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4 Committee for Medicinal Products for Human Use (CHMP)
5 Committee for Medicinal Products for Veterinary Use (CVMP)
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7 **Guideline on the quality of water for pharmaceutical use**
8 **Draft**

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

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14 Comments should be provided using this [template](#). The completed comments form should be sent to
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Guideline on the quality of water for pharmaceutical use

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16 Executive summary

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

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

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

27 1. Introduction (background)

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

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

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

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

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

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

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

58 2. Scope

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

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

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

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

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

80 3. Legal basis

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

84 4. Requirements of the European Pharmacopoeia

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

- 86 • Water for Injections
- 87 • Purified Water
- 88 • Water for preparation of extracts

89 4.1. Potable Water

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

97 4.2. *Water for Injections (WFI)*

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

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

106 4.3. *Purified Water*

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

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

111 For a detailed description of the production and control of Purified Water refer to Ph. Eur. monograph
112 0008.

113 4.4. *Water for preparation of extracts*

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

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

121 5. Quality of Water for Pharmaceutical Use

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

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

128 The following tables provide some general examples for guidance:

129 5.1. *Water present as an excipient in the final formulation*

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

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

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

140 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

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

145 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

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

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

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

155 *5.2. Water used during manufacture of active substances and medicinal*
 156 *products excluding water present as an excipient in the final formulation*

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

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

162 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

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

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

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

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

169 Table 4: Water used during manufacture of medicinal products but not present in the final
170 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

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

174 5.3. Water used for cleaning/rinsing of equipment, containers and closures

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

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

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

183 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

184 * CIP = Clean In Place

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

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

191 References

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

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