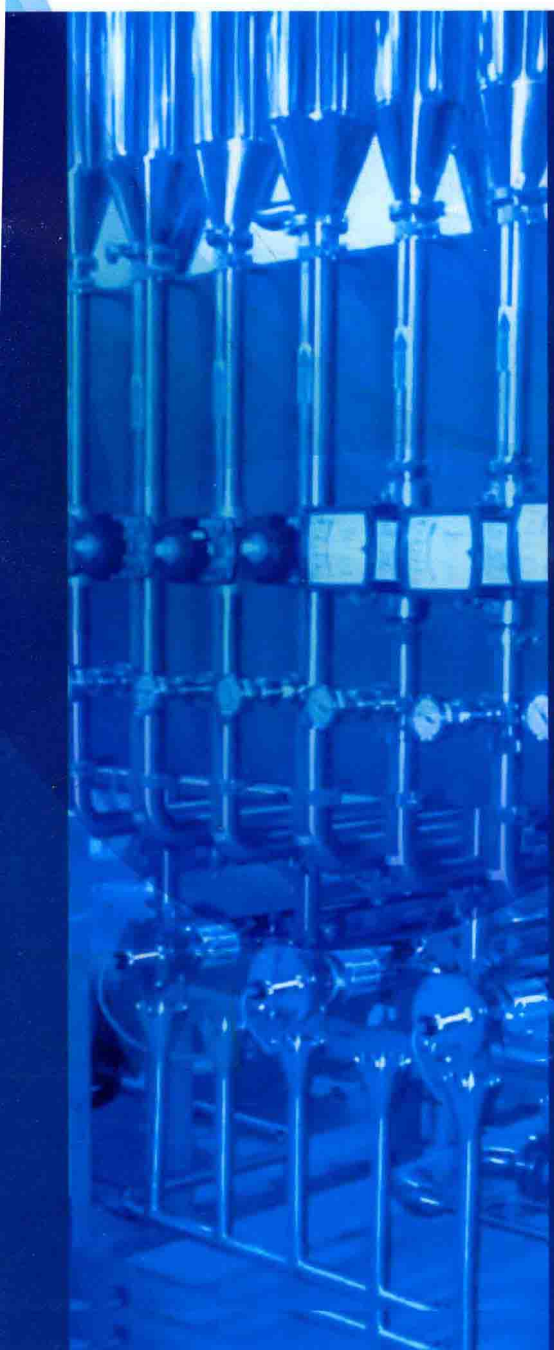
Pharmaceutical Water Systems

制药用水系统 英文版



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化学工业出版社

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·北京·

本书为英文版，结合多年工程实践实验，对制药用水系统进行了深入的总结和归纳。

本书大量采用实际工程案例和图片，结合 ISPE 及 ASME BPE 的理论经验，力求真实、形象、准确地介绍制药用水系统的基本概念和设计思路。本书基于“质量源于设计、预防微生物污染与预防颗粒物污染”的理念，重点介绍了制药用水系统的设计、安装、调试以及验证的基本原理与具体实践。本书还提供了制药用水系统组成材料的质量控制标准，以保证制药用水系统能稳定地为制药生产提供所需的制药用水和纯蒸汽。

本书适用于制药行业从事研究、设计、生产制药用水系统的技术人员，也可供制药工程相关专业高校师生阅读参考。

This book uses a large number of actual engineering cases and photos, and combines that with the theoretical experience of the International Society for Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers Bioprocessing Equipment (ASME BPE) to introduce the basic concepts and design approaches of pharmaceutical water systems in a vivid and accurate manner. This book is based on the concepts of the "quality by design, prevention of microbial contamination and particles contamination" to introduce the rationale of design, installation, commissioning and validation of pharmaceutical water systems. It also provides the readers with the quality control specifications for materials used in a Pharmaceutical Water Systems to ensure it can provide the pharmaceutical water and pure steam required for pharmaceutical production stably.

This book is of particular relevance to technicians who are engaged in researching, designing and manufacturing clean stainless steel fluid process systems. At the same time, it can be used as reference material for majors related to pharmaceutical engineering etc.

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Preface

Pharmaceutical water systems are an important subject in the *Good Manufacturing Practice*. Compared with developed countries. With gradual development of design, installation and validation activities, the pharmaceutical water systems are becoming the leading element in new or renovated projects of the modern pharmaceutical industry. All pharmaceutical enterprises will make the design, installation and validation activities the key of drug quality assurance, and realize that pharmaceutical water systems with reliable quality can provide competitive advantages of consistent quality assurance and cost savings for the enterprises.

For the pharmaceutical industry, pharmaceutical water systems is very important not only due to compliance requirements of regulations and product quality in the pharmaceutical industry, but also for the development of science and technology, and the benefits of cutting edge knowhow on drug quality improvement and risk control. With the continuous technological development of environmental protection, energy conservation and process safety in world, the design concepts and quality standards of pharmaceutical water systems have changed accordingly; this requires the pharmaceutical enterprises to adapt to the new requirements of the water generation equipment and storage and distribution systems. The original purpose for writing this book was to promote the understanding of the continuously improved quality requirements of pharmaceutical water systems, and the challenges faced by product manufacturing companies in pharmaceutical industry at present.

As a direct practitioner of design, installation and validation of pharmaceutical fluid process systems in the pharmaceutical industry, the author of this book has a rich technical expertise and practical experience with respect to pharmaceutical water systems, with 1000+ success project cases. The book provides an overview of the practical methods used in the day to day purified water systems, water for injection systems and pharmaceutical steam systems operations. These methods comply with advanced international advanced GMP regulations and guidelines and standardized applications of relevant content, including current innovative methods such as risk assessment concepts and GEP management. The book is an excellent reference text for pharmaceutical water systems, and a must read for those seeking to improve the level of design and validation activities in the pharmaceutical industry.

The author

January, 2017 in Shanghai, China

Foreword

Pharmaceutical Water Systems is a practical reference text that will facilitate a comprehensive understanding of pharmaceutical water systems; it provides clear explanations of pharmaceutical technologies, chemical principles, physical chemistry, pharmacopoeia, the Good Manufacturing Practice and relevant scientific theory and engineering technology. This book uses practical examples of unit operation, cleaning technology and microbiology to demonstrate the basic characteristics of pharmaceutical water systems in a comprehensive and vivid manner.

The Good Manufacturing Practice (2010 *Revision*) was formally issued and implemented in the Chinese mainland on March 1st, 2011. Many advanced design concepts and process analytical technologies are promoted in the pharmaceutical industry. The author published *Pharmaceutical Water Systems* (*First Edition in Chinese*) in 2012; it was widely accepted by the industry, and provided a comprehensive theory summary and practical experience insights for pharmaceutical enterprises and institutions of higher education.

After five years, the author edited and compiled *Pharmaceutical Water Systems* (*First Edition in English*) using a more comprehensive and in depth approach with successful system operation examples chosen from thousands of actual pharmaceutical water systems. This book introduces new and innovative technological concepts, including WFI generation with the purification method, online microorganism detecting technology, design and practice of WFI systems at normal temperature, residual chlorine removal technology with UV radiation, rouge remediation and prevention, etc. It is expected that this book will help practitioners in the pharmaceutical industry acquire a deeper and more visual understanding of pharmaceutical water systems, and promote the popularization of design, manufacturing and validation ability of pharmaceutical water systems in the industry.

The *Pharmaceutical Water Systems* has 13 chapters; Chapter 1 to Chapter 3 are mainly covering laws and regulations, design concepts and unit operation; Chapter 4 to Chapter 7 introduce the concept of quality by design as the starting point for a pharmaceutical water systems of high quality, including purified water generation systems, WFI generation systems, storage and distribution systems and pure steam systems; Chapter 8 takes the prevention of microbial contamination as starting port to systematically describe sanitation and sterilization technologies, and make detailed analyses and summaries of various sanitation/sterilization measures; Chapter 9 and Chapter 10 take the prevention of particles contamination as the starting point of a description of the hazards of rouge formation and derouging measures, and propose reasonable suggestions for maintenance of pharmaceutical water systems; Chapter 11 covers the principle of quality control with emphasis on the importance of welding, pickling and passivation; Chapter 12 and Chapter 13 are describing the process an-

alytical technology, commissioning and qualification methods of pharmaceutical water systems from the perspective of automatic control technology and validation.

This book uses a large number of actual engineering cases and photos, and combines that with the theoretical experience of the International Society for Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers Bioprocessing Equipment (ASME BPE) to introduce the basic concepts and design approaches of pharmaceutical water systems in a vivid and accurate manner. This book is based on the concepts of the "quality by design, prevention of microbial contamination and particles contamination" to introduce the rationale of design, installation, commissioning and validation of pharmaceutical water systems. It also provides the readers with the quality control specifications for materials used in a pharmaceutical water systems to ensure it can provide the pharmaceutical water and pure steam required for pharmaceutical production stably.

The author thanks Gordon Farquharson, ISPE senior lecturer, for his support and encouragement. Mr Gordon Farquharson devotes his enthusiasm to the transfer of scientific knowledge of water and steam systems promoting the development of the pharmaceutical industry. At the same time, the compilation of this book has been assisted by Dr Anthony Bevilacqua, head of R&D at Mettler Toledo, he is serving on USP Chemical Analysis Expert Committee and the ISPE Critical Utilities COP Steering Committee, and has made great contributions to the development of pharmacopoeia water. It is expected that this book will not only help the operators involved in the use and maintenance of pharmaceutical water, but also meet the requirements of in-depth understanding of pharmaceutical water systems by technicians who work on the design, installation, commissioning, validation and management of pharmaceutical water systems.

This book is authored by Gongchen Zhang. Relevant regulatory authorities, biopharmaceutical enterprises, institutes of higher education, engineering consulting companies and brand suppliers participated in the writing and proofreading of this book. All participant units and authors have exerted great efforts to the compilation of *Pharmaceutical Water Systems*. The author thanks the following writers and entities who have participated in the compilation of this book.

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This book is translated by professional translation team. All participant translators have exerted great efforts to the compilation of *Pharmaceutical Water Systems*. The author thanks the following translators who have participated in the compilation of this book.

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This book is of particular relevance to technicians who are engaged in researching, designing and manufacturing clean stainless steel fluid process systems, as well as the technical, production and engineering maintenance personnel from the pharmaceutical, chemical, daily chemicals manufacturing and semiconductor industry. At the same time, it can be used as reference material for majors related to materials chemistry, metal anticorrosion, pharmaceutical engineering, pharmaceutical preparation, bioengineering, etc. in institutes of higher education. Due to the limitation of knowledge level of the author and urgent time, the inappropriateness and error may exist in the book. The author will appreciate comments and suggestions from the readers regarding this book.

Gong Chen Zhang

Biography

Gongchen Zhang, Chinese senior GMP compliance and engineering design consultant expert, has over 19 years of practical experience and many patents in the pharmaceutical industry. He graduated in pharmaceutical engineering and chemical & biological engineering from Wuhan Engineering University and Huazhong University of Science and Technology of China. He is the training lecturer for the course "Water and Steam Systems" offered by the International Society for Pharmaceutical Engineering (ISPE), and the writer of GB 50913—2013 *Design Specification of Pharmaceutical Process Water Systems*. He mainly works on the design and R&D of pharmaceutical clean liquid process systems (pharmaceutical water systems, pharmaceutical process liquid preparation systems, CIP/SIP systems). He strongly supported the concept of Water Loop SKID and the pharmaceutical water systems Turn-key project in pharmaceutical industry (the typical cases such as Sinopharm Group, Boehringer Ingelheim, ReckittBenckiser, P&G, Novozymes, Apptec, Innovent, Tasly, Hualan, Kanghong etc.), and was involved in the research and implementation of many innovative design concepts such as Biopharmaceutical USP/DSP/Preparation processes with batch control systems (including antibody, insulin, vaccine and blood products), intelligent LVP preparation systems (the biggest 316L preparation tank volume is 35000L), intelligent fat emulsion injection (LVP/SVP) process preparation systems (the typical cases such as Kanglaite fat emulsion injection), and intelligent suppository and ointment process preparation systems (the typical cases such as Mayinglong suppository and ointment). He also had important contributions to the development of many innovative design concepts such as WFI systems with superheated water sterilization, heat storage/bypass circulation at normal temperature (the typical cases such as Innovent antibody and Protgen insulin), WFI storage and circulation at 4 degree temperature (the typical cases such as Blood Products), scientific derouging and passivation (the typical cases such as P&G and Lily), generation of high purity water or WFI with the purification method, applications of water electrolysis ozone sanitation, subloop cold point of use cooling modularization, etc. The author participated in the editing of the *Chemical Engineering Cartography* which is a teaching material for major of pharmaceutical engineering in national institutes of higher education involved in the 12th Five-Year Plan of the Ministry of Health, and the national standard GB 50913—2013 *Design Specification of Pharmaceutical Process Water Systems*; he supervised the editing and publishing of books such as *Pharmaceutical Water System*, *Pharmaceutical Fluid Process Manual*, and *Pharmaceutical Derouging Process Manual*, and participated in the editing of books such as *Pharmaceutical Engineering Process Design*, *Pharmaceutical Preparation Process Equipment* and *Engineering Design*, *Microbial Control in Pharmaceutical Cleanrooms*, *Pharmaceutical Process Validation Manual*, and *Compilation of EU GMP/GDP Regulations*.

Abbre viations

Abbreviations	English
AHU	Air Handing Unit
AOAC	Association of Official Analytical Chemists
AMV	Analytical Method Validation
API	Active Pharmaceutical Ingredient
ASME	American Society of Mechanical Engineers
ASME BPE	American Society of Mechanical Engineers Bioprocessing Equipment
ASTM	American Society for Testing and Materials
BD	Bowie-Dick
BI	Biological Indicator
BMS	Building Management System
CAPA	Corrective and Preventative Action
CCA	Component Criticality Assessment
CCP	Critical Control Point
CD	Cycle Development
CEHT	Clean Equipment Hold Time
CFR	Code for Federal Regulations
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CHO	Chinese Hamster Ovary
CIP	Clean in Place
ChP	Chinese Pharmacopeia
C_p/C_{pk}	Process Capability Index
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSV	Computer System Validation
CVP	Cleaning Validation Plan

cont

Abbreviations	English
DCS	Distributed Control System
DDS	Detailed Design Specification
DEHT	Dirty Equipment Hold Time
DNA	Deoxyribonucleic Acid
DoE	Design of Experiment
DOP	Dioctyl Phthalate(or Equivalent,Dispersed Oil Particulate)
DQ	Design Qualification
DS	Design Specification
ED_{50}	50% Effective Dose
EDI	Electrodeionization Deionization (US Filter)
EHS	Environment Health Safety
ELISA	Enzyme-linked Immuno Sorbent Assay
EMA	European Medicines Agency
EMS	Environmental Monitoring System
EP	European Pharmacopoeia
EPA	Environmental Protection Agency
ERP	Enterprise Resource Planning
ETOP	Engineering Turnover Packages
EU	European Union
FAT	Factory Acceptance Testing
FDA	Food and Drug Administration
FDS	Functional Design Specification
FMEA	Failure Modes and Effects Analysis
FS	Function Specification
FTA	Fault Tree Analysis
FQCP	Field Quality Control Plan
GAMP	Good Automated Manufacturing Practice
GDP	Good Document Practice
GEP	Good Engineering Practice

cont

Abbreviations	English
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GxP	Good x Practice
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard and Operability Analysis
HDS	Hardware Design Specification
HEPA	High Efficiency Particulate Air
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HMI	Human Machine Interface
HPLC	High Performance Liquid Chromatography
HVAC	Heating, Ventilation, and Air Conditioning
I/O	Input and Output
IC_{50}	The Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	International Electro technical Commission
IQ	Installation Qualification
ISO	International Standards Organization
ISPE	International Society for Pharmaceutical Engineering
IUPAC	International Union of Pure and Applied Chemistry
LIMS	Laboratory Information Management System
LOD	Limit of Detection
LOQ	Limit of Quantizatity
MB/L	Methylene Blue
MCB	Master Cell Bank
MES	Manufacturing Execution System
MTDD	Minimum Treatment Daily Dosage
OOS	Out of Specification

cont

Abbreviations	English
OQ	Operational Qualification
OSD	Oral Solid Dosage
P&ID	Piping and Instrumentation Diagrams
PAO	Poly-alpha-olefin
PAT	Process Analytical Technology
PBS	Phosphate Buffer Saline
PCB	Primary Cell Bank
PCR	Polymerase Chain Reaction
PDA	Parenteral Drug Association
PDI	Pre-delivery Inspection
PEP	Project Execution Plan
PFD	Process Flow Diagram
PHA	Preliminary Hazard Analysis
PIC/S	Pharmaceutical Inspiration Convention and Pharmaceutical Inspection Co-operation Scheme
PLC	Programmable Logic Controller
PM	Project Managemnet
PP	Polypropylene
PPE	Personal Protective Equipment
PPQ	Process Performance Qualification
PQ	Performance Qualification
PS	Pure Steam
PTFE	Polytetrafluoroethylene
PV	Process Validation
PVC	Polyvinyl Chloride
PVP	Process Validation Plan
PW	Purified Water
QA	Quality Assurance
QbD	Quality by Design

cont

Abbreviations	English
QC	Quality Control
QMS	Quality Management System
QPP	Quality and Project Plan
QRM	Quality Risk Management
RA	Risk Assessment
RABS	Restricted Access Barrier System
RH	Relative Humidity
RNA	Ribonucleic Acid
RO	Reverse Osmosis
RPN	Risk Priority Number
RSD	Relative Standard Deviation
RTM	Requirements Traceability Matrix
RTP	Rapid Transfer Port
SAL	Sterility Assurance Level
SAT	Site Acceptance Testing
SCADA	Supervisory Control and Data Acquisition
SCR	Source Code Review
SDA-PAGE	Sodium Dodecyl Sulfate-polyacrylamide gel
SDI	Silt Density Index
SDS	Software Design Specification
SFDA	State Food and Drug Administration
SIA	System Impact Assessment
SIP	Sterilize In Place
SME	Subject Matter Expert
SMS	Software Module Specifications
SMT	Software Module Test
SOP	Standard Operating Procedure
SV	Sindbis Virus
TM	Traceability Matrix

cont

Abbreviations	English
TOC	Total Organic Carbon
TR	Technical Report
UAF	Unidirectional Airflow
UCL	Upper Confidence Limit
UPS	Uninterruptable Power Supply
URB	User Requirements Brief
URS	User Requirements Specification
USP	United States Pharmacopoeia
UV	Ultraviolet Light
VHP	Vaporized Hydrogen Peroxide
VMP	Validation Master Plan
VP	Validation Plan
VSR	Validation Summary Report
VSV	Vesicular Stomatitis Virus
WCB	Working Cell Bank
WFI	Water for Injection
WHO	World Health Organization
WIP	Wetting in Place

Contents