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Guideline on the quality of water for pharmaceutical use

Draft

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This guideline replaces the Note for guidance on quality of water for pharmaceutical use (CPMP/QWP/158/01 EMEA/CVMP/115/01) and CPMP Position Statement on the Quality of Water used in the production of Vaccines for parenteral use (EMEA/CPMP/BWP/1571/02 Rev.1).

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

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Executive summary

This guideline replaces the Note for Guidance on quality of water for pharmaceutical use (CPMP/QWP/158/01, EMEA/CVMP/115/01) originally adopted in May 2002, and the CPMP Position Statement on the Quality of Water used in the production of Vaccines for parenteral use (EMEA/CPMP/BWP/1571/02 rev.1).

The note for guidance has been updated to reflect the following changes in the European Pharmacopoeia:

- revised monograph for Water for Injections (0169) allowing the possibility to use methods other than distillation for producing water of injectable quality;
- new monograph for Water for preparation of extracts (2249);
- suppression of the monograph for Water, highly purified (1927).

1. Introduction (background)

Water is one of the major commodities used by the pharmaceutical industry. It may be present as an excipient or used for reconstitution of products, during synthesis, during production of the finished product or as a cleaning agent for rinsing vessels, equipment, primary packaging materials etc.

Different grades of water quality are required depending on the different pharmaceutical uses. Control of the quality of water, in particular the microbiological quality, is a major concern and the pharmaceutical industry devotes considerable resource to the development and maintenance of water purification systems.

The European Pharmacopoeia (Ph. Eur.) provides quality standards for grades of water for pharmaceutical use including Water for Injections (WFI), Purified Water and Water for preparation of extracts.

Until April 2017, the production of Water for Injections (WFI) had been limited to production by distillation only. Following extensive consultation with stakeholders, the Ph. Eur. monograph for Water for Injections (0169) was revised in order to allow the production of WFI by a purification process equivalent to distillation, such as reverse osmosis coupled with appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration. The revised monograph was published in the Ph. Eur. Supplement 9.1 and became effective on 1 April 2017.

This change brings the Ph. Eur. more closely in line with the US Pharmacopeia and the Japanese Pharmacopoeia, allowing production of WFI by distillation or by a purification process proven "equivalent or superior to distillation", and "by distillation or by reverse osmosis and/or ultrafiltration", respectively.

In addition, the Ph. Eur. Commission has adopted a new policy for the test for bacterial endotoxins, reflected in the revision of general chapter 5.1.10 Guidelines for using the test for bacterial endotoxins and the general monograph for Substances for pharmaceutical use (2034). As a consequence, new monographs for substances for pharmaceutical use will no longer include the test for bacterial endotoxins (with possible exceptions). This aspect is now covered by the general monograph, which includes recommendations for establishing limits and information on how to evaluate the pyrogenicity of substances and where, according to the monographs on Parenteral preparations (0520) and Preparations for irrigation (1116), the requirements apply to the finished product.

The opportunity has also been taken to update terminology and requirements to reflect current expectations.

2. Scope

This document is intended to provide guidance to the industry on the pharmaceutical use of different grades of water in the manufacture of active substances and medicinal products for human and veterinary use and should be considered for new marketing authorisation applications, as well as any relevant variation application to existing marketing authorisations.

This guidance also applies to Advanced Therapy Medicinal Products (ATMPs). Where applicable, guidance is provided to include preparation of critical starting materials such as viral vectors and on cell based medicinal products where terminal sterilisation is not possible. For additional specific guidance for Advanced Therapy Medicinal Products, applicants and manufacturers are advised to consult the EC guidelines on Good Manufacturing Practice (GMP) specific to Advanced Therapy Medicinal Products (ATMPs).

Where relevant, the principles of this guideline may also be applied to investigational medicinal products.

This guidance is not intended to cover situations where medicinal products are prepared extemporaneously or where preparations are reconstituted/diluted with water prior to use by a pharmacist (e.g. water for reconstituting oral antibiotic mixtures, water for diluting haemodialysis solutions) or in the case of veterinary products, by the user (e.g. sheep dips).

This guideline complements the "Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies EMA/INS/GMP/443117/2017 GMP/GDP Inspectors Working Group" which has been published following the implementation of the revised monograph for Water for Injections (0169) and it is intended that the guideline and Q&A should be read together.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles sections 4 & 5 of Annex I to Directive 2001/83/EC and the introduction and general principles section 2 & 3 of Annex I to Directive 2001/82/EC.

4. Requirements of the European Pharmacopoeia

The European Pharmacopoeia provides quality standards for the following grades of water:

- Water for Injections
- Purified Water
- Water for preparation of extracts

4.1. Potable Water

Potable Water is not covered by a pharmacopoeial monograph but must comply with the regulations on water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC, or laid down by the competent authority. Testing should be carried out at the manufacturing site to confirm the quality of the water. Potable water may be used in chemical synthesis and in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water. It is the prescribed source feed water for the production of pharmacopoeial grade waters.

4.2. Water for Injections (WFI)

Water for Injections (WFI) is water for the preparation of medicines for parenteral administration when water is used as a vehicle (water for injections in bulk) and for dissolving or diluting substances or preparations for parenteral administration (sterilised water for injections).

For a detailed description of the production and control of Water for Injections refer to Ph. Eur. monograph 0169. It should be noted that when reverse osmosis is to be introduced at the local manufacturing site, notice should be given to the GMP supervisory authority of the manufacturer before implementation as described in the *Compilation of Community Procedures on Inspections and Exchange of Information*.

4.3. Purified Water

Purified Water is water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised.

Purified Water which satisfies the test for endotoxins described in Ph. Eur. monograph 0008 may be used in the manufacture of dialysis solutions.

For a detailed description of the production and control of Purified Water refer to Ph. Eur. monograph 0008.

4.4. Water for preparation of extracts

Water for preparation of extracts is water intended for the preparation of Herbal drug extracts (0765) which complies with the sections Purified water in bulk or Purified water in containers in the monograph Purified water (0008), or is water intended for human consumption of a quality equivalent to that defined in Directive 98/83/EC which is monitored according to the Production section described in the monograph.

For a detailed description of the production and control of Water for preparation of extracts refer to Ph. Eur. Monograph 2249.

5. Quality of Water for Pharmaceutical Use

Validation and qualification of water purification, storage and distribution systems are a fundamental part of GMP and form an integral part of the GMP inspection.

The grade of water used at different stages in the manufacture of active substances and medicinal products should be discussed in the marketing authorisation application. The grade of water used should take account of the nature and intended use of the finished product and the stage at which the water is used.

The following tables provide some general examples for guidance:

5.1. Water present as an excipient in the final formulation

Water is the most commonly used excipient in medicinal products: the minimum quality of water selected depends on the intended use of the product, according to a risk based approach to be applied as part of an overall control strategy.

Table 1 summarises the main categories of sterile products. WFI is required for those products intended for parenteral administration and this includes solutions for haemofiltration and haemodiafiltration, and peritoneal dialysis.

Sterile ophthalmic, nasal/ear and cutaneous preparations should be prepared using materials (water) designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms. According to the risk assessment, this could require the use of water of higher quality than purified water.

Table 1: Sterile Medicinal Products

Sterile medicinal products	**Minimum acceptable quality of water**
Biologics (including vaccines and ATMP)	WFI
Parenteral	WFI
Ophthalmic (excluding ATMP)	Purified Water
Haemofiltration Solutions Haemodiafiltration Solutions	WFI
Peritoneal Dialysis Solutions	WFI
Irrigation Solutions	WFI
Nasal/Ear Preparations	Purified Water
Cutaneous Preparations	Purified Water

Table 2 summarises the main categories of non-sterile dosage forms. With the exception of non-sterile vaccines for non-parenteral use and some nebuliser preparations, Purified Water is the acceptable grade of water for all non-sterile products.

Table 2: Non-sterile Medicinal Products

Non-sterile medicinal products	**Minimum acceptable quality of water**
Vaccines for non-parenteral use	Purified Water*
Oral Preparations	Purified Water
Nebuliser Solutions	Purified Water**
Cutaneous Preparations	Purified Water***
Nasal/Ear Preparations	Purified Water
Rectal/Vaginal Preparations	Purified Water

* WFI is recommended in order to ensure the vaccines' safety and product quality (avoid introduction of undesirable microorganisms in the finished product formulation) unless otherwise justified (i.e. for some non-sterile veterinary vaccines for non-parenteral use, purified water might be accepted).

** In certain disease states (eg. cystic fibrosis), medicinal products administered by nebulisation are required to be sterile and non-pyrogenic. In such cases, WFI should be used.

*** For some products such as veterinary teat dips, it may be acceptable to use potable water where justified and authorised taking account of the variability in chemical composition and microbiological quality.

5.2. Water used during manufacture of active substances and medicinal products excluding water present as an excipient in the final formulation

The acceptable grade of water will depend heavily on the stage at which it is to be used during manufacture, the subsequent processing steps and the nature of the final product, according to a risk based approach to be applied as part of an overall control strategy.

Table 3 summarises the minimum acceptable quality of water for the manufacture of active substances.

Table 3: Water used during the manufacture of Active Substances (AS)

Type of manufacture	**Product requirements**	**Minimum acceptable quality of water**
Synthesis of all intermediates of AS prior to final isolation and purification steps	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable Water*
Fermentation media	AS is intended for manufacturing of chemical entities (i.e. semi-synthetic products, antibiotics).	Potable Water*
Fermentation media and cell culture media	AS is intended for manufacturing of biologics (i.e. vaccines and recombinant biologicals).	Purified Water
All steps including fermentation media, cell culture media, initial purification, final isolation and purification.	AS is intended for manufacturing of ATMPs. Also applicable to starting materials such as viral vectors intended for the manufacture of ATMPs.	WFI
Extraction of herbals	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used	Water for preparation of extracts **
Any step excluding final isolation and purification (e.g. fermentation, initial purification)	AS is biological and intended for parenteral use (excluding ATMP).	Purified Water
Final isolation and purification	No requirement for sterility or apyrogenicity in AS or the pharmaceutical product in which it will be used.	Potable Water*
Final isolation and purification	AS is not sterile, but is intended for the preparation of non-sterile vaccines for non-parenteral use.	Purified Water
Final isolation and purification	AS is not sterile, but is intended for use in a sterile, non-parenteral product.	Purified Water
Final isolation and purification	AS is sterile and not intended for parenteral use.	Purified Water
Final isolation and purification	AS is not sterile, but is intended for use in a sterile, parenteral product.	Purified Water***

Type of manufacture	Product requirements	Minimum acceptable quality of water
Final isolation and purification	AS (biological) is in solution, not sterile, but is intended for use in a sterile, parenteral product.	WFI
Final isolation and purification	AS is sterile and apyrogenic	WFI
Final purification	AS is biological and intended for parenteral use.	WFI

* Purified Water should be used where there are technical requirements for greater chemical purity.

** Refer to the monograph 2249 "Water for preparation of extracts".

*** Appropriate specifications have to be set for endotoxins and specified micro-organism testing of the active substance as per the relevant Ph. Eur. chapters.

Table 4 summarises the acceptable quality of water for the manufacture of sterile and non-sterile medicinal products.

Table 4: Water used during manufacture of medicinal products but not present in the final formulation

Manufacture	Minimum acceptable quality of water
Granulation	Purified Water*
Tablet coating	Purified Water
Used in formulation prior to non-sterile lyophilisation	Purified Water
Used in formulation prior to sterile lyophilisation	WFI

* For some veterinary premix products eg. granulated concentrates it may be acceptable to use potable water where justified and authorised taking account of the variability in chemical composition and microbiological quality.

5.3. Water used for cleaning/rinsing of equipment, containers and closures

Washing procedures of the equipment, primary containers and closures normally fall within the field of GMP and are not described routinely in the MA dossier, but may, in certain circumstances, be requested by the competent authority.

In general, the final rinse used for equipment, containers/closures should use the same quality of water as used in the final stage of manufacture of the AS or used as an excipient in a medicinal product.

Table 5 summarises the acceptable quality of water used for cleaning/rinsing of equipment, containers/closures for all medicinal products.

Table 5: Water used for cleaning/rinsing.

Cleaning/Rinsing of Equipment, Containers, Closures	PRODUCT TYPE	Minimum Acceptable quality of water
Initial rinse	Intermediates and AS	Potable Water
Final rinse	AS	Use same quality of water as

Cleaning/Rinsing of Equipment, Containers, Closures	PRODUCT TYPE	Minimum Acceptable quality of water
		used in the AS manufacture
Initial rinse including CIP* of equipment, containers and closures, if applicable.	Medicinal products – non sterile	Potable Water
Final rinse including CIP* of equipment, containers and closures, if applicable.	Medicinal products – non sterile	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Initial** rinse including CIP* of equipment, containers and closures, if applicable.	Sterile products	Purified Water
Final rinse*** including CIP* of equipment, containers and closures, if applicable.	Sterile non-parenteral products	Purified Water or use same quality of water as used in manufacture of medicinal product, if higher quality than Purified Water
Final rinse*** including CIP* of equipment, containers and closures, if applicable.	Sterile parenteral products	WFI

* CIP = Clean In Place

** Some containers, e.g. plastic containers for eyedrops may not need an initial rinse, indeed this may be counter-productive since particulates counts could be increased as a result. In some cases e.g. blow-fill-seal processes rinsing cannot be applied.

*** If equipment is cleaned with diluted detergents or/and dried after rinsing with diluted alcohol, the alcohol or the detergent should be diluted in water of the same quality as the water used for the final rinse.

References

1. Note for Guidance on Quality of water for pharmaceutical use (CPMP/QWP/158/01-EMEA/CVMP/115/01).
2. Ph. Eur. monograph “Water for Injections” (0169).
3. Ph. Eur. monograph “Water for preparation of extracts” (2249).
4. Ph. Eur. monograph “Water, purified” (0008).
5. Ph. Eur. monograph “Parenteral preparations” (0520).
6. Ph. Eur. monograph “Preparations for irrigation” (1116).
7. Ph. Eur. monograph “Substances for pharmaceutical use” (2034) .
8. CPMP Position Statement on the Quality of Water used in the production of Vaccines for parenteral use (EMEA/CPMP/BWP/1571/02 Rev.1).
9. ICH Q9 (Quality risk management), EMA/CHMP/ICH/24235/2006.

10. Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies EMA/INS/GMP/443117/2017 GMP/GDP Inspectors Working Group.
11. Ph. Eur. chapter 5.1.10 "Guidelines for using the test for bacterial endotoxins"
12. Compilation of Community Procedures on Inspections and Exchange of Information, (EMA/572454/2014).