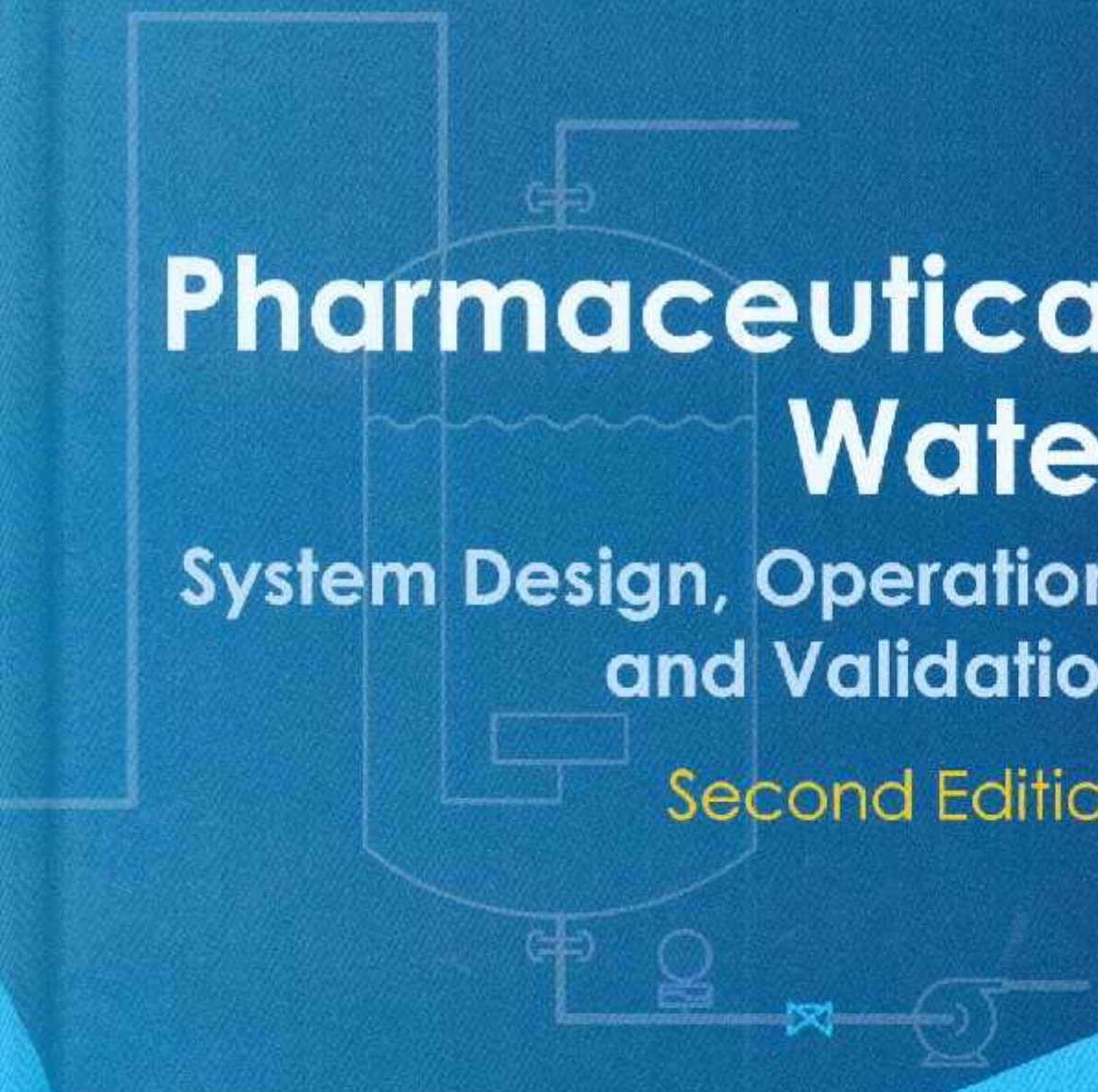
Pharmaceutical Water

System Design, Operation, and Validation

Second Edition



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Preface to the second edition

The preface of the first edition of *Pharmaceutical Water* discusses the numerous seminars, conferences, and training sessions conducted each year that specifically discuss water purification and compendial water systems. It is interesting to note how much the world has changed in the last 12 years. Perhaps, the Internet explosion with virtual instant access to material coupled with budget restriction explains the limited number of events with fewer attendees. Despite this, the relative number of citations associated with compendial water systems continues to grow. Perhaps, it is time to go "back to basics," acknowledging that compendial water systems consist of multiple unit operations with demanding design, installation, operation, validation, and preventative maintenance requirements. Further, unique feed water properties for different systems significantly influence these parameters. In summary, while some may imply, there is no standard system or "magic bullet."

During preparation of this second edition, several enhancements were performed. The original text has been completely reviewed and edited to incorporate changes in technology, feed water quality, and regulatory requirements. Significant expansion and entirely new sections have been added discussing the following:

- Expanded use of chloramines in raw water supplies
- Use of ozone for microbial control in Purified Water systems
- Discussion of biofilm theory and operating experience
- Chemical sanitization material selection and execution
- The effects of disinfection byproducts in raw water supplies
- Reverse osmosis membrane performance and system design
- Continuous electrodeionization enhancement
- System documentation
- System commissioning

Twelve more years of experience has provided a significant number of observations. Many of these observations have been included as "case histories," with data inserted into the text at several locations. While theory, design, operation, validation, and maintenance considerations are discussed, the second edition reflects actual observations and expands on the "hands-on" presentation philosophy of the original text.

References have been added or updated throughout the text. These should be used by the reader as an expansion of the material presented in the text. On many occasions, "older" references are retained. These are like a good wine, improving with age, often proving information of significant importance.

Knowledge is good, but sharing that knowledge and experience is excellent.

Preface to the first edition

Each year, I am fortunate enough to present several workshops, seminars, and courses associated with pharmaceutical water systems. At the beginning of my presentation, mostly for sessions lasting longer than a few hours, I generally discuss some ground rules. I explain how I will do everything possible to avoid speaking from the podium. Often, I remove the microphone and simply walk in front of or around the attendees. It is important to emphasize that the material being presented is an attempt to share my personal experience associated with pharmaceutical water systems on a daily basis. I encourage questions since they demonstrate that the attendees have been properly stimulated by the subject matter. I have approached the preparation of this text in a manner similar to my approach to workshops, with the thought that it provided me with a forum to discuss topics without a time limit.

I am constantly amazed by the number of presentations offered each year regarding pharmaceutical water systems. I rarely review a brochure for a major conference without noting a session on water systems. Certainly, the number of seminars presented for pharmaceutical water systems over the past several years is disproportional to the balance of technical emphasis for all other systems, components, and functions at a facility. It is my belief that this situation has evolved due to improper "horizontal-vertical" integration of disciplines and management with regard to information associated with pharmaceutical water systems. Horizontal integration is extremely important since it relates to interdisciplinary exchange of information associated not only with pharmaceutical water systems but also the regulatory, operating, maintenance, and similar issues associated with these systems. From an organizational viewpoint, it is critical that all appropriate disciplines be involved in aspects of the pharmaceutical water system. This role should not be limited to an engineering department or, more specifically, a facilities engineering department. Regulatory, quality control, analytical, manufacturing, and other input is vital to the success of design, operation, validation, and maintenance of any pharmaceutical water system. Of equal importance is a vertical integration of knowledge. This entails a transfer of items such as the details associated with routine operation of a system from operating personnel, through supervisory personnel, all the way to senior management personnel. It is impossible for senior managers to determine proper system design and related budgets or to address regulatory concerns without "hands-on" knowledge of detailed system operation. When proper horizontal and vertical integration are performed, all the necessary tools required to weave interdisciplinary input through a project is achieved.

In preparing this text, I elected to personally write all of the material myself. This appears to contradict the weaving concept indicated above. However, I believe that the contrary is true. When multiple individuals attempt to prepare a text addressing all aspects of pharmaceutical water systems, the lack of proper horizontal and vertical integration becomes very obvious. Continuity of the presentation is affected. This text deals with pharmaceutical water systems by addressing the compendial requirements, the nature of raw water supplies, specification preparation, and validation documentation. Occasionally, it may appear that certain items are repeated. I am extremely sensitive to the fact that an individual focusing on a particular topic may review a certain section of this text without reviewing another section, which may discuss related items in greater detail. To avoid this situation, some repetition, coupled with a table of contents and a complete index, ensures that all aspects associated with a particular topic have been reviewed.

Finally, I have attempted to simplify the somewhat overpowering nature of engineering aspects associated with specific water purification unit operations by presenting a brief overview of the theory and application of the technology, a discussion of design considerations, and a discussion of operating and maintenance considerations that

incorporates extensive field experience and "case histories." Throughout the entire text, regulatory and related issues are woven into the presentation. The resulting tapestry may occasionally present opinions. These are clearly designated by indicating that I am suggesting, based on experience associated with over 400 pharmaceutical and related water purification systems, that my opinion should be considered. If this generates a difference of opinion, my objective has still been met since it has stimulated the reader to consider a different view of a particular topic.

Acknowledgements

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Contents

1 | Introduction

DEFINITION OF PHARMACEUTICAL WATERS

- Water and steam used in the pharmaceutical industry and related disciplines are classified by various pharmacopeias. The U.S. Pharmacopeia (USP) classifies compendial waters as follows:
  - Water for Injection
  - Bacteriostatic Water for Injection
  - Sterile Water for Inhalation
  - Sterile Water for Injection
  - Sterile Water for Irrigation
  - Purified Water
  - Sterile Purified Water
  - Water for Hemodialysis
  - Pure Steam
  - Drinking Water (indirectly)
- With the exception of Drinking Water, USP Purified Water, USP Water for Injection, and USP Pure Steam, the classifications listed above refer to "packaged water" (USP, 2010(a)). Drinking Water, USP Purified Water, and USP Water for Injection are the primary waters used for most pharmaceutical applications, and are the primary topic of this book. Validation is required for all compendial water systems producing USP Purified Water or USP Water for Injection, with the exception of Drinking Water. Drinking Water used in a specific application generally requires "commissioning/qualification" to an "internal" specification, verifying that the quality of the product water, from both a chemical and microbiological standpoint, does not vary from established internal specifications with time. This qualification process is often used not only to maintain control of product water but also to document the nature of the system by preparing and executing documents similar to those used for compendial water systems. Obviously, the internal specifications established for a qualified system may parallel a particular USP official monograph specification, such as that for Purified Water. Finally, certain applications may expand the USP requirements for a particular grade of water. As an example, many biotechnology water specifications require "low bacterial endotoxin" Purified Water. For such application, the biotechnology company would validate the system as a USP Purified Water system and incorporate an internal bacterial endotoxin specification. Chemical, bacteria, bacterial endotoxin, and other parameters associated with each of the pharmaceutical grades of water identified above are addressed individually in this chapter.
- USP is prepared and published by The United States Pharmacopeial Convention, a private organization. The material within USP is established by "Expert Committees," circulated to the general public for comment and review, and revised after acceptance. The Expert Committees as well as the review processes include U.S. Food and Drug Administration comment, review, and approval. Since new volumes of USP are published periodically, it is suggested that reference to USP states the number of the most recent addition and/or most recent edition including all "Supplements."

DEFINITION OF PHARMACEUTICAL WATERS—EP, JP, BP, etc.

- As indicated, water and steam used in the pharmaceutical industry and related disciplines are also classified by other pharmacopeias, including the European

Pharmacopeia (EP), Japanese Pharmacopeia (JP), and the British Pharmacopeia (BP). Over the past several years, there have been many attempts to "harmonization" descriptions, specifications, and method of production for compendial waters. While significant progress has been achieved, specific differences of importance will be addressed within this chapter.

CHEMICAL SPECIFICATIONS

Drinking Water

- From a chemical standpoint, water classified as Drinking Water, for applications such as some initial rinsing operations and active pharmaceutical ingredient manufacturing operations, must meet the U.S. Environmental Protection Agency's (EPA) National Primary Drinking Water Regulations (NPDWR), or comparable regulations of the European Union, Japan, and/or World Health Organization, as applicable, for "Drinking Water." This would include but not be limited to the parameters presented in Table 1.1 for U.S. EPA Drinking Water (EPA, 2010). It is important to note that the NPDWR *will* change with time, incorporating additional parameters or changing regulated item concentrations. It should be emphasized that all validated USP systems, as well as systems using Drinking Water, should have access to correspondence identifying changes to these regulations.
- As discussed further in subsequent chapters of this book, it is highly recommended that supplemental analysis for Drinking Water, including feedwater to a USP Purified Water or USP Water for Injection system, be considered. The nature and type of analyses are dictated by the intended use of the Drinking Water. For example, if groundwater is used for an initial rinsing step during applications such as "clean-in-place" (CIP) or the production of an active pharmaceutical ingredient, it may be appropriate to treat the water through a particulate removal filter and/or water softening system. If water softening is used, the presence of high molecular weight multivalent cations, such as barium, strontium, and aluminum, in the feedwater should be identified. As discussed in chapter 3, these compounds will affect the Standard Operating Procedures (SOPs), specifically the regeneration salt dosing and concentration, during regeneration of the water softening system. Multivalent cations, such as calcium and magnesium, are *not* included in the NPDWR, but affect the performance of the system.
- Other specific components are critical to different water purification unit operations. Another example is the level of naturally occurring organic material (NOM) in a surface water supply to a USP Purified Water system. Both anion resin and reverse osmosis (RO) membranes will foul with organic material. The level of the NOM in feedwater will not only dictate the nature of pretreatment equipment but also establish an analytical monitoring program clearly demonstrating that the selected pretreatment operations "protect" the anion resin within the ion exchange system or RO membranes from fouling.

Purified Water

- Chemical specifications for USP Purified Water are outlined in the *Official Monograph* by referencing *Physical Tests* chapters for conductivity and total organic carbon (TOC). *Physical Tests* Section <643> provides the TOC specification, capability of the TOC analyzer, "system suitability" requirements, and calibration requirements. The section does *not* set forth requirements for online measurement versus "grab" sampling and laboratory analysis. Further, the section does not state the frequency of analysis. The TOC limit for USP Purified Water is 0.50 mg/L. The specification agrees with the current EP specification.
- USP *Physical Tests* Section <645> outlines the specification for conductivity, method of determination, instrument (meter and probe), calibration requirements, etc. This section outlines a three-stage test method that compensates for the presence of carbon dioxide and pH. The most restrictive specification, "Stage 1," is 1.3 μS/cm at 25°C or