European Medicines Agency
*Inspections*

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# Reflection Paper on Water for Injection Prepared by Reverse Osmosis



## SCOPE

This paper outlines why it is currently not considered acceptable to use reverse osmosis for the production of water for injections (WFI).

In view of recent technological advancements in this field, this paper aims to stimulate discussion on this topic.

## INTRODUCTION

Today the use of reverse-osmosis to prepare WFI is considered acceptable by the US Pharmacopoiea, however stringent requirements regarding validation and maintenance are required by the US FDA.

The European Pharmacopoeia requires that WFI must be prepared by distillation. Reverse osmosis is not considered acceptable in the EEA, according to the recommendations of the Note for Guidance on Quality of Water for Pharmaceutical Use (CPMP/QWP/158/01 - EMEA/CVMP/115/01).

Considering economical and practical industrial aspects, it is often claimed that this technological approach should be accepted by EEA Competent Authorities. The major objections concern range of separation for reverse osmosis, validation and maintenance of devices and microbiological aspects.

## RANGE OF SEPARATION FOR REVERSE OSMOSIS

Municipal water may contain contaminants such as chlorine and volatile organic chemicals. Because these contaminants are physically smaller in size than water, the semi-permeable membrane used in reverse osmosis cannot prevent them from passing through with the treated water. Moreover, there are no test methods currently available that would effectively identify all possible toxic contaminants in water.

## VALIDATION AND MAINTENANCE OF DEVICES

The reverse osmosis device must be validated to prepare a quality of water identical with water prepared by distillation. It appears that many devices available on the market are not designed for such a use.

Maintenance of systems used for reverse osmosis is considered critical particularly regarding mechanical resistance of organic membranes subjected to high pressure and because of microbiological concerns. The development of ceramic membranes may allow these problems to be resolved.

## MICROBIOLOGICAL ASPECTS

The major microbiological problem is biofilm formation.

- Biofilm formation on both sides of the RO membrane begins within minutes of the unit being switched on.

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- The biofilm on the upstream side concentrates a wide variety of metabolic by-products. The concentration is sufficient for these to pass through the membrane.
- Biofilm consists of a wide variety of gram positive and gram negative bacteria.
- Pathogenic bacteria are commonly found in biofilms, especially Mycobacteria.
- Biofilms cannot be destroyed. Any attempt by using biocides, temperature, etc. results in a rapid increase in growth following treatment.
- Biofilm can form on the permeate side of the membrane in the following ways:
    - Through microscopic holes and tears in the membrane.
    - If the permeate side of the membrane is not sterile.
    - Through flexing and bending as pressure increases due to decreasing flux as the biofilm builds up.
- Biofouling of membranes will begin within a few minutes of operation of the system.
- The biofilm will build up and become increasingly resistant to sanitisation by hot water or chemicals because of the glycocalyx material.
- RO is a percentage removal system: the higher the concentration of micro-organisms, the more metabolic by-products, exotoxins, etc.will pass through the membrane.
- The net effect is that the RO membrane will become, in practice, a bacterial fermenter. As bacteria in the biofilm grow and metabolise, a range of metabolic by products will be secreted which will include proteins and carbohydrates, some of which may be biologically active. These contaminants are not easily identified and quantified.

**CONCLUSION**

Today it is not possible to assume that the quality of WFI prepared by reverse-osmosis is as safe as water prepared by distillation according to the requirement of the European Pharmacopoeia.