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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
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NOTE FOR GUIDANCE ON QUALITY OF WATER FOR PHARMACEUTICAL USE

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Changes are in:

- Table 3 (Final isolation and purification of API - not sterile but intended for use in sterile parenteral product)
- Table 5 - Initial rinse of containers/closures for sterile products
- Table 5 - Final rinse of containers closures for sterile parenteral products (addition of footnote).

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00
Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int http://www.emea.eu.int
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NOTE FOR GUIDANCE ON QUALITY OF WATER FOR PHARMACEUTICAL USE

1. INTRODUCTION

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.

2. BACKGROUND

The European Pharmacopoeia (Ph Eur) contains standards for grades of water for pharmaceutical use including Water for Injections (WFI) and Purified Water. The use of reverse osmosis (RO) as a means of preparing WFI has been the subject of ongoing discussion within the Ph Eur Commission for a number of years. In 1999, in response to requests from national delegations to permit the use of RO for WFI production, a major international symposium was organised to discuss the issue. The meeting concluded that there was insufficient evidence at the present time to support the use of RO to produce WFI and in view of the safety concerns, WFI should be prepared only by distillation as laid down in the Ph Eur.

The meeting agreed that further guidance on the use of the different grades of pharmaceutical water would be beneficial to the industry as the Ph Eur monographs themselves do not address some of the aspects of when particular grades should be used. Furthermore as a result of this activity a new Ph Eur monograph entitled 'Highly Purified Water' has been adopted and will be implemented in the Ph Eur from 1st January 2002.

The CPMP/CVMP Quality Working Party and Inspectors Working Party have recently reconsidered the use of RO water for the preparation of WFI. They have concluded on the available evidence, that the production of water by RO and associated technologies is considered to lack the robustness of distillation and concerns remain about the potential risks associated with, for example, fouling of the membrane (chemical and biological), failure of membrane integrity and lack of effective validation. Hence the current view is that Highly Purified Water is not acceptable for WFI.

3. 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 pharmaceutical ingredients and medicinal products for human and veterinary use.

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

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4. REQUIREMENTS OF THE EUROPEAN PHARMACOPOEIA

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

- Water for Injections
- Purified Water
- Highly Purified Water

4.1 **Potable Water** is not covered by a pharmacopoeial monograph but must comply with the regulations on water 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) 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 before use (sterilised water for injections).

Production

Control of the chemical purity of WFI presents few major problems. The critical issue is that of ensuring consistent microbiological quality with respect to removal of bacteria and bacterial endotoxins. Distillation has a long history of reliable performance and can be validated as a unit operation, hence it currently remains the only official method for WFI.

WFI in bulk is obtained from water that complies with the regulation on water intended for human consumption laid down by the competent authority, or from purified water, by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or suitable metal and which is fitted with an effective device to prevent the entrainment of droplets. The correct maintenance of the apparatus is essential. During production and storage, appropriate measures are taken to ensure that the total viable aerobic count is adequately controlled and monitored.

WFI complies with the tests for Purified Water with additional requirements for bacterial endotoxins (not more than (nmt) 0.25 IU of endotoxin per ml), conductivity and Total Organic Carbon.

4.3 **Purified Water** is water for the preparation of medicinal products other than those that require the use of water which is sterile and/or apyrogenic. Purified Water which satisfies the test for endotoxins may be used in the manufacture of dialysis solutions.

Production

Purified Water is prepared by distillation, by ion exchange or by any other suitable method, from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

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4.4 Highly Purified Water is intended for use in the preparation of products where water of high biological quality is needed, except where Water for Injections is required.

Production

Highly Purified Water is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority. Current production methods include, for example, double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionisation. Highly Purified Water meets the same quality standards as WFI but the production methods are considered less reliable than distillation and thus it is considered unacceptable for use as WFI.

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 the active pharmaceutical ingredients and pharmaceutical products should be discussed in the pharmaceutical dossier. The grade of water used should take account of the nature and intended uses 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. 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.

For convenience the pharmaceutical industry often uses WFI for the preparation of ophthalmic, sterile nasal/ear and cutaneous preparations. In such situations, Highly Purified Water represents a useful alternative with the added advantage of satisfying the industry's need for large volumes.

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Table 1: Sterile Medicinal Products

Sterile medicinal products	Minimum acceptable quality of water
Parenteral	WFI
Ophthalmic	Purified
Haemofiltration Solutions Haemodiafiltration Solutions	WFI
Peritoneal Dialysis Solutions	WFI
Irrigation Solutions	WFI
Nasal/Ear Preparations	Purified
Cutaneous Preparations	Purified

Table 2 summarises the main categories of non-sterile dosage forms. With the exception of 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
Oral Preparations	Purified
Nebuliser Solutions	Purified*
Cutaneous Preparations	Purified **
Nasal/Ear Preparations	Purified
Rectal/Vaginal Preparations	Purified

* In certain disease states eg. cystic fibrosis, medicinal products administered by nebulisation are required to be sterile and non-pyrogenic. In such cases WFI or sterilised Highly Purified Water 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 pharmaceutical ingredients 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. Tables 3 and 4 summarise the acceptable quality of water for the manufacture of active pharmaceutical ingredients and for sterile and non-sterile medicinal products.

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Table 3: Water used during the manufacture of Active Pharmaceutical Ingredients (APIs)

Type of manufacture	Product requirements	Minimum acceptable quality of water
Synthesis of all intermediates of APIs prior to final isolation and purification steps	No requirement for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used.	Potable Water*
Fermentation media	No requirement for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	Potable Water*
Extraction of herbals	No requirement for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	Potable Water**
Final isolation and purification	No requirement for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	Potable Water*
Final isolation and purification	API is not sterile, but is intended for use in a sterile, non-parenteral product	Purified Water
Final isolation and purification	API is sterile and not intended for parenteral use	Purified Water
Final isolation and purification	API is not sterile, but is intended for use in a sterile, parenteral product	Purified Water with an endotoxin limit of 0.25EU/ml and control of specified organisms.
Final isolation and purification	API is sterile and apyrogenic	Water For Injections

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

** The Applicant would need to demonstrate that potential variations in the water quality, particularly with respect to mineral composition, would not influence the composition of the extract.

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

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

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

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 API or used as an excipient in a medicinal product.

Table 5: Water used for cleaning/rinsing.

Cleaning/Rinsing of Equipment, Containers, Closures	Product type	Minimum Acceptable quality of water
Initial rinse	Intermediates and API	Potable Water
Final rinse	API	Use same quality of water as used in the API manufacture
Initial rinse including CIP* of equipment, containers and closures, if applicable.	Pharmaceutical products – non sterile	Potable Water
Final rinse including CIP* of equipment, containers and closures, if applicable.	Pharmaceutical 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 dried after rinsing with 70% alcohol, the alcohol should be diluted in water of the same quality as the water used for the final rinse.

**** Where a subsequent depyrogenisation step is employed the use of Highly Purified Water may be acceptable subject to suitable justification and validation data.

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