Evolving Dialysis Water and Fluid Quality Standards in Portugal

Rui Lucena[1,2*], *Mário Raimundo*[3,5], *Artur Mendes*[4,5]

1. Fresenius Medical Care, Portugal
2. International Organization for Standardization (ISO) TC150/SC2 Working Group on Renal Replacement, Detoxification & Apheresis
3. Serviço de Nefrologia, Unidade Local de Saúde Loures-Odivelas, Loures, Portugal
4. Serviço de Nefrologia, Unidade Local de Saúde Lisboa Ocidental, Lisboa, Portugal
5. DaVita- Portugal

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Abstract

Dialysis water and dialysis fluid quality have evolved from operational concerns into central components of hemodialysis safety, quality management and service resilience. Early experience showed that water considered safe for drinking could still expose hemodialysis patients to clinically relevant chemical and microbiological hazards, owing to the large volumes of dialysis fluid used, the semipermeable interface with blood, and patients' limited renal capacity to eliminate contaminants. In Portugal, this evolution was shaped by early regulatory milestones, including *Decreto-Lei n.º 392/93,* and by successive editions of the *Manual de Boas Práticas,* from the first *Manual de Boas Práticas de Hemodiálise* in 2001 to the 2011 and 2017 editions of the *Manual de Boas Práticas de Diálise Crónica.* The 2025 edition, officially released in 2026, marks a further step in this pathway, adopting a modular structure and updating guidance on hemodialysis water treatment systems, dialysis water, dialysis fluids, and sustainability. This article places the 2025 revision in historical context and analyses its alignment with the ISO 23500 series, focusing on terminology, chemical and microbiological quality requirements, ultrapure dialysis fluid, online-produced substitution fluid, validation, surveillance, documentation and responsibilities. The revised Manual supports a more integrated approach in which patient safety depends on the full quality chain, from incoming water and water treatment infrastructure to concentrates and final dialysis fluid, with additional validated safeguards for ultrapure dialysis fluid and online-produced substitution fluid when required by the prescribed treatment modality. In the context of climate change, water scarcity, and increasing variability in feed-water quality, efficient, safe, and resilient water treatment systems are essential. Sustainability must therefore be integrated into dialysis practice without compromising chemical or microbiological safety.

Keywords: Dialysis Solutions; Environmental Sustainability; Hemodialysis Solutions; Renal Dialysis/adverse effects; Water; Water Microbiology

INTRODUCTION

The evolution of dialysis water and fluid quality standards is inseparable from the history of hemodialysis itself. In the earliest scientific and experimental phases of dialysis, attention focused mainly on diffusion principles and creating appropriate concentration gradients, rather than on chemical or microbiological contaminants in the water used to prepare dialysis fluid.[1,2] As hemodialysis transitioned from an experimental therapy to a clinical treatment between the 1940s and 1960s, the composition of dialysis fluid emerged as a critical technical concern, particularly regarding the preparation of solutions with suitable electrolyte and buffer characteristics. However, systematic control of water contaminants had not yet become a defining aspect of dialysis practice.[3]

In the early years of chronic hemodialysis, dialysis fluid was often prepared from municipal water with added salts and, in some formulations, glucose. As the immediate technical challenges of dialysis, such as vascular access and machine function, were progressively addressed and patients began to survive longer, it became apparent that dialysis fluid prepared from untreated or inadequately treated water could contain substances harmful to patients or damaging to dialysis equipment.[1-3] For instance, high concentrations of calcium and magnesium in municipal water were associated with carbonate precipitation within

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* **Corresponding Author:** Rui Lucena | rui.lucena@inuvai.com | Rua Professor Salazar de Sousa Lote 12; 1750-233 Lisbon.

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dialysis machine fluid pathways and clinical manifestations of hypercalcemia, leading to the implementation of water softening prior to dialysis fluid preparation.[1,3-5]

By the mid-1970s, aluminum, chloramines, copper, and fluoride had been identified as definitely or probably toxic to hemodialysis patients; for aluminum and chloramines, toxicity could occur at concentrations found in municipal water supplies.[1] Concurrently, the microbiological aspect of dialysis fluid quality became increasingly evident. Pyrogenic reactions and temporary bacteremia during hemodialysis were linked to excessive counts of Gram-negative bacteria and/or endotoxin concentrations in dialysis fluid, and subsequent observations on cytokine activation contributed to the interleukin hypothesis, which associates contaminated dialysis fluid with acute and chronic inflammatory consequences.[3,6] These findings established the principle that water used for dialysis fluid preparation requires dialysis-specific purification and quality limits.

These observations marked the emergence of formal water and fluid quality standards for hemodialysis, initially focused on preventing acute chemical toxicity and gross microbiological contamination associated with pyrogenic reactions. Over time, these standards evolved into a structured risk-control framework, with chemical requirements organized into three main clusters: contaminants with documented toxicity in dialysis patients, electrolytes typically used in dialysis fluid preparation, and other inorganic trace elements. In parallel, microbiological requirements were refined to include total viable microbial counts, explicit endotoxin limits, action levels, more sensitive culture methods, dialysis fluid purity targets, and broader quality-management requirements.[1,3]

The initial formal efforts towards standardization originated in North America. The Association for the Advancement of Medical Instrumentation (AAMI) and the American Society for Artificial Internal Organs began work on hemodialysis machine standards in the late 1960s, and the first AAMI standard for hemodialysis systems was published in 1982.[7] A parallel process occurred in Canada, where the Canadian Standards Association issued a draft standard in 1978.[1] These early standards established maximum allowable levels for chemical contaminants and bacteria in dialysis water, as well as microbiological limits for the final dialysis fluid.[1] The rationale for these standards was informed by the distinct exposure profile of hemodialysis patients: contaminants may cross the dialyzer membrane into the bloodstream, exposure volumes significantly exceed those of typical drinking-water exposure, and patients with renal failure possess limited capacity to eliminate accumulated contaminants.[1,3] This risk is further amplified in contemporary practice by the use of high-permeability membranes and high-volume convective therapies, underscoring the need for rigorous chemical and microbiological control of both dialysis water and dialysis fluid, supported by an efficient, resilient and appropriately monitored water treatment system (Fig. 1).

Portugal followed this international trajectory, yet its regulatory evolution was also influenced by national safety concerns. In the early 1990s, an incident of aluminum intoxication among Portuguese hemodialysis patients was reported by Simões *et al* under the cautionary title "Aluminum intoxication only happens in the other nephrologist's dialysis center" and subject to a subsequent investigation by Ordem dos Médicos.[8,9] During the same period, Portugal enacted *Decreto-Lei n.º 392/93*, which established the licensing and inspection framework for healthcare units providing hemodialysis in both ambulatory and home settings.[10] This decree-law marked an early national regulatory milestone for hemodialysis safety, mandating regular monitoring of contaminants in water supplied to and treated within hemodialysis units, verification of the proper functioning of the unit's water treatment system (WTS), and communication by public water suppliers of changes that could affect relevant contaminants. Following *Decreto-Lei n.º 392/93,* Portuguese good-practice guidance evolved through successive editions of the *Manual de Boas Práticas*. The inaugural edition, the *Manual de Boas Práticas de Hemodiálise*, was approved by *Despacho n.º 14 391/2001* and published in the *Diário da República* in 2001, explicitly to define rules and processes for quality assurance in dialysis units.[11] A subsequent 2006 revision of the *Manual de Boas Práticas de Hemodiálise* is documented by later editions of the Manual. The 2011 document adopted the broader title *Manual de Boas Práticas de Diálise Crónica* and stated that it superseded the 2001 and 2006 versions.[12] The 2017 edition, in turn, explicitly replaced the 2001 and 2006 editions of the *Manual de Boas Práticas de Hemodiálise* and the 2011 edition of the *Manual de Boas Práticas de Diálise Crónica*, confirming a sequence of periodic national revisions.[13] More recently, *Portaria n.º 94/2024/1* reinforced the operational relevance of the *Manual de Boas Práticas de Diálise* by requiring dialysis units to have a dedicated WTS that permanently ensures water quality according to the Manual's requirements.[14]



Figure 1. Schematic layout of a contemporary dialysis water treatment system (adapted from Lucena[26]).

The configuration shown includes tap water inlet (with water meter) and storage tank with dedicated booster pumps to stabilize flow and pressure, pre-treatment [sediment filtration, ion exchange/softening, carbon adsorption, and microfiltration], followed by a double-stage reverse-osmosis (RO) system with integrated heat disinfection capability, enabling interface heat disinfection (IHD). The distribution system supplies the dialysis ward (dialysis machines) and other validated points of use, such as in-house concentrate preparation. The configuration illustrated represents one contemporary example; alternative constellations, including single-stage RO systems and chemical disinfection, may also comply with applicable standards when appropriately validated and operated in accordance with manufacturer instructions.

The 2025 edition of the *Manual de Boas Práticas de Diálise Crónica*,[15] officially released in 2026, marks a significant step in the ongoing revision process. The introduction describes the Manual as an essential reference for ensuring the quality of clinical follow-up and therapy for patients undergoing chronic dialysis, while underscoring the need for continuous, regular updates. The new edition adopts a modular structure guided by flexibility, openness, and sustainability considerations, with independent chapters that can be updated over time and allow the inclusion of new chapters. Within this framework, Part II, Chapter 2 covers the WTS for dialysis, while Chapter 5, also in Part II, addresses environmental sustainability considerations in dialysis units. This revision occurs within a clinical and technological context that has evolved significantly from earlier standards. Contemporary hemodialysis increasingly utilizes high-flux membranes (including medium cut-off dialyzers), bicarbonate-based dialysis fluid, ultrafiltration-controlled systems, online hemodiafiltration (HDF), and high-volume convective therapies.[16-18] These therapies have improved treatment performance but also require tighter control of microbial contamination, endotoxins and other biologically active contaminants in the dialysis fluid pathway.[3] Consequently, ultrapure dialysis fluid has become a central component of modern hemodialysis practice, with reported benefits including improved biocompatibility, reduced inflammatory markers, better erythropoietin responsiveness and mitigation of dialysis-related complications.[17]

International standards now reflect this system-based approach. The ISO 23500 series provides the current international framework for the preparation and quality management of fluids for hemodialysis and related therapies. ISO 23500-1:2024 specifies general requirements for the preparation and quality management of dialysis water, dialysis fluid, and online substitution fluid.[19] ISO 23500-3:2024 delineates minimum chemical and microbiological requirements for water used to prepare dialysis fluids and concentrates.[20] ISO 23500-5:2024 specifies quality requirements for dialysis fluids used in hemodialysis and related therapies, including ultrapure dialysis fluid and online-produced substitution fluid.[21]

This article situates the 2025 revision of the *Portuguese Manual de Boas Práticas de Diálise Crónica* within a historical context and examines how its updated approach to dialysis water and fluid quality management aligns with the ISO 23500 series. The focus is on the quality chain from incoming water to dialysis water, dialysis fluid, ultrapure dialysis fluid, and online-produced substitution fluid, with particular emphasis on the innovations in the 2025 Manual regarding terminology, quality requirements, validation, monitoring, documentation, responsibilities, and sustainability considerations.

FROM REGULATORY CONTROL TO QUALITY MANAGEMENT: THE PORTUGUESE PATHWAY, 1993–2025

The evolution of Portuguese dialysis water and fluid quality guidance reflects a shift from early regulatory control of hemodialysis safety to a broader good-practice and quality-management framework (Table 1). The first major milestone was *Decreto-Lei n.º 392/93*,[10] which established the licensing and inspection regime for healthcare units providing hemodialysis in ambulatory and home settings. Although broader than water quality alone, this decree-law represented an important national response to safety concerns in hemodialysis, including the need to control WTS performance and prevent exposure to clinically relevant contaminants.

A second phase began with the publication of the first *Manual de Boas Práticas de Hemodiálise*, approved by *Despacho n.º 14 391/2001* and published in the *Diário da República*.[11] This document explicitly aimed to define rules and processes for quality assurance in dialysis units,

thereby moving beyond licensing requirements toward a more structured description of technical and procedural expectations for hemodialysis practice. In the area of water and dialysis fluid, the 2001 Manual already addressed water purification, quality assurance, maximum allowable chemical and microbiological values, laboratory monitoring, responsibilities and the quality of dialysis fluid used in different hemodialysis modalities. The quality requirements incorporated into the first Manual followed a deliberately conservative approach, based on reviewing internationally available standards and recommendations and generally adopting the most stringent values for the relevant chemical and microbiological parameters. This reflected the national safety concerns that followed the aluminum intoxication episode and the need to establish a robust protective framework for Portuguese hemodialysis units.

Table 1. Evolution of Portuguese dialysis water and fluid quality guidance, 1993–2025

Year	Milestone	Main relevance to water and dialysis fluid quality
1993	*Decreto-Lei n.º 392/93*	Early regulatory milestone for haemodialysis licensing and inspection; reinforced the need for water treatment control, monitoring of relevant contaminants and communication with public water suppliers.
2001	*Despacho n.º 14 391/2001: Manual de Boas Práticas de Hemodiálise*	First formal Manual; introduced structured good-practice requirements for haemodialysis quality assurance, including water purification, chemical and microbiological limits, dialysis fluid quality, laboratory monitoring and responsibilities.
2006	Revision of the *Manual de Boas Práticas de Hemodiálise*	Documented by later Manuals as an intermediate revision; content not analysed (original document not available).
2011	*Manual de Boas Práticas de Diálise Crónica*	Broadened the title and scope from haemodialysis to chronic dialysis; replaced the 2001 and 2006 haemodialysis manuals; reinforced the concept of the Manual as a dated and continuously updated guidance document.
2017	Revision of the *Manual de Boas Práticas de Diálise Crónica*	Consolidated the previous sequence of revisions; retained a dedicated chapter on haemodialysis water treatment, including quality parameters, equipment, monitoring, responsibilities, documentation and non-conformity management.
2024	Portaria n.º 94/2024/1	Updated the legal framework for dialysis units and explicitly referred to the *Manual de Boas Práticas de Diálise* as the reference for the required water quality assurance by the water treatment system, under Article 34, nº 8.
2025	*Manual de Boas Práticas de Diálise Crónica* 2025 edition, officially released in 2026	Introduced a modular structure guided by flexibility, openness and sustainability; Part II, Chapter 2 focuses on hemodialysis water treatment systems and Part II, Chapter 5 addresses environmental sustainability in dialysis units.

The timeline illustrates the transition from early licensing and inspection requirements toward successive good-practice manuals and, ultimately, a modular framework that allows dialysis water and fluid quality to be interpreted within contemporary quality-management, ISO-alignment and sustainability principles.

Subsequent revisions progressively broadened the scope and structure of Portuguese dialysis good-practice guidance.

The 2017 edition[13] further consolidated this process. It described itself as the fourth version of the Manual and explicitly replaced the 2001 and 2006 editions of the *Manual de Boas Práticas de Hemodiálise* and the 2011 edition of the *Manual de Boas Práticas de Diálise Crónica*.[12] In relation to water treatment, the 2017 Manual retained a dedicated chapter on the hemodialysis WTS, including objectives, quality parameters, equipment selection, installation requirements, water treatment elements, dialysis fluids, laboratory quality control, responsibilities, documentation and actions in case of non-conformity.

The 2025 edition, officially released in 2026, marks a further step in this trajectory. Within this new structure, Part II is dedicated to technical specifications, with Chapter 2 specifically addressing the hemodialysis WTS and Chapter 5 addressing environmental sustainability in dialysis units.[15] This reorganization is relevant because it allows water and dialysis fluid quality to be interpreted not only as a set of technical limits, but as part of a broader framework that includes quality management, validation, monitoring, documentation, responsibilities and sustainability commitment. This historical pathway supports the rationale for analyzing the 2025 Manual in relation to the ISO 23500 series. Earlier Portuguese documents focused primarily on ensuring safe water treatment, defining maximum allowable values, and assigning responsibilities within dialysis units. The 2025 revision provides an opportunity to reassess these requirements in light of contemporary hemodialysis practice, including high-flux dialysis, online HDF, ultrapure dialysis fluid and online-produced substitution fluid. In this context, alignment with ISO 23500 is particularly relevant because it frames dialysis water and dialysis fluid safety as a full quality chain, extending from incoming water and water treatment equipment to dialysis water, concentrates, standard dialysis fluid, ultrapure dialysis fluid and online substitution fluid.

MAIN TECHNICAL EVOLUTIONS IN WATER AND FLUID QUALITY MANAGEMENT

The most relevant evolution is not only the individual numerical limits, but the progressive expansion of what is

considered part of dialysis water and fluid quality. In 1993, the focus was mainly on defined chemical and bacterial contaminants in dialysis water. From 2001 onward, endotoxin testing, high-flux dialysis, and online convective therapies, including HDF requirements, became more visible. The 2011 and 2017 Manuals introduced a clearer structure for chemical clusters, microbiological action levels, validation and routine monitoring. The 2025 Manual consolidates these elements within a broader quality-management model, closer to the ISO 23500 framework, in which safety depends on the entire chain from incoming water to dialysis water, dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid.

Evolution of dialysis water chemical quality requirements

Table 2 illustrates the progressive evolution of Portuguese dialysis water chemical quality requirements from the early regulatory framework of 1993 to the 2025 Manual. While *Decreto-Lei n.º 392/93* already established maximum allowable levels for several clinically relevant contaminants, subsequent editions of the *Manual de Boas Práticas* progressively reorganized these requirements into a more structured framework, distinguishing contaminants with documented toxicity in hemodialysis, electrolytes normally included in dialysis fluid prescription, other inorganic trace elements, and relevant process-control parameters. This evolution reflects a broader transition from prescriptive contaminant limits toward a quality-management approach to dialysis water production and surveillance.

Compared with the 2017 Manual, the 2025 revision brings Portuguese dialysis water chemical requirements closer to ISO 23500-3:2024, particularly for several parameters with documented toxicity in hemodialysis and for electrolytes usually included in dialysis fluid prescription. Relevant changes include realignment of selected maximum allowable levels, such as aluminium, sulfate, magnesium, potassium and sodium, and the continued use of total chlorine as the practical control parameter for chlorine/chloramine exposure.

The 2025 revision also removes selected parameters previously included in Portuguese guidance when the evidence base or routine-monitoring rationale was weak. Thallium was removed from the list of contaminants, as no studies have reported data indicating that this contaminant is of particular concern in the hemodialysis setting. Iron was also removed as a routine chemical requirement. Although iron can foul water purification devices, including reverse osmosis (RO) membranes, and may interfere with softening processes, its inclusion was primarily related to system performance rather than acute patient toxicity. Ammonium was likewise not retained, reflecting its absence from ISO 23500-3 chemical requirements and the limited evidence supporting its routine surveillance as a dialysis water parameter.

Some differences between the 2025 Manual and ISO 23500-3:2024 remain and should be interpreted as local guidance rather than lack of alignment. In particular, the 2025 Manual retains chloride as an electrolyte-related parameter, although ISO 23500-3 does not define a maximum allowable chloride level. The Manual also maintains conductivity and RO rejection rate as process-control indicators, as they remain useful operational tools for assessing WTS performance and identifying when further investigation or corrective action may be required.

Table 2. Evolution of Portuguese dialysis water chemical requirements and comparison with ISO 23500-3:2024

		Dialysis water maximum allowable level/concentration (mg/L)[a]						
Class of contaminants	**Contaminant / parameter**	**Decreto-Lei n.º 392/93**	**Manual 2001**	**Manual 2011**	**Manual 2017**	**Manual 2025**	**ISO 23500-3 (2024)**	**Typical RO rejection rate[b]**
With documented toxicity in haemodialysis	Aluminium	0.01	0.004	0.004	0.004	0.01	0.01	96%-99%c
	Chloramines	0.1	0.1	see total chlorine	see total chlorine	see total chlorine	see total chlorine	P
	Free chlorine	0.5	0.5	see total chlorine	see total chlorine	see total chlorine	see total chlorine	P
	Total chlorine[d]	Not established	Not established	0.1	0.1	0.1	0.1	P
	Copper	0.1	0.1	0.1	0.1	0.1	0.1	96%-99%
	Fluoride	0.2	0.2	0.2	0.2	0.2	0.2	92%-99%
	Lead	0.05	0.05	0.005	0.005	0.005	0.005	95%-99%
	Nitrate (measured as N)	2	2	2	2	2	2	90%-95%[c]
	Sulfate	100	100	50	50	100	100	96%-99%
	Zinc	0.1	0.1	0.1	0.1	0.1	0.1	96%-99%

Dialysis water maximum allowable level/concentration (mg/L)[a]								
Class of contaminants	**Contaminant / parameter**	**Decreto-Lei n.º 392/93**	**Manual 2001**	**Manual 2011**	**Manual 2017**	**Manual 2025**	**ISO 23500-3 (2024)**	**Typical RO rejection rate[b]**
Electrolytes usually included in dialysis fluid prescription	Calcium	2 (0.10 mEq/L)	2 (0.10 mEq/L)	2 (0.10 mEq/L)	2 (0.10 mEq/L)	2 (0.10 mEq/L)	2 (0.05 mmol/L)	93%-99%[c,P]
	Chloride	Not established	Not established	50 (1.41 mEq/L)	50 (1.41 mEq/L)	50 (1.41 mEq/L)	Not established	92%-99%
	Magnesium	4 (0.33 mEq/L)	4 (0.33 mEq/L)	2 (0.16 mEq/L)	2 (0.16 mEq/L)	4 (0.33 mEq/L)	4 (0.16 mmol/L)	93%-99%[c,P]
	Potassium	8 (0.20 mEq/L)	8 (0.20 mEq/L)	2 (0.05 mEq/L)	2 (0.05 mEq/L)	8 (0.20 mEq/L)	8 (0.20 mmol/L)	92%-99%
	Sodium	70 (3.04 mEq/L)	70 (3.04 mEq/L)	50 (2.17 mEq/L)	50 (2.17 mEq/L)	70 (3.04 mEq/L)	70 (3.04 mmol/L)	92%-99%
Other inorganic trace elements	Ammonium (NH_4)	Not established	Not established	0.2	0.2	Not established	Not established	80%-99%[c]
	Antimony	Not established	Not established	0.006	0.006	0.006	0.006	>90%
	Arsenic	0.05	0.05	0.005	0.005	0.005	0.005	50%-99%
	Barium	0.1	0.1	0.1	0.1	0.1	0.1	99%
	Beryllium	Not established	Not established	0.0004	0.0004	0.0004	0.0004	>90%
	Cadmium	0.01	0.01	0.001	0.001	0.001	0.001	93%-99%
	Chromium	0.05	0.014	0.014	0.014	0.014	0.014	85%-99%
	Iron	Not established	Not established	0.02	0.02	Not established	Not established	96%-99%[c,P]
	Mercury (inorganic)	0.02	0.0002	0.0002	0.0002	0.0002	0.0002	94%-98%
	Selenium	0.01	0.01	0.09	0.09	0.09	0.09	99%
	Silver	0.05	0.05	0.005	0.005	0.005	0.005	93%-97%
	Thallium	Not established	Not established	0.002	0.002	Not established	Not established	>90%
Other relevant water process parameters	pH	Not established	< 7	According to IFU	According to IFU	According to IFU	Not established	NA
	Conductivity (µS/cm @ 20ºC)	Not established	35	25	25	25	Not established	95%-99%
	Temperature (°C)	Not established	According to IFU	According to IFU	According to IFU	According to IFU	Not established	NA
	Reverse Osmosis Rejection Rate (%)[f]	Not established	≥ 90%	> 95%[e]	> 95%[e]	> 95%[e]	Not established	NA

[a] Unless stated otherwise
[b] Typical RO rejection shows expected ranges for clean, intact polyamide Thin-Film Composite (TFC) RO at ~25 °C and neutral pH; actual performance is site-specific and dependent on the overall water chemical profile and conditions (e.g. pH and oxidation status). Rejection also varies with system configuration, single-pass vs two-pass/second-stage RO, and with recovery strategy (e.g., concentrate recirculation or partial concentrate reuse to improve efficiency), which increases concentration factor and can shift observed rejection and permeate quality
[c] Rejection efficiency may be significantly compromised when contaminant concentrations exceed critical thresholds
[d] Determining the level of chloramine typically involves measuring both total chlorine and free chlorine and assigning the difference in concentrations to chloramine. To permit a single test to be used, a maximum allowable level for total chlorine is set at the maximum allowable level for chloramine (0.1 mg/L)
[e] A rejection rate below 95% may be acceptable when the feedwater to the reverse osmosis unit has a low degree of mineralization, for example <100 µS/cm, provided that the conductivity of the produced water remains below the specified limit
[f] Reverse osmosis rejection rate (%) is calculated from paired feedwater and permeate measurements of Total Dissolved Solids or conductivity, corrected to 20 °C
[P] Indicates a potential WTS performance concern. RO rejection alone should not be used to assure control: chlorine/chloramine require upstream removal; hardness-related constituents and iron may promote scaling or fouling. Selected organic compounds may require compound-specific verification or additional treatment.
IFU: Instructions for use; NA: Not applicable
Values are presented as maximum allowable levels/concentrations for dialysis water, unless otherwise stated. Historical Portuguese requirements are compared with ISO 23500-3:2024. Typical RO rejection rates are indicative and may vary according to feed-water chemistry, membrane type, operating conditions and system configuration.

Evolution of dialysis water and dialysis fluids microbiological quality requirements

The evolution of microbiological requirements shows an important shift from a limited focus on bacterial contamination in dialysis water toward a more comprehensive framework covering dialysis water, dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid. In *Decreto-Lei n.º 392/93*, the microbiological requirement was limited to total viable microbial counts in dialysis water, with no defined maximum allowable endotoxin level and

no requirements for dialysis fluids. This reflects the historical stage of regulation, where microbiological control was recognized but not yet translated into the broader bacterial/endotoxin surveillance framework used in later standards.

The 2001 Manual expanded the microbiological scope by introducing endotoxin limits and by distinguishing conventional hemodialysis from high-flux hemodialysis and HDF. However, it also reflected a terminology issue that was later corrected: stricter microbiological limits that should apply to dialysis fluid used in high-flux therapies and HDF were effectively linked to the water used for those therapies. This could suggest the need for a special category of "high-flux/HDF dialysis water," whereas later guidance clarified that the key distinction is between dialysis water, standard dialysis fluid, ultrapure dialysis fluid and substitution fluid.

The 2011 revision was a major step forward. It introduced the concept of action levels, defined here as threshold values obtained through routine monitoring that require immediate investigation and corrective action to prevent further deterioration of water or dialysis fluid quality. This is consistent with the ISO rationale that action levels allow corrective action before maximum allowable levels are exceeded. The 2011 Manual also clarified terminology, removed the implied need for a special dialysis water quality category for high-flux HD or HDF, and defined microbiological requirements for dialysis water, standard dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid. Importantly, it stated that online substitution fluid must be sterile and non-pyrogenic and recognized that conformity cannot be demonstrated by conventional end-product testing but depends on a validated device or process. Another relevant development in 2011 was the introduction of more explicit laboratory methodology. The Manual specified recommended culture conditions, including membrane filtration, R2A/TGEA media and incubation at 17°C–23°C for 168 hours, and identified LAL testing for endotoxin measurement. It also included yeasts and filamentous fungi as microbiological indicators in dialysis water, with action and maximum allowable levels.

The 2017 revision largely preserved this structure but corrected the microbiological requirement for ultrapure dialysis fluid, aligning it with the expected limit of <0.1 CFU/mL, equivalent to <1 CFU/10 mL, and <0.03 EU/mL for endotoxin.

Compared with the 2017 edition, the 2025 Manual introduces no major change in the core microbiological limits. It maintains the established requirements for dialysis water, standard dialysis fluid, ultrapure dialysis fluid and online substitution fluid, while preserving the action-level approach for dialysis water and the practical monitoring framework for routine surveillance. In the 2025 Manual, monthly microbiological monitoring of dialysis water includes total viable microbial counts, yeasts and filamentous fungi, and endotoxins, with action levels for dialysis water set at 50 CFU/mL for viable microbial counts, 50 CFU/10 mL for yeasts and filamentous fungi, and 0.125 EU/mL for endotoxins.

The comparison with the ISO 23500 series shows broad alignment for total viable microbial counts and endotoxin limits for dialysis water and dialysis fluids. One intentional difference is the Portuguese decision to retain yeasts and filamentous fungi as routine microbiological indicators for dialysis water. ISO 23500-3 recognizes that fungi can coexist with bacteria and endotoxin in dialysis water but does not define routine maximum limits because further evidence is needed regarding their role in biofilm formation and clinical significance. The 2025 Manual therefore maintains a more conservative local surveillance requirement in this area, while remaining aligned with the ISO framework for the main bacterial and endotoxin parameters.

Table 3 compares the microbiological requirements of the 2025 Manual with the ISO 23500 series. Overall, the 2025 Manual preserves the microbiological structure introduced in earlier Portuguese guidance while aligning with the ISO distinction between dialysis water, standard dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid. The requirement that online substitution fluid be sterile and non-pyrogenic also aligns with ISO 23500 and reinforces the principle that validated devices and processes ensure conformity, not conventional end-product testing alone.

Table 3. Comparison of microbiological requirements in the 2025 Portuguese Manual and ISO 23500 series (2024)

		Manual 2025		ISO 23500:2024		
Fluid Type	**Parameter**	**Maximum Allowable Level**	**Typical Action Level**	**Maximum Allowable Level**	**Typical Action Level**	**Comment**
Dialysis Water	TVMC	< 100 CFU/mL	50 CFU/mL	< 100 CFU/mL	50 CFU/mL	Aligned
	Yeasts and Filamentous fungi	< 100 CFU/10mL	50 CFU/10mL	not established	not established	Portuguese Manual retains additional surveillance
	Endotoxin	< 0.25 EU/mL	0.125 EU/mL	< 0.25 EU/mL	0.125 EU/mL	Aligned
Standard Dialysis Fluid	TVMC	< 100 CFU/mL	not established	< 100 CFU/mL	50 CFU/mL	MAL aligned; ISO defines action level
	Endotoxin	< 0.25 EU/mL	not established	< 0.5 EU/mL	0.25 EU/mL	2025 Manual is more stringent
Ultrapure Dialysis Fluid	TVMC	< 0.1 CFU/mL	not applicable	< 0.1 CFU/mL	not applicable	Aligned
	Endotoxin	< 0.03 EU/mL	not applicable	< 0.03 EU/mL	not applicable	Aligned
Substitution Fluid	TVMC	Sterile	not established	Sterile	not established	Aligned; conformity depends on validated process
	Endotoxin	Non-pyrogenic	not established	Non-pyrogenic	not established	Aligned; conformity depends on validated process

CFU: colony-forming units; EU: endotoxin units; MAL: maximum allowable level; TVMC: Total Viable Microbial Counts.
For ultrapure dialysis fluid and online substitution fluid, action levels are generally not applicable in the same way as for dialysis water because limits approach the detection capability of conventional methods and, in the case of online substitution fluid, conformity depends on a validated production process rather than routine end-product testing.

ALIGNMENT WITH ISO 23500

The extent to which the 2025 *Manual de Boas Práticas de Diálise Crónica* is aligned with the ISO 23500 series is relevant because ISO 23500 currently provides the international reference framework for the preparation and quality management of fluids for hemodialysis and related therapies, covering dialysis water, concentrates, dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid. Accordingly, alignment should not be assessed solely by comparing numerical limits, but also by considering terminology, quality-management principles, validation and revalidation requirements, routine monitoring, documentation, allocation of responsibilities and the interpretation of requirements for online HDF.

Overall, the 2025 Manual closely aligns with the ISO 23500 series in its distinction between dialysis water, dialysis fluid, ultrapure dialysis fluid, and online-produced substitution fluid, and in its use of chemical and microbiological quality requirements for the relevant fluid categories. The strongest areas of alignment are dialysis water requirements, dialysis fluid microbiological quality, online substitution fluid production through validated devices or processes, and the broader quality-management approach based on validation, monitoring, documentation and corrective action (Table 4).

Table 4. Alignment of the 2025 Portuguese Manual with the ISO 23500 series

Domain	2025 Manual	Relevant ISO 23500 part	Alignment	Comment
Terminology	Distinguishes dialysis water, dialysis fluid, ultrapure dialysis fluid and substitution fluid	ISO 23500-1,-3,-5	High	Supports correct distinction between water and dialysis fluids
Water treatment system design and configuration	Provides guidance on WTS components, configuration, installation and operational controls required to produce dialysis water.	ISO 23500-1,-2	High	Supports alignment with ISO 23500-2 by linking system design and configuration to the required dialysis water quality.
Concentrates and in-house concentrate preparation	Addresses concentrates as part of the dialysis fluid preparation chain, with specific attention to in-house preparation, handling, storage, distribution, quality control and traceability within the dialysis unit.	ISO 23500-1,-4	High	Aligns with ISO 23500-4 by reinforcing that final dialysis fluid quality depends not only on dialysis water, but also on controlled concentrate preparation and management.
Dialysis water chemical requirements	Largely aligned with ISO 23500-3	ISO 23500-3	High	Some local additions retained (Chloride and process parameters)
Dialysis water and dialysis fluid microbial requirements	Defines microbiological requirements for dialysis water, standard dialysis fluid, ultrapure dialysis fluid and online-produced substitution fluid, including total viable microbial counts, endotoxin limits and action levels where applicable.	ISO 23500-3,-5	High	Broadly aligned with ISO microbial limits and fluid categories. The 2025 Manual retains yeasts and filamentous fungi as additional routine indicators for dialysis water, representing a conservative local surveillance requirement.
Validation/revalidation	Required after installation and relevant technical changes	ISO 23500-1	High	Supports quality-management approach
Routine monitoring	Includes operational checks and laboratory surveillance	ISO 23500-1,-3,-5	High	Supports trend-based interpretation
Documentation and responsibilities	Defines expectations for protocols, records and responsible functions	ISO 23500-1	High	Supports auditability and accountability
Sustainability	Addressed in dedicated chapter	Not central in ISO 23500	Additional national focus	Relevant if implemented without compromising fluid quality

Importantly, the alignment between the 2025 Manual and ISO 23500 is not limited to dialysis water and dialysis fluid limits. The Manual also addresses WTS design/configuration and in-house concentrate preparation, corresponding to ISO 23500-2[22] and ISO 23500-4.[23] This reinforces the interpretation of fluid quality as a complete preparation chain, from water treatment infrastructure and concentrates to the final dialysis fluid and online-produced substitution fluid.

Remaining differences should mostly be interpreted as local guidance rather than lack of alignment. The 2025 Manual retains chloride as an additional electrolyte-related parameter and includes conductivity and RO rejection rate as process-control indicators. Although these are not ISO 23500-3 maximum allowable contaminant limits, they remain useful tools for monitoring WTS performance and triggering investigation when system performance deteriorates. Similarly, the continued inclusion of yeasts and filamentous fungi reflects a more conservative Portuguese surveillance approach, whereas ISO 23500-3 recognizes their potential relevance but does not establish maximum limits. This shows that alignment with ISO 23500 does not require identical wording or parameter lists, provided the national guidance preserves the same quality and safety principles.

REMAINING CHALLENGES AND OPPORTUNITIES

Although the 2025 Manual represents a substantial step toward ISO-aligned quality management, several areas will require continued development during implementation. These challenges are not primarily related to the definition of maximum allowable levels, but to how dialysis units translate guidance into surveillance practice, documentation, operational resilience and sustainable water stewardship. Three areas are particularly relevant: microbial monitoring, integrated WTS surveillance and sustainability.

Moving beyond culture-based microbial surveillance

Microbiological monitoring remains an area where future developments may further strengthen dialysis water and dialysis fluid quality management. Current standards rely

primarily on culture-based methods, such as heterotrophic plate counts, together with endotoxin testing. These methods remain essential for routine compliance monitoring, but they have inherent limitations. Colony counts provide only a relative estimate of microbial burden and are influenced by sample handling, culture medium, incubation temperature and incubation time.[24] Moreover, culture-based methods detect only organisms capable of growing under the selected laboratory conditions and may therefore underestimate viable but non-culturable microorganisms or other microbial-derived components relevant to biofilm formation and inflammatory risk.

ISO 23500 series already recognizes that alternative microbial methods may be used when appropriately validated and comparable to established methods. This creates an opportunity to complement conventional surveillance with faster or more sensitive technologies. Flow cytometry (FCM) is one such approach, allowing rapid quantification of total and intact microbial cells using fluorescent DNA staining. In a recent study comparing FCM with heterotrophic plate counts for dialysis water microbial monitoring, Lucena *et al*[25] reported higher sensitivity with flow cytometry and suggested that the method may enable earlier detection of microbial deterioration and more timely corrective actions. The potential for rapid, automated or at-line microbial screening using FCM offers a promising avenue for earlier detection of microbial deterioration in dialysis settings. If FCM is adopted, method-specific maximum levels, action thresholds and interpretation rules will need to be established for dialysis water and dialysis fluids.

From periodic testing to integrated WTS surveillance and audit-ready documentation

WTS surveillance involves both online and offline measurements. Real-time or near-real-time monitoring of parameters such as conductivity, flow, hardness, pressure, temperature, RO performance and total chlorine can support early detection of deviations and enable prompt corrective action. In contrast, reliance solely on scheduled offline sampling provides only intermittent snapshots of a continuous process and may miss transient or evolving deviations occurring between sampling intervals.

Offline laboratory testing remains essential for demonstrating compliance with chemical, microbiological and endotoxin requirements. However, its value is greatest when interpreted together with routine operational data, maintenance records, disinfection history and trends in system performance. This is particularly relevant for microbiological surveillance, where culture-based results may require several days and therefore cannot provide immediate warning of system deterioration.

A mature quality-management approach should therefore combine formal laboratory verification with continuous or frequent operational monitoring. Online measurements can identify early warning signals, while offline testing confirms compliance with maximum allowable levels and supports investigation of deviations. The practical objective is to move from periodic confirmation of quality toward proactive assurance of WTS performance, using trends and deviations from baseline values to trigger investigation before patient safety or hydraulic system integrity is compromised.

Integrated WTS surveillance also requires audit-ready documentation. Online measurements, offline laboratory results, maintenance activities, disinfection records, deviations, investigations and corrective actions should be documented in a way that allows reconstruction of system performance over time. This is particularly important when isolated analytical results remain within maximum allowable levels but trends suggest deterioration, such as progressive loss of RO rejection, increasing conductivity, recurrent chlorine breakthrough or rising microbial counts. In this context, documentation should not be viewed only as administrative evidence of compliance, but as a core quality-management tool supporting traceability, accountability and timely decision-making.

Integrating sustainability into dialysis water and dialysis fluids quality management

The 2025 Manual explicitly introduces environmental sustainability as one of the guiding principles of its new structure and includes a dedicated chapter on sustainability in dialysis units. This is an important step because dialysis water and fluid quality management can no longer be separated from the broader need to improve resource efficiency and resilience. However, the translation of sustainability principles into routine dialysis practice requires a pragmatic, measurable and safety-oriented approach. Water-saving strategies should not be implemented as isolated initiatives, but as part of the same quality-management framework that governs WTS design, validation, monitoring, maintenance and corrective actions.

Practical implementation should begin with understanding current water use. A professional water audit, supported by direct measurements at critical points of the clinic and WTS, can help distinguish fixed losses from treatment-related consumption, identify avoidable waste and define realistic internal key performance indicators. Such an approach is consistent with recent recommendations emphasizing water audits, metering, RO recovery, reject-water reuse where permitted, optimization of pretreatment cycles and alignment of RO operation with treatment schedules as feasible strategies to reduce water consumption.[26]

Sustainability measures must remain subordinate to dialysis water and dialysis fluid safety. Increasing RO recovery, modifying disinfection frequency, using standby or eco-flow modes, reusing RO reject water or changing concentrate logistics may reduce water use, but each intervention should be evaluated within a validated

operating envelope and in accordance with feed-water quality, manufacturer instructions, local regulation and microbiological trends. In this sense, the opportunity created by the 2025 Manual is not simply to "save water," but to integrate water stewardship into a controlled, auditable and ISO-aligned quality-management system.

A more pragmatic next step for Portuguese dialysis units would therefore be to convert the sustainability guidance of the Manual into operational practice: quantify water use, define site-specific Key Performance Indicators such as liters per treatment and RO recovery, document the local feasibility of reuse options, review disinfection and pretreatment cycles, and ensure that any efficiency measure is supported by surveillance data. Lucena[27] further explored inefficiencies in current dialysis water use and proposed strategies to optimize consumption without compromising safety. This approach allows environmental goals to be pursued without compromising the chemical and microbiological quality requirements that remain fundamental to patient safety.

Conclusion

The 2025 *Manual de Boas Práticas de Diálise Crónica* represents an important evolution in Portuguese guidance for dialysis water and fluid quality management. Compared with earlier versions, it moves beyond a predominantly prescriptive approach to water treatment and consolidates a broader quality-management framework, supported by clearer terminology, updated chemical and microbiological requirements, validation, routine surveillance, documentation, defined responsibilities and specific considerations for online HDF. Its closer alignment with the ISO 23500 series reinforces the interpretation of fluid quality as a complete preparation chain, extending from incoming water and water treatment infrastructure to dialysis water, concentrates and final dialysis fluid, with additional requirements for ultrapure dialysis fluid and online-produced substitution fluid when required by the prescribed treatment modality.

This evolution is particularly timely. Contemporary hemodialysis depends on efficient, safe and resilient water treatment systems capable of maintaining performance under variable feed-water conditions, increasing treatment complexity and growing environmental pressures. Climate change, water scarcity, infrastructure vulnerability and potential deterioration in source-water quality reinforce the need for systems that are not only compliant at a single point in time, but continuously monitored, well documented, properly maintained and able to support timely corrective action. Recent sustainability-focused guidance in nephrology also emphasizes that water stewardship should become part of routine dialysis practice, including water audits, metering, RO recovery optimization, reduction of avoidable fixed losses and reuse strategies where technically and legally appropriate.

The challenge for Portuguese dialysis units is therefore to translate the revised Manual into a proactive quality-assurance culture, rather than treating it as a static compliance checklist. Sustainability measures must be pursued without compromising chemical or microbiological safety, and any efficiency strategy should remain embedded within a validated and auditable quality-management system. In this sense, the 2025 Manual provides an opportunity to modernize Portuguese practice by combining ISO-aligned fluid quality management with a stronger commitment to operational resilience and responsible water use.

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Ethical Disclosures

Conflicts of Interest: Rui Lucena is an employee of Fresenius Medical Care and participates in ISO TC150/SC2 activities related to the ISO 23500 series.

Mário Raimundo and Artur Mendes are employees of DaVita-Portugal and have consulting roles in Ordem dos Médicos.

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accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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