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2 **PRODUCTION OF WATER FOR INJECTION**  
3 **BY MEANS OTHER THAN DISTILLATION**

4 (July 2019)

5 *DRAFT FOR COMMENTS*

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms ([kopps@who.int](mailto:kopps@who.int)), with a copy to Ms Claire Vogel ([vogelc@who.int](mailto:vogelc@who.int)) by **20 September 2019**.

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/19.786:

**PRODUCTION OF WATER FOR INJECTION  
BY MEANS OTHER THAN DISTILLATION**

<b>Description of activity</b>	<b>Date</b>
Preparation of the document following recommendation of the Fifty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	December 2018 to January 2019
Mailing of working document inviting comments, including to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP), and posting of the working document on the WHO website for public consultation.	February - March 2019
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	April 2019
Discussion of working document and feedback received during the informal Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	2-3 May 2019
Discussion of working document and feedback received during the informal Consultation on Regulatory Guidance For Multisource Products.	17-18 May 2019
Consolidation of comments received and review of feedback.	June 2019
Discussion of working document and feedback received during the public consultation and the above meetings in the informal	2-5 July 2019

Consultation on Good Practices for Health Products Manufacture and Inspection.	
Mailing of the revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for the second round of public consultation.	July – 20 September 2019
Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	End of September 2019
Presentation to the Fifty-fourth ECSPP meeting.	14-18 October 2019
Any other follow-up action as required.	

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Draft for comments

46 **PRODUCTION OF WATER FOR INJECTION**  
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48  
49 **BACKGROUND**

50  
51 In recent years, several pharmacopoeias adopted revised monographs on water for injection  
52 (WFI) allowing production by non-distillation technologies. Until now, the production of WFI  
53 in many countries was limited to distillation only. The monograph revisions in a number of  
54 pharmacopoeias were the result of extensive consultations with stakeholders and now allow  
55 production of WFI by a purification process equivalent to distillation – such as reverse osmosis  
56 – coupled with appropriate techniques. During the Fifty-second meeting of the World Health  
57 Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations  
58 (ECSPP) in October 2017, members of the Expert Committee recommended that the WHO  
59 Secretariat should collect feedback on whether or not to revise the WHO specifications and  
60 good manufacturing practices (GMP) in relation to the production of WFI. In light of this,  
61 feedback was sought on whether or not the WHO specifications and GMP text(s) should be  
62 revised in relation to the production of WFI, allowing other purification processes and, if yes,  
63 whether details on additional requirements should be added and, if so, which requirements  
64 these should be. A working document for public inquiry was circulated in March 2018 and  
65 comments received were consolidated in April 2018. The issue was discussed at an informal  
66 Consultation on Screening Technologies, Sampling and Specifications for Medicines held in  
67 May 2018 and then again during an informal Consultation on Good Practices for Health  
68 Products Manufacture and Inspection held in July 2018. Comments and feedback were then  
69 consolidated before presentation of the document and all comments to the Expert Committee  
70 in October 2018.

71  
72 During the Fifty-third ECSPP meeting, the Expert Committee members discussed and agreed  
73 that the monograph in *The International Pharmacopoeia*, Water for Injections (1) and WHO  
74 Good Manufacturing Practices: Water for Pharmaceutical Use (2) be revised to allow different  
75 technologies for production of WFI other than distillation.

76  
77 This specific text was drafted to clarify the use of alternative production of WFI.

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- 81 1. Introduction  
82 2. Scope  
83 3. Monographs  
84 4. Life cycle approach  
85 5. Risk assessment  
86 6. Control strategy  
87 7. Good practices in the production of WFI  
88

89 References

90 Further reading  
91

92 **1. INTRODUCTION**  
93

94 1.1. Water is widely used in the pharmaceutical industry. It is often used as a raw material,  
95 an ingredient in formulations, to prepare reagents, in cleaning and in the manufacture  
96 of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical  
97 products (FPP).  
98

99 1.2. Water for pharmaceutical use must meet quality requirements and specifications as  
100 published in standards and Pharmacopoeia. Water of required quality for its intended  
101 use should be produced by appropriate methods.  
102

103 **2. SCOPE**  
104

105 2.1. This document provides guidance for the production of WFI by means other than  
106 distillation. The principles described in this guideline may be applied to other grades  
107 of water produced, meeting other specifications.  
108

109 2.2. The document is not exhaustive but aims to provide guidance on the main principles to  
110 be considered. Other guidelines and literature should also be consulted (1,2).  
111

### 112 3. MONOGRAPHS

113  
114 3.1. Manufacturers should have appropriate specifications for WFI.  
115

116 3.2. Monographs for WFI are published in *The International Pharmacopoeia*, as well as  
117 various national Pharmacopoeia, and provide for the minimum requirements for the  
118 quality of WFI.  
119

120 3.3. WFI should meet the specification as published in current monographs of the  
121 Pharmacopoeia, recognized by the Medicines Regulatory Authority.  
122

### 123 4. LIFE CYCLE APPROACH

124  
125 4.1. Good practices during each stage of the life cycle in the production and control of WFI  
126 should be considered.  
127

128 4.2. Stages in the life cycle in production include, but are not limited to, the collection and  
129 treatment of source water, treatment of potable water and purified water used in  
130 production of WFI, production of WFI, storage, distribution, control and use of WFI.  
131

132 4.3. Principles of risk management and data governance should be applied in each relevant  
133 stage of the life cycle.  
134

### 135 5. RISK ASSESSMENT

136  
137 5.1. An appropriate method for the production of WFI should be used.  
138

139 5.2. Risks and controls should be identified for each stage of the life cycle of the production,  
140 storage, distribution, use and control of WFI.

141 5.3. Risks identified should be assessed to determine the scope and extent of validation and  
142 qualification of the system, including the computerized system, used for the production,  
143 control and monitoring of WFI.  
144

145 5.4. Where production methods other than distillation are used, specific controls should be  
146 taken to ensure:

147

- 148 - that there is no risk of contamination of water;
- 149 - the appropriateness of user requirement specifications (URS);
- 150 - feed-water quality;
- 151 - sequence of purification stages required;
- 152 - the extent of pre-treatment required;
- 153 - appropriately designed and located sampling points;
- 154 - controls are in place to prevent dead legs and contamination; and
- 155 - in-line monitoring.

156

## 157 **6. CONTROL STRATEGY**

158

159 6.1. The WFI system should be appropriately qualified and validated.

160

161 6.2. There should be no risk of contamination of WFI produced, stored or circulated.

162

163 6.3. An appropriate control strategy should be defined to ensure that all risks identified are  
164 eliminated, or reduced to an acceptable level.

165

166 6.4. Attention should be given to, for example, the selection of components, their material  
167 of construction, preventive maintenance, life cycle and sanitization.

168

169 6.5. Treatment (also referred to as pre-treatment) of water entering the system should ensure  
170 adequate removal of chemicals (organic and inorganic), particles, matter and  
171 microbiological impurities. The treatment should not have a detrimental effect on  
172 materials of construction or downstream components of the water system.

173 6.6. Techniques such as deionisation, ultrafiltration, water softening, descaling, pre-  
174 filtration and degasification, ultraviolet treatment, along with other techniques, may be  
175 considered in conjunction with a double pass reverse osmosis (RO) system).

176

177 6.7. The materials of construction of all parts of the system, including components selected  
178 for the production, storage and distribution of WFI systems, should be appropriately  
179 designed and constructed, should not be reactive, additive, absorptive or adversely  
180 affect the quality of water. Examples of suitable materials include SS 316L and a  
181 variety of polymers (e.g. Polyvinylidene Fluoride (PVDF) and Polypropylene (PP)).

182

183 6.8. These should allow for routine sanitisation (thermal or chemical, or a combination  
184 thereof). The method of sanitization should be appropriate, effective and validated.  
185 Sanitization should be done at specified intervals in accordance with a documented  
186 procedure.

187

188 6.9. Appropriate sampling techniques should be used to sample water for analysis, at  
189 defined sampling locations, in accordance with a documented sampling procedure and  
190 a schedule.

191

## 192 **7. GOOD PRACTICES IN THE PRODUCTION OF WFI**

193

194 7.1 WFI should be prepared either from water that complies with WHO guidelines for  
195 drinking-water, national standards for drinking water or purified water as a minimum  
196 quality feedwater.

197

198 7.2. An appropriate method should be used to produce WFI.

199

200 7.3 Where RO is used, single or double-pass RO, coupled with other appropriate techniques  
201 such as electro-deionisation (EDI), ultrafiltration (UF) or nanofiltration, should be  
202 considered. The purification process employed should be proven to be at least  
203 equivalent to distillation.

204



- 205 7.4 WFI should meet the relevant pharmacopoeia specifications for chemical and  
206 microbiological purity (including endotoxin).  
207
- 208 7.5 Water testing results should be trended. Trend data should be reviewed routinely in  
209 order to determine the potential for deterioration in the system.  
210
- 211 7.6 Appropriate action and alert limits in addition to specification limits should be  
212 specified. Alert and action limits should be reassessed routinely to enable, where  
213 possible, a re-evaluation of those control limits.  
214
- 215 7.8 The system should be monitored for its ongoing performance within defined  
216 parameters, including but not limited to, conductivity, pH, total organic carbon (TOC)  
217 and microbial contamination.  
218
- 219 7.9 A combination of online and offline monitoring of WFI should be done to ensure that  
220 the appropriate water specification is maintained. TOC and conductivity should be  
221 monitored with on-line instruments.  
222
- 223 7.10 RO membranes should be monitored for any potential integrity breaches.  
224
- 225 7.11 The system should remain in a validated state throughout its life cycle.  
226

## 227 **References**

- 228
- 229 1. *The International Pharmacopoeia*, 8<sup>th</sup> edition, 2018 (update in progress).  
230
- 231 2. WHO Good Manufacturing Practices: Water for Pharmaceutical Use, WHO Technical  
232 Report Series, No. 970, Annex 2. 2011 (update in progress).  
233  
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235  
236

237 **Further reading**

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239 ISPE Baseline. Water and Steam Systems. Volume 4

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