



Water Production for Pharmaceutical Manufacturing: *Looking Beyond Compliance at the Entire Manufacturing Process*

Grantek is a Systems Integrator focused on automation with extensive expertise and partnerships throughout the pharmaceutical manufacturing industry, including water purification.

Introduction

In pharmaceutical manufacturing, water is used for several purposes: as a product ingredient; as a solvent in the manufacturing process; for cleaning; and as an analytical reagent. Though incoming source water must meet the requirements of the Environmental Protection Agency's (EPA's) National Primary Drinking Water Regulation (40 CFR 141), it is not pure enough for use in pharmaceutical manufacturing processes.

Pharmaceutical manufacturing facilities must include water treatment equipment capable of purifying potable feed water to United States Pharmacopeia (USP) standards, with water for injection (WFI) being the most stringent classification. As a systems integrator with deep experience working in regulated pharmaceutical manufacturing facilities, Grantek can oversee all aspects of water purification system implementation.

General Chapter <1231> of the USP defines three grades of monographed water for pharmaceutical purposes: purified water, water for injection and water for hemodialysis. Though USP defines the water quality standards, it does not specify the methods for treating water to meet USP standards.



Water Purification Systems in Pharmaceutical Manufacturing

Water purification system components that require water for pharmaceutical manufacturing processes are determined by need and by the feed water's quality.

Testing of the feed water is required to accurately identify contaminants it may contain, including particulates, inorganics, organics and microorganisms. The contaminants present determine the technologies required for the water purification system design. A typical system that produces purified water may require three stages:

- **Pretreatment**, consisting of filtration to remove particulates and some organics, and de-chlorination to remove chlorine added by the municipal water treatment system. Chlorine will degrade stainless steel over time and therefore must be removed from the water before the water enters the

pharmaceutical production equipment. Activated carbon filters are typically used to remove chlorine, which can also damage reverse osmosis (RO) membranes over time. Sediment filters may be used to remove particulates.

- **Final treatment**, in which the water is purified via ion exchange, RO, electro deionization, or a combination of methods. Disinfection methods include RO and continuous electro deionization (CEDI), which uses electricity, ion exchange membranes, and resin to deionize water. CEDI does not require the use of chemical treatments.
- **Polishing** steps, including electrodeionization (EDI), which is usually a polishing treatment to RO. Continuous EDI units use the electric current to regenerate the resin mass continuously. This technique can achieve very high purity, with conductivity below 0.1 $\mu\text{S}/\text{cm}$. Ultraviolet light systems leave no residue in the water and deactivate the DNA of bacteria and viruses that may be present.

A typical WFI production system consists of a water purification system, distillation equipment, and storage tanks specifically for WFI.

What other processes require purified water?

- Steam cleaning systems: Clean steam systems also require purified water as their input. Sterilization with high-pressure steam typically takes place after cleaning. For steam cleaning,



purified water is run through a clean steam generator piped to the water system. The steam may be introduced via steam-in-place ports on the equipment. The equipment and lines are pumped full of steam at 121° C, and the steam is allowed to cool, at which time the condensate is pumped out. Grantek assures that steam systems are pressure-tested to ensure there are no leaks before use.

Steam cleaning is not completed on water production equipment that can be damaged by application of steam. RO systems provide for both back-flushing to clean the membranes, as well as, a means to remove the disinfecting chemicals after cleaning.

- Clean in Place (CIP): The water used to clean pharmaceutical production equipment must be as high-quality as the water used for production. This means that purified water capacity must be sufficient to meet the needs of cleaning in addition to production volume. Typically, systems are also taken apart twice a year for cleaning, utilizing chemicals stronger than those of the typical CIP cleaning cycle.
- Supporting production of final product, including sterile filling, mixing/compounding, and buffer/media preparation.

Why Grantek?

As an engineering and integration company with over 30 years of pharmaceutical industry experience, Grantek provides end-to-end services to ensure our customers' purified water systems are installed and integrated into the facility in accordance with current industry standards.

Grantek does not build water purification systems, we integrate them into your processes and your facility. We are a pharmaceutical integrator focusing on systems automation with strengths including working with a deep network of partners with expertise throughout the pharmaceutical manufacturing industry. In addition to integration and automation skills, Grantek offers extensive experience in development of project lifecycles, validation and qualification documentation. We perform fully documented facility acceptance testing, site acceptance testing, and IQ/OQ/PQ testing, providing our customers with a validated system and the full complement of required documentation.

Data integrity is instrumental in pharmaceutical manufacturing. The experience Grantek has built in the pharmaceutical space allows us to see beyond the compliance of 21 CFR Part 11 when overseeing projects. While requirements behind regulations are important, data integrity and assurance at the point of recording data results in cost savings and efficiencies later in the manufacturing process. This is something Grantek keeps top of mind during all phases of the projects we oversee.

Finally, projects can be completed more efficiently, saving time and money, if a pharmaceutical manufacturer uses a single integrator for water purification and for production of final product.

Planning Your Project

If your company is considering the construction of a new pharmaceutical production facility or a greenfield project, Grantek recommends that the Director of Engineering or the Director of Operations initiate the consultative process with Grantek six months to one year before groundbreaking takes place. This allows adequate time for Grantek to perform detailed analysis of the system integration needs and to create a project plan that ensures all business and regulatory requirements are met. The project plan identifies all required testing and documentation as well as schedule and integration activities.

If a facility is adding capacity and/or new production capability to an existing manufacturing facility, Grantek recommends that the Facilities Manager or Engineering Manager contacts us to begin strategic planning three to six months before final project approval.

Whether a greenfield facility or an expansion, Grantek's detailed project plan serves to define customer and project requirements at a level of detail not typically provided in the Request for Proposal. Grantek prepares the Functional Requirements Specification, providing the technical details on how the customer's requirements will be fulfilled. When Grantek and the customer agree on the Functional Requirements Specification, Grantek prepares a detailed technical design specification.



The design phase also includes layout of the purification system components in the plant. If a purification system already exists and a new product is to be produced, the existing purification system design must be evaluated and redesigned as required to meet the new needs.

The design phase also includes adding the necessary sensors, such as sensors that check for Total Organic Carbon (TOC) and ions (contaminants), temperature, flow rate, back pressure, etc. to integrate the water purification system with the Supervisory Control and Data Acquisition (SCADA) system. This ensures seamless integration of the water purification subsystem with the plant's other subsystems in the facility's monitoring system. Proper design of monitoring systems ensures reliability and maintainability during operation and compliance to applicable regulations, as well as providing alerts if a process falls out of specified tolerances.

For expansion projects, project planning includes outlining of installation and configuration activities to minimize impact to the existing systems and production. When done correctly, most installation activities can be performed without affecting production or ongoing activities. Scheduling required disruptions is crucial to minimize the impact on production. Inclusion of electronically controlled valves in system design not only helps to reduce cutover costs, but also provides optimal control of water flow during operation, such as allowing low priority outlets to be shut off as necessary to provide water to high priority processes, and for maintenance such as repair or cleaning.



When planned correctly, expansion installation can proceed without negatively affecting operations. Many purification systems and system components, such as an RO subsystem, are built on a frame that is simply dropped in place and then connected to the plant's purified water piping or to other components. Installing skids helps simplify installation but requires adequate access to move them to their installation location. This form factor also allows for simplified system upgrade if new components are required. Automation/monitor system wiring must also be routed to the installation location.

Control and Monitoring

Control systems are central to pharmaceutical manufacturing for several reasons, including business intelligence, reliability and maintainability of the entire production system, regulatory compliance, and security. Therefore, it is important that companies choose a system integrator capable of thoroughly evaluating existing automation/monitoring systems to ensure proper incorporation of water purification system sensors. Grantek's extensive experience in system integration ensures that each system is properly configured, secure, and provides real time information for decision making, regulatory compliance, and audit trails.

Grantek installs and integrates SCADA and Historian monitoring systems, and has developed our own Building Automation System (BAS) in house using Wonderware. For smaller facilities, Grantek installs and integrates local skid-based historians that connect water system components to the building automation system, which is typically tied into the site security system to provide 24-hour monitoring. Site-wide historians may also be installed, primarily for maintaining a production record of water quality records over time, and to provide an audit train of user logins, manual interventions, and other system events. The Historian system is 21 CFR Part 11 compliant, as it provides two-factor user authentication. Grantek can integrate the historian with the site's domain controller so login authorization can efficiently be based on the facility's existing network users and groups. The historian system provides full audit trail records for incident investigations if necessary.

Conclusion

Grantek's deep experience as a system integrator in the food and pharmaceutical industries spans more than 30 years, and throughout our history we have worked with numerous water purification systems. We have extensive experience integrating production systems in compliance with current Good Automated Manufacturing Practice (GAMP 5), and 21 CFR Part 11 for electronic signatures, as well as the industry and regulatory standards applicable to the product.

Our experience with infrastructure requirements — networking, computerized systems, operating systems, hardware, custom fabrication, and power requirements — enables Grantek to provide computerized and automated water purification systems that also meet business needs and help to mitigate potential risks, including cyber security and physical infrastructure failures.

As the project moves forward, Grantek develops test protocols with full traceability to requirements in accordance with GAMP 5.



Grantek is an agile company experienced in working with fluctuating schedules and business situations, so we accommodate schedule changes and delays upstream. Our expertise provides

us the capability of designing, integrating, and qualifying water purification systems to ensure the required production capacity, product quality, and regulatory compliance. As a trusted partner, Grantek works with other process design and power engineering firms to integrate the water production equipment with the rest of the production line as well as facility alarm and monitoring systems, historian systems to ensure a complete audit trail, and ERP systems to tie the water production equipment into the company's business systems, resulting in a fully integrated facility capable of operating in a highly efficient manner.

For over 30 years, top manufacturers in Food & Beverage, CPG, Pharmaceuticals and Energy have called upon Grantek to solve their most complex business and manufacturing challenges. Grantek's team of professionals located in 17 offices across the globe deliver solutions to complex problems in Smart Manufacturing, Industrial Networking, Automation and Industrial Safety. Call 1.866.936.9509 or email info@grantek.com to learn more.