Agua Purificada para uso farmacéutico según OMS
WHO TRS 970 (Informe 47), Anexo 2

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22 Abr 2020

Educational Background

•Pharmacist, Universidad Central del Ecuador, Quito-Ecuador, 1996
•“Introduction to GMPs for Pharmaceutical Products”, Universidad de Puerto Rico / FDA
•“Project Management”, Universidad Politécnica de Madrid, August 2006
•Advanced English, Wall Street Institute, Quito-Ecuador, November 2010
•Mastery in Process and Quality Management, Universidad Central del Ecuador - 2020

Associations membership and participation

- American Society for Quality (ASQ)
  - Certified Pharmaceutical GMP Professional
  - Regular member
- Ecuadorian Association of Innovative Laboratories
  - Subject Matter Expert of GMP/GSP related topics in representation of Pfizer Ecuador
  - Regular member
- Pichincha-Ecuador, Association of Chemist and Biochemist Professionals
  - Speaker in GMP/GDP related conferences
  - Regular member

Work Experience

- Pfizer – Quality Assurance Manager
- Grünenthal GmbH
  - Quality Assruance Manager
  - Regional QA Manager
  - GMP Corporate auditor – 40 + GMP audits performed in China, India, Europe and Latam
- GMP Training & Cosulyting
  - GMP senior consultant

OBJETIVOS del Webinar:

- Entender de manera sucinta, pero integral, el **Anexo 2 del Informe 46 de la Organización Mundial de la Salud** "WHO good manufacturing practices: water for pharmaceutical use"

- Conocer y diferenciar el **uso de los distintos tipos de Agua** para Uso Farmacéutico.

- Conocer y diferenciar los **sistemas** de: Purificación, Almacenamiento y Distribución de agua según OMS y los principios de Calificación/Validación del sistema.

World Health Organization

Qué son los TRS de la WHO?

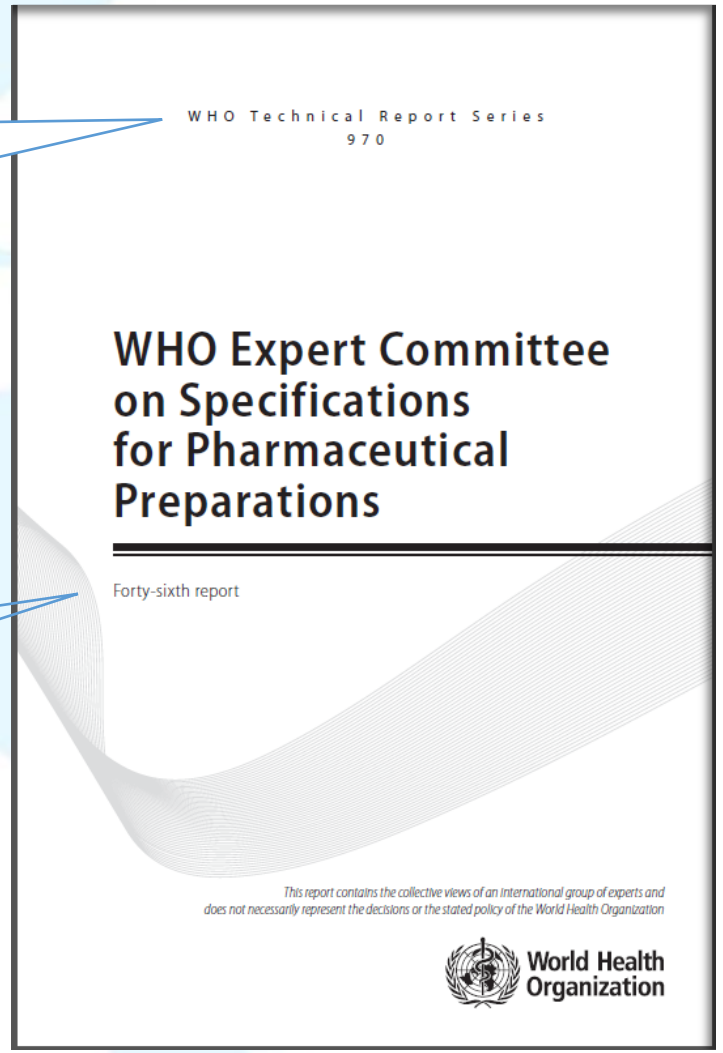
http://www.who.int/medicines/publications/pharmprep/en/

" El *Comité de Expertos en Especificaciones para Preparaciones Farmacéuticas* se reúne todos los años y sus Informes incluyen todas las Guías adoptadas en forma de ***Anexos***"

Los TRS
El Comité de Expertos emite anualmente los **Technical Report Series** – TRS

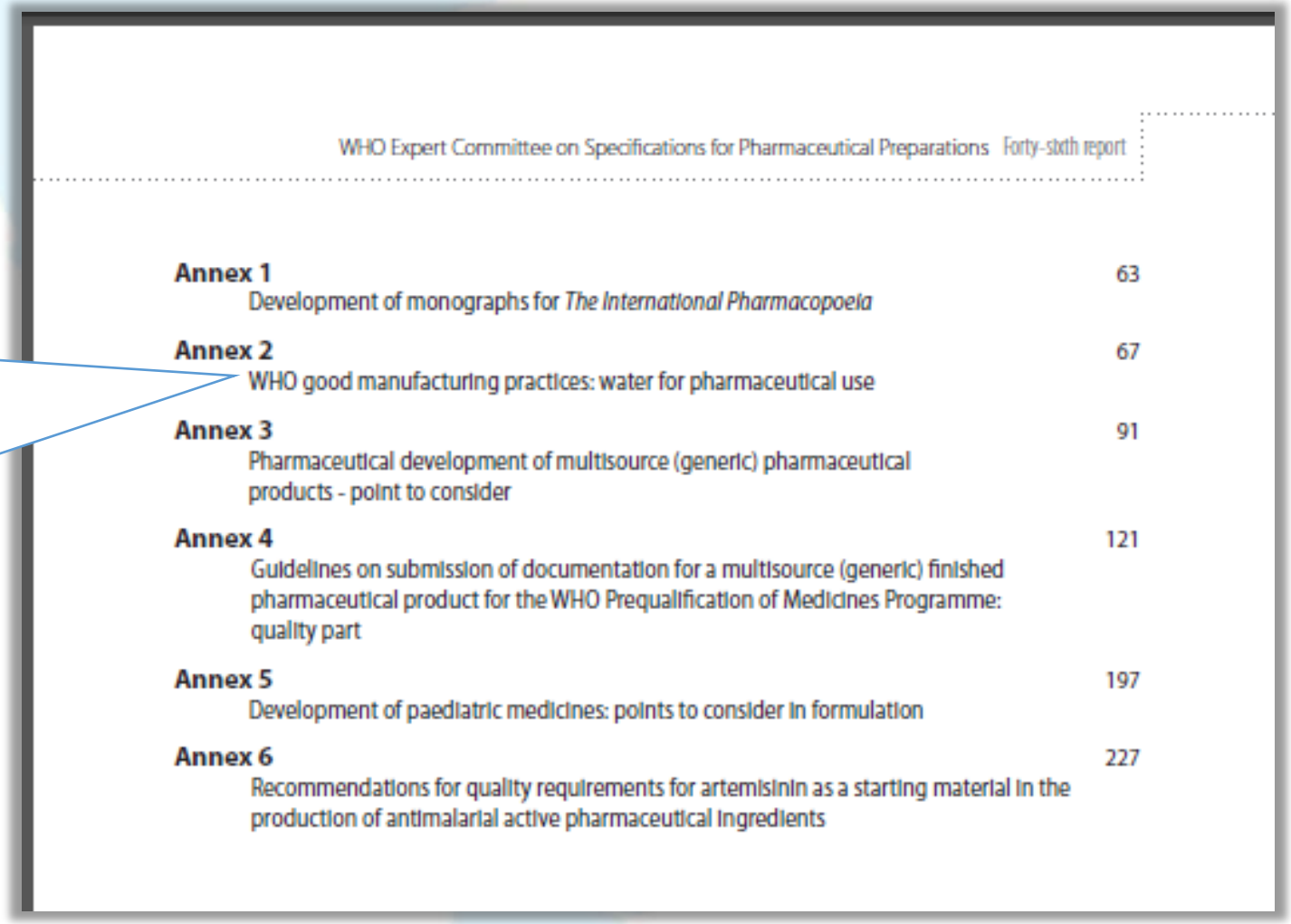
Nomenclatura:

- "WHO Technical Report Series 970"
- Informe 47, 2013



Annex 2

"Good Manufacturing Practices: Water for Pharmaceutical Use"



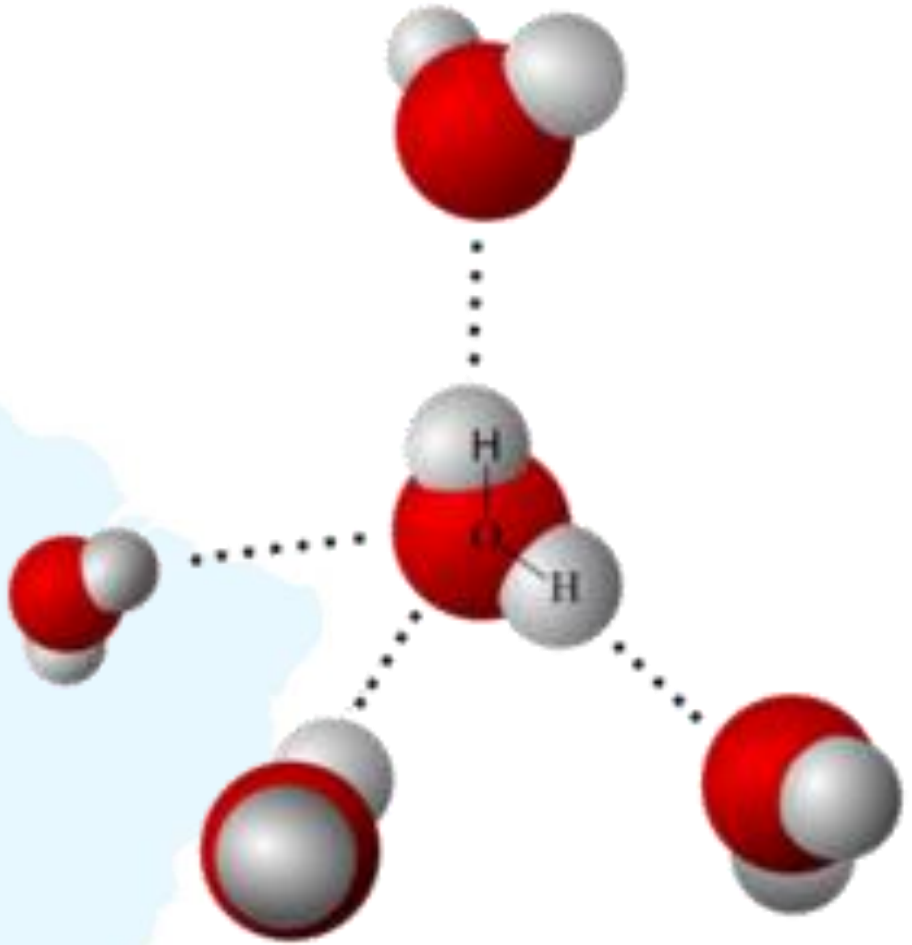
ALCANCE y PROPOSITO DEL ANEXO 2, Informe 47

- **which quality of water to use** for specific applications ?
- Guidance on **specifications** (referred to Pharmacopoeias)
- The guidelines may also be relevant to **other industrial** or specific uses
    - *Nota*: no cubre agua para administración a pacientes o el uso de pequeñas cantidades de agua en farmacias como componente individual en prescripciones.

INTRODUCCION:

- **Agua es la sustancia mas ampliamente utilizada**
    - **Materia prima**
    - **Estructura química** única debido a su polaridad y puentes de hidrógeno
    - Capaz de disolver, absorber o suspender muchos compuestos.

- **Riesgos**
    - Contaminación o reacción con los componentes de una fórmula
    - Crucial eliminar toda posibilidad de contaminación microbiana.
- **Quality Control**
    - Alta prioridad
    - Control Químico y Microbiológico.
    - Durante producción, Almacenamiento y distribución.



2. Principios Generales de los Sistemas de Agua Purificada

- Diseñados, instalados, calificados y mantenidos para asegurar producción de agua de Calidad

- **Capacidad** adecuada

- Los sistemas de producción deben estar **Validados** (IQ, OQ, PQ) … y tener mantenimiento regular

- **Cambios**, aprobados por quality assurance (QA) usando Change Control

- **Sanitización** es parte de los programas de biocontaminacion

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3. Especificaciones

Drinking Water (DW)

Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required

Typical treatment includes **desalinization**, **softening**, **removal of specific**
ions, **particle reduction** and **antimicrobial treatment**.

Derived from a public water supply that may be a combination of more than one of the natural sources listed above.

It is also common for public water supply organizations to conduct **tests** and guarantee that the drinking-water delivered is of drinking quality.

3. Water quality specifications

Drinking-water

It is the **responsibility** of the **pharmaceutical manufacturer** to assure that
the source water supplying the purified water (PW)

Drinking-water quality is covered by the **WHO drinking-water guidelines**, standards from the International Organization for Standardization (**ISO**)and other **regional** and **national** agencies.

3. Water quality specifications

Bulk purified water (BPW)

- Prepared from a drinking-water source as a minimum-quality feed-water.
- It should meet the relevant pharmacopoeial specifications for **chemical** and **microbiological purity** with appropriate action and alert limits.
- It should also be **protected** from **recontamination** and microbial proliferation.
- BPW may be prepared by:
  - Reverse osmosis (RO)
  - RO/electro-deionization (EDI)
  - Vapour compression (VC).

3. Water quality specifications

Bulk highly purified wáter (BHPW)

Prepared from drinking water as a minimum-quality feed-water.

BHPW is a unique specification for water found only in the *European Pharmacopoeia*.

This grade of water must meet the same quality standard as water for injections (WFI), including the limit for endotoxins, but the water-treatment process used may be different.

Current production methods include:

- **Double-pass RO** + **ultrafiltration** and **deionization**.

3. Water quality specifications

Bulk water for injections (**BWFI**)

- BWFI) should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feedwater.

- BWFI is not sterile water and is not a final dosage form.
  - It is an intermediate bulk product
  - BWFI is the highest quality of pharmacopoeial WPU.

The International Pharmacopoeia and the *European Pharmacopoeia* allow only **distillation** as the final purification step.

BWFI should meet **pharmacopoeial specifications** for chemical and microbiological purity (including **endotoxin**)

4. Application of specific types of water to processes and dosage forms

- The grade of water used should **take into account the nature** and **intended use**.

- B**HP**W can be used in the preparation of products when water of high quality (very low in microorganisms and endotoxins) is needed.

- BW**FI** should be used in the **manufacture** of **injectable** and for manufacture of **sterile water** for **preparation** of **injections**.

- BW**FI** should also be used for the **final rinse** after cleaning of equipment and

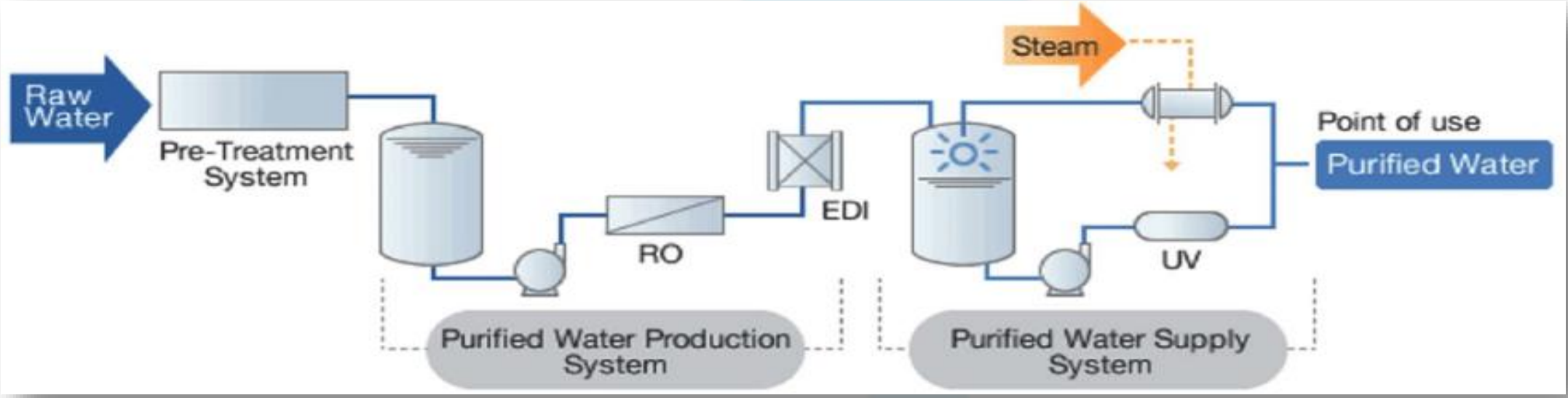
components that come into contact with **injectable products**

Steam in contact with an injectable product in its final container should conform to the **specification** for **BWFI** when condensed.

5. Water purification systems

General Considerations:

- water quality **specification**
- **quantity** of water required
- **feed-water** quality and the variation over time (seasonal changes)
- **support facilities**
  - Raw water, electricity, heating steam, chilled water, compressed air, sewage system, exhaust air
- **sanitization** strategy;
- **support** and **maintain** the water purification equipment;
- **continuity** of operational usage considering hours/days, days/years and planned downtime;
- **life-cycle costs** (capital and operational including maintenance).



5. Water purification systems

General considerations

- **location** of the plant room
- **temperature** that the system will encounter
- the **risk** of **contamination**
- the adverse impact of **adsorptive contact** materials;
- **hygienic or sanitary design**, where required;
- **corrosion** resistance
- a system **configuration** to avoid **proliferation** of **microbiological organisms**
- **tolerance** to cleaning and sanitizing **agents** (thermal and/or chemical)
- ability to collect **simples**

should be monitored routinely

5. Water purification systems

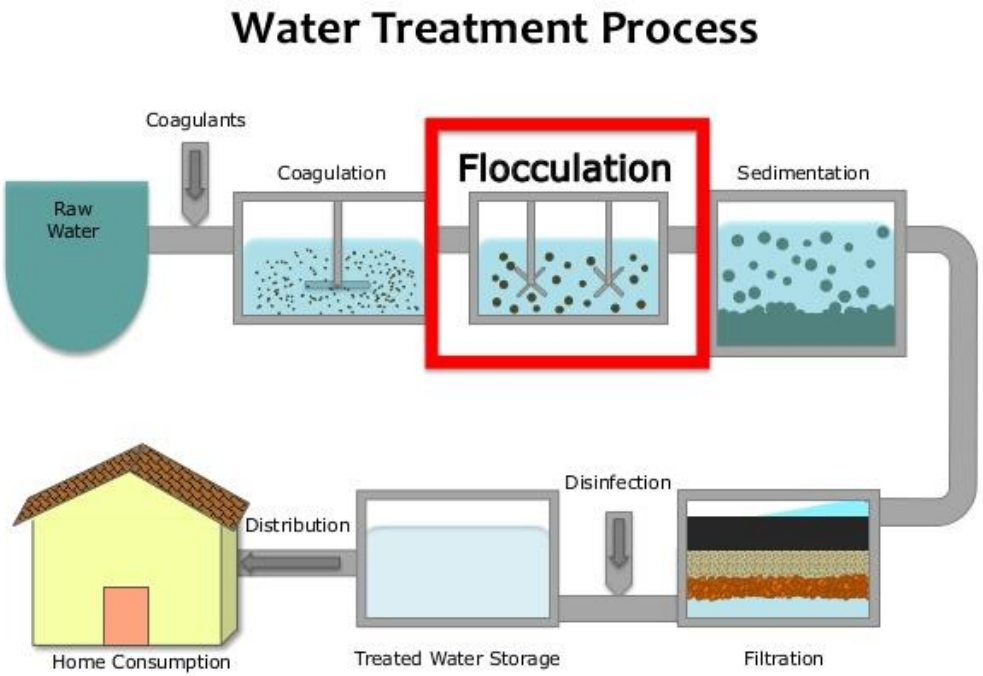
Production of **drinking wáter (DW)**

DW is derived from a **raw water source** such as a well, river or reservoir.

There are **no prescribed methods for the treatment** of raw water to produce drinking-water from a specific raw water source.

Typical processes employed include:

- Desalinization
- **filtration**
- **softening**
- **disinfection** or sanitization (e.g. by sodium hypochlorite)
- **iron** (ferrous) removal;
- precipitation
- reduction of concentration of specific inorganic and/or **organic materials**



DW should be monitored routinely (consider seasonality)
Trend review may be used to identify chan - the **storage** systems must not allow degradation of the water quality

5. Water purification systems

Production of **purified water (PW)**

The following should be considered:

- the **feed-water** quality and its variation over seasons;
- **quantity** of water required by the user;
- water-quality **specification (USP)**
- **appropriately located sampling points**
- **U**nit process steps should be provided with appropriate instrumentation to measure parameters:
  - ✓ Flow
  - ✓ pressure,
  - ✓ Temperature
  - ✓ Conductivity
  - ✓ total organic carbon (TOC).

Ambient-temperature systems are especially **susceptible** to **microbiological** contamination, particularly when equipment is **static** during periods of no or low demand for water.
It is essential to consider the **mechanisms for microbiological control** and **sanitization**.
The method for sanitizing each stage of purification needs to be defined. There should be document evidence
The following should be considered:
– maintenance of minimum flow through the water generation
system is recommended at all times;

5. Water purification systems

Production of **purified water (PW)**

The following should be considered:

- **maintenance**
- **control of temperature** in the system
- provision of **ultraviolet disinfection**
- selection of **water-treatment components** that can periodically be thermally sanitized;
- application of **chemical sanitization** (including agents such as **ozone, hydrogen peroxide and/or peracetic acid**)
- thermal sanitization at **> 65 °C.**

5. Water purification systems

Production of water for injection(WFI)

Distillation is the preferred

The following should be considered :

- the **feed-water** quality
- the required water quality **specification**
- the **quantity** of water

The storage and distribution system should be considered as a key part of the system.

The storage and distribution system should be **configured** to **prevent microbial proliferation** and recontamination of the water (PW, BHPW, BWFI).
It should be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained

6. Water storage and distribution systems

Production of water for injection(s)

pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.

■ ***Compatibility***. - working temperature and potential chemicals that will come into contact with the system at rest, in operation and during sanitization.

■ ***Prevention of leakage***. All materials that come into contact with WPU should be non-leaching at the range of working and sanitization temperatures of the system.

■ ***Corrosion resistance***. PW, BHPW and BWFI are highly corrosive.

When stainless steel is used it should be **at least grade 316**. In general **316L or a higher grade of stainless steel is used**.

6. Water storage and distribution systems

Production of water for injection(s)

The system should be **passivated** after **initial installation** or **after significant modification**.

Smooth internal surfaces help to avoid roughness that can be the source of contamination because of possible accumulation of microorganisms and formation of biofilms.

6. Water storage and distribution systems

Production of water for injection(s)

- The internal material finish should have an arithmetical **average surface roughness** of not
- greater than **0.8 micrometre (Ra).**
- When stainless steel is used, mechanical and **electro-polishing techniques** may be employed.
- ■ ***Jointing***. **welding** in a controlled manner.:
  - qualification of the operator
  - documentation of the welder set-up
  - work session test pieces (coupons)
  - logs of all welds and visual inspection of a defined proportion of welds, e.g. 100% hand welds, 10% automatic welds.
- ■ *Design of protuberances, unions and valves*. unions or valves are used they should be **of a hygienic or sanitary design**. **Appropriate checks** should be carried out to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- ■ *Documentation.* All system components should be fully documented **and be supported by original or certified copies of material certificates.**
- ■ ***Materials****.* Suitable materials that may be considered for sanitary elements of the system include 316L (low carbon) stainless steel, polypropylene, polyvinylidene-difluoride and perfluoroalkoxy. The

7. Operational considerations

Qualification

should follow the validation convention of design review or design qualification
(DQ), IQ, OQ, and PQ.

- Tests on the **source water** must be included within the validation
- The source water should meet the **requirements** for **drinking-water** and any internal specification.

Phase 1. Sample daily the incoming feed-water to verify its quality.
A test period of **two weeks** should be spent monitoring the system
intensively.
System should operate continuously without failure or performance deviation. Usually **water is not used** for finished pharmaceutical product.

■ **Sample** or continuously monitor the incoming feed-water **daily** to verify its quality.
■ Sample or continuously monitor after **each step** in the purification **process.**
■ Sample or continuously monitor **at each point of use** and at other defined sample points.
■ Develop and finalize operating, cleaning, sanitizing and maintenance **procedures (SOPs)**
■ Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
■ Verify provisional **alert levels**.
■ Develop and refine test-failure procedure.

7. Operational considerations

Qualification

Phase 2.
A further test period of **two weeks** should be spent carrying out further **intensive monitoring** while deploying all the refined SOPs after the satisfactory completion of phase 1. :
– **demonstrate consistent operation** within established ranges;
– **demonstrate consistent production** and delivery of water of the required **quantity and quality** when the system is operated in accordance with the SOPs.

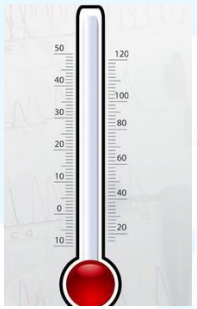
Phase 3. **one year** after the satisfactory completion of phase 2.
Water **can be used** for FFP manufacturing purposes during this phase which has the following objectives:
■ **to demonstrate reliable performance** over an extended period;
■ **to ensure that seasonal variations** are evaluated.

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.

7. Operational considerations

Continuous system monitoring

- A **routine monitoring plan** should be established based on the results of phase 3.
- Parameters:
  - Flow
  - Pressure
  - Temperature
  - Conductivity
  - Total organic carbon (TOC) – online
  - Offline:
    - sample testing for physical, chemical and microbiological attributes.
    - Offline samples should be taken from points of use
    - All water samples should be taken using the same methodology as detailed in production procedures.



Monitoring data should be subject to **trend analysis** (trending should typically be within **2 sigma**).
Suitable **alert and action levels should be established** based on historical reported data.

Any trend towards frequently exceeding alert limits should trigger a thorough investigation of the root cause, followed by appropriate corrective actions.

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