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BioPure HX2®

Research Report: Endotoxin Results

Introduction

The BioPure HX2 is a Double Pass Reverse Osmosis (RO) System designed to meet international ISO hemodialysis water requirements and it is currently licensed as a class 3 medical device by Health Canada. The system is built with automatic heat disinfection capability resulting in a simplified endotoxin and bacteria control process. This technical report examines the endotoxin removal capability of the BioPure HX2 in a pilot test environment.

BioPure HX2

The BioPure HX2 Double Pass Water Purification System is Mar Cor Purification's next generation central RO unit for hospitals and clinics alike. This direct feed system ensures the highest quality of water is delivered to the patient, while the added feature of automatic hot water disinfection allows for greater endotoxin and bacteria removal, as well as, control, reducing the need for chemicals and operator attention.

The two-pass design is an improvement over Mar Cor Purification's currently FDA 510(k) registered single pass RO systems. The BioPure HX2 is intended to purify water specifically targeted for the hemodialysis marketplace with system performance meeting dialysis grade water standards according to CAN/CSA-ISO13959-11 and Health Canada requirements.

The BioPure HX2 Double Pass RO system is a stand-alone water purification system and is designed to be fed with pretreated potable water; its main function is to remove organics, inorganics, particles and microbial contaminants from water used in hemodialysis and related therapies. The purified product water meets the quality requirements of CAN/CSA-ISO26722-11, CAN/CSA-ISO13959-11 and CAN/CSA-ISO11663-11. This technical report focuses on the endotoxin removal capability of the BioPure HX2.

Test Procedure

Hot water disinfection is recognized by CAN/CSA/ISO26722-11 as an effective means of controlling bacterial proliferation. Testing and verification of cycle temperature and time parameters were performed prior and during the pilot test to verify the functional performance of routine hot water disinfection and allow endotoxin level measurement under normal operating and maintenance conditions. The baseline water sampling taken during the pilot test was submitted to a recognized independent third party agency for analysis of the microbiological and chemical requirements as specified in CAN/CSA-ISO26722-11 and CAN/CSA-ISO13959-11. The baseline sample was potable water from the city of Oakville, Ontario, locally softened and dechlorinated with carbon media tanks and measured at sample port 2 (See Appendix A). The analysis returned consistent results:

Table 1: Pretreated Potable Feed Water Analysis
CAN/CSA-ISO26722-11 and CAN/CSA-ISO13959-11

Endotoxin concentration	> 0.5 EU/ml

The BioPure HX2 is equipped with a scheduler that can fully automate the operation of the system. The scheduler was set up to mimic the normal operating schedule of dialysis clinics: Monday through Saturday from 7:00 am to 11:00 pm.

- The BioPure HX2 was set to automatically perform a combo heat sanitization (1st pass, 2nd pass and loop) on the first Sunday at 6:00 pm where the system would reach and hold a temperature of 80°C for 60 minutes. Heat sanitization was not performed for the remainder of the sampling period.
- The BioPure HX2 was set to automatically start at 6:30 am every weekday and Saturdays to ensure the system was already running when the clinic opened.
- The BioPure HX2 was set to automatically turn off at 11:00 pm every weekday and Saturdays and perform auto-flush sequences overnight.
- The water sampling was performed between 8:00 am and 10.00 am on Monday, Wednesday and Friday for three consecutive weeks at sample port 4.

Test Methodology

The LAL Test (Limulus Amebocyte Lysate) is based on an aqueous extract of blood cells from the horseshoe crab, which reacts with bacterial endotoxin allowing for the detection and quantification of endotoxins in a sample. To test the endotoxin levels on the BioPure HX2® final water product, a Charles River Endosafe® PTS™ reader was used, which measures the color intensity of the sample specimen to determine endotoxin concentrations. This device is based on an FDA-registered endotoxin detection system and uses multi-channel cartridges that automatically perform a duplicate sample test and a duplicate positive control test, which together satisfies both the harmonized USP Bacterial Endotoxin Test (BET) and the FDA guideline for LAL testing. The cartridge sensitivity can determine if the BioPure HX2 can produce water that is at or below an endotoxin level of 0.01 EU/ml.

Results

The final testing of product water quality was evaluated to meet the acceptance criteria below:

Table 2: Product Water Acceptance Criteria CAN/CSA-ISO13959-11 and CAN/CSA-ISO11663-11

	Standard	*Ultrapure*
Endotoxin concentration	*< 0.5 EU/ml*	*< 0.03 EU/ml*
Total viable microbial count	*< 100 cfu/ml*	*< 0.1 cfu/ml*

The analysis of each sample occurred within one hour of sampling. The results were validated based on the assay acceptance criteria established by the test methodology. The analysis returned consistent results:

Table 3: BioPure-HX2 Product Water Analysis Extracted Data from Charles River Endosafe® PTS™

Endotoxin concentration	*< 0.01 EU/ml*

Cartridges of a higher sensitivity (<0.005 EU/ml) used in parallel with 0.01 EU/ml cartridges also recorded non-detectable results throughout the testing period. The results were not formally recorded but the findings indicate that the BioPure HX2 is capable of producing water at much lower endotoxin levels.

Discussion

Quality requirements for dialysis fluid used in hemodialysis and related therapies are split into two classes: standard dialysis fluid and ultrapure dialysis fluid. The quality requirements for contaminants are the same, except for the maximum allowable levels of microbial contaminants (see table 2).

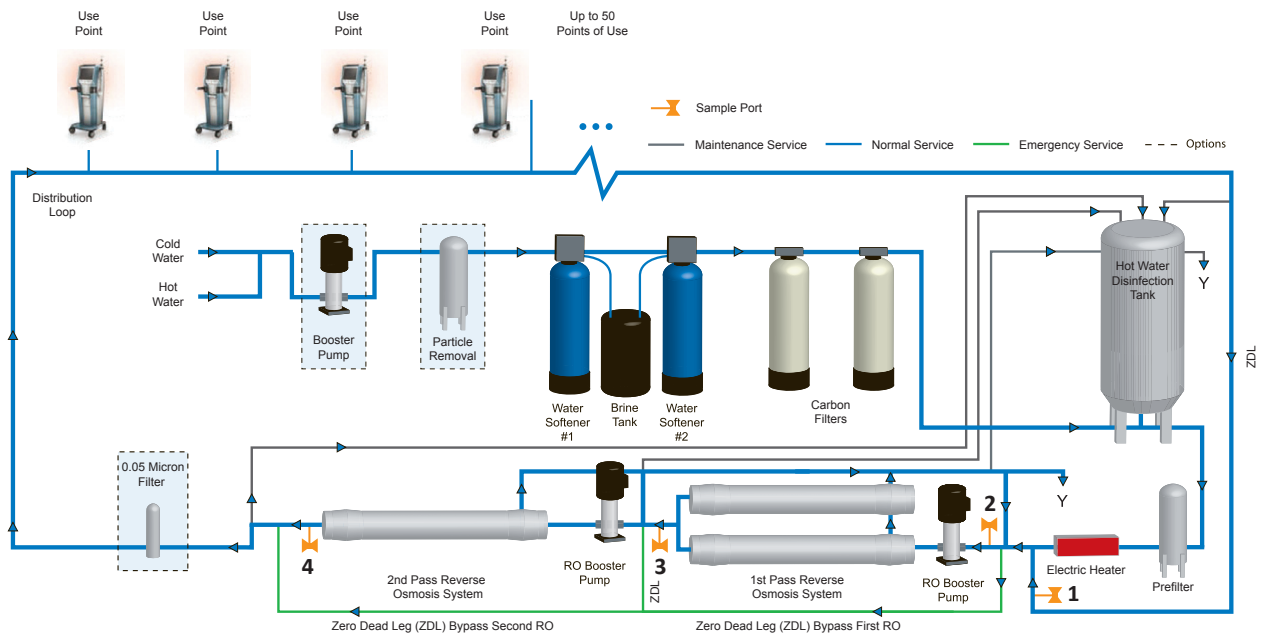
Although dialysis fluids complying with the requirements for the standard dialysis fluid is the acceptable minimum quality for routine hemodialysis, ultrapure dialysis fluid is recommended based on clinical and experimental observations that reducing microbiological contaminants in the dialysis fluid has been linked with reduced levels of inflammation and associated morbidity of hemodialysis patients.

As a forward-looking medical device manufacturer, Mar Cor Purification endeavors to encourage healthcare professionals and those responsible for the management of dialysis towards the use of ultrapure dialysis fluid as a voluntary standard. The BioPure HX2 system is equipped with advanced features that will revolutionize the way hospitals and clinics manage their water for dialysis. Most importantly, it will reliably and consistently meet or exceed the water quality requirements for ultrapure dialysis fluid.

Mar Cor Purification

A subsidiary of Cantel Medical Corp., Mar Cor Purification is the largest supplier of dialysis water systems and services in North America. Mar Cor Purification is dedicated to providing innovative solutions through filtration, water, and disinfection technologies to the medical, life science and industrial marketplaces. Mar Cor Purification has service offices in 21 cities in the U.S. and Canada, with 7 resin regeneration plants strategically located in Atlanta, Boston, Chicago, Philadelphia, San Antonio, Montreal and Toronto. For more information please visit www.mcpur.com.

Appendix A: Process Flow Diagram & Sample Port Locations



Appendix B: Terminology and References

AAMI	Association for the Advancement of Medical Instrumentation AAMI TIR43: 2011: Ultrpure dialysate for hemodialysis and related therapies, a technical information report
ANSI	American National Standards Institute ANSI/UL 61010-1: Standard for Safety Electrical Equipment For Measurement, Control, and Laboratory Use Part 1: General Requirements
CFU	Colony-Forming Unit. Viable bacterial or fungal can estimated in CFU. The appearance of a visible colony requires significant growth of the initial cells plated, as a result, the measurement is given as CFU/mL (colony-forming units per milliliter) for liquids to reflect this uncertainty.
CMDCAS	Canadian Medical Devices Conformity Assessment System - Canadian Medical Device Standards
CSA	Canadian Standards Association CSA C22.2 No 601.1-M90: Medical Electrical Equipment - Part 1: General Requirements for Safety
EU	Endotoxin Units. Endotoxin is a major component of the outer cell wall of gram-negative bacteria. It is measured in Endotoxin Units per milliliter (EU/mL). One EU equals approximately 0.1 to 0.2 ng endotoxin/mL of solution.
FDA	Food and Drug Administration FDA Guidance Document (May 30, 1997): Guidance for content of 510k for Water Purification Systems for Haemodialysis
ISO	International Organization for Standardization CAN/CSA-ISO11663:2011: Quality of Dialysis Fluid for Hemodialysis and Related Therapies CAN/CSA-ISO26722:2011: Water Treatment Equipment for Haemodialysis Applications and Related Therapies CAN/CSA-ISO13959:2011: Water for Haemodialysis and Related Therapies ANSI/AAMI-ISO23500:2011: Guidance for the Preparation & Quality Management of Fluids for Hemodialysis and Related Therapies
MCP	Mar Cor Purification Inc. Endotoxin Test Plan Oct 19 2012: BioPure HX2 Endotoxin Test Plan TR-8400HX22PASS rev 1, 5-Nov-12: BioPure HX2 2 Pass Technical Assessment Report
PTS	Portable Test System. Charles River Endosafe®-PTS™ is a handheld spectrophotometer that utilizes FDA-licensed disposable cartridges for endotoxin testing.

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