INQUIRY REGARDING PRODUCTION OF “WATER FOR INJECTION” (March 2018) DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to: Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopps@who.int; and to Mrs Xenia Finnerty (finnertyk@who.int) by 15 May 2018.

Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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INQUIRY REGARDING PRODUCTION OF WATER FOR INJECTION

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1. Background

Several pharmacopoeias, including the European Pharmacopoeia, during the past years and months adopted revised monographs on water for injections (WFI) allowing production by non-distillation technologies.

Up until now, the production of WFI had been limited to distillation only in many countries. The monograph revisions in the context of several pharmacopoeias were the result of extensive consultations with stakeholders. They newly allow for production of WFI by a purification process equivalent to distillation such as reverse osmosis, coupled with appropriate techniques.

The Japanese Pharmacopoeia and the US Pharmacopeia, for example, allow for production of WFI by distillation or a purification process proven to be equal or superior to distillation, and by distillation or reverse osmosis followed by ultrafiltration, respectively.

In the European context, EDQM conducted a survey in 2010 to gather data on the use of non-distillation technologies for producing WFI and organized an expert workshop in March 2011. The revised monograph in the European Pharmacopoeia foresees that the use of non-distillation technologies for the production of WFI requires that notice is given to the supervisory authority of the manufacturer before implementation.

Any non-distillation technology for producing WFI should be equivalent in quality to that produced by distillation, where equivalence in quality does not simply mean compliance with a specification but also takes into account the robustness of the production method. This is why the ongoing general revision of Annex 1 “Manufacture of sterile medicinal products” to the European Union good manufacturing practices (GMP) guidelines will include new guidance on production methods for WFI. In order to ensure the necessary guidance is available for the newly revised European monograph implementation, a question-and-answer (Q&A) document was prepared by the GMP/GMDP Inspectors Working Group of the European Medicines Agency.
2. WHO CONTEXT

At an informal WHO consultation on good practices for health products manufacture and inspection held in April 2017, it was noted that new technologies were being adopted for the manufacture of WFI internationally, as outlined above. The monograph on “Water for injections” included in *The International Pharmacopoeia* and the GMP for water describe a distillation process only when used as WFI, whereas other technologies, such as reverse osmosis, have been included in other pharmacopoeias.

This was reported to the 52nd the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Expert Committee members noted the report and recommended that the WHO Secretariat should collect feedback on whether to revise the WHO specifications and GMP in relation to the production of WFI.

Within the context of the WHO publications the following contain information on the production of WFI by distillation only:

- WHO good manufacturing practices: water for pharmaceutical use (WHO Technical Report Series, No. 970, Annex 2, 2012);
  [http://www.who.int/medicines/areas/quality_safety/quality_assurance/GMPWatePharmaceuticalUseTRS970Annex2.pdf?ua=1](http://www.who.int/medicines/areas/quality_safety/quality_assurance/GMPWatePharmaceuticalUseTRS970Annex2.pdf?ua=1);

- Monograph on “Water for injections” in *The International Pharmacopoeia*:

In light of the above, feedback is being sought on whether the WHO specifications and GMP text(s):

- should be revised in relation to the production of WFI allowing other purification processes as well,
  - and if yes, if details on additional requirements should be added,
    - and if yes, which additional requirements should be added.