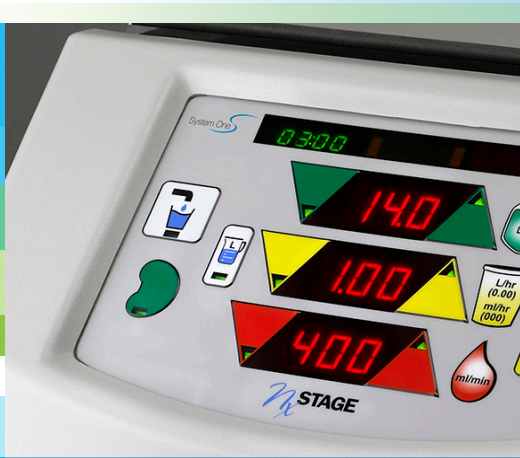
NxSTAGE® Home Therapies

Therapy Handbook

NxStage® Hemodialysis Treatment



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Introduction

The simplicity and portability of the NxStage System One™ has ignited a new wave of home hemodialysis (HHD) and flexible in-center therapy adoption. The system has been used to perform millions of treatments, on thousands of patients, revolutionizing the way patients and providers think about hemodialysis therapy.[1]

NxStage's innovative system design is:

Simple to learn and operate

- Drop-in cartridge
- Simple interface
- No significant home modifications

Portable and flexible

- Compact
- No unique electrical requirements

Allows therapy choice

- Treatment schedule and location

Pays attention to safety

- Comprehensive self-tests automatically performed before each treatment

This document outlines some key concepts of hemodialysis therapy with the NxStage System One. It incorporates the perspectives of some of the clinical investigators and advisors to NxStage, and assumes knowledge of the system's components. For additional details on the system components, see The NxStage System One product brochure, APM494 or outside of the US: APM964. NxStage has prepared this document as an introduction; it does not address all topics critical for managing a patient on the NxStage System One therapy. It is always the physician's responsibility to ensure the appropriate prescription, therapy, and care plan for an individual patient.

Personal and Partner Responsibility in the Home

Home hemodialysis with NxStage requires a patient and partner who are committed to being trained on and following the guidelines for proper system operation. If a patient chooses home hemodialysis, he or she will be responsible for complying with the dialysis prescription, which may require treatments up to six days per week. Each treatment can take about 2½ to 3 hours or more including set-up and tear-down.

If the patient chooses to do home hemodialysis, the patient and his/her partner will need to take on the responsibility for tasks that would normally be taken care of by center staff when receiving treatment in-center. They will need to perform all aspects of the dialysis treatment from start to finish, including setting

up the dialysis equipment, needle insertion, responding to and resolving all system alarms, and system tear-down at the end of treatment.

In addition, patients must monitor their blood pressure, ensure that proper aseptic technique is followed, and follow all of the training material and instructions given by the training nurses. Patients and their partners will also be trained on and need to know how to respond to any health emergencies that might happen during treatment at home, including dizziness, nausea, hypotension, and fluid or blood leaks.

Home Treatment Environment

To do home hemodialysis successfully, patients must take care to ensure that they have a clean and safe environment for their treatments. They will also need to set aside space in the home for the needed supplies.

Risks Associated with All Forms of Hemodialysis

All forms of hemodialysis, including treatments performed in-center and at home, involve some risks. These may include high blood pressure, fluid overload, low blood pressure, heart-related issues, vascular access complications, cramps, backache, headache, dizziness, nausea, an “off” taste in the mouth, fatigue, fever, chills, joint pain, itching, seizures or sinusitis.

All hemodialysis therapies also involve the use of medical devices that introduce the potential for additional risks including air entering the bloodstream, damage of red blood cells, inflammatory reactions, blood chemistry imbalances, blood loss due to clotting of the blood tubing set or accidental blood line disconnection or other leak, allergic reactions, and excess warming or cooling of the dialysate. In addition, dialysis patients may have other underlying diseases that may, in some cases, make it more difficult for them to manage their hemodialysis treatments.

Home Nocturnal Hemodialysis

The NxStage System One may be used at night while the patient and care partner are sleeping. Treatment with nocturnal therapy may require adjustments to medications, including but not limited to iron, Erythropoiesis-Stimulating Agents (ESA), insulin/oral hypoglycemics, anticoagulants, and phosphate binders.

Product Disclaimer: Not all products are cleared or available for sale in all countries.

SECTION ONE:
ADEQUACY AND DOSING

Determining Treatment Options

NxStage System One is designed around the intersection of portability and flexibility, empowering patients to fit dialysis into their unique lifestyle. System One patients can choose from an array of possible therapy options such as conventional thrice weekly to more frequent dialysis, all while having the option to travel with their cycler.

The NxStage Dosing Calculator allows you and your patients to work together to see what fits into their schedule while meeting clinical needs. Designed and built from scientific formulas and peer-reviewed journals, the calculator quickly and easily provides patient-specific therapy treatment schedules including frequency, treatment duration and volume, dialysate and blood flow rates. Compatible with desktop and mobile devices, the calculator is available when and wherever you need it.

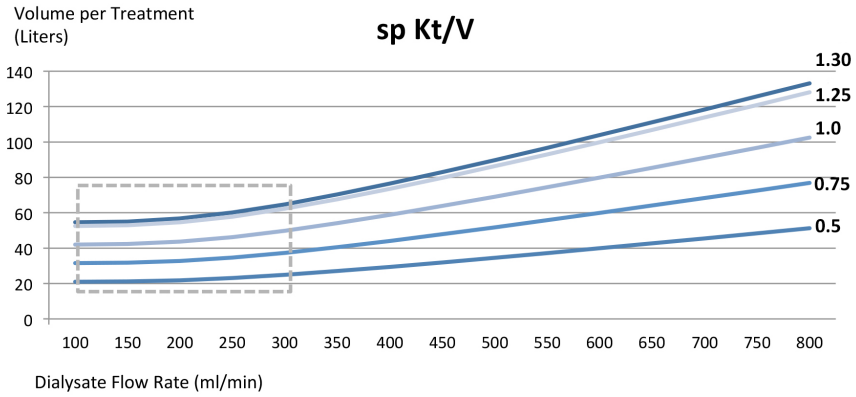
Visit https://dosingcalculator.nxstage.com to try the dosing calculator today.

It is essential to remember these methods only provide starting estimates which will need to be adjusted based on actual patient experience. A physician must ultimately decide, prescribe, and adjust the appropriate fluid volume for a patient.

Time Efficiency (Conventional) vs Water Efficiency (NxStage); High Dialysate Saturation

In conventional hemodialysis, the objective is to deliver as much therapy (and clearance) as possible, in a set amount of time (3-4 hours, 3 times weekly). As shown in Figure 1, this is accomplished by running dialysate flow rates over 500 mL/min. At these high flow rates, clearance rate per unit of dialysate is lower and the spent dialysate is less saturated. A good analogy for this is found in peritoneal dialysis (PD), where less saturated dialysate means there is a low ratio of solute concentrations in dialysate and plasma [D/P ratio]. As a result, conventional in-center dialysis requires large volumes of water to achieve targeted clearance through on-line dialysate production systems.

Figure 1*



Generating large volumes of high quality fluid may be challenging, especially in the home setting. In the home or flexible in-center setting, a therapy should be efficient in its use of fluid, and dialysate should be used to its fullest potential. When the therapy can be scheduled with greater flexibility, time efficiency is no longer a primary driver.

As depicted in Figure 1, NxStage therapy achieves high fluid efficiency by optimizing the effective dwell time of the dialysate in the dialyzer itself. This occurs when blood flow rate is high relative to the dialysate flow rate. Dialysate saturation exceeds 90% when blood flow rate is approximately 3 times dialysate flow rate.[2]

Figure 1 References:

Daugirdas et al, Solute-solver: a web-based tool for modeling urea kinetics for a broad range of hemodialysis schedules in multiple patients. Am J Kid Dis. 2009;54(5):798-809

Gotch et al, Effective diffusion volume flow rates (Qe) for urea, creatinine, and inorganic phosphorus (Qeu, Qecr, QeiP) during hemodialysis. Sem Dial. 2003;16(6):474-476

* Assumes patient total body water of 42 Liters.

spKt/V vs eKt/V vs stdKt/V

Kt/V, or clearance normalized to patient total body water, is the commonly used standard by which therapy dose is measured and compared. However, there are multiple variants of Kt/V:

- **spKt/V (single pool):** The most common "per-treatment" dose, measured in hemodialysis using pre-Blood Urea Nitrogen (BUN) and post-BUN levels and a conversion formula (as described in K-DOQI). spKt/V does not incorporate posttreatment rebound, and may lead to incorrect conclusions when comparing treatments of different durations and/or frequencies.
- **eKt/V (equilibrated):** Also a "per-treatment" dose. Generally accepted to be a more meaningful measure of actual dose delivery in a given dialysis session, as it incorporates postdialysis rebound. Rebound becomes more significant when clearance rates are high and/or treatment times are short. eKt/V is difficult to measure directly in routine clinical practice. Because it's difficult to measure eKt/V directly, several formulas ("rate equations") have been established to translate spKt/V to eKt/V. Daugirdas-Schneidtz, HEMO, Tatersall, Leypoldt, etc. The Daugirdas equation[3] is widely used to estimate actual rebound across a range of therapy rates and durations. However, as with spKt/V, eKt/V may lead to incorrect conclusions when comparing treatments at different frequencies.
- **stdKt/V (standardized):** A "weekly" dose, originally proposed by Gotch[4],has become widely accepted. This measure was developed to allow comparison of therapies of different durations and schedules (as referenced above, neither spKt/V or eKt/V can be simply added together for comparison). Therapy regimens are considered to deliver equivalent doses if the average pretreatment BUN concentrations are equal. This model takes into consideration the kinetics advantages of more frequent and/or longer therapies. **stdKt/V is not directly measured, but can be calculated using spKt/V, treatment time, and frequency.** K-DOQI Guidelines[5] recommend an spKt/V which translates into a minimum stdKt/V of 2.0.
  The NxStage Dosing calculator allows users to set a target weekly stdKt/V. This value sets the stdKt/V that will be provided by all choices in the Options table.
- **URR (urea reduction ratio):** The ratio of post and pretreatment BUN levels. It is an integral component of the spKt/V calculation. However, it does not capture the impact of net fluid removal, or the duration of therapy. As such, K-DOQI discourages the sole use of URR.

Several sample therapy schedules, delivering the same stdKt/V, are depicted below:*

Figure 2*

	Regimen A	Regimen B	Regimen C	Regimen D
Schedule	3x4 Hours	3.5x4 Hours	3.5x8 Hours	6x2 Hours
stdKt/V (calculated weekly dose)	**2.0**			
spKt/V[a] (what is measured)	1.30	0.98	0.89	0.50
eKt/V[b†] (what can be calculated)	1.12	0.86	0.83	0.41
stdKt/V[b‡] (calculated weekly dose)	**2.4**			
spKt/V (what is measured)	1.70	1.24	1.10	0.61
eKt/V (what can be calculated)	1.46	1.07	1.01	0.50

Higher clearances can be achieved. For example, a stdKt/V of 4.0 could be achieved by the following regimens:

Figure 3*

	Regimen A	Regimen B
Schedule	4x8 Hours	5x2 Hours
stdKt/V (calculated weekly dose)	**4.0**	
spKt/V[a] (what is measured)	2.36	1.95
eKt/V[b*] (what can be calculated)	2.00	1.47

References:

Daugirdas et al, Solute-solver: a web-based tool for modeling urea kinetics for a broad range of hemodialysis schedules in multiple patients. *Am J Kid Dis* 2009; 54(5): 798-809

Gotch et al, Effective diffusion volume flow rates (Qe) for urea, creatinine, and inorganic phosphorus (Qeu, Qecr, QeiP) during hemodialysis. *Sem Dial* 2003; 16(6): 474-476

* Assumes patient total body water of 42 Liters.

$$^{\dagger} eKt/V = spKt/V\left(0.924 - \frac{0.395}{t}\right) + 0.056;\ eKt/V \leq spKt/V$$

$$^{\ddagger}\ stdKt/V = \frac{\frac{10080\left(1-e^{-eKt/V}\right)}{t}}{\frac{1-e^{-eKt/V}}{spKt/V} + \frac{10080}{Nt} - 1}$$

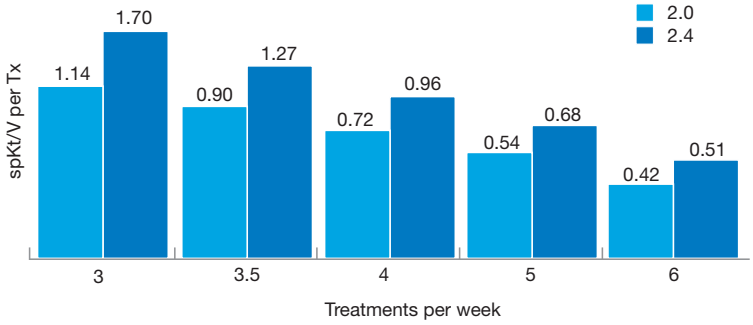
[a]Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993;4:1205-1213.

[b]Leypoldt et al, Predicting treatment dose for novel therapies using urea standard Kt/V. *Semin Dial* 2004; 17(2):142-145.

Choosing a Target per Treatment spKt/V

A weekly stdKt/V target dose can be translated into a per-treatment spKt/V for any given treatment regimen (frequency and duration). The spKt/V is important because it can be routinely measured with pretreatment and posttreatment blood samples to monitor therapy delivery.

Approximate per session Kt/V (spKt/V) to achieve equivalent urea clearances
(weekly standardized Kt/V (stdKt/V) ≥ 2.0)



While many different treatment schedules are utilized, NxStage therapy has often been administered 5x or 6x weekly for 2.5-3 hours per treatment. In this schedule, a spKt/V of 0.42-0.51 for 6 days per week, and 0.54-0.68 for 5 days per week, deliver a weekly stdKt/V of approximately 2.0 and 2.4, respectively, which meets or exceeds the K-DOQI minimum threshold of 2.0. It is important to remember that no consensus on the ideal dose exists, so prescriptions must be tailored to individual patient needs based on physician judgment.

Effluent ("Drain") Volume Divided by Body Water Approximates spKt/V

Formulae aside, Kt/V is intended to convey a relatively simple concept – volume cleared divided ("normalized") by total volume. Total volume is approximated by a patient's total body water (determined by an appropriate anthropometric formula or otherwise). Also, when the dialysate is highly saturated (fluid efficiency), effluent volume approximates total volume cleared.

For NxStage therapy delivered more frequently, Kt/V can be very roughly approximated by dividing total effluent (dialysate plus net ultrafiltration) by estimated total body water. So, to deliver a spKt/V of 0.5 to a patient with 40 L of total body water, approximately 20 L of effluent (e.g.,18 L of dialysate and 2 L of net ultrafiltration) may be required.

SECTION TWO:
THE DIALYSATE

Fluid processing has traditionally been a major obstacle in making hemodialysis more accessible. NxStage has risen to this challenge and offers both easy-to-use portable premixed fluids as well as space-saving concentrate options.

CONSTITUENT	CONV. HD	NXSTAGE
Sodium	135-145 mEq/L (135-145 mmol/L)	140 mEq/L (140 mmol/L)
Buffer/Base	30-38 mEq/L [bicarb] (30-38 mmol/L [bicarb]) 2-4 mEq/L [acetate] (2-4 mmol/L [acetate])	35, 40, 45 mEq/L [lactate] (35, 40, 45 mmol/L [lactate])
Potassium	0-4 mEq/L (0-4 mmol/L)	1, 2, 3 mEq/L 1, 2, 3 mmol/L
Calcium	2.0-3.5 mEq/L (1.25-1.75 mmol/L)	3-3.5 mEq/L (1.5-1.75 mmol/L)
Magnesium	0.5-1 mEq/L (0.25-0.5 mmol/L)	1 mEq/L 0.5 mmol/L
Glucose	2 g/L	1.1 g/L
Quality Standards Adhered To	AAMI	Bags: USP, and BP, European Pharmacopeia (EP) PureFlow SL: AAMI and ISO

NxStage fluids have some differences from those generally offered:

- **Potassium concentrations are available in a range of 1-3 mEq/L (1-3 mmol/L).** To-date, most patients using the System One are treating more than thrice weekly. Due to increased frequency of therapy, potassium fluctuations are typically less extreme. As a result, the amount of potassium added or removed per session is also smaller.
- **The buffer/base level is higher.** Lactate is a 50% larger molecule than bicarbonate ($C_3H_5O_3^-$: molecular weight [MW] of 89 vs. HCO_3^- : MW of 61), and thus the rate at which it diffuses across the dialyzer membrane is slightly lower. A higher concentration helps to ensure adequate buffer balance (see "Lactate Based Dialysate" on the next page).

- **Calcium concentrations are available in a more narrow range.** Calcium does not rapidly exchange between compartments in the body. Between dialysis treatments, calcium accumulates in the patient due to the inability to excrete calcium in the urine. This has led to the use of lower calcium baths (2.0-2.5 mEq/L [1.0-1.25 mmol/L]) in the majority of chronic hemodialysis patients treating thrice weekly in-center in an effort to remove more calcium per treatment. More frequent dialysis may lessen this accumulation as calcium is removed on a more recurrent basis. Thus, less calcium needs to be removed per treatment.

Dialysate Prescription Considerations with Nocturnal NxStage® Therapies

- Evidence for an optimal dialysate composition for nocturnal hemodialysis is lacking. The below information is intended to provide a general overview of basic prescription trends for nocturnal hemodialysis (NHD). "Dialysate composition should be individualized to achieve pre-and postdialysis levels in the local laboratory 'normal' range."[3] At dialysate volumes similar to more frequent hemodialysis, the existing patient dialysate composition prescription may be a good starting point.
- **Lactate Prescription, Patient Co2 Levels** "[Bicarbonate] concentration should be adjusted to achieve a predialysis bicarbonate of 22-24 mmol/L. […] Especially with frequent, long NHD, the dialysis solution [buffer] should be set toward the lower end to limit the occurrence of post-dialysis alkalemia."[3]
- **Calcium Prescription, Patient Calcium Levels** "Patients receiving frequent, long NHD can deplete their total-body calcium unless a slightly higher-than-usual dialysis solution is used. […] the ideal dialysate calcium concentration for an individual patient will vary with dietary calcium intake (including calcium-based phosphorus binder), vitamin D analog use, ultrafiltration volume, and the level of parathyroid gland activity. […] The CSN clinical practice guideline for intensive HD (Nesrallah, 2013) currently recommends using a dialysate calcium of 1.5mM (3.0mEq/L) or higher for long, frequent HD."[3]
- **Patient Phosphorus Levels** "To control serum phosphorus in patients ingesting a usual amount of protein, about 24-28 hours per week of dialysis is required in the absence of phosphorus binder ingestion."[1] The NxStage Nocturnal Hemodialysis (NHD) study utilizing the same frequency of treatments and dialysate volume as Short-daily Hemodialysis (SDHD) demonstrated "improved serum phosphorus (4.6 vs. 5.4 mg/dL, $p<0.001$)."[6]
- **Potassium Prescription, Patient Potassium Levels** With increased frequency of therapy, potassium fluctuations are typically less extreme. As a result, the amount of potassium exchanged between the dialysate and blood per session is also smaller. Per K/DOQI, measures to prevent and manage hyperkalemia should be based on baseline serum potassium (target: 4.5-5.5 mEq/L).[7]

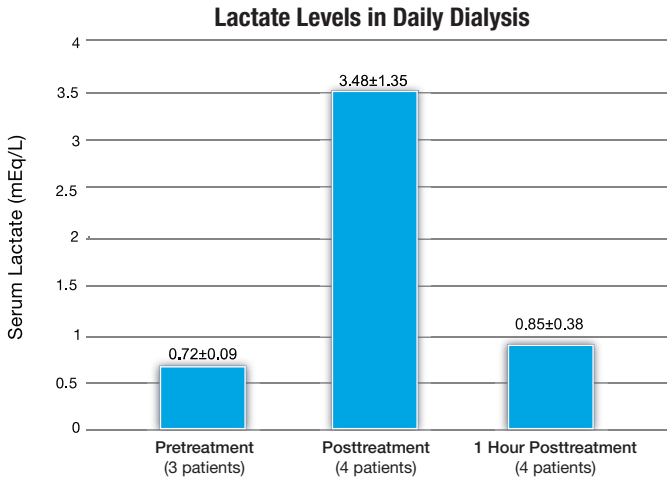
Lactate-based Dialysate

Most conventional hemodialysis uses bicarbonate-based dialysate, which typically uses acetate as an acid concentrate. Therapies using prepackaged fluids, such as PD or the NxStage System One, use lactate based dialysate. Lactate provides a practical buffer alternative, as it is converted by the patient rapidly to bicarbonate on a 1:1 basis primarily by the liver and also the skeletal muscle.

Lactate should not be confused with acetate in terms of patient tolerance and cardiovascular stability. Acetate has known vasodilatory effects that far exceed lactate.[8] In addition, today's lactate-based solutions are comprised entirely of L-Lactate, whereas the mixture of D and L-Lactate stereoisomers used during the 1970s was associated with poor patient tolerance (related to D-Lactate).[9] L-lactate has been studied as a dialysate buffer base, with the following conclusion:[10-12]

"In patients with reduced lactate metabolism, for example, concomitant hepatic failure, after liver transplantation or lactic acidosis, bicarbonate-buffered solutions should be used as the replacement fluid. In nearly all other critically-ill patients, the physiological capacity of lactate metabolism allows the use of lactate-buffered solutions."[10]

Clinicians prescribing hemodialysis with the NxStage System One have observed that lactate-buffered dialysate is well-tolerated by patients. Data shown at the 2004 American Society of Nephrology Annual Meeting (see graph below), showed that moderate elevation of serum lactate levels at the end of treatment is less than that observed in low to moderate physical exertion and returns to baseline levels soon after treatment.



Moran, Doss, Leypoldt, Friederichs, "Lactate Dialysate Requirements in Short Daily Hemodialysis Therapies" 2004 American Society of Nephrology Annual Meeting

Dialysate Options

NxStage offers two sources for dialysate: premixed dialysate bags and dialysate produced by the PureFlow SL Dialysate Preparation System.

Premixed, 5-liter dialysate bags are portable along with the System One. This offers patients the freedom to travel, with a physician prescription, without interrupting their treatment schedule. Usage by the patient has been simplified. The physician determines the number of bags the patient requires; the patient simply hangs and connects the bags for treatment.

Premixed fluid bags are manufactured to European Pharmacopoeia standards and USP. Premixed dialysate bags are terminally sterilized and non-pyrogenic (<0.25 EU/mL). Premixed fluid bags also meet ISO 10993 Biological Evaluation of Medical Devices, which consists of a series of tests intended to address potential biological risks arising from the use of a medical device.

The other source of dialysate is via the PureFlow SL Dialysate Preparation System. The PureFlow SL, together with the System One, is a preconfigured and FDA-cleared hemodialysis system, designed, tested, and validated to yield AAMI/ANSI/ISO quality (which includes standards for chemical and chlorine/chloramine testing) water and dialysate for in-center and home use. This compact system is designed to produce ultrapure product water from ordinary tap water,* which is then precisely mixed with sterile-filtered concentrate to produce ANSI/AAMI/ISO 13958 and 11663 quality dialysate. PureFlow SL minimizes the delivery, storage, management and disposal challenges associated with prepackaged bags of dialysis fluid. Each bag of concentrate replaces between eight and twelve 5-liter bags of premixed dialysis fluids, depending on the patient's prescription. Dialysate concentrate SAKs are manufactured to European Pharmacopoeia standards/USP specifications and have a capacity up to 60 L once mixed. The sterile-filtered concentrate is mixed with ultrapure water† via the PureFlow SL Dialysate Preparation System and meets AAMI RD52:2004 and the more recent versions, ANSI/AAMI/ISO 13958 and 11663 standards.

Sterile and/or ultrapure fluids have been associated with many potential clinical benefits in the general hemodialysis literature, including improved treatment tolerance, improved nutrition, reduced inflammatory markers (e.g., dialysate-associated amyloidosis), and maintained residual renal function.[13]

*Refer to section 4: "The PureFlow SL System" for more details.

† Bench Testing demonstrated that the PureFlow SL system produces water that has <0.1 CFU/ml bioburden and <0.03 EU/ml endotoxins for up to 12 weeks. All concentrate is sterile-filtered prior to entering the presterilized SAK.

SECTION THREE:

GETTING STARTED

Choosing the Lactate Level

NxStage dialysate comes in three lactate buffer concentrations, 35, 40 and 45 mEq/L. It has been reported to us that clinicians typically target a mid-week pretreatment bicarbonate level of 22-25 mEq/L with NxStage therapy. There is no set rule on which formulation a patient might use, but the following table outlines some observations:

Factor	May consider 40 mEq/L	May consider 45 mEq/L
Bicarbonate levels on conventional therapy	≥ 24 mEq/L	≤ 20 mEq/L

Attention should be paid to the patient's concomitant medication regimen and its potential impact on acid/base status. In the NxStage Investigational Device Exemption (IDE) study[12], acid/base was managed patient-by-patient within the targeted range using 40 and 45 lactate formulations. Because physician judgment plays a role in selecting the appropriate formulation, most programs start all patients on one of the formulations (either 40 or 45 mEq/L) and closely monitor bicarbonate levels during the training period, changing if necessary once bicarbonate levels equilibrate (It has been reported to us that this typically happens quickly in the first 1-2 weeks). For instance, if bicarbonate levels are deemed too low when starting with the 40 lactate formulation, a switch to 45 lactate may be made and vice versa. In the less likely case where bicarbonate levels are still too low on the 45 lactate solution, additional methods may need to be employed (e.g., administering oral bicarbonate, or reducing dialysate flow rate).

Monitoring Phosphorus Level

Phosphorus does not rapidly exchange between compartments, making removal time-intensive. Conventional dialysis sessions may not clear all of the excess phosphorus. This has led to the use of phosphate binders in the majority of chronic hemodialysis patients. Serum phosphorus levels may decrease during dialysis, but may rise following treatment as the compartments equilibrate.

To-date, most patients on hemodialysis with the System One are treating more than thrice weekly. It has been shown conversion to more frequent hemodialysis may significantly decrease serum phosphorus.[13]

According to the Handbook of Dialysis, the "serum inorganic phosphorus level drops sharply during dialysis, and then remains at a very low plateau level during the session. For this reason, as for urea, there is some degree of increased level phosphorus removal with SDHD [short daily hemodialysis] relative to three times per week dialysis even when the weekly dialysis time of both therapies is the same. When SDHD is given six times per week with shorter (1.5- to 2.0-hour) session lengths, phosphorus control is not markedly improved, despite a moderately increased amount of phosphorus removal, probably because patients receiving SDHD sometimes feel better, have increased appetite, and increase their phosphorus intake. However, increasing total weekly dialysis time will substantially increase phosphorus removal, to the point that clinical benefits are observed. For example, when SDHD was given six times per week, 3 hours per session, control of serum phosphorus and Ca x P product was markedly improved, and the amount of phosphorus binders administered could be reduced (Ayus et al., 2005)."

As dietary intake may be liberalized with more frequent therapy, patients may take in more phosphorus.[3] This may nullify the gains of more frequent removal, which may explain why patients remain on binders after switching from thrice-weekly therapy.

Choosing a Blood Flow

Since the NxStage cycler blood pump achieves similar blood flows from a given patient access as conventional dialysis machines, we understand that most clinicians prescribe the same blood flows as for conventional dialysis. However, as with conventional dialysis, "overdriving" a vascular access can lead to loss in therapy efficiency and alarms that interrupt treatment. Monitoring access (or arterial) pressure on the system and ensuring that it does not exceed -250 mmHg helps to ensure "overdriving" does not occur.

Anticoagulating the Circuit

Physicians typically prescribe systemic heparin anticoagulation for patients on NxStage therapy. Multiple protocols exist, depending on physician preference. Selection of the type of anticoagulation and dosing protocol is the responsibility of the physician. For short (3.5 hours or less) therapies, anti-coagulation is typically achieved with an initial loading dose of heparin. For longer therapies, an external syringe pump can be connected to the NxStage blood circuit to provide continuous anticoagulant administration. Alternatively, low molecular weight heparin (LMWH) may be an appropriate option for some patients; limited experience has shown that LMWH has been used in conjunction with the NxStage System One.[16] It is worth noting that the System One is designed to eliminate the blood-air interface which may reduce the need for anticoagulation.[17]

Proactively Addressing Blood Pressure (BP) Medications

A near universal finding in studies of more frequent dialysis is that the need for antihypertensive medications to manage blood pressure falls significantly, or may even be eliminated.[14,18] A failure to reduce blood pressure medications as appropriate early in the treatment regimen may contribute to patient malaise and may increase risk of hypotensive events.

Blood pressure response to frequent therapy often begins within the first few days of therapy. We understand that many clinicians proactively adjust medications at the onset of more frequent therapy, then monitor blood pressure closely thereafter during the training period. However, this is not a hard-and-fast rule, as some blood pressure medications may be prescribed for reasons other than blood pressure control. At a minimum, blood pressure and medication response should be closely followed and addressed as needed.

SECTION FOUR:
INTRODUCTION TO THE PUREFLOW SL DIALYSATE PREPARATION SYSTEM

The NxStage System One with PureFlow SL is a preconfigured FDA-cleared hemodialysis system, designed, tested, and validated to yield AAMI/ANSI/ISO quality (which includes standards for chemical and chlorine/chloramine testing) water and dialysate for in-center and home use.
PureFlow SL minimizes the delivery, storage, inventory management, and disposal challenges associated with prepackaged bags of dialysate. Each bag of concentrate replaces between eight and twelve 5-liter bags of prepackaged dialysate, depending on the patient's prescription.

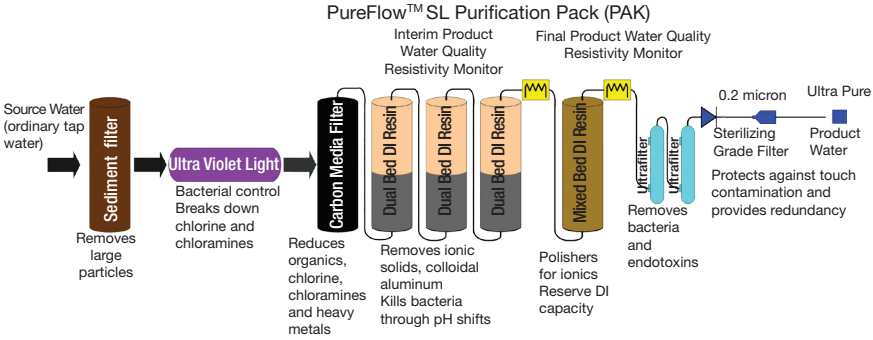
Water Purification and Dialysate Production in One Integrated Unit

Home hemodialysis may benefit the patient, the provider, and overall health care economics. To date, however, complexity and infrastructure of traditional dialysis systems make it difficult to offer these therapies to patients, and as a result, a limited number of patients have gained access.

In contrast, the PureFlow SL, together with the System One, is a preconfigured FDA-cleared hemodialysis system. It incorporates all water treatment and dialysate mixing technology into one small, easy-to-use package. The system produces ANSI/AAMI/ISO 13958 and 11663 quality dialysate in 40 to 60 L batches in the patient's home. As a fully integrated system, the PureFlow SL is designed to prevent the patient from using dialysate that does not meet quality specifications.

Overview of Water Purification With the PureFlow SL

Purified water for dialysate preparation is processed from tap water which meets the PureFlow incoming water specifications (published in APPENDIX C) via the mechanisms outlined below:



The PureFlow SL Purification Pack (PAK) bundles the filters, resin beds, and sensors highlighted in the preceding figure, in an easy-to-replace, disposable box. Once purified, the system is designed to mix a precise volume with the sterile-filtered dialysate concentrate to prepare a batch of the desired dialysate formulation and volume. The system is designed to confirm final concentration of electrolytes in the dialysate by an automated conductivity test, so no external or manual conductivity testing is required. Key purification components of the PAK include:

- **A carbon filter** which reduces organic contaminants, chlorine, chloramines, iron, and hydrogen sulfide. The carbon filter provides a minimum of 10 minutes empty bed contact time (EBCT).
- **A dual bed De-ionization (DI) resin** which removes ionic contaminants (anions and cations) such as mercury, lead, magnesium, silver, calcium, nitrates, sulfates, chlorine, and fluorine.
- **A resistivity sensor** to determine exhaustion.
- **A mixed bed DI resin** which polishes the intermediate product water for ionic contaminants.
- **A final resistivity sensor** to ensure greater than 1.0 Megaohm-cm purity.
- **An ultrafilter array** which removes bacteria and endotoxins.

In addition to the PAK, the PureFlow SL water purification process includes:

- **A high-powered Ultraviolet (UV) Light** in the control unit for bacterial control and breaking down chlorine and chloramines for removal by the carbon filter.
- **A sediment filter** which removes large particles from source water.

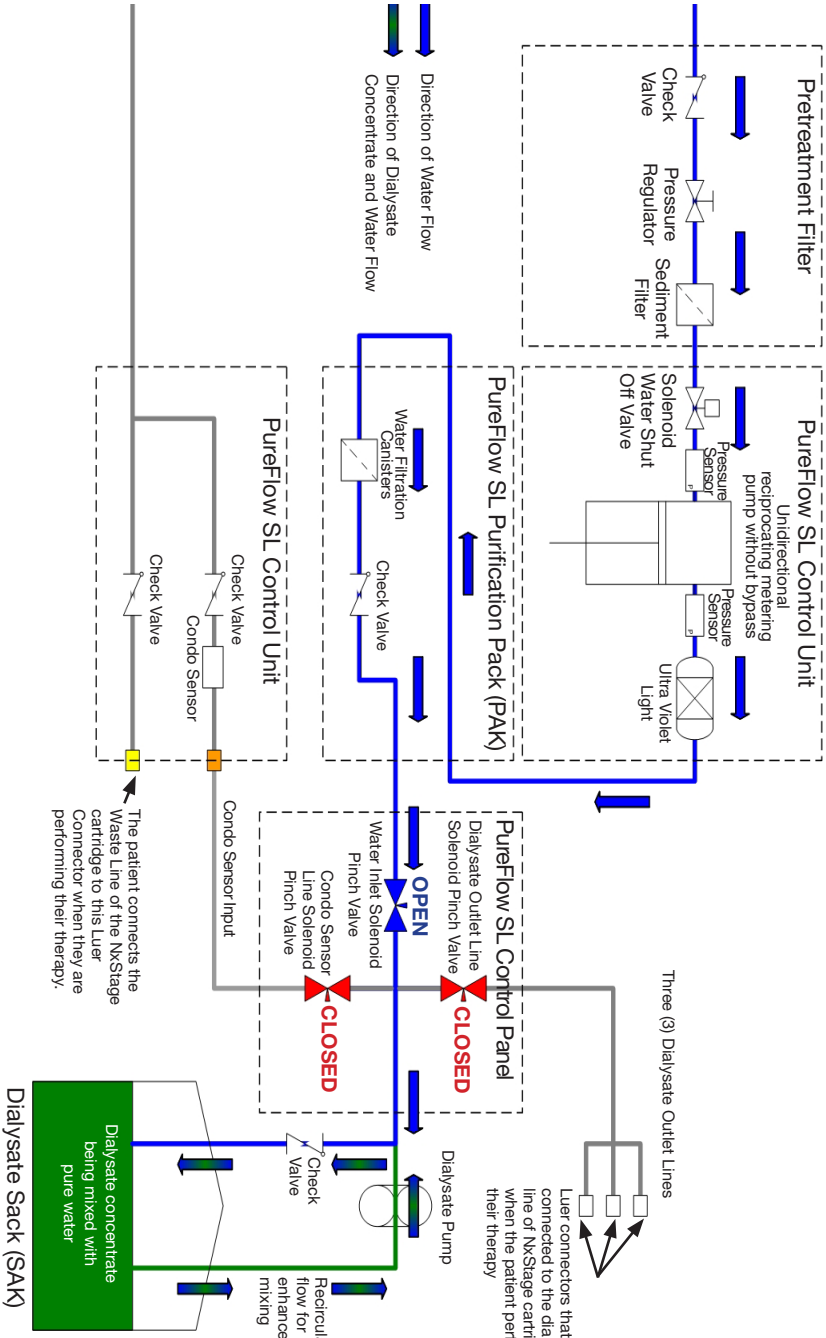
For a more detailed description of the water purification system of the PureFlow SL, see APPENDIX B. For a detailed description of the quality of water produced compared to international standards, see APPENDIX C.

Making and Using a Batch of Dialysate

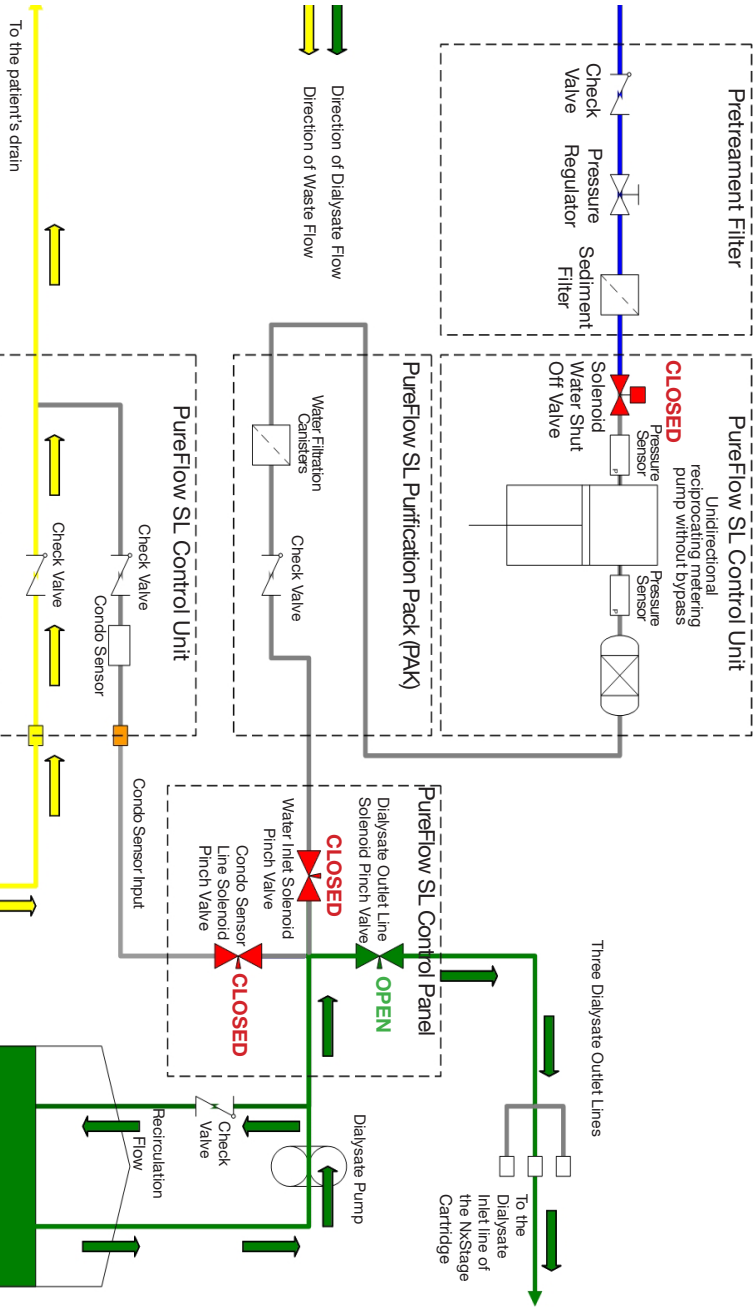
The PureFlow SL is designed to perform a number of operations to make a batch of ANSI/AAMI/ISO quality dialysate including:

- Controlling the precision water metering pump, peristaltic dialysate pump and solenoid valves which command the flow of water and/or dialysate through the PureFlow SL system.
- Purifying the incoming source water using the carbon media, DI resin beds, and dual ultrafilters to produce ultrapure product water.
- Monitoring the resistivity of product water.
- Filling the dialysate sack with the correct amount of ultrapure product water.
- Mixing and heating the resultant dialysate.
- Monitoring the conductivity of the dialysate.
- Providing a sample of chlorine/chloramines testing.
- Monitoring the time to Dialysate Sack (SAK) expiration (or mix-to-use time).
- Monitoring the expiration status and exhaustion of the PAK: The PAK has been verified for 12 weeks and will expire at that time. High levels of Total Dissolved Solids (TDS) and hardness in the source water will, however, result in PAK exhaustion sooner than 12 weeks.

Page 22 shows the fluid flow path through the PureFlow SL while a batch is being made and page 23 shows the fluid flow while a batch is being used. Note, the PureFlow SL system is isolated from the incoming source water when a batch of dialysate is being used for treatment.


Pretreatment Filter
Check Valve
Pressure Regulator
Sediment Filter
PureFlow SL Control Unit
Unidirectional reciprocating metering pump without bypass
Pressure Sensor
Solenoid Water Shut Off Valve
Ultra Violet Light
Direction of Water Flow
Direction of Dialysate Concentrate and Water Flow
PureFlow SL Purification Pack (PAK)
Water Filtration Canisters
Check Valve
PureFlow SL Control Panel
Dialysate Outlet Line Solenoid Pinch Valve
OPEN
CLOSED
Water Inlet Solenoid Pinch Valve
Condo Sensor Line Solenoid Pinch Valve
CLOSED
Three (3) Dialysate Outlet Lines
Luer connectors that are connected to the dialysate line of NxStage cartridge when the patient performs their therapy
Dialysate Pump
Check Valve
Recirculation flow for enhanced mixing
PureFlow SL Control Unit
Check Valve
Condo Sensor
Check Valve
Condo Sensor Input
The patient connects the Waste Line of the NxStage cartridge to this Luer Connector when they are performing their therapy.
Dialysate concentrate being mixed with pure water
Dialysate Sack (SAK)

Using a batch of dialysate



The Disposable Purification Pack (PAK)

The PAK uses proven DI water purification technology to produce AAMI- and ISO quality product water for dialysis. Ions are charged parts of molecules and deionization is a process which uses specially-designed resins to remove the mineral ions from source water:

- Cationic (positively charged ions) contaminants such as aluminum (Al3+), iron (Fe2+), copper (Cu2+), sodium (Na+), magnesium (Mg2+), silver (Ag+), zinc (Zn2+), and calcium (Ca2+), are exchanged with hydrogen ions (H+).
- Anionic (negatively charged ions) contaminants, such as nitrate (NO3-), bicarbonate (HCO3-) sulfate (SO42-), chloride (Cl-), fluoride (Fl-) and bromide (Br-), are exchanged with hydroxide (OH-) ions.

Capturing ionic-based contaminants from the source water displaces hydrogen and hydroxide ions which combine to form water. The resins used in DI systems have finite ion exchange capacities and must be replaced when the hydrogen and hydroxide ions in the resins have been exhausted (i.e., completely replaced by the ionic contaminants in the source water). The removal of ions from the source water by the DI system will produce purified water that is characterized by significantly higher resistivity values (and conversely, lower conductivity values) than the average drinking water supplied by most municipalities.

Exhaustion of the DI resins can therefore be detected by measuring the resistivity of the water once it has passed through the DI resin beds. The PureFlow SL continuously monitors the resistivity of the water once it has passed through the DI resin beds. Exhaustion is determined by a fall in resistivity below the 1MΩcm purity threshold.

PAK life is constrained by both exhaustion and expiration. Exhaustion occurs when resistivity values of the product water fall below a preset purity level. Expiration occurs automatically after 12 weeks of use. After the PAK has exhausted or expired, the control unit will automatically prevent the user from making another batch.

For optimal system performance, PureFlow SL uses two basic configurations of DI resins in the PAK:

- Dual Bed DI Resin configuration: Cation and anion resins are housed in separate layers in the same cartridge or tank.
- Mixed Bed DI Resin configuration: Cation and anion resins are blended together in the same cartridge or tank.

In the PureFlow SL, like most other applications where water purity is critical, dual bed DI resins are followed by mixed bed DI resins.

Advantages of the PureFlow SL System

The PureFlow SL offers a number of advantages:

1. **Removal of incoming contaminants through ionic capture:**
   The single most important advantage of a DI system over many of the competing filtration technologies is the ability to capture and hold incoming contaminants at a preset level rather than simply reducing their levels.

   Other water purification systems, such as RO, work on the principle of relative reduction. These systems are typically designed to reduce incoming water contaminants by 90% or more. If contaminant levels inadvertently rise in the incoming water due to such causes as seasonal variations, drought conditions, or floods, RO systems will typically fall to a lower recovery rate, i.e., they will flush more waste water down the drain to produce the same amount of product water. This can result in increased utility costs.

   If contaminant levels inadvertently rise in the incoming water due to such things as seasonal variations, drought conditions or floods, contaminant levels in the product water used to prepare the dialysate will also rise and may present patient safety issues.

   If contaminant levels in the source water rise, the replaceable PureFlow SL PAK will continue to remove them to AAMI- and ISO quality levels. This ensures PureFlow SL produces AAMI- and ISO quality water and dialysate from a wide variety of water sources without water quality variations affecting the product water quality.

2. **Filtration efficiency not affected by the temperature of the incoming water:** The purification efficiency of a DI system is not dependent on, or affected by, the temperature of the incoming water. Therefore, warm water blending or other temperature compensation techniques are not needed to efficiently operate the PureFlow SL system. Furthermore, since DI systems do not have membranes to foul, as in traditional RO systems, water softening is not required.

3. **Conversion of all incoming water into product water with no waste water as a byproduct:** All incoming source water is converted to high purity product water on a 1:1 basis so one liter of product water is prepared from one liter of source water. The PureFlow SL system prepares either a 40 L, 50 L, or 60 L batch of dialysate which, depending on the patient's prescription, can be used for up to three treatments. The water consumed during a week's worth of treatments on the PureFlow SL is, on average, equivalent to one load of laundry in a typical top-loading washing machine.

   Traditional RO systems require larger volumes of water for each treatment compared to a similarly sized DI system. The ratio of source water to product water in an RO system can be as high as 10:1* (i.e., for every liter of product water produced by the RO system, 10 liters of source water is needed, with 9 liters of water going down the drain as waste water) which could place significant demands on the water supply and result in costly water bills.

4. **Easy installation and lower infrastructure requirements of the PureFlow SL system:** PureFlow SL requires only one simple connection to the source water so no major plumbing modifications are required to install the system. The source water connection is via a simple adapter to the faucet, washer or under the sink. Some may choose to attach the waste line to the drain via a connector as well.

   PureFlow SL runs on standard household power. It uses a standard power cord so an electrician is not needed to wire the power connection of the PureFlow SL system.

   Furthermore, the peak electrical rating of the PureFlow SL is 400 VA which occurs intermittently when the dialysate heaters in the tub of the PureFlow SL cabinet are *ON* so that a dedicated electrical circuit is generally not required of the PureFlow SL.

   The average electrical load of PureFlow SL when operated at room temperature (65 to 72°F / 18 to 22°C) is equivalent to a single continuously operated 100 W light bulb or approximately 70 kilowatt-hours (kwh) per month.

* Mar Cor Purification. http://www.mcpur.com/main/library/tech/TechNotes/general/TN102-Recovery-3002413.pdf. 3002413 Rev E 3/12/2013.

5. **Easy operation of the DI system used in the PureFlow SL PAK:** The PureFlow SL system features continuous on-line monitoring of the product water quality produced by the PAK. When the monitoring system detects the PAK has exhausted, it automatically prevents the user from making a batch of dialysate. A new PAK must be installed and primed and a new SAK loaded in order to make a new batch of dialysate.

   The system also automatically determines when a PAK has expired (i.e., reached the end of its maximum 12 week life) and the PureFlow SL prevents the user from making a new batch of dialysate until a new PAK has been installed and primed. With these automatic systems in place, users do not have to log and analyze the resistivity values of the product water over time in order to predict when the PAK will exhaust, nor do they have to maintain written records on when the PAK was installed in order to determine the PAK expiration date. The system continuously monitors the PAK status and will automatically prevent the user from using a PAK that is either exhausted or expired.

6. **Removal of requirements for sterilization or decontamination of the water purification system:** The PAK has been validated to produce product water that meets AAMI and ISO requirements for bacteria and endotoxins for a period of up to 12 weeks without the need for manually sterilizing, cleaning, or decontaminating any of its water purification components. When the PAK reaches its expiration date, which is automatically determined and tracked by the PureFlow SL system, the user simply replaces it with a new PAK. Furthermore, the SAK disposable, which consists of sterile-filtered dialysate concentrate, sterilized fluid lines, and a sterilized dialysate storage sack, or bag, is a single-use batch product.

DI Technology, Reinvented

DI systems have been used for a long time for traditional dialysis, but their use had been subject to a number of tradeoffs. The PureFlow SL system and NxStage therapy were designed to overcome these potential tradeoffs.

Historical Tradeoff	PureFlow SL and Therapy with the NxStage System One
Shorter lifespan, especially when providing the water volumes used for traditional in-center hemodialysis.	NxStage therapy fully saturates the dialysate, thus requiring less water than traditional in-center therapy.
DI replacement is difficult and requires specially trained personnel.	PureFlow DI resins are easily replaced by changing the PAK periodically, taking advantage of low water usage with PureFlow SL.
There is a potential risk of the breakthrough of chemical contaminants when DI resins near exhaustion.	PureFlow integrates multiple automatic, on-line purity sensors which are designed to continuously monitor the quality of the product water. The system also incorporates an automatic shut-down feature designed to ensure the integrity of the product water and that a breakthrough has not occurred.
Traditional mixed bed DI resins can sometimes harbor bacteria.	Highly acidic and basic dual bed resins help inhibit bacteria growth; redundant ultrafilters are designed to prevent bacteria and endotoxins from entering into the product water. The PAK has been validated to produce AAMI RD52:2004 and ANSI/AAMI/ISO 11663-quality product water for a period of up to 12 weeks. At 12 weeks of operation, the PAK will expire and the system will automatically prevent the user from using the PAK to make a new batch of dialysate.

Simplicity in Handling and Storage

NxStage therapy using premixed dialysate has inherent benefits: portability, simplicity, safety, consistency, and flexibility. The PureFlow SL builds upon these strengths with the additional benefit of:

- **Reduced shipments and storage:** Four weeks of hemodialysis treatments with a bag system will typically require 480 liters, or 48 cases, of bagged dialysate to be shipped. The PureFlow SL requires just 24 liters, or 4 cases, of concentrate for four weeks of dialysis treatments.

- **Reduced handling, setup, and clean-up:** With the PureFlow SL system, there are no dialysate bags to be opened, hung, and connected at the start of each treatment. Instead, the user loads the SAK into the PureFlow SL tub. Once a batch of dialysate has been mixed, the time and effort to set up the dialysate fluid circuit for each treatment is streamlined to simply connect the SAK dialysate outlet line to the System One cartridge. The Drain Line Cleaning Kit (NX25-0561) is shipped automatically on a quarterly basis. It is designed to help remove organic build-up from the PureFlow SL drain line.

The LINX® Water Pretreatment System

Source water quality varies by geography and may impact PAK life. For source water with high levels of Total Dissolved Solids (TDS) and hardness (calcium, magnesium), the LINX Water Pretreatment System may be deployed along with the PureFlow SL. The LINX System is not a medical device. It is designed to reduce levels of TDS and hardness in source water. As such, employing the LINX System with the PureFlow SL may prolong PAK life.

By prolonging PAK life, the user experience with the NxStage System One with PureFlow SL is improved by:

- reducing time spent priming new PAKs,
- decreasing inventory space at the home needed for extra PAKs, and
- reducing the physical burden of frequently disposing exhausted PAKs.

Source Water, Product Water, and Dialysate Defined

To understand the water and dialysate requirements associated with the PureFlow SL system, it is important to understand the differences between source water, product water, and dialysate.

- **Source Water** – This is the water used to supply the PureFlow SL and/or LINX systems. The source water is supplied by a municipality, water district or from a well. This is the same water used for drinking.
- **Product Water** – This is purified water produced by the PureFlow SL PAK that meets the quality requirements of ANSI/AAMI/ISO 13959. The product water is mixed with the dialysate concentrate in the SAK to produce ANSI/AAMI/ISO 11663-quality dialysate.
- **Dialysate** – This is the precise mixture of fluid made from product water and a concentrated aqueous solution of electrolytes, salts, and glucose used for hemodialysis. The quality of dialysate is also defined by ANSI/AAMI/ISO 11663.

Source Water Requirements for PureFlow SL

AAMI and ISO have identified a list of 20+ chemicals of concern which could pose a risk to dialysis patients. The maximum levels for these contaminants in the product water used to prepare dialysate have been determined and documented in ANSI/AAMI/ISO 13959. The system was therefore designed and tested to consistently, reliably, and safely produce PRODUCT water which meets the ANSI/AAMI and ISO requirements from SOURCE water which meets the US EPA Safe Drinking Water Act (SDWA) for the 20+ chemical contaminants of concern to AAMI and ISO. A complete list of the ANSI/AAMI and ISO contaminants of concern and the users PureFlow SL source water requirements can be found in APPENDIX C.

Source water quality can be confirmed for all new PureFlow SL patients by performing a standard AAMI or ISO test panel of the user's tap water and then comparing each contaminant level to the corresponding *PureFlow Requirements for Source Water* limits as listed in APPENDIX C.

If needed, the source water to the PureFlow SL can be pretreated by a RO system, ion exchange system, or other systems which reduce specific chemical contaminants (such as Nitrates, Sulfates, Radium, etc.), so long as the pretreated water meets the *PureFlow Requirements for Source Water.*

Other systems typically require rigid and restrictive specifications for source water because they are not as fluid-efficient and do not incorporate the design and safety features of the PureFlow SL. See the next page for a comparison of PureFlow SL to alternative technologies.

Comparison to Alternative Home Purification Technologies

Parameter	Alternative Water Purification System for Dialysis[a]	PureFlow SL
Filtration Technology	Reverse Osmosis (RO) filtration with recirculation capabilities	DI filtration
Product Water Quality	Product water quality proportionally related to source water quality[a,b]	Product water quality independent of source water quality. The PureFlow SL consistently produces AAMI and ISO quality product water from source water which meets the *PureFlow SL Source Water Purity Requirements* listed in APPENDIX C.
Source Water Purity Requirements:		
Chlorine	< 0.1 mg/L[c]	< 4.0 mg/L
Total Hardness	Max. 10 grains (pH dependent)[b]	No operational limits on total hardness and TDS, although there may be contractual limits.
Source Water Temperature	1.7-32°C (35-90°F)[b] Water production decreases approximately 3% per 1°C (1.5% per 1°F) incoming water temperature drop.[b] Ideal 25°C (77°F)[c]	5° to 32° C (40° F to 90° F)
Source Water Flow Rate	> 3.0 L/min[d] - 7.6 L/min[b] (0.8-2.0 gallons/min)	> 0.2 L/min (0.05 gallons/minute)
Yield (% of incoming water which is converted to product water)	15-50% depending on source water quality, temperature, pH, flow rate, and pressure[a-d]	100%
Operator Monitoring Requirements	Source water must be monitored, since changes in product water may exceed acceptable limits if source water deteriorates significantly[a-d]	None required. Continuous monitoring by the PureFlow SL system.
Disinfection	Required every other week or monthly:[c] • Product water sampling for incubation and analysis • Disinfection	None required due to the disposable nature of the PAK.

[a] Luehmann D, Keshaviah P, Ward R, Klein E. Water Treatment for Hemodialysis. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, 2006.

[b] Mar Cor Purification. Millenium HX Portable Water Purification System w/Automatic Hot Water Disinfection. P/N:3027573 Rev.C, 2012.

[c] AmeriWater, Degremont Technologies. http://www.ameriwater.com/wp-content/PDF/MROS_Portable_Reverse_Osmosis_System_for_Dialysis.pdf and http://awewater.com/pdf/OwnersManuel_PA2000.pdf. Dialysis MROS Portable Reverse Osmosis. 2012.

[d] Mar Cor Purification. WRO 300 H Portable Water Purification System with Automated Hot Water Disinfection P/N:3027263 Rev.C, 2012.

Specific Conductance of Source Water

"Specific conductance" is commonly used by the water treatment industry to measure water quality as it provides a good measure of the amount of dissolved material in the water. Specific conductance is a measure of the ability of water to conduct an electrical current. The specific conductivity of water is affected by the concentration of Total Dissolved Solids (TDS) in the water. Therefore, higher TDS results in higher specific conductivity. These solids may originate from various sources, such as organic materials, agricultural runoff, sewage, industrial wastewater, road runoff, and chemicals which have been added by the water supplier to treat the water.

The most common solids with high specific conductance in drinking water include: calcium, sodium, magnesium, chloride, carbonate, and sulfate. These solids are designed to be easily removed by the PureFlow SL system. The water produced by the PureFlow SL has a very low specific conductance (guaranteed to be less than 1 µS/cm). Typical drinking water, on the other hand, has specific conductance values between 150 µS/cm and 750 µS/cm. Values greater than 750 µS/cm are not recommended for drinking.

The PureFlow SL system does not have specific operational requirements for the specific conductance of source water. It should be noted, because higher specific conductance means more dissolved solids in the water, PAK life is shortened by high specific conductance. For users with high specific conductance in their water, additional source water pretreatment with the LINX System (page 29) may be indicated.

PureFlow SL and Water Softeners

Water softeners should be avoided with the PureFlow SL system. Commercially available, residential water softeners use an ion exchange process to replace incoming calcium (Ca2+) and magnesium (Mg2+) ions which typify hard water with sodium (Na+) ions which do not precipitate out in pipes or react adversely with soap. For every calcium or magnesium ion removed by the water softener, two sodium ions are released. This process places additional demands on the ion removal capacity of the PureFlow SL PAK which will shorten its life.

Product Water and Dialysate

The NxStage System One with PureFlow SL is a preconfigured FDA-cleared hemodialysis system, designed, tested, and validated to yield AAMI/ANSI/ISO quality (which includes standards for chemical and chlorine/chloramine testing) water and dialysate for in-center and home use that consistently meet the purity requirements specified in the standards listed in the following table:

Standard Number	Title
ANSI/AAMI/ISO 11663	Quality of Dialysis Fluid for Hemodialysis and Related Therapies
ANSI/AAMI/ISO 13958	Concentrates for Hemodialysis and Related Therapies
ANSI/AAMI/ISO 13959	Water for Hemodialysis and Related Therapies
ANSI/AAMI/ISO 26722	Water Treatment Equipment for Hemodialysis Applications and Related Therapies
EN 13867	Concentrate for Hemodialysis and Related Therapies
AAMI RD52:2004	Dialysate for hemodialysis

The PureFlow SL system, when operated in accordance with its labeling, is designed to consistently produce product water and dialysate which meet the ANSI/AAMI and ISO requirements for chemical contaminants, bacteria, and endotoxins. These requirements are summarized in APPENDIX C.

Requirements for Product Water and Dialysate

Product water produced by the PureFlow SL must be tested for chlorine/chloramines

The PureFlow SL requires total chlorine/chloramines testing after the preparation of each batch of dialysate. Once a batch is made, no change to the chemical composition can occur with respect to chlorine and chloramines. If the test fails, the user must drain the batch, install and prime a new PAK, and then prepare another user batch.

The PureFlow SL has been validated to remove chlorine to ANSI/AAMI/ISO standard levels (0.1 mg/L for total chlorine), even when challenged with elevated levels of chlorine and chloramines. For best results, it is recommended the test for total chlorine be performed within two hours of making a batch or with ultra low total chlorine test strips which are insensitive to interference components.

NxStage minimum requirements for water and dialysate quality testing with the PureFlow SL

The following monitoring is required by NxStage labeling to ensure the proper operation of the PureFlow SL:

1. **Source water quality verification prior to installing and using the PureFlow SL:** This test is required to ensure the tap water meets the *Source Water Purity Requirements for the PureFlow SL.* These requirements are published in the *NxStage PureFlow SL User's Guide* and reproduced in Appendix C of this document.
2. **Total chlorine (free total chlorine [free chlorine and combined chlorine/ chloramines]) test of the product water prior to the first use of each batch:** The total chlorine levels must be no more than 0.1 mg/L (or 0.1 ppm). For more information on how to perform this test, refer to the *NxStage PureFlow SL User's Guide.*

   Note, NxStage labeling does not require testing of the dialysate.

NxStage PureFlow SL Testing Requirements

	Bacteria, Endotoxin	Chemical Contaminants	Chlorine/ Chloramines
Source Water	X	✓ Prior to installing and using PureFlow SL	✓ Prior to installing and using PureFlow SL
Product Water	X	X*	✓ Prior to first use of each batch
Dialysate	X*	X	X

✓ Testing is required by NxStage.

X Testing is NOT required by NxStage; refer to your local laws and regulations for potential additional requirements.

Quality of fluids validated at production site.

* U.S. Center for Medicare and Medicaid Services (CMS) In 2008, CMS published the "Medicare and Medicaid Programs, Conditions of Coverage for End-Stage Renal Disease Faculties; Final Rule" that relaxed the frequency of testing of dialysate for bacteria and endotoxins from monthly to a minimum of once a quarter. State and foreign regulations on testing requirements may vary from those of CMS

Sampling Dialysate Prepared by the PureFlow SL

Although NxStage does not require dialysate testing, this may be a requirement in your location. If testing is required, NxStage sells a dialysate sampling bag (DTK-001) which draws dialysate from the SAK while minimizing the potential for the introduction of external contaminants to the drawn sample.

Refer to Appendices D and E for guidelines on evaluating the dialysate culture and endotoxin test results from a dialysate sample drawn from the SAK. Note, do not use samples collected with the dialysate sampling bag for analysis of chemical contaminants.

Conductivity of Dialysate Produced by the PureFlow SL

Traditional hemodialysis systems proportion two or more streams of concentrate. These systems use conductivity measurement to ensure the proper ratio of water, electrolytes and buffer. These systems typically have a final dialysate conductivity measurement to divert dialysate to the drain that does not meet the appropriate level pf conductivity.

The PureFlow SL has a similar automatic protection system. After a batch of dialysate is prepared the system automatically tests the final dialysate conductivity of each batch. If it meets the appropriate level, the user is allowed to use the batch of dialysate. If it does not meet the conductivity limits, the system notifies the user then automatically diverts it down the drain. Therefore, by the PureFlow SL automatically confirming the conductivity of each batch of dialysate, the manual conductivity confirmation by an operator is eliminated. The final dialysate conductivity ranges by SAK type.

PH of Dialysate Produced by the PureFlow SL

Traditional hemodialysis systems proportion multiple source of concentrates that use multiple dilution (mixing) ratios with water. Because the concentrates are not preconnected, and multiple mixing ratios can be selected, there is a risk of proportioning the wrong concentrate (connect the wrong concentrate to the wrong port). There are concentrate errors where dialysate with the correct conductivity is not at a physiologic pH. It is typical to test the pH of the dialysate before treating a patient to eliminate this potential misuse error. It should be noted, however, that the combination of conductivity and pH testing will not detect all incorrect dialysate mixing errors in traditional hemodialysis systems.

The PureFlow SL prefilled SAK disposable eliminates the possibility of connecting the wrong concentrate to the wrong port thereby adding to patient safety by removing this potential human error. The PureFlow SL eliminates the possibility of ever having the wrong pH by using prefilled SAK disposables. By eliminating this misuse possibility, the pH test is not required by the FDA-cleared labeling.

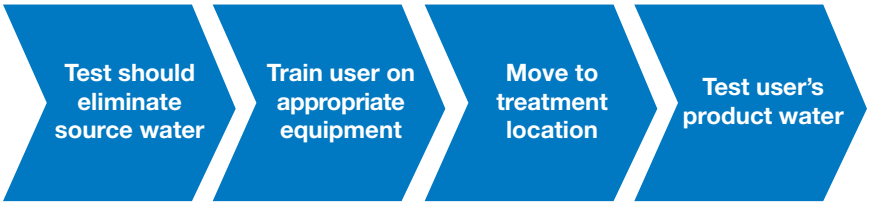
SECTION FIVE:

TRAINING AND LOGISTICS

New User Training

For a new user, it is important to understand the source water quality prior to training the user on using the System One with anything other than premixed dialysate bags. Depending on the source water quality, the user may need to be trained on:

- Only bags,
- The PureFlow SL, and
- The LINX Water Pretreatment System.



New Home Patient Logistics

When a new patient prescription is received, NxStage or your local distribution partner will deliver the necessary equipment and supplies to the center training the patient and his/her partner, including:

- The System One Cycler,
- The PureFlow SL control unit (which easily slides into the PureFlow SL cabinet),
- The PureFlow SL cabinet (if the center does not currently have one),
- Supplies and manuals for training purposes, and
- The home connection "how-to" guide and parts kit that the patient can use to identify which water connection option would be most appropriate for his/her home.

When it is clear the patient will successfully complete training and be transitioned home, NxStage or your local distribution partner will send the following directly to the home (if applicable):

- PureFlow SL cabinet
- LINX Water Pretreatment System
- Monthly supplies (PAKs, SAKs, Cartridges, etc.)
- Reserve supplies and premixed dialysate bags. At the end of the in-center training period, each patient will take home his or her cycler (with verified treatment parameters) as well as the PureFlow SL control unit (with verified treatment parameters), if applicable.

If a patient is currently using premixed dialysate bags and wishes to convert to PureFlow SL he/she should bring in their Cycler for training and software updates, as required. A source water test must be completed to verify the source water meets the requirements outlined in Appendix C. All other training logistics described above remain the same.

Setting up the PureFlow SL at Home

The training center provides a connection kit, which includes the following components for connecting to the patient's source water:

- Faucet (tap) adapter connection
- Under-sink connection
- Washer Hook-up connection

The patient will be able to take this kit home early-on during training, in order to determine which connection is most convenient. Simple instructions on how to make these connections are provided. The instructions are designed to be "do-it-yourself," although patients or centers may decide to employ the services of a plumber to make the necessary water and drain connections. Instructions for sliding the PureFlow into the cabinet and placing the System One Cycler on top of the cabinet are provided in the *PureFlow SL User Guide.*

In the case of a service swap, the PureFlow SL is designed to be modular and easily exchanged. NxStage Technical Support or your local distribution partner will assess which module needs replacement, and initiate a service swap for the patient.

Providing Ongoing Home Care

As with any other chronic treatment regimen, patient conditions may change over time and patients should be followed and seen on, at least, a monthly basis. NxStage requires that a trained partner be present during treatment. As such, NxStage patients and their partners take on the significant new responsibility of administering treatments. With this, they may be subject to the significant stress of self-care. Patients as well as partners should be regularly seen by social workers, nurses and doctors to monitor for signs of developing burnout.

In order to manage this risk, organizations working with NxStage around the country have implemented programs intended to manage patient and partner burn-out risk by:

- Creating community among patients
- Employing the Dosing Calculator to help develop prescriptions tailored to the patient's clinical and lifestyle objectives
- Employing PureFlow SL
- Providing respite care as an option

NxStage offers a number of tools to help identify patients at risk of dropping, maximize patient retention from initial start through the first 90 days at home and beyond. Our Clinical Educators can help you develop and execute a custom retention plan through personalized workshops. Please contact NxStage or your local distribution partner for more information.

APPENDIX A:
DIALYSATE CATALOG

Premixed Dialysate Bag Formulations

Constituents (mEq/L)	RFP-204	RFP-205	RFP-207	RFP-209	RFP-211
Lactate	40 mEq/L (40 mmol/L)	35 mEq/L (35 mmol/L)	45 mEq/L (45 mmol/L)	45 mEq/L (45 mmol/L)	40 mEq/L (40 mmol/L)
Potassium	1 mEq/L (1 mmol/L)	3 mEq/L (3 mmol/L)	1 mEq/L (1 mmol/L)	2 mEq/L (2 mmol/L)	2 mEq/L (2 mmol/L)
Sodium	140 mEq/L (140 mmol/L)				
Calcium	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3.5 mEq/L (1.75 mmol/L)
Magnesium	1 mEq/L (0.5 mmol/L)				
Chloride	105 mEq/L (105 mmol/L)	112 mEq/L (112 mmol/L)	100 mEq/L (100 mmol/L)	101 mEq/L (101 mmol/L)	106.5 mEq/L (106.5 mmol/L)
Glucose	1.1 g/L				
Osmolar–ity (calculated)	294 mOsmol/L	298 mOsmol/L	294 mOsmol/L	296 mOsmol/L	296 mOsmol/L

All RFP-2XX fluids are packaged in 5.0 liter bags and will typically have up to 1.5% overfill.

Dialysate Concentrates

The PureFlow SL System prepares batches of dialysate in the following formulations and volumes:

Constituents (mEq/L)	SAK-301/401	SAK-302/402	SAK-303/403	SAK-304/404	SAK-305/405	SAK-306/406	SAK-307/407
Lactate	45 mEq/L (45 mmol/L)	40 mEq/L (40 mmol/L)	45 mEq/L (45 mmol/L)	45 mEq/L (45 mmol/L)	45 mEq/L (45 mmol/L)	45 mEq/L (45 mmol/L)	40 mEq/L (40 mmol/L)
Potassium	1 mEq/L (1 mmol/L)	1 mEq/L (1 mmol/L)	1 mEq/L (1 mmol/L)	2 mEq/L (2 mmol/L)	1 mEq/L (1 mmol/L)	2 mEq/L (2 mmol/L)	1 mEq/L (1 mmol/L)
Sodium	140 mEq/L (140 mmol/L)						
Calcium	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)	3 mEq/L (1.5 mmol/L)
Magnesium	1 mEq/L (0.5 mmol/L)						
Chloride	100 mEq/L (100 mmol/L)	105 mEq/L (105 mmol/L)	100 mEq/L (100 mmol/L)	101 mEq/L (101 mmol/L)	100 mEq/L (100 mmol/L)	101 mEq/L (101 mmol/L)	105 mEq/L (105 mmol/L)
Glucose	100 mg/dL						
Batch Size	60 L	60 L	50 L	60 L	40 L	50 L	50 L

APPENDIX B:
WATER PURIFICATION WITH THE PUREFLOW SL SYSTEM

The following system components are designed to achieve the purposes set forth below:

Component	Purpose
Sediment Filter	Removes sand, sediment, and other large particles. The PureFlow SL monitors the incoming water pressure and can detect if the filter becomes clogged, thus requiring replacement.
UV Light	Controls bacteria. Breaks down chlorine, chloramines, and other organics into ions that are readily absorbed by the DI resins (the lamp intensity is at a level 2-3x the typical sufficient dose to break down chloramines).
Carbon Media	Removes chlorine/chloramines, and organic compounds. As specified by AAMI and ISO, empty bed contact time (EBCT) is greater than 10 minutes.
Dual Bed DI	Serves as primary deionization bed; removes the bulk of the ionic contaminants. Sequesters colloidal aluminum. Kills bacteria through pH changes between the acid and base regions.
Resistivity Sensor #1	Situated after the dual bed DI resins, this first sensor monitors the quality of the water exiting the dual bed DI resins. Once the resistivity falls below its threshold, the resin is deemed to be close to exhaustion, and the mixed bed DI resin performs purification to complete the batch. The water purification system will go into a “last batch” state with audible and visible warnings, and allow current batch to complete. Once the current batch is completed the system will force user to replace the PAK prior to making another batch.
Mixed Bed DI	Serves as a polishing deionization bed. The resin helps to remove any ions that may pass through the three dual bed DI’s, acting as a backup. (CONTINUED NEXT PAGE)

Resistivity Sensor #2	Situated after the mixed bed resin, the second resistivity sensor acts as a final check to ensure that the quality of the water exiting the system meets AAMI and ISO standards for water requirement of >1 Megaohm-cm resistivity, or total ionic dissolved components. If this sensor is tripped, indicating an exhausted PAK condition, the dialysate will automatically be drained (visible and audible alarms) thereby not allowing the patient to make or use a batch with the product water from an exhausted PAK.
Dual Ultrafilter	Removes bacteria and endotoxins. The series of system ultrafilters have been validated to provide water which meets AAMI and ISO microbiological requirements (and purity standards) for up to 12 weeks. Once the PAK expires, the PureFlow SL will automatically prevent further use of the PAK (visible and audible alarms).
0.2 Micron Filter	Eliminate any bacteria from reaching the dialysate solution in the SAK. The 0.2 micron filter is located on the water inlet line of the SAK. Any bacteria transferred by touch contamination or use of non-aseptic techniques in the operation of the system will not reach the patient.

APPENDIX C:
SUMMARY OF DRINKING WATER STANDARDS AND SPECIFICATIONS

The table below lists the source water requirements for the PureFlow SL system, as well as the maximum contaminant levels in safe drinking water.

	Contaminant	Source Water (mg/L)	Product Water (mg/L) ANSI/AAMI/ISO 13959:2009
Contaminants with documented toxicity in hemodialysis	Aluminum[a]	0.2	0.01
	Chloramines[b]	4.0	Not specified[c]
	Free Chlorine[b]	4.0	Not specified[c]
	Total Chlorine	4.0	0.1
	Copper	1.3	0.1
	Fluoride	4.0	0.2
	Lead	0.015	0.005
	Nitrates (as N)	10	2
	Sulfate[a]	250	100
	Zinc[a]	5	0.1
Normally included in dialysate	Calcium	No limit	2
	Magnesium	No limit	4
	Potassium	No limit	8
	Sodium	No limit	70
Other contaminants	Antimony	0.006	0.006
	Arsenic	0.01	0.005
	Barium	2	0.1
	Beryllium	0.004	0.0004
	Cadmium	0.005	0.001
	Chromium	0.1	0.014
	Mercury	0.002	0.0002
	Selenium	0.05	0.09
	Silver[a]	0.1	0.005
	Thallium	0.002	0.002

In addition to the above limits, there may be contractual limits for Total Dissolved Solids (TDS) and water hardness (Calcium, Magnesium). Please contact NxStage or your local distribution partner for more information.

Appendix C References:

a. Contaminant is listed in the US EPA SDWA as a National Secondary Drinking Water Standard.

b. Chlorine and chloramines are generally added to public water supplies to control bacteria levels. The acceptability of the incoming concentrations of free chlorine and chloramines in the patient's source water for use with the PureFlow SL can be easily verified by using commercially available test strips for total chlorine. Following the test strip manufacturer's instructions check that the total chlorine result for the source water is less than or equal to 4.0 mg/L.

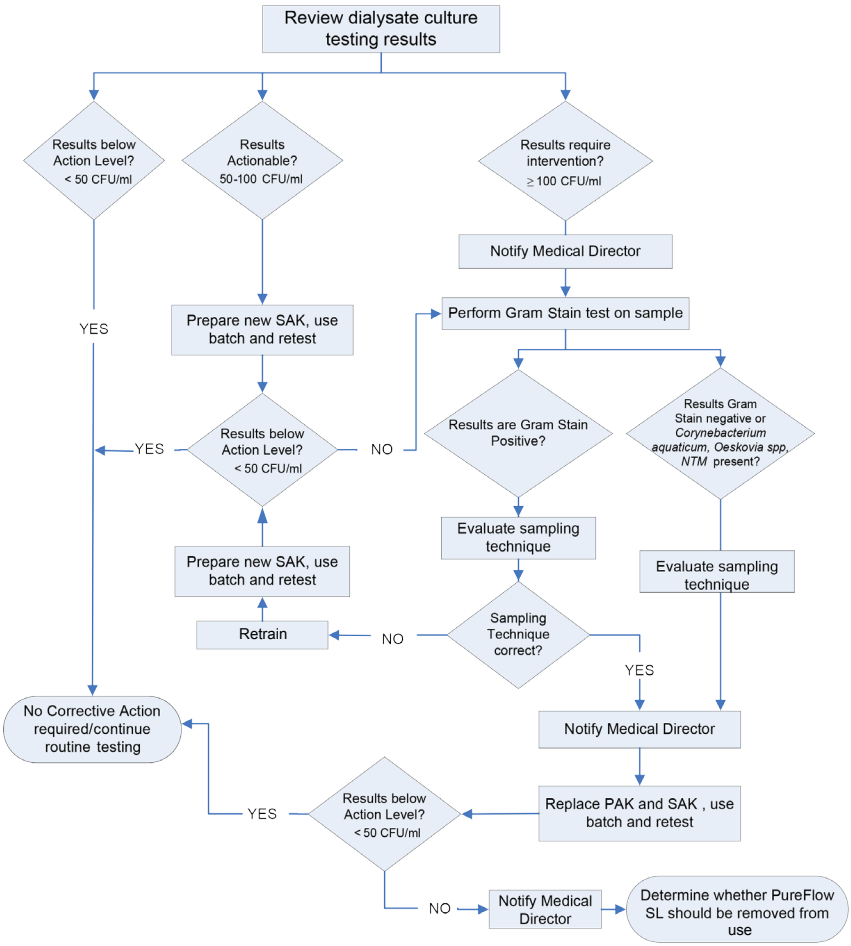
c. Total chlorine consists of free chlorine and chloramines (i.e., total chlorine = free chlorine + chloramines) so the concentration levels of these contaminants are related.

In addition to chemical contaminants, ANSI/AAMI/ISO also specify the following limits for the presence of bacteria and endotoxins in dialysate:

	ANSI/AAMI/ISO 11663 Requirement for Dialysis Fluid
Bacteria	< 100 CFU/ml (action level of 50 CFU/ml)
Endotoxins	< 0.5 EU/ml

APPENDIX D:

GUIDANCE FOR EVALUATING THE DIALYSATE CULTURE TEST RESULTS*

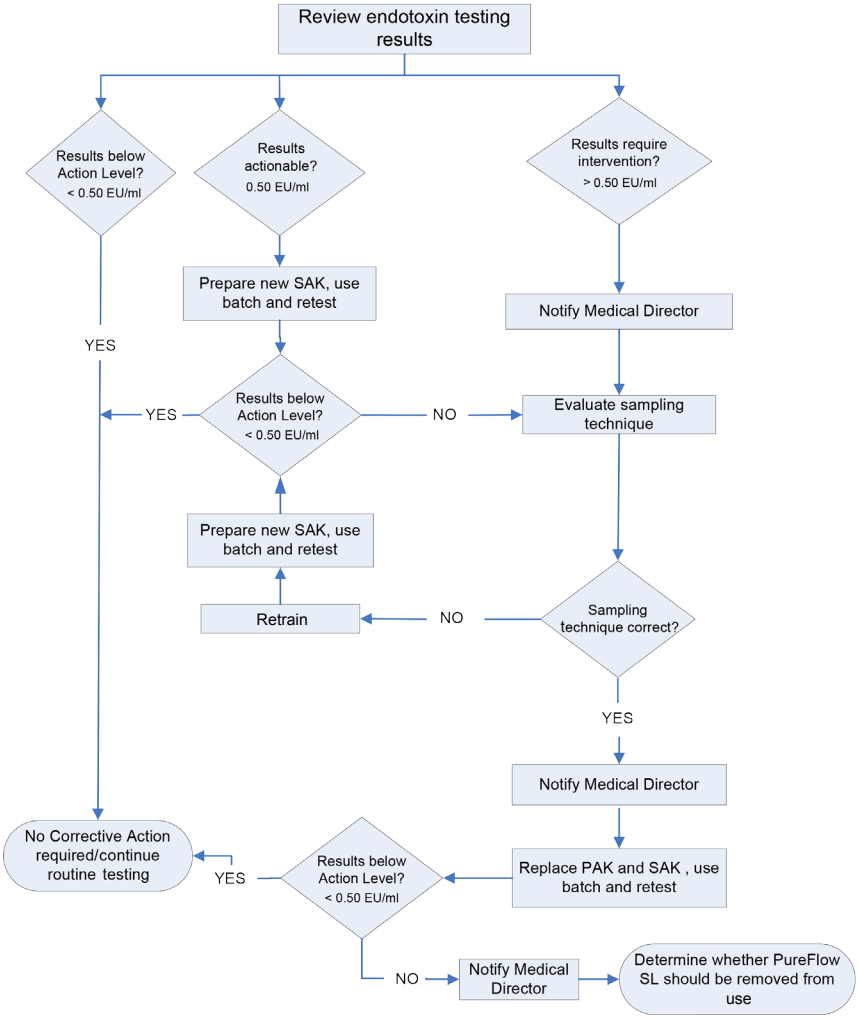


Action Level	50 CFU/ml
Intervention Level	100 CFU/ml

*In the European Union and Australia the following action and intervention levels shall be used
Action level: None specified, therefore 0.1 CFU/ml used. Intervention level: 0.1 CFU/ml

APPENDIX E:

GUIDANCE FOR EVALUATING THE DIALYSATE ENDOTOXIN TEST RESULTS*



Action Level	None specified; therefore 0.50 EU/ml used
Intervention Level	0.50 EU/ml

*In the European Union and Australia the following action and intervention level shall be used
Action level: None specified, therefore 0.03 EU/ml used. Intervention level: 0.03 EU/ml

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