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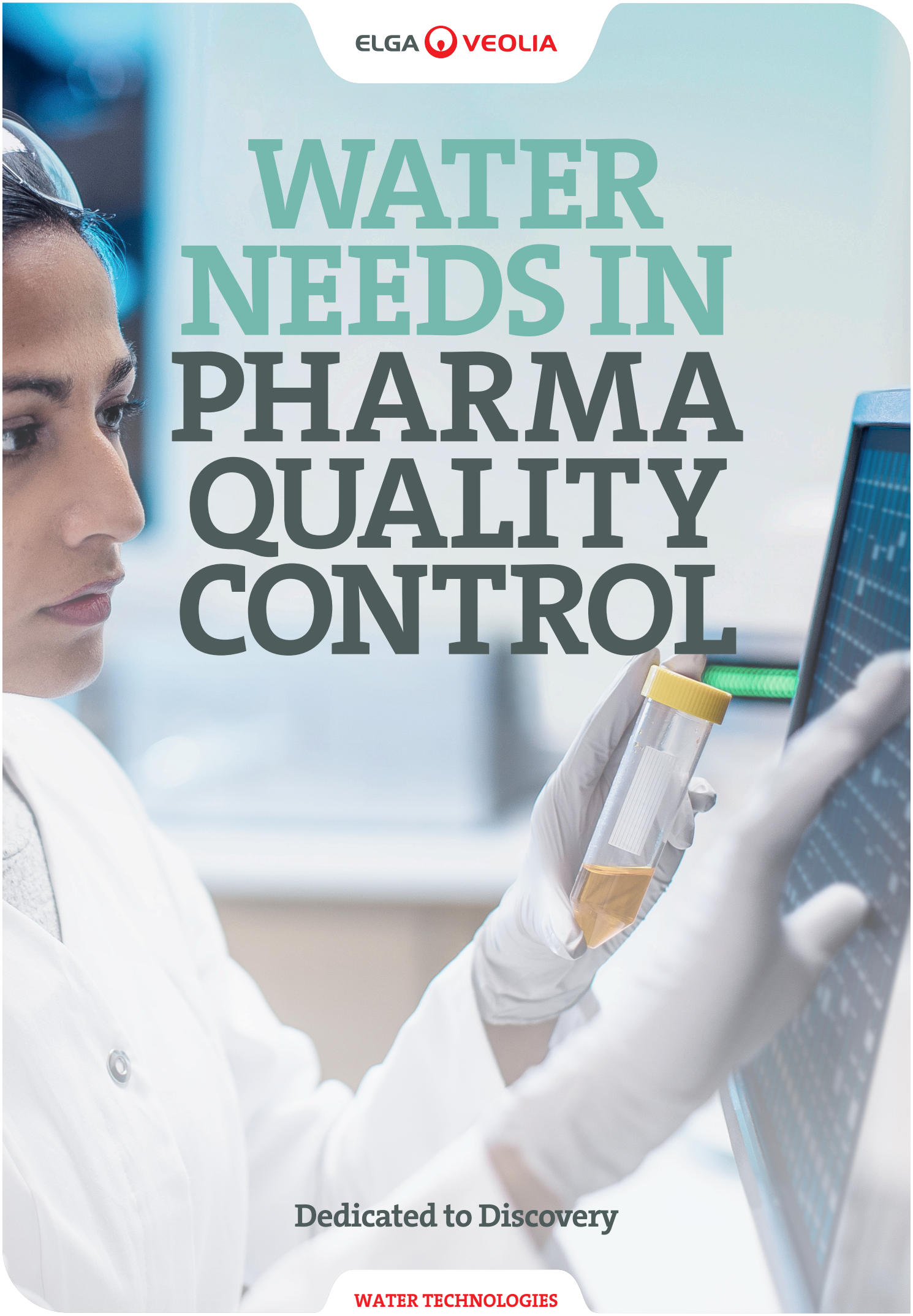
WATER NEEDS IN PHARMA QUALITY CONTROL



Dedicated to Discovery

WATER TECHNOLOGIES

Inside

SECTION 1

Water and pharma

CHALLENGE: ENSURING WATER IN PHARMA QC LABS IS COMPLIANT

Water is one of the most widely used substances in the pharmaceutical industry. It functions as an ingredient, a cleaning agent, a reagent, a solvent and a product, throughout the drug discovery process, from the initial identification of potential drug targets, all the way to the manufacture and quality control of the final product.

However, water also can dissolve, soak up, collect, or be used to suspend many different compounds and gasses, so it can be subject to a broad range of particulate, chemical, and microbiological contaminants, any of which may be potential health hazards. This means that water quality in pharmaceutical manufacturing operations must be effectively controlled.

At what stage of the drug production and QC process does the water used need to meet regulatory compliance standards, or is it enough that it simply meets GxP requirements? How is water used when things go wrong in production, to get to the bottom of QC issues? How can we be sure that any QC issues arising do not come from the water itself? These are just a few of the questions we need to answer when considering suitable water purification systems for QC labs.

Pharmaceutical manufacturers and their quality control laboratories are subject to extensive requirements arising from numerous governmental regulating bodies. Water systems and their associated validation support services must also meet the most stringent GxP regulatory requirements. The Food and Drug Administration (FDA) in the USA, the State Food and Drug Administration (SFDA, in China), the European Medicines Agency (EMA in the EU) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) all play a critical role.

An overview of the different authorities and standards is briefly outlined in Fig. 1.

Government & World Regulatory Organizations	Industry & Government Authorities	Standards, Accreditations & Regulations	Processes
Government Agencies set standards & regulations for industries. Usually geo-specific but can adopt similar regulations from other entities.	Industry authorities interpret & define how to implement standards, accreditations & regulations set by International Regulatory Organizations.	The formal recognition to work to specified standards. All accreditation, regulations and standards include the principles of quality management systems.	Detailed instructions or processes required to meet the specified standards, regulations or accreditations defined by industry and Government Agencies.
• FDA (Food & Drug Agency) • MHRU (Medicines and Healthcare products Regulatory Agency) • EMA (European Medicines Agency) • SFDA (China State Food & Drug Administration) • CDSCO (India Central Drugs Standard Control Organization) • Japanese Pharmaceuticals and Medical Devices Agency	• cGMP (current Good Manufacturing Practices) GLP (Good Lab practices) GDP (Good Document Practices) • GAMP (Good Automated Manufacturing Practice) • PHARMACOPEIA (Japanese/ European/ British/United States Pharmacopeia bodies) • ASTM (American Society for Testing and Materials) • CLSI (Clinical and Laboratory Standards Institute) • ISO	• CFR21 - USP643 - USP645 • ASTM D1193 standard specification for reagent water • CLSI: reagent water • ISO 3696: Water for analytical laboratory use • USP 32, 1.1.2009 US Pharmacopoeia Purified Water Specification • EP 6th Edition, 2009 European Pharmacopoeia Purified Water Specification	• SOPs (Standard Operating Procedures) • Validation

Fig. 1: Pharmaceutical manufacturers and their quality control laboratories are subject to extensive requirements arising from numerous governmental regulating bodies.

QC labs are responsible for auditing the safety of their outputs, so they are subject to additional regulatory standards compared with standard analytical or research labs.

For water purification this means:

- **An electronic signature audit trail for water used in QC (21 CFR Part 11)**
- **Compliance with specific TOC measurement text (USP 643)**
- **A cell constant of +/-2% to meet tighter accuracy requirements (USP 645)**

Challenges with the production and QC process

We will now look at the challenges and solutions in three different areas:

- Water used in the drug production and QC process: ensuring labs stay compliant
- Water needs for manufacture of active pharmaceutical ingredients (APIs): transparent processes and strict adherence to specifications
- What happens when QC goes wrong, and how water can help: leveraging plug and play compliance.

SECTION 2

Water in drug production and QC

CHALLENGE: ENSURING LABS STAY COMPLIANT WHEN WATER IS USED IN THE DRUG PRODUCTION AND QC PROCESS

Given that water is produced "on demand", with all the variables this entails, how can we be sure that any QC issues arising do not come from the water itself? This is just one of the challenges we need to address when considering water purification systems for pharmaceutical QC labs. Some of these challenges are:

i. How do we produce water suitable for QC "on-demand"?

Control of water quality for pharmaceutical production and QC, throughout the production, storage, and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, the challenge across the whole of the drug production and QC process is that water is usually drawn from a system on demand and is not in itself subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is thus essential: hence

the need for compliant water purification systems with associated Standard Operating Procedures (SOPs) that are traceable and can be validated.

SOLUTION:

Water purification systems for drug production and QC must be considered to be direct impact, quality-critical systems that should be qualified. That qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). More information on how to do performance qualification on water purification systems can be found in section 4.

ii. How do we avoid microbial contamination in water for QC?

Checking and controlling the microbiological quality of water for pharmaceutical QC is a high priority, especially given that certain microbiological tests may require periods of incubation, so that results are likely to lag behind the water use. Some types of microorganism may proliferate in water treatment components, and in the storage and distribution systems, producing biofilms. It is very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation, and for that to be a traceable process that can be validated, ideally managed digitally.

SOLUTION:

Water treatment equipment, storage and distribution systems used in QC processes should have features that control the proliferation of microbes during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system, and their performance proven during the commissioning and qualification activities.

iii. How do we ensure water for injection is pure?

Water for injection (WFI) is the highest quality of pharmacopeial water for pharmaceutical use and refers to **any water that is destined for human ingestion.** WFI should be prepared from potable water as a minimum-quality feedwater. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections.

WFI should also be used for the **final rinse** after cleaning of equipment and components that **come into contact with injectable products**, as well as for the final rinse in a washing process in which no subsequent heat is applied. When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it also should conform with the specification for WFI when condensed.

SOLUTION:

To ensure that water meets WFI specifications in its level of purity, and be fully confident that any QC issues are due to the ingredients and not to QC issues with the water itself, the only way is to use a water purification system that is compliant, meeting CGMP or equivalent regulations, so that the water is fully controlled ahead of its use in production and QC processes.

SECTION 3

Water for manufacture of APIs

CHALLENGE: ENSURING TRANSPARENT PROCESSES AND STRICT ADHERENCE TO SPECIFICATIONS

Water is used extensively as a starting material in the **production, processing, and formulation of active pharmaceutical ingredients (APIs)**, intermediates and finished pharmaceutical products (FPP). What can go wrong with these raw materials that go into the production of a drug? How can compliant water help control the challenges involved?

The quality of APIs has a significant effect on the efficacy and safety of medications. Indeed, poorly manufactured, or compromised APIs can result in serious issues, including illness, or even death. The **quality of water required depends on the stage of synthesis of the API:** we may be talking about an intermediate API, the final API, or API cleaning.

TYPES OF PROCESS/PRODUCT	TYPE OF WATER SYSTEM REQUIRED
Initial and Intermediate API Steps	Water equivalent to the local drinking water requirements (i.e., municipal water). Normally deionized water is used as municipal water
API Cleaning (except final API rinse steps)	Water equivalent to the local drinking water requirements (i.e., process water)
API Final	USP/EP purified water
API Cleaning (final rinse steps)	USP/EP purified water

Fig. 2 Determining the required water quality grade for an API process.
USP: United States Pharmacopeia; EP: European Pharmacopeia.[1]

The acceptable grade of water will also depend heavily on the stage at which it is to be used during manufacture, the subsequent processing step, and the nature of the final product. **Not all stages require ultrapure, compliant** water, however, as can be seen in Fig.2.

The justification for a lower water grade quality to be used in the API initial and intermediate steps is as follows:

- **There is typically further solvent addition and/or distillation prior to commencing the manufacture of the final API.**
- **Solvent additions and/or a distillation minimize the growth of microorganisms.**
- **The risk impact to the final API is minimized by the subsequent solvent addition and/or distillation prior to commencing the manufacture of this step.**

Where there is no further subsequent solvent addition or distillation preceding the water addition **- typically API final isolation - a higher water grade is required, to minimize the impact to the final API.** In general, the final rinse of the equipment and containers/closures should be with the same quality of water as that used in the final stage of manufacture of the API or the water that is used as an excipient in a medicinal product.

SOLUTION:

At this last stage (API final isolation and formulation) it is critical to use a water purification system that meets regulatory compliance standards. Such systems minimize risk, ensuring that the water quality is easily measured and automatically recorded as part of the QC process. They also minimize the likelihood of human error, minimizing downtime.

SECTION 4

The role of water in QC failure

CHALLENGE: USING WATER TO GET TO THE BOTTOM OF WHAT HAS HAPPENED WHEN QC GOES WRONG

Pharmaceutical quality control laboratories perform one of the most important functions in pharmaceutical production.

A significant portion of the CGMP regulations pertain to the quality control laboratory and product testing. Similar concepts apply to bulk drugs.[2]

What happens when things go wrong with the link between QC lab and production, in the testing of a drug? How can compliant water help in resolving these challenges?

Serious problems can occur if poor-quality medicines slip through the quality control net. These include but are not limited to:

- **Lack of therapeutic effect that may lead to prolonged illness or death**
- **Toxic or adverse reactions**
- **Waste of limited financial resources**
- **Diminished effectiveness of (and confidence in) the entire healthcare system.**

The following characteristics of a drug determine its quality:

DETERMINANTS OF DRUG QUALITY

Identity	The correct active ingredient is present
Purity	The medicine is not contaminated with potentially harmful substances
Potency	The correct amount of active ingredient is present, usually between 95 and 110 percent of the labelled amount
Uniformity	Consistency of shape and size of the dosage form
Bioavailability*	Must be consistent to provide a predictable therapeutic result
Stability	The activity of the medicine is ensured for the period of time stated on the product label, that is, until the expiration date
Pharmacopeia standard	A drug is deemed to be "good quality" if its characteristics meet the standards described in a widely accepted pharmacopoeia such as the British Pharmacopoeia (BP), European Pharmacopoeia (EP), International Pharmacopoeia (IP), or United States Pharmacopeia (USP).

*Bioavailability is defined here as the speed and completeness with which an administered medicine enters the blood stream. Bioavailability differences exist between manufacturers of the same product. Therefore, careful evaluation of generic medicines may be necessary before purchase and use.

TYPES OF QC TESTS

Quality assurance (QA) protocols include the measurement and recording of the relevant QC tests for drugs prior to their release and distribution.

Efficient QA and QC processes are key to the integrity of the pharmaceutical industry, and to the credibility of the healthcare system. They ensure that when things go wrong, the problem can be easily traced and the product taken out of the system, whether it is underdoing batch release tests prior to distribution or has already been released into the market.

A drug will need to be recalled if it is found to be substandard and is already in the market. There must be rapid communication processes in place, including inventory control systems that track distribution to facilities by batch number, and the recalls need to be classified according to risk to the consumer, varying from no adverse clinical effect, through temporary or mild illness, through to potential for serious illness or death.

QC testing can be split into analytical techniques, microbiological testing and compendial analysis.

The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants. Suitable methods that are sensitive and specific should be used where possible, and may include chromatographic methods.

Other methods may include (alone or in combination) measurement of total organic carbon (TOC), pH, or conductivity; ultraviolet (UV) spectroscopy; and enzyme-linked immunosorbent assay (ELISA).

So as not to implicate the water itself directly in any QC problems, and to get maximum sensitivity in these analytical tests, it is recommended to use water purification systems that are compliant. Type I water is used for most analytical techniques. The microbiological analysis tests will require the water to be sterile, although Type II water will normally suffice.

SOLUTION:

The water purification systems used in pharmaceutical QC testing should follow WHO guidelines for qualification (DQ/IQ/OQ/PQ).[3] In addition, these systems should be simple to use, with plug and play compliance, such that the water from them is constantly monitored and validated upstream of all QC tests.

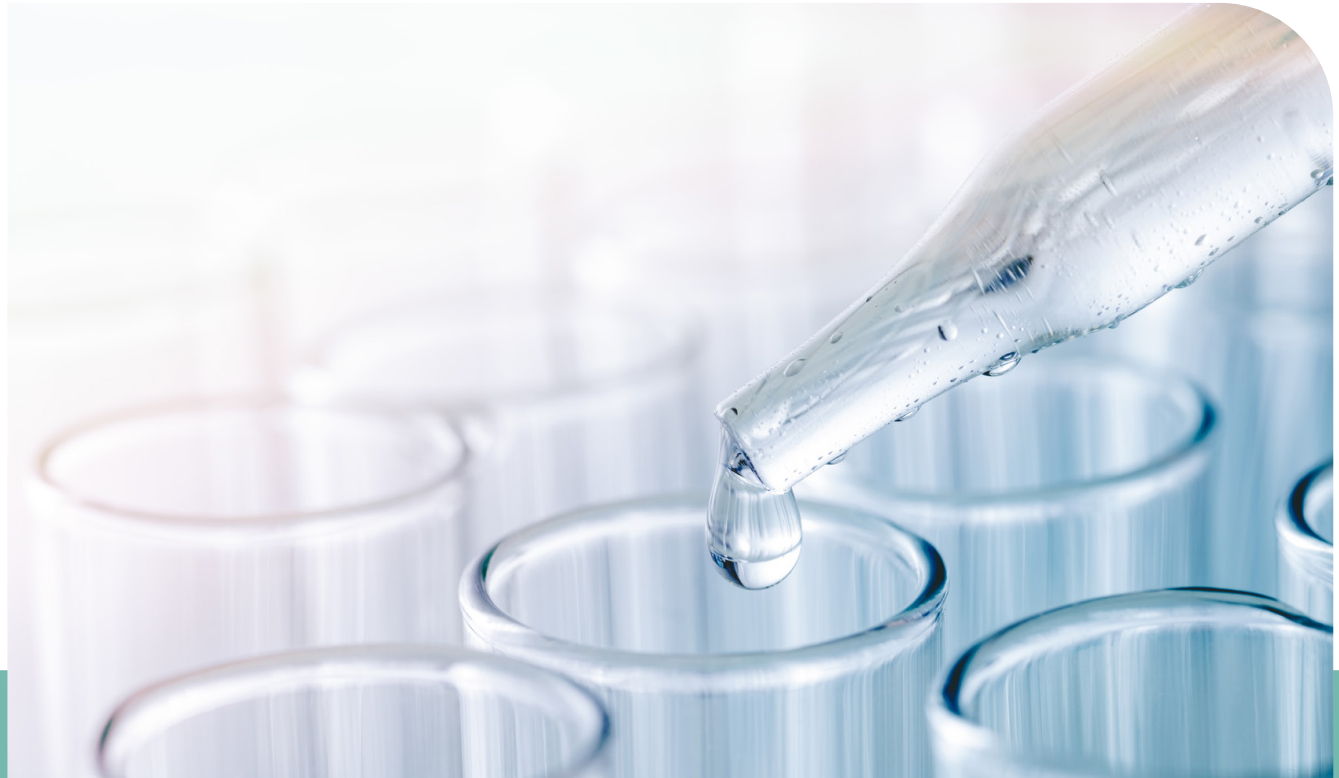
When it comes to performance qualification, these guidelines have been defined in some detail, with a three-phase approach to prove the reliability and robustness of the system over an extended period.

QC TESTING SPLIT INTO ANALYTICAL TECHNIQUES

Analytical techniques
HPLC, UPLC, LC/MS/MS, ELISA, SDS-PAGE

Microbiological testing
Bacterial endotoxin testing, bioburden analysis (e.g., total viable counts), microbial identification, microbiological antibiotic assays

Compendial analysis
A range of tests, including some of the techniques above, to ensure the final product meets pharmacopeia standards.



PHASE 1

A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following procedures should be included in the testing approach.

- **Undertake chemical and microbiological testing in accordance with a defined plan.**
- **Sample the incoming feed water to verify its quality.**
- **Sample after each step in the purification process daily.**
- **Sample at each point of use and at other defined sampling points daily.**
- **Develop appropriate operating ranges.**
- **Develop and finalize operating, cleaning, sanitizing and maintenance procedures.**
- **Demonstrate production and delivery of water of the required quality and quantity.**
- **Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization, and troubleshooting.**
- **Verify provisional alert and action levels.**
- **Develop and refine the test-failure procedure.**

PHASE 2

A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase.

The approach should also:

- **Demonstrate consistent operation within established ranges; and**
- **Demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.**

PHASE 3

Typically runs for one year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features:

- **Demonstrate extended reliable performance.**
- **Ensure that seasonal variations are evaluated.**
- **The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.**

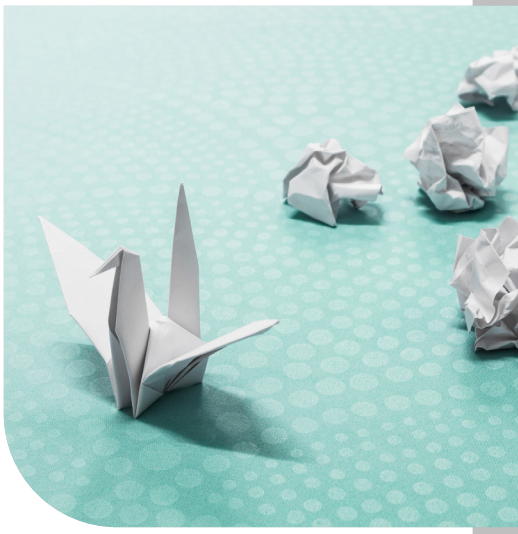
SECTION 5

Water: both ingredient and reagent

COMPLIANT WATER SYSTEMS ARE KEY TO SUCCESSFUL QC

QC is a crucial step in the pharma production process: its failure can be catastrophic for the reputation of a company and the motivation of its staff. Providing QC teams with simple, automated, and validated solutions for the different steps in the QC process will significantly reduce the chances of failure, potentially resulting in decreased downtime, and increased productivity. This is especially important when it comes to water.

The ubiquitous nature of water in the pharmaceutical production and QC process means that we must take care of water quality from both the perspective of being a pure ingredient in its own right, as well as being a key component amongst the reagents used in the QC testing portfolio. By leveraging the inbuilt capabilities of compliant water purification systems, together with pharmacopeia and WHO guidelines, this ironic knot can be resolved, to ensure the success of the drug production and QC process.



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