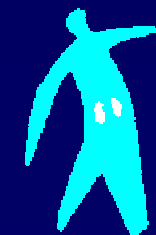
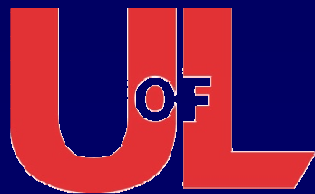


# INTERNATIONAL STANDARDS ON FLUID PREPARATION FOR CONVECTIVE THERAPIES

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Kidney  
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# THE EVOLUTION OF CONVECTIVE THERAPIES

- Convective therapies enhance large molecule removal by using ultrafiltration rates exceeding those required to achieve dry weight; volume balance is maintained by infusing substitution solution directly into the blood line.
- In the original practice of convective therapies, substitution solution was provided using pre-packaged bags or bottles of fluid sterilized using conventional terminal sterilization methods.
- The logistics of using pre-packaged fluids restricted the volume of substitution solution that could be used for a single treatment.
- This limitation was removed by the development of systems that prepared substitution solution on-line by sequential filtration of dialysate through bacteria- and endotoxin-retentive filters.
- The fluid produced by these systems should comply with relevant quality standards.

# INTERNATIONAL STANDARDS FOR HEMODIALYSIS AND RELATED THERAPIES

- ❖ ISO 13958:2009, *Concentrates for haemodialysis and related therapies*
- ❖ ISO 13959:2009, *Water for haemodialysis and related therapies*
- ❖ ISO 11663:2009, *Quality of dialysis fluid for haemodialysis and related therapies*
- ❖ ISO 26722:2009, *Water treatment equipment for haemodialysis applications and related therapies*
- ❖ ISO 23500:2011, *Guidance for the preparation and quality management of fluids for haemodialysis and related therapies*

# QUALITY STANDARD FOR SUBSTITUTION SOLUTION

- According to ISO 11663:2009, Clause 4.1.4, *Microbiological requirements for on-line prepared substitution fluid*:

**“This fluid shall be sterile and non-pyrogenic.”**

**Sterile:** Free from viable microorganisms with a sterility assurance level (SAL) of  $10^{-6}$ .

One in a million chance of contamination.

**Non-pyrogenic:** Having less than 0.03 EU/mL [of endotoxin].

5 EU/kg/h is considered the minimum dose required to produce a fever. For a 70 kg person receiving 6 L/h of substitution solution, an endotoxin concentration of 0.03 EU/mL corresponds to a dose of 2.6 EU/kg/h.

## **COMPLIANCE WITH THE QUALITY STANDARD**

“Compliance of online produced fluid with the requirements of this International Standard [ISO 11663:2009] cannot be demonstrated with traditional test procedures. For this reason, compliance with this International Standard shall be ensured by proper operation of a validated system, verified according to the manufacturer's instructions at the time of installation, and confirmed by the user with a regular monitoring and maintenance schedule.”

**ISO 23500:2011 provides guidance to users on how to routinely achieve compliance with the quality requirements of ISO 11663:2009.**

# ISO 23500:2011

## *Guidance for the preparation and quality management of fluids for haemodialysis and related therapies*

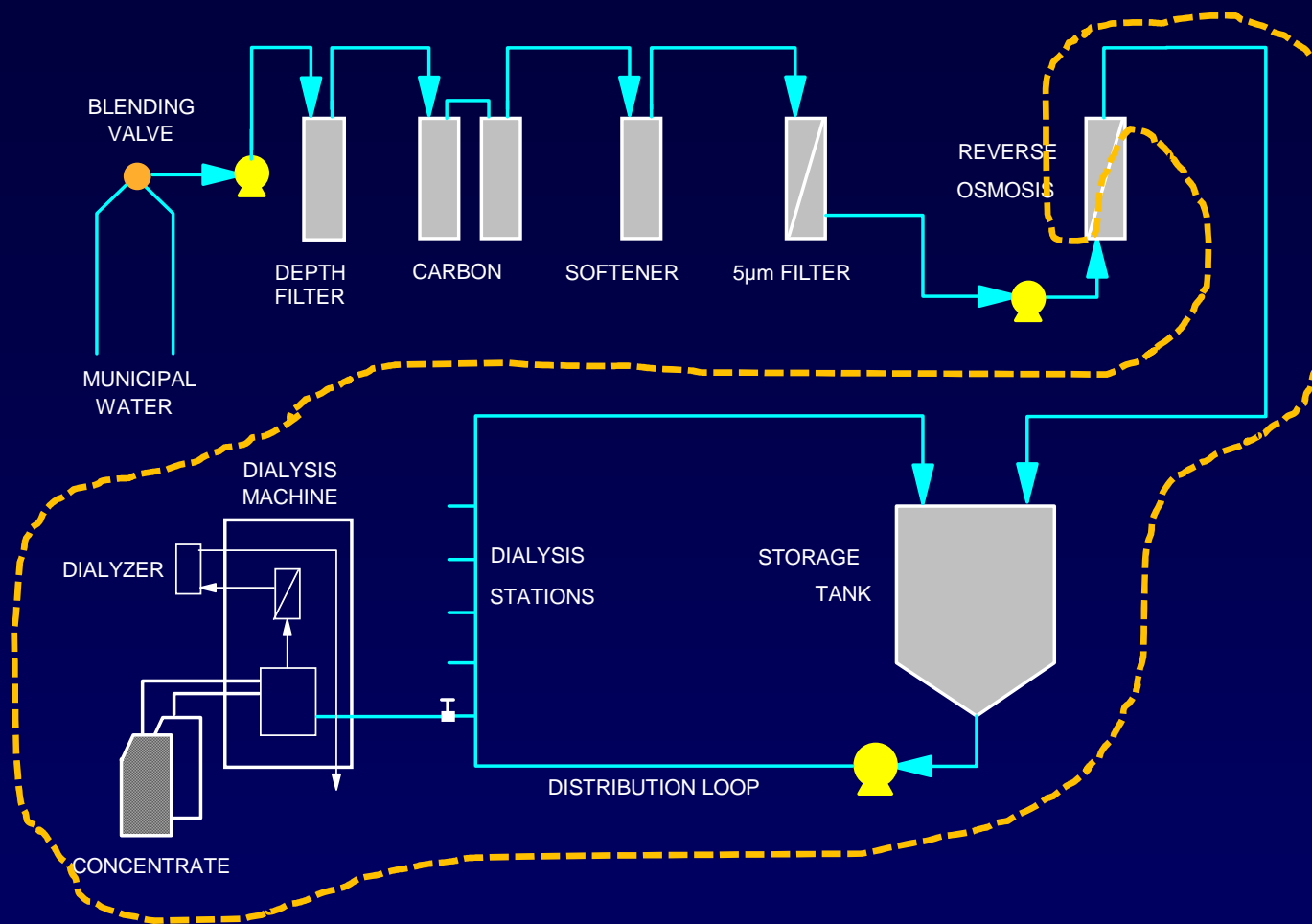
1. Scope
2. Normative references
3. Terms and definitions
4. Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663
5. Critical aspects of system design
6. Validation of system performance
7. Quality management
8. Strategies for microbiological control
9. Environment
10. Personnel

# PREPARATION OF SUBSTITUTION SOLUTION BY SEQUENTIAL FILTRATION

- Substitution solution is produced by sequential filtration through bacteria- and endotoxin-retentive filters capable of reducing the level of bacteria and endotoxin by  $> 10^6 - 10^7$  and  $10^3 - 10^4$ , respectively
- The manufacturer's validation of these systems is applicable only when they are operated under specified conditions.
- In particular, the incoming fluid quality must comply with the maximum contaminant levels set by the manufacturer of the system. For example:
  - Dialysis water contains  $< 100$  CFU/mL and  $< 0.25$  EU/mL; or,
  - Standard dialysis fluid contains  $< 1000$  CFU/mL and  $< 1$  EU/mL.

# PREPARATION OF SUBSTITUTION SOLUTION BY SEQUENTIAL FILTRATION

The challenge for a dialysis facility is to establish a ***Quality Management System*** that ensures the manufacturer's requirements for the incoming fluid are routinely met.



The goal of the **Quality Management System** is to maintain an intact hygienic chain between the product water side of the reverse osmosis module and the point at which dialysis fluid enters the dialyzer or becomes substitution solution.

# QUALITY MANAGEMENT SYSTEM

The *Quality Management System* should be designed to prevent bacterial infiltration and limit biofilm formation.

Critical aspects of the *Quality Management System* include:

- Equipment design (ISO 23500:2011, Annex B);
- Installation and operational verification of equipment (ISO 23500:2011 clause 6);
- Maintenance of equipment (ISO 23500:2011 clause 8); and,
- Monitoring of system performance (ISO 23500:2011 clauses 7, 8 and Annexes C and D).

## SYSTEM DESIGN

- All fluid handling systems should be designed to allow frequent disinfection.
- The preferred methods are hot water pasteurization and ozone since neither requires extensive rinsing to eliminate residuals.
- All fluid handling systems should be constructed from materials that allow the use of hot water or ozone.

# SYSTEM OPERATION

The operation of all fluid preparation systems (dialysis water, concentrate, dialysis fluid) should be subject to formal documentation that:

- Clearly and concisely describes the systems and their operational status;
- Provides detailed procedures for ongoing maintenance and operational verification of the systems performance;
- Defines responsibility for the systems; and,
- Establishes training requirements for all personnel involved in any aspect of fluid preparation.

***This documentation should be consistent with the manufacturer's instructions for use of the system used to prepare the substitution solution.***

# INSTALLATION AND OPERATIONAL VERIFICATION AND QUALIFICATION

Installation should be followed by:

- Formal verification that the installed system matches the pre-approved plans.
- Verification that system performance meets the functional specifications of the system, including the operation of safety systems and compliance with applicable standards for all contaminants.
- A period of normal operation during which there is frequent data acquisition to demonstrate consistent performance.

## SYSTEM MAINTENANCE

- The single most important aspect of maintenance is **regular disinfection** to suppress the formation of mature biofilm.
- Once established, biofilms are extremely difficult to eliminate. Therefore, disinfection must be proactive – designed to suppress biofilm formation, not eliminate biofilm after it has formed.
- Hot water pasteurization or ozone are preferred. They are effective against biofilm and allow frequent disinfection because they leave no chemical residuals (hot water) or residuals with a very short half-life (ozone).

# ESTABLISHING MAINTENANCE AND MONITORING SCHEDULES

Data obtained during the initial period of performance qualification should be used to establish initial disinfection schedules, monitoring plans, and action levels.

**CAUTION:** Cultures and endotoxin tests may not accurately reflect the bacterial burden in a newly installed system because biofilm takes time to form and mature.

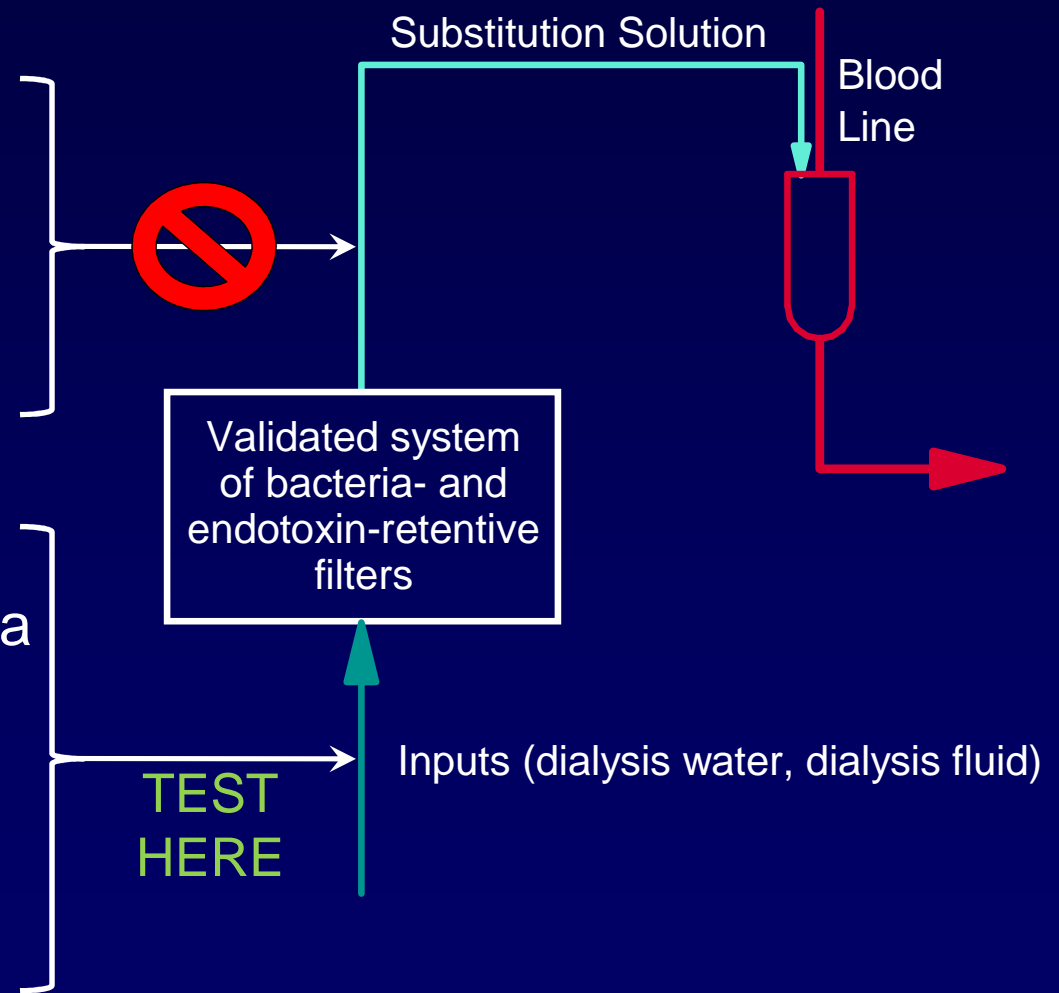
# MONITORING

The purpose of monitoring is to demonstrate the adequacy of maintenance procedures and to ensure that the inputs to the system used to prepare substitution solution meet the requirements of that system's manufacturer.

- Chemical contaminants:
  - Rejection by reverse osmosis and conductivity of product water (continuous)
  - Total chlorine (at least daily when present as monochloramine)
  - Chemical analysis (at least annually)
- Microbial contaminants:
  - Cultures
  - Endotoxin testing

# MONITORING FOR MICROBIAL CONTAMINANTS

- Available culturing methods are not sufficiently sensitive to demonstrate sterility by testing the final substitution solution.
- Sterility of the substitution solution is assured by using a validated system and testing the inputs to that system to show that they comply with the system manufacturer's specifications.



# SUMMARY

- Equipment to perform on-line convective therapies is widely available and has been shown to perform safely and effectively in large numbers of patients in multiple centers and over long periods.
- Equipment for on-line convective therapies incorporates many safety systems; however, the user is responsible for certain residual risks.
- One important user responsibility is maintaining the quality of the fluids supplying the on-line equipment within the limits for which the equipment performance has been validated.
- This responsibility requires the user to establish a **Quality Management System** that encompasses all aspects of fluid preparation, including system design, performance validation, on-going performance verification , and staff training.
- ISO 23500:2011 provides a road map to guide users in establishing their quality management system.