The guidance contained in this document is intended to provide information about the available specifications for water for pharmaceutical use (WPU), guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms, and to provide guidance on the good manufacturing practice (GMP) regarding the design, installation and operation of pharmaceutical water systems. Although the focus of this document is on water for pharmaceutical applications, the guidelines may also be relevant to other industrial or specific uses where the specifications and practices can be applied.

本文件指南主要阐述制药用水(WPU)的现有规定，对特殊应用下如生产原料药（API）和制剂的水质要求给出指导，同时对制药用水系统的设计，安装和运行提供GMP指南。尽管本文档侧重于制药用水，其指导方针同样可适用于其他相关行业或特殊用途。

The GMP guidance for WPU contained in this document is intended to be supplementary to the general GMP guidelines for pharmaceutical products published by WHO (*WHO Expert Committee on Speci- fications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4).

本文档的制药用水（WPU）GMP指南是对WHO发表的制药产品GMP大纲的补充。（WHO专家委员会关于制剂的要求，报告第37篇，日内瓦，世界卫生组织，2003《WHO技术报告系列，第908号》附件4）

This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material.

本文档参考了相关规定，如药典和散装水的使用，生产，储存和分配工业指南。为避免误解，本文档未对这些材料进行复制。

Note: This document does not cover waters for administration to patients in their formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines. The guidance provided in this document can be used in whole or in part as appropriate to the application under consideration.

备注：本文档不涉及病人制剂用水的管理或药房配备处方药时的小剂量用水，本文档的规定可以全部或部分为这些应用提供参考。

Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorization

submitted to the national drug regulatory authority.
本文档与药典规定存在细微差异，生产商可根据国家药物管理局提供的相关销售权威选择相应的条款。

1.2 Background to water requirements and uses
水质要求和使用的背景

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.
水是药品生产，加工和配制中最普遍使用的物质，原料或起始原料。由于其极性和氢键，水具有独特的化学属性。水能够溶解，吸收或悬浮多种不同的物质。这些物质可能是污染物，或者本身含有有害物质，或者能够与所需产品产生反应，从而对健康造成危害。

Different grades of water quality are required depending on the route of administration of the pharmaceutical products. One source of guidance about different grades of water is the European Medicines Evaluation Agency (EMEA) *Note for guidance on quality of water for pharmaceutical use* (CPMP/QWP/158/01).
根据制药产品的管理方式的不同，对水质要求等级也不同。对水质等级区分可以参考欧洲药物评审委员会(EMEA) 的文件《制药用水水质指导原则(CPMP/QWP/158/01)》.

Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use. Control of the microbiological quality of WPU is a high priority. Some types of microorganism may proliferate in water treatment components and in the storage and distribution systems. It is very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation.
在生产,储存和分配工艺中，最主要的问题是对水质包括微生物和化学性能进行控制。跟其他的产品和工艺原料不同，根据需求从系统中取水，而不是使用前进行测试和取量。因而，保证需求的质量是非常重要的。此外，部分微生物测试需要一定的培养期，因此，很可能在用水之后才能测试结果。控制制药用水的微生物质量是首要问题，有些微生物可能在水处理部件和储存分配系统中滋生繁衍。所以很有必要进行常规消毒以减少微生物污染，采用相应的方式阻止微

生物繁衍。

1.3 Applicable guides

应用指南

In addition to the specific guidance provided in this document, the Bibliography lists some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

除了本文档列出的详细指南，参考书目中也列出了一些相关的刊物，对于规划、安装和使用制药用水系统可以提供更详细的背景资料。

2. General requirements for pharmaceutical water systems

制药用水系统的基本要求

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

制药用水的制备，储存和分配系统，需要进行设计、安装、调试、认证以及维护，以保证水质要求。系统不得在设计产能范围之外运行，水的生产、储存和分配应该遵循避免有害微生物、化学或物理（如灰尘）污染的原则。

The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for planned preventive maintenance tasks, they need not be approved after implementation.

对系统的使用包括安装、调试、认证和其他未计划的维护或修改工作，应当经过质量认证部门的批准。如果获批准后进行预防性维护任务，在执行之后不需要被认证。

Water sources and treated water should be monitored regularly for quality and for chemical, microbiological and, as appropriate, endo-toxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results and any actions taken should be maintained for an appropriate length of time.

应该定期对水源和处理水的水质和化学、微生物、内毒素污染成分进行监测。 同时要对水净化、储存和分配系统的性能进行监控。要对监测结果以及因此采取的行动进行记录并备案一段时间。

Where chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed to ensure that the sanitizing agent has been effectively removed.

如果微生物控制系统采用化学消毒的水系统，应当执行认证规程，保证有效清除其中的消毒剂。

3. Water quality specifications
水质规定

3.1 General
总则

The following requirements concern water processed, stored and distributed in bulk form. They do not cover the specification of waters formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form waters.

下列要求是关于散装水的加工、储存和分配，不涉及病人管理所需的配方水。药典中对散装水和剂型用水都有规定。

Pharmacopoeial requirements for WPU are described in national and international pharmacopoeias and limits for various contaminants are given. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

对制药用水的药典要求，国内和国际药典都有规定，同时可以查到对各种污染物质的限制。计划进入国际市场的企业应当制定相关的条款，以符合各种相关药典的严格规定。

3.2 Drinking-water
饮用水

Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

饮用水的供应，管道系统应该不含任何可能导致产品污染的缺陷，采用持续正压进行供给。

Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes softening, removal of specific ions, particle reduction and antimicrobial treatment. It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It is also common for public water-supply organizations to conduct tests and guarantee that the drinking-water delivered is of potable quality.

一般饮用水不需要处理，而天然水资源或水库资源，则需要简单处理。天然资源一般包括泉水，井水，河流，湖泊和大海。对这类水资源处理主要是保证人类消耗（饮用），典型的处理方式包括软化，去离子，减少杂质以及抗微生物处理。有些提供饮用水的公用水供应可能来源于以上提到的几种不同的天然资源，所以，公用水供应机构需要对饮用水质进行测试，保证提供的

饮用水达到符合饮用水质量标准。

Drinking-water quality is covered by the WHO drinking-water guidelines, standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

WHO饮用水指南中规定了饮用水的水质，按照国际标准化组织（ISO）和其他地区和国家机构的标准进行了规定。饮用水应该符合主管当局制定的相关条款规定。

If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site to confirm that the quality meets the standards required for potable water.

如果饮用水直接用于制药的某个环节，或者用作制备高质量药用水的进水，则应该在使用点定期进行测试，以保证水质符合饮用水标准。

3.3 Purified water

纯化水

Purified water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

纯化水（PW）原水进水的最低水质要求是饮用水源，应当符合药典化学和微生物纯度的规定，同时要防止再污染和微生物繁衍。

3.4 Highly purified water

高纯水

Highly purified water (HPW) should be prepared from potable water as a minimum-quality feed-water. HPW is a unique specification for water found only in the *European Pharmacopoeia*. This grade of water must meet the same quality standard as water for injections (WFI) including the limit for endotoxins, but the water-treatment methods are not considered to be as reliable as distillation. HPW may be prepared by combinations of methods such as reverse osmosis, ultrafiltration and deionization.

高纯水（HPW）的原水进水的最低水质要求为饮用水。只有在欧洲药典中才有对高纯水的规定。该等级的水必须达到注射用水（WFI）的水质标准，包括对内毒素的限制，但是高纯水的水处理方法不如蒸馏可靠。可以采用几种方式相结合制备高纯水，如：反渗透，超滤和去离子。

3.5 Water for injections

注射用水

Water for injections (WFI) should be prepared from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

注射用水（WFI）原水进水的最低水质要求为饮用水. 注射用水不是无菌水，也不是最终的剂型，而是中间产品，注射用水符合药典规定的制药用水的最高水质。

Certain pharmacopoeias place constraints upon the permitted purifi-cation techniques as part of the specification of the WFI. *The International Pharmacopoeia* and *The European Pharmacopoeia*, for example, allow only distillation as the final purification step.

某些药典对纯化技术加作限制条件，作为注射用水的要求。例如，国际药典和欧洲药典，规定纯化的最后一步为蒸馏。

3.6 Other grades of water

其他水

When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

当特定工艺要求特殊的非药典级别水时，需要进行特别说明，同时必须满足制药用水药典要求中对这一剂型或工艺步骤的要求。

4. Application of specific waters to processes and dosage forms

水在工艺和剂型中的应用

Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.
产品许可权威机构对使用特定等级的制药用水用于不同的剂型和生产步骤清洗、配液、合成、制备、或配方等进行了规定。

The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.
用水等级取决于中间体和最后成品的特性和用途,以及用水的生产工艺阶段.

HPW can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for WFI.
高纯水可以用来制备对水质要求比较高(如微生物和内毒素含量很低)的产品, 但是工艺阶段或产品要求对于制备方式的限制没有一些药典文章对注射用水的规定那么明确.

WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI should also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.
注射用水用于注射产品制剂, 一般用于注射用(肠胃外给药)物质或制剂使用前的溶解或稀释, 或用于注射液制剂的无菌水.一般与注射类产品接触的设备和部件的清洗的最后阶段也一般使用注射用水冲，同时，后续工艺如果没有热清洗或化学清洗，一般也采用注射用水作为的最后一级清洗。

When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it should conform with the specification for WFI when condensed.
在制备注射类产品的最后容器或设备中，如果存在与注射产品接触的蒸汽，那么蒸汽在凝结之后也需要符合蒸馏水水质。

5. Water purification methods
水净化方式

5.1 General considerations
总则

The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI (refer to section 3.5).
大纲(如药典)制药用水的规定中对水的净化方式的要求，没有像注射用水制备方式那样严格界定（参考章节3.5）

The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method:
水净化的方法或净化步骤的顺序的选择，必须跟应用相适应。选择水处理方式，应当考虑以下一些因素

— the water quality specification;
水质要求
— the yield or efficiency of the purification system;
净化系统的产量或效率
— feed-water quality and the variation over time (seasonal changes);
进水水质和时间变化
— the reliability and robustness of the water-treatment equipment in operation;
水处理设备运行期间的可靠性和稳定性
— the availability of water-treatment equipment on the market;
水处理设备市场的供货能力
— the ability to adequately support and maintain the water purification equipment; and
对水处理设备能够提供充足的支持和维护，以及
—the operation costs.
运行成本

The specifications for water purification equipment, storage and distribution systems should take into account the following:
水处理设备、储存和分配系统的规格应当考虑以下一些因素：

— the risk of contamination from leachates from contact materials;
接触材料的沥出物可能造成的污染
— the adverse impact of adsorptive contact materials;

吸附型接触材料的负面影响

— hygienic or sanitary design, where required;
规定要求的卫生设计

— corrosion resistance;
抗腐蚀能力

— freedom from leakage;
无渗漏

— configuration to avoid proliferation of microbiological organisms;
防止微生物滋生的配置

— tolerance to cleaning and sanitizing agents (thermal and chemical);
对清洗和消毒剂的兼容能力（热力和化学方面）

— the system capacity and output requirements; and
系统容量和输出要求；以及

— the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.
系统是否能够对所有必要仪表，测试和取样点的相关重要质量参数进行监控，。

The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:
水净化设备、储存和分配系统的设计、配置和布局，需要考虑下列物理因素：

— the space available for the installation;
安装所需的空间

— structural loadings on buildings;
建筑的结构负荷

— the provision of adequate access for maintenance; and
维护所需的足够通道的规定

— the ability to safely handle regeneration and sanitization chemicals.
能够安全处理再生和消毒化学品的能力

5.2 Production of drinking-water

饮用水的制备

Drinking-water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce potable drinking-water from a specific raw water source.
饮用水取自原水水源如井，河流或水库。对于如何处理原水，使其达到饮用水标准，没有特定

的方法。

Typical processes employed at a user plant or by a water supply authority include:
用户或水供应机构主要采用下列工艺：

— filtration;
过滤

— softening;
软化

— disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
杀菌或消毒（例如：加氯）

— iron (ferrous) removal;
去铁离子

— precipitation; and
沉淀

— reduction of specific inorganic/organic materials.
降低特定无机/有机物质

The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking-water quality changes significantly, the direct use of this water as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented.
饮用水水质应当进行常规监测。如果原水水源、处理技术或系统配置有任何变化，则应该另作测试。如果饮用水水质变化显著，而此水又是用作制药用水或下一步处理阶段地进水，则应当重新评审并对评审结果备案。

Where drinking-water is derived from an “in-house” system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or its operation should not be made until a review has been completed and the change approved by the QA department.
如果饮用水从室内系统提供，用作处理的原水，应当对水处理的步骤以及系统的配置进行备案。若有更改，则需重新评审并得到质量认证部门的认同之后方可开始运行。

Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, its use should ensure a turnover

of the stored water sufficient to prevent stagnation.
如果用户自身储存和分配饮用水，在使用储存系统前必须保证能够不降低水质。储存之后，应当采用特定方式定期进行测试。在储水之处，应当保证储水能够流动以防止出现死水。
The drinking-water system is usually considered to be an “indirect impact system” and does not need to be qualified.
饮用水系统一般被认为是“间接影响系统”，不需要进行认证。
Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.
购买的散装饮用水通过罐运输到使用者手中，则存在其特殊的问题，与通过管道输送的风险有所不同。供应商评估、授权认证，包括对运输车辆的认可确认，应当与选用其他任何起始原料类似的认证。
Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained, or flushed, and sanitized.
用于生产饮用水的设备和系统，应当具备排污能力和消毒能力。储罐应当是密闭的，装有合适的保护性排气口，能够进行视觉检查，同时具备排污能力和消毒能力。分配管路必须能够排污，冲洗以及消毒。
Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back-flushing, chemical or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be maintained with continuous water flow to inhibit microbial growth.
对于砂滤、碳滤、软化器，需要采用特殊手段控制微生物污染。一旦系统受到微生物感染，污染能够迅速形成生物膜并在整个系统当中蔓延开来。防止污染的方式有多种，如反洗，化学或热水消毒，频繁再生等方式。此外，所有的水处理部件需要保持不间断水流量，以防止微生物滋生。

5.3 Production of purified water
纯水制备

There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate

qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. Distillation can also be used.
药典当中未对纯水制备方式进行特殊规定，因此任何合适的经认证的纯化技术或者技术顺序均可用来制备纯水。目前主要采用离子交换、超滤和/或反渗透工艺。此外，蒸馏技术也是主要手段之一。

The following should be considered when configuring a water purification system:
配备一套纯水系统时，应当考虑到下列因素：

— the feed-water quality and its variation over seasons;
进水水质以及季节变化导致的水质变化；

— the required water-quality specification;
要求达到的水质参数

— the sequence of purification stages required;
所需的纯化阶段顺序

— the energy consumption;
能量消耗

— the extent of pretreatment required to protect the final purification steps;
为保护最终纯化步骤所需的预处理范围

— performance optimization, including yield and efficiency of unit treatment-process steps;
性能优化，包括产出和设备处理工艺步骤的效率

— appropriately located sampling points designed in such a way as to avoid potential contamination; and
设计合理的取样点，以防止潜在的污染，以及

— unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.
设备工艺步骤采用合适的仪表，可对流量、压力、温度、电导，PH以及有机碳总量等参数进行测量。

Ambient-temperature PW systems are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbiological control and sanitization.
常温下，纯水系统极容易受到微生物感染，尤其是无需用水或用水需求很低时，设备长期处于静止状态。所以，就必须考虑微生物控制和消毒装置。

The following techniques should be considered:
应当考虑下列技术：

— maintenance of flow through water-purification equipment at all times;
始终保持纯水设备流量
— control of temperature in the system by pipeline heat exchange or plant-room cooling to reduce the risk of microbial growth (guidance value <25 °C);
通过管道中热交换器或厂房冷却来控制系统的温度， 从而降低微生物生长的风险（建议值<25 °C）
— provision of ultraviolet disinfection;
采用紫外线消毒装置
— selection of water-treatment components that can be thermally sanitized; and/or
选择能够进行热水消毒的水处理部件；以及/或
— application of chemical sanitization (including agents such as ozone).
采用化学消毒（包括臭氧等介质）

5.4 Production of highly purified water

高纯水制备

There are no prescribed methods for the production of HPW in any major pharmacopoeia, including the *European Pharmacopoeia*. Any appropriate qualified purification technique or sequence of techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used.
The guidance provided in section 5.3 for PW is equally applicable to HPW.
主要药典一般都没有对高纯水的制备方式进行规定，包括欧洲药典也不例外。因此任何合适的经认证的纯化技术或者技术顺序均可用来制备高纯水。目前采用的方式主要有离子交换、超滤和/或反渗透等方式。
章节5.3中提到的制备纯水的方式同样适用于高纯水制备。

5.5 Production of water for injections

注射用水制备

The pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. Distillation is the preferred technique; it is considered a more robust technique based on phase change, and in some cases, high temperature operation of the process equipment.
药典中对蒸馏水的生产的最后净化阶段做了规定或限制。蒸馏是优选技术，根据各个阶段的变化，蒸馏是其中最稳定的技术，有时候工艺设备可以在高温条件下运行。
The following should be considered when designing a water purification system:
设计水净化系统时，应当考虑到下列因素：

— the feed-water quality;
进水水质

— the required water quality specification;
要求达到的水质参数

— the optimum generator size to avoid over-frequent start/stop cycling;
最佳的产量，防止过频启动或停止循环。

— blow-down and dump functions; and
吹扫和排放功能

— cool-down venting to avoid contamination ingress.
冷却通风防止外界污染（是不是防止冷凝水？）

6. Water purification, storage and distribution systems
水净化、储存和分配系统

This section applies to WPU systems for PW, HPW and WFI. The water storage and distribution should work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment.
本章节针对纯水、高纯水和注射用水详细介绍制药用水系统。水储存和分配应该和水纯化设备连接以保证水能够源源不断地输入到用水点，以确保水净化设备的最佳运行。

6.1 General
总则

The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.
储存和分配系统可以认为是整个系统的重要组成部分，所以设计应该和系统的水净化部件连成一体。

Once water has been purified using an appropriate method, it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following text describes the requirements for storage and distribution systems.
水经过一定的方法净化之后，可以直接使用，更多时候，净化水会被装入储罐，由后面的分配系统输送到用水点。下面将对储存和分配系统的要求进行阐述。

The storage and distribution system should be configured to prevent recontamination of the water after treatment and be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.
储存和分配系统的配置应该能够防止处理后的水再次受到污染，通过一系列的在线和离线监控，可以保证水保持在规定的水质范围内。

6.2 Materials that come into contact with systems for water for pharmaceutical use
制药用水系统的接触材料

This section applies to generation equipment for PW, HPW and WFI, and the associated storage and distribution systems.
本章节主要介绍纯水、高纯水和注射用水的制水设备以及相配套的储存和分配系统。

The materials that come into contact with WPU, including pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.
和制药用水的接触材料，包括管路、阀门和管件、密封件、隔膜以及仪表，需要符合下列标准：

• *Compatibility.* All materials used should be compatible with the temperature and chemicals used by or in the system.

兼容性。所有使用的材料应当能够和系统中使用的或系统本身的温度和化学物质兼容。

• *Prevention of leaching.* All materials that come into contact with WPU should be non-leaching at the range of working temperatures.

防止浸出。所有和制药用水接触的材料在工作温度范围内不得浸出其它化学物质。

• *Corrosion resistance*. PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipework used. Appropriate sanitary specification plastics and stainless steel materials are acceptable for WPU systems. When stainless steel is used it should be at least grade 316L. The system should be passivated after initial installation or after modification. When accelerated passivation is undertaken, the system should be thoroughly cleaned first, and the passivation process should be undertaken in accordance with a clearly defined documented procedure.

抗腐蚀性。纯水、高纯水和注射用水具有很强的腐蚀性。为防止系统出现故障从而对水造成污染，必须选择适宜的材料，保证严格密封，所有管件和部件必须和使用的管道相兼容。制药用水系统可采用合适的卫生级塑料或不锈钢。所使用的不锈钢至少要达到316L。系统初次安装或修改之后需要进行钝化。在进行加速钝化时，需要对系统进行全面彻底的清洗，同时钝化工艺需要符合清晰明确的备案规程。

• *Smooth internal finish*. Once water has been purified it is susceptible to microbiological contamination, and the system is subject to the formation of biofilms when cold storage and distribution is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre arithmetical mean roughness (Ra). When stainless steel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless steel material to surface corrosion.

光滑的内部抛光。水经过净化之后，很容易造成微生物污染，如果采用低温储存和分配，则极容易形成微生物膜。光滑的内部表面可以防止制药用水系统粗糙不平或出现裂缝。裂缝之处容易引发腐蚀。内部抛光应该达到平均表面粗糙度不高于0.8μm（Ra）。如果使用不锈钢，可以采用机械抛光和电化学抛光。电化学抛光可以加强不锈钢材料的表面抗腐蚀能力。

• *Jointing*. The selected system materials should be able to be easily jointed by welding in a controlled manner. The control of the process should include as a minimum, qualification of the operator,

documentation of the welder set-up, work-session test pieces, logs of all welds and visual inspection of a defined proportions of welds.

密封性. 所选的系统材料应该能够通过焊接能够很好的连接。该工艺控制必须包括有资质的工人、焊工资质文件、施工测试件，所有焊点的焊接日志以及对一定比例的焊接进行视觉检查。

• *Design of flanges or unions.* Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals are used and that they are fitted and tightened correctly.

*法兰或活接头设计。*采用法兰或活接头时，则应当是卫生设计。同时需要进行适当的检测，确保使用正确的密封件，确保正确紧密地安装。

• *Documentation.* All system components should be fully documented and be supported by original or certified copies of material certificates.

*文档备案。*所有系统部件需要进行完整的文件备案，提供材质证明原件或认证的复印件。

• *Materials.* Suitable materials that may be considered for sanitary elements of the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

*材料。*系统的卫生级元件所采用的材料包括316L（低碳）不锈钢，聚丙烯（PP），聚偏二氟乙烯（PVDF）和过氟烷氧基（PFA）。其它材料如未增塑聚氯乙烯（uPVC）可以用作低纯度水处理设备设计中，如离子交换器和软化器等。

6.3 System sanitization and bioburden control

系统消毒和生物控制

Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualification activities.

纯水、高纯水和注射用水的水处理设备、储存和分配系统的设计，在正常使用中应当能够控制微生物滋生，同时在调停进行维护或修改之后能够对系统进行消毒或杀菌。在系统设计中应当考虑到这一技术并在调试和确认中对性能进行认证。

Systems that operate and are maintained at elevated temperatures, in the range of 70–80 °C, are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed or

the temperature requirements for the water in use，then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.5.3 for guidance).
将温度提高到70–80 °C运行设备并保持该温度运行，相对于在较低温度下运行设备，抵抗微生物污染的效果更明显。如果由于工艺要求或者使用水的温度要求，需要保持较低的温度，则需要采取相应的手段防止微生物污染进入并滋生。（参考章节6.5.3）

6.4 Storage vessel requirements
储罐要求

The water storage vessel used in a system serves a number of important purposes. The design and size of the vessel should take into consideration the following.
系统中的水储罐具有重要的角色，容器的设计和尺寸需要考虑以下因素。

6.4.1 Capacity
容量

The capacity of the storage vessel should be determined on the basis of the following requirements.
储罐的容量取决于下列几个要求。

• It is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points.
应当选择一个缓冲容量，该容量介于水处理设备的稳定产能和用水点可能同时需水水量之间

• The water treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and equipment stress that occur when the equipment cycles on and off too frequently.
水处理设备应当能够长时间持续运行，防止设备频繁启动或关闭从而导致设备效率低下或对设备本身造成压力。

• The capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session or other logical period of demand.
在水处理设备出现故障，或者由于消毒或再生过程而无法制水时，该容量能够提供短期的备用容量。备用容量的计算，需要保证能够完成一个工艺批次，工作周期或其它逻辑需求周期。

6.4.2 Contamination control considerations
污染控制

The following should be taken into account for the efficient control of contamination.

如何有效控制污染，需要考虑以下因素。

• The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.

储罐的上部空间由于水珠和空气接触，在适当温度下会导致微生物滋生。因此，水分配回路的设计需要保证上部空间被水流有效湿润。可以考虑使用清洗球或分配装置将表面浸湿。

• Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.

储罐中的喷嘴应当可以防止死角的出现，以防微生物污染聚集。

• Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered to prevent condensation within the filter matrix that might lead to filter blockage and to microbial growthrough that could contaminate the storage vessels.

储罐上安装的排气过滤器，使得内部液位可以波动。过滤器应当具有除菌功能，具有疏水性，并能够在线进行一体性测试，同时也可以进行离线测试。为了避免形成滤波矩阵从而导致过滤器堵塞以及微生物滋生，可采用可加热排气过滤器，防止对储罐造成污染。

• Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.

如果为了防止储罐压力过大，在储罐上安装了减压阀和爆破片，则应当采用卫生级设计。爆破片应当安装外部裂缝显示，以防止事故损失破坏系统的完整性。

6.5 Requirements for water distribution pipework

水分配管路

The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled.

纯水、高纯水和注射用水的分配应当采用持续的循环管路回路。储罐和分配回路系统应当防止污染物的扩散。

Filtration should not usually be used in distribution loops or at takeoff user points to control

biocontamination. Such filters are likely to conceal system contamination.
在分配回路中以及在用水点开始处，应当较少使用过滤，这样可以控制微生物污染，因为该过滤可能藏匿系统污染物。

6.5.1 Temperature control and heat exchangers
温度控制和热交换器

Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or double plate and frame con- figuration should be considered. Where these types are not used, an alternative approach whereby the utility is maintained and monitored at a lower pressure than the WPU may be considered.
在系统中如果采用热交换器对制药用水进行加热或冷却,则需要注意防止加热或冷却设施对水造成污染。因此可以考虑更为安全的双管板或双板框式热交换器。如果为使用以上类型的交换器，则可以考虑将热源或冷源设施压力保持和监控在制药用水的压力以下。

Where heat exchangers are used they should be arranged in continually circulating loops or subloops of the system to avoid unacceptable static water in systems.
如果使用热交换器，则系统应该保持持续的循环回路和子回路，以防止系统中处于静止状态。

When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.
如果由于工艺要求需要降低温度，则应当在最短的时间内降低。因此，应当在系统确认时对冷却周期和持续时间进行认证。

6.5.2 Circulation pumps
循环泵

Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.
循环泵应当符合卫生设计，并采用合适的密封，以防止系统污染。如果安装有备用泵，则需要防止安装和使用中系统出现死角。

6.5.3 Biocontamination control techniques
微生物污染控制技术

The following control techniques may be used alone or more commonly in combination.

可以单独使用下列控制技术防治微生物污染，但是更常见的是结合使用。

• Maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms. The maintenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short-term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur.

在水分配系统中保持持续的湍流循环，可以阻止微生物膜的形成。对于特定系统的设计速率应当在系统确认时验证， 并对性能是否效果明显进行监控。在分配系统的运行过程中，如果不出现停流、倒流或压损等情况，则流速中出现短暂的波动不会引起污染。

• The system design should ensure the shortest possible length of pipework.

系统设计应当确保最短的管路。

• For ambient temperature systems, pipework should be isolated from adjacent hot pipes.

对于常温系统，管路应当和毗邻的热管路隔离开来。

• Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.

管路安装中避免出现直径是1.5倍以上分支直径的盲管段。

• Pressure gauges should be separated from the system by membranes.

压力表应该采用隔膜和系统分开。

• Hygienic pattern diaphragm valves should be used.

应当采用卫生级隔膜阀。

• Pipework should be laid to falls to allow drainage.

管路应该有一定的坡度，以保证排污。

• The growth of microorganisms can be inhibited by:

可以采用下列方式杜绝微生物的生长：

— ultraviolet radiation sources in pipework;
管道中加入紫外线辐射源；

— maintaining the system heated (guidance temperature 70– 80 °C);
对系统加热并保持温度（指导温度70– 80 °C）

— sanitizing the system periodically using hot water (guidance temperature >70 °C);
定期对系统使用热水消毒（指导温度>70 °C）

— sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
采用过热水或洁净蒸汽定期对系统进行杀菌或消毒；以及

— routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water.

Ozone can be effectively removed by using ultraviolet radiation.
采用臭氧或其它化学品进行常规化学消毒。化学消毒之后，在使用水之前，需要确保化学品被完全清除。可以采用紫外线辐射将臭氧有效去除。

7. Operational considerations

操作要求

7.1 Start-up and commissioning of water systems

水系统的启动和调试

Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

计划周全、定义明确、成功完整备案的调试是水系统成功认证的重要前提。调试工作包括工作设定，系统启动，控制回路调整以及记录所有系统性能参数。如果在认证工作中需要使用或参考调试数据，调试工作质量和相关的数据和文档必须和认证计划要求相称。

7.2 Qualification

确认

WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualifi- cation should follow the validation convention of design review or、design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

制药用水、纯化水、高纯水和注射用水系统均作为直接影响质量的重要系统，因此需要确认。确认需要遵循设计评审的认证原则或设计确认（DQ）、安装确认（IQ）、运行确认（OQ）和性能确认（PQ）。

This guidance does not define the standard requirements for the conventional validation stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

本指南未对常规的认证阶段DQ， IQ和OQ等定义标准要求，而集中对应该用作制药用水系统的特殊PQ方法进行阐述，以实现系统的连贯性和可靠性等性能。三阶段法能够实现性能确认的目标，通过一段较长时间的服务，可以证明系统的可靠性和稳定性。

Phase 1. A test period of 2–4 weeks should be spent monitoring the system intensively. During this

period the system should operate continuously without failure or performance deviation. The following should be included in the testing approach.
阶段1. 需要花费2-4周时间对系统集中监控。在该阶段，系统应当能够持续运行，不出现故障或性能偏离。测试方法应当包括以下几个方面。

• Undertake chemical and microbiological testing in accordance with a defined plan.
根据明确的计划进行化学和微生物测试。

• Sample the incoming feed-water daily to verify its quality.
每日对进水水质取样，确定其水质。

• Sample after each step in the purification process daily.
每日对每一步净化工艺之后的水分别取样。

• Sample at each point of use and at other defined sample points daily.
每日对用水点和规定的其它取样点分别取样。

• Develop appropriate operating ranges.
建立合适的运行范围。

• Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
建立和确定运行、清洗、消毒和维护规程。

• Demonstrate production and delivery of product water of the required quality and quantity.
按照要求的水质和水量进行水生产和输送演示。

• Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
使用和精炼操作、维护、消毒和故障维修的标准操作规程（SOPs）

• Verify provisional alert and action levels.
校验临时警报和行动等级。

• Develop and refine test-failure procedure.
选择和精炼故障测试规程。

Phase 2. A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase. The approach should also:
阶段2。在成功完成第一阶段测试之后，需要采用精炼的标准操作规程进行2-4周的进一步测试，对系统展开进一步集中监控。取样计划一般跟第一阶段相同。这一阶段的水可以用于生产用途。具体方法还包括：

— demonstrate consistent operation within established ranges; and

对已经建立好的范围进行持续运行演示；以及

— demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.
严格参照标准操作规程，按照要求的水质和水量进行持续生产和输送演示。

Phase 3. Phase 3 typically runs for 1 year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features.
阶段3。 在第二阶段成功完成之后，第三阶段一般运行一年时间。该阶段的产水可以用于生产目的，该阶段具备以下目标和特征。

• Demonstrate extended reliable performance.
长期可靠的性能演示。

• Ensure that seasonal variations are evaluated.
确保对季节变化进行评估。

• The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.
根据阶段1和2建立的规程，相应减少取样点，取样频率和测试到正常常规节奏。

7.3 Continuous system monitoring
持续系统监控

After completion of phase 3 of the qualification programme for the WPU system, a system review should be undertaken. Following this review, a routine monitoring plan should be established based on the results of phase 3.
完成制药用水系统的第三阶段的确认项目以后，需要对系统进行评审。在评审之后，需要根据第三阶段的结果建立常规的监控计划。

Monitoring should include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use and specific sample points. Samples from points of use should be taken in a similar way to that adopted when the water is being used in service.
监控分为在线仪表的监控，参数包括流量、压力、温度、电导和全部有机碳等，以及离线取样测试，包括物理、化学和微生物属性。离线取样点包括用水点取样和特定的取样点。用水点取样的水应当跟正在使用的水相同。

Tests should be carried out to ensure that the selected pharmacopoeia specification has been satisfied,

and should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, total viable count, presence of specific pathogens and endotoxins.
需要开展相应的测试，确保水质符合选择的药典规格。测试包括电导率、PH、重金属、硝酸盐、总的有机碳、总的活菌数、是否存在特殊病原体和内毒素等。

Monitoring data should be subject to trend analysis.
监控数据应当根据趋势分析进行调整。

7.4 Maintenance of water systems

水系统的维护

WPU systems should be maintained in accordance with a controlled, documented maintenance programme that takes into account the following:
制药用水系统的维护应当符合严格控制的、已备案的维护计划，并考虑以下要素：

— defined frequency for system elements;
系统元件规定的频率

— the calibration programme;
校验计划

— SOPs for specific tasks;
标准操作规程中规定的特殊任务

— control of approved spares;
对批准的易损件控制

— issue of clear maintenance plan and instructions;
发行明确的维护计划和说明

— review and approval of systems for use upon completion of work; and
工作结束后对所使用的系统评审和批准；以及

— record and review of problems and faults during maintenance.
记录和评审维护过程中出现的问题和故障。

7.5 System reviews

系统评审

WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance. The review should consider matters such as:
需要定期间隔对制药用水（纯化水，高纯水和注射用水）系统进行评审。评审团应当包含工程

技术、质量认证、运行和维护代表，评审包括以下内容：

— changes made since the last review;
上次评审起所作的更改

— system performance;
系统性能

— reliability;
可靠性

— quality trends;
质量趋势

— failure events;
故障事件

— investigations;
调查

— out-of-specifications results from monitoring;
监控出的超出规范的结果

— changes to the installation
安装所进行的更改

— updated installation documentation;
更新的安装文件

— log books; and
日志；和

— the status of the current SOP list.
现有的标准操作流程清单状态

8. Inspection of water systems

水系统的检查

WPU (PW, HPW and WFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audit and self-inspection of established water systems. This GMP guidance can be used as the basis of inspection. The following list identifies items and a logical sequence for a WPU system inspection or audit:

常规检查的主体主要是制药用水（纯化水，高纯水和注射用水）系统。用户应当考虑对建设完毕的水系统执行常规审计和自查。本GMP指南可以用作检查依据。以下列举了鉴定项目和制药用水系统检查或审计的逻辑顺序：

— a sampling and monitoring plan with a drawing of all sample points;

取样和监控计划，绘有所有取样点的图纸

— the setting of monitoring alert and action levels;
监控报警和行动等级设定；

— monitoring results and evaluation of trends;
监控结果和趋势评估

— inspection of the last annual system review;
对上一年度系统评审进行检查

— review of any changes made to the system since the last audit and check that the change control has been implemented;
对上一次审计之后系统所作的任何更改进行评审，检查更改控制是否已执行；

— review of deviations recorded and their investigation;
对记录的偏离评审以及调查；

— general inspection of system for status and condition;
系统状态和条件的总体检查；

— review of maintenance, failure and repair logs; and
维护、故障和修理日志评审；以及

— checking calibration and standardization of critical instruments.
检查重要仪表的校验和标准化。

For an established system that is demonstrably under control, this scope of review should prove adequate.
对于已经建成的并明显处于控制下的系统，该范围的评审是足够的。

For new systems, or systems that display instability or unreliability, the following should also be reviewed:
对于新系统，或者表现不稳定或不可靠的系统，还要对以下方面评审：

— performance qualification;
性能确认

— operational qualification; and
运行确认；以及

— installation qualification.
安装确认。

Bibliography

参考书目（略）