Contents

1	Foreword & Introduction	8
2 2.1 2.1.1 2.1.2 2.1.3 2.1.4 2.1.5	Regulatory Requirements Regulatory Requirements for the Production of Water for Injections (WFI) WFI Monograph (0169) of the European Pharmacopoeia (Ph. Eur.) International Requirements for the Production of WFI Guideline on the quality of water for pharmaceutical use EMA – Questions and Answers on Production of Water for Injections by Non-Distillation Methods – Reverse Osmosis and Biofilms and Control Strategies Annex 1 of the GMP Guidelines	10 10 11 12 12 12
2.1.6	Annex 15 (Qualification & Validation)	14
3 3.1 3.1.2 3.1.2.1 3.1.2.2 3.1.2.3 3.1.2 3.2.3 3.2.1 3.2.2.1 3.2.2.2 3.2.2.1 3.2.2.2 3.2.2.2 3.2.2.3 3.2.2.4 3.2.3	Production of Water for Injection (WFI) Water Purification up to the Final Treatment Stage Process Selection Suitable Processes and Process Combinations Introduction Pretreatment Purification Processes Operating Design Concepts Final Purification Stage Process Selection Ultrafiltration Module Types Service Life and Shelf Life Requirements Placed on Manufacturer and Quality Assurance Standardization UF Modes of Operation (Low Cross-Flow–Dead-End)	17 17 18 18 19 20 22 23 23 23 23 23 25 26 26 26 26
4 4.1 4.2 4.3 4.4 4.5 4.5.1 4.5.2	Discussion of Risks Risk Assessment: Intended Usage of the Water Risk Assessment for the Water Treatment Processes Risk Assessment for Storage & Distribution Risk Assessment for Operation & Maintenance Biofilm Control Strategy for Membrane-Based WFI Generators System Design Routine Monitoring	31 33 38 40 40 41 42
5 5.1 5.2 5.3 5.3.1 5.4 5.5 5.5.1 5.5.2	Measurement Technology Definition of Measurement Points Online/Offline Measurement Rapid Microbial Test Methods Measurement Points for Online Measurement of Microbial Counts Rapid Methods for Determination of Endotoxins Measurement Parameters Conductivity TOC	45 45 45 46 47 47 47 47
6 6.1 6.1.1 6.1.2 6.1.3 6.2	Storage and Distribution System Design Introduction Microbiological Control Strategies Design of Extraction and Sampling Points Materials of Construction	51 51 51 51 52 53

6.3 6.4	Temperature of Storage and Distribution Systems Operational Concepts	53 53
7 7.1 7.1.1 7.2 7.2 7.3 7.3.1 7.4 7.5	Sanitization Methods Pretreatment Purification Sanitization of the Purification Stages – Risks and Monitoring Sanitization of the Storage and Distribution System Storage Tank Ventilation Filter Sanitization of the Storage and Distribution System – Risks and Monitoring Development of a Sanitization Concept	56 56 58 59 60 61 62 62
8 8.1 8.2 8.3 8.4 8.4.1 8.4.2 8.4.3 8.4.4 8.5 8.6 8.7 8.8	Qualification and ValidationIntroductionProcess ExpertiseWater QualityPurificationPretreatmentReverse OsmosisEDIUltrafiltrationStorage and DistributionSanitizationUpgrading HPW Systems to WFI SystemsRequalification of a Cold WFI System	65 66 66 67 67 68 69 73 73 73 74 75
9 9.1 9.2 9.3 9.4 9.5	Monitoring and Controls Sampling Methods, Locations and Frequencies Sample Volumes Objectionable Microorganisms Warning and Action Limits Trending & Statistics	77 77 78 78 78 78 79
10	Economic Aspect	81
11	Conclusion and Outlook	83
12 12.1 12.2 12.3	Attachments List of Tables List of Figures List of Abbreviations	85 85 85 86