GUIDANCE FOR THE CONTENT OF PREMARKET NOTIFICATIONS FOR WATER PURIFICATION COMPONENTS AND SYSTEMS FOR HEMODIALYSIS

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Food and Drug Administration
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Office of Device Evaluation
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Gastroenterology and Renal Devices Branch

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While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to:

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health

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This document reflects the current review guidance for water purification components and systems for hemodialysis. It is based on 1) current scientific knowledge, 2) clinical experience, 3) previous submissions by manufacturers to the Food and Drug Administration (FDA), and 4) the Safe Medical Devices Act of 1990 and FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and medicine, and changes occur in implementation of Congressional legislation, these review criteria will be re-evaluated and revised as necessary.

This document is an adjunct to the CFR and other FDA Guidance documents for the preparation and review of 510(k) submissions. It does not supersede those publications, but provides additional clarification on what FDA believes is needed before a device can be cleared for marketing. The submission must provide evidence that the device is substantially equivalent in safety and effectiveness to a predicate device legally marketed in the United States.

A water purification system for hemodialysis is described in the FDA regulation, 21 CFR 876.5665(a), as a "device that is intended for use with a hemodialysis system and that is intended to remove organic and inorganic substances and microbial contaminants from water used to dilute dialysate concentrate to form dialysate. This generic type of device may include a water softener, sediment filter, carbon filter and water distillation system." The classification for this device is class II as stated in 21 CFR 876.5820(b) and its product code is 78 FIP.

Water purification is one of the most important aspects of safe and effective hemodialysis. The potential adverse clinical effects of inadequate or malfunctioning water purification equipment include anemia, bone disease, hemolysis, metabolic acidosis, nausea, vomiting, neurological deterioration, pyrogenic reactions and death. Water purification systems are designed to remove metals (e.g., aluminum, copper, zinc, magnesium), electrolytes (e.g., calcium, sodium, fluoride, chlorine, sulphate) and bacteria and pyrogens from feed water. Due to the great variation in feed water quality across the United States, the water purification needs of individual dialysis clinics may vary. Suppliers of water purification systems commonly customize a system for an individual clinic that takes into account the feed water quality and the required capacity.

This guidance document is addressed to both the manufacturers of individual water purification *components* and the suppliers and/or manufacturers of water purification *systems*. For the purposes of this document, *component* refers to the building blocks of a water purification system, such as reverse osmosis units, deionization tanks, water softeners, etc. The term *system* refers to the complete assembly of water purification components that are used in concert to produce purified water. The term *auxiliary component* refers to a component which does not directly affect water quality, such as pumps, valves, tubing, pressure gauges, etc. Manufacturers or suppliers of water purification *systems* who market their product for use in hemodialysis are required to submit premarket notifications (510(k)s). Manufacturers of water purification *components* (including *auxiliary*) are not required to submit 510(k)s unless they intend to label and/or market the products for use in hemodialysis. In this case, a 510(k) will be required and, as described in section 9 of this document, the level of detail required in the 510(k) will vary depending on the complexity of the component. Manufacturers and/or suppliers of portable water purification systems for use in acute dialysis or in the home setting may have slightly different requirements than those described in sections 9 and 10 below. We recommend that these manufacturers and/or suppliers contact FDA to discuss their particular application.

The primary reference for the information required to be in a premarket notification (510(k)) for a medical device is set forth in 21 CFR 807.87. Additional information on the required elements for a premarket notification submission is contained in the "DRAERD Premarket Notification [510(k)] Screening Checklist." A copy may be obtained from the Center for Devices and Radiological Health's Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597 or on the World Wide Web at http:\\www.fda.gov\cdrh\dsmamain.html. In addition to the general requirements, FDA recommends that each premarket notification for a water purification component or system include the information below in order to ensure that the submission is adequate to permit a determination of substantial equivalence to a predicate device.

1. List the device name, including the trade or proprietary name and the classification name (Water purification system for hemodialysis) of the device as described in 21 CFR 807.87(a).

2. List the establishment registration number, if applicable, of the owner or operator submitting the premarket notification as described in 21 CFR 807.87(b).

3. List the generic class (class II) in which the device has been placed and the appropriate panel (78 Gastroenterology/ Urology) as described in 21 CFR 807.87(c).

4. Provide a statement of the action taken by the registered manufacturer to comply with the requirements of the Act under section 514 for special controls, as required in 21 CFR 807.87. (Note that special controls are not currently required for water purification systems).

5. The Safe Medical Devices Act of 1990 (SMDA) requires all persons submitting a premarket notification submission to include either (1) a summary of the safety and effectiveness information in the premarket notification submission upon which an equivalence determination could be based (510(k) summary), OR (2) a statement that safety and effectiveness information will be made available to interested persons upon request (510(k) statement). Safety and effectiveness information refers to information in the premarket notification submission, including adverse safety and effectiveness information, that is relevant to an assessment of substantial equivalence. The information could be descriptive information about the new and predicate device(s), or performance or clinical testing information.

6. Provide copies of the proposed labels, labeling, and advertisements sufficient to describe the water purification component or system, its intended use, and the directions for use (including maintenance, operation, cleaning and troubleshooting). The labeling should include a specific intended use statement and any warnings, contraindications, or limitations clearly displayed as described in 21 CFR 807.87(e). The labeling may be provided in draft form. The labeling should bear the caution statement as outlined in 21 CFR 801.109(b)(1): "CAUTION: When used as a medical device, Federal law restricts this device to sale by or on the order of a physician." A device label is any identification on the water purification components or system and/or on the package in which it is stored and shipped. Additional guidance on labeling issues for medical devices is described in Bluebook Memo G91-1 "Device Labeling Guidance (3/18/91)." A copy may be obtained from DSMA at the telephone numbers listed above. (NOTE: Additional labeling requirements for specific water purification components are described in Section 9 of this document.)

7. The water purification component or system should be compared to a legally-marketed predicate device. A legally-marketed predicate device is defined as one which was in commercial distribution prior to May 28, 1976, the enactment data of the Medical Device Amendments (pre-amendment), or one which has been cleared for marketing in the United States under Section 510(k) of the Act. State whether the substantially equivalent device is a pre-amendment device or a device which has been cleared for marketing through the 510(k) process, providing the 510(k) number if known. The predicate and proposed device

should be compared with regard to the intended use, design (hardware, software, safety features, and other applicable characteristics), water-contact materials, performance specifications and capacity. The FDA recommends that the comparison be provided in a manner that is clear and comprehensible (e.g., tabular form).

8. For a device or device labeling that has undergone a change or modification that could significantly affect the safety or effectiveness of the device, the 510(k) should include any additional supporting data to show that the manufacturer has considered the consequences and effects that the change or modification might have on the safety and effectiveness of the device as described in 21 CFR 807.87(g).

9. DESCRIPTIVE INFORMATION AND TEST REQUIREMENTS FOR WATER PURIFICATION COMPONENTS

The following specific requirements are listed for each component of a water purification system.

A. REVERSE OSMOSIS (R.O.)

1. Provide a diagram of the R.O. system, including the location of all valves, and all pressure, temperature, conductivity/total dissolved solids (TDS) and flow sensors. The conductivity/TDS meter should be temperature compensated for accuracy.

2. Identify all water contact materials, separating them into those that contact feed water and product water. For all product water materials, results of leach testing should be provided that identify and characterize the potential leachables using appropriate chemical analyses.

3. Provide a complete description of the membranes utilized, including the physical design and materials of construction. A diagram of the membrane cartridge is recommended. Provide a graph of the range of permeate flow rates as a function of the recommended temperature range.

4. Specify the nominal performance of each type of R.O. membrane, including the rejection of total dissolved solids (TDS), monovalent and polyvalent ions, bacteria and endotoxin; organic size cut-off; chlorine and pH tolerance; and temperature and pressure limits. Provide data to demonstrate that the membranes, as utilized in the R.O. system, meet the

performance specifications for removal of TDS, bacteria and endotoxin.

5. Provide a full description of the control system for the unit. Describe the audible and visual alarms, including the recommended location, and the consequent action(s). To ensure patient safety, FDA believes that alarms (audible and visual) and system shutdown or divert to drain should occur whenever the high product water conductivity alarm is activated. If the R.O. does not include this feature, a justification should be provided on how other alarms or sensors are used to maintain patient safety in the event of this alarm condition.

6. Describe any software used to control the R.O. system. If the unit is software controlled, provide a description of the software requirements, a listing of any modules or subroutines and a description of how each fulfills the requirements. A description of the software quality assurance procedures and verification/validation activities that were performed should also be provided. Additional information can be obtained by referring to the "Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review." A copy of this guidance can be obtained by contacting DSMA at the telephone numbers listed above.

7. Provide the values of the factory-set default values for the setpoints of the control system and provide instructions to the user on how to change them, if applicable.

8. Provide a user's manual that includes detailed instructions for installing, operating, monitoring, maintaining, troubleshooting, cleaning and disinfecting the device as well as any associated warnings or precautions. Recommended schedules for monitoring, maintaining, cleaning and disinfecting the device should be included, along with a monitoring log. The cleaning and disinfection instructions should include, at a minimum, the identity of appropriate cleaning agents and disinfectants, the recommended cleaning and disinfection frequency and the procedure for measuring residuals. If the unit includes an autoflush feature, explain how the frequency or duration of the autoflush can be changed.

B. DEIONIZATION (D.I.)

1. Provide a device description that includes a generic diagram of the system, all sizes and capacities supplied (i.e., the range of feed and product flow rates and the reduction of specific solutes), and the identity of the resins (including the quality).

2. Describe all monitors and alarm systems. The D.I. should include a temperature-compensated audible and visual alarm to indicate when the bed is exhausted. The FDA recommends that ultrafilters or submicron filters be installed on the outlet line from the D.I. tanks to ensure removal of bacteria and endotoxin which are known to be harmful to dialysis patients. If ultrafilters or submicron filters are not included, a justification should be provided on how other alarms or sensors are used to maintain patient safety in the event of bacterial contamination and bed exhaustion. If the D.I. is intended to serve as the primary purification component (instead of an R.O. system), a system shutdown or divert to drain should occur whenever the product water resistivity alarm is activated. If the D.I. does not include this feature, a justification should be provided on how other alarms or sensors are used to maintain patient safety in the event of this alarm condition.

3. Provide data to demonstrate that the unit(s) supplied meet the performance specifications, such as the exchange capacity.

4. Identify all water contact materials, separating them into those that contact feed water and product water. For all product water contact materials, results of leach testing should be provided that identify and characterize the leachables using appropriate chemical analyses.

5. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device. The manual should provide the expected life of the resin bed in terms of the quality and volume of water treated. The manual should identify the recommended quality of replacement tanks or resins. Due to the potential problems of sudden exhaustion of the D.I. bed, the instructions should have clear and adequate warnings to respond immediately to any alarm conditions. The labeling should also include a Warning that D.I. units should only be used with water that has been treated with carbon filtration, to prevent contamination by nitrosamines.

C. WATER SOFTENERS

1. Provide a device description that includes the capacity (i.e., feed and product flow rates), ranges of feed water hardness treated, and the identity of all water contact materials.

2. Describe the control features provided with the unit. The FDA recommends that these units include regeneration lock-outs that will keep the R.O. from operating whenever the water softeners are regenerating.

3. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device including the recommended regeneration schedule as a function of usage. Labeling should also include the recommended grade of replacement salt and resins. If the manufacturer intends to market water softeners directly to dialysis facilities, the labeling should state that water softeners are to be used only for pre-treatment of water prior to R.O. or D.I.

D. CARBON FILTRATION TANKS

1. Provide a device description that includes the bed volume, maximum flow rates, empty bed contact times (EBCT) and the identity of all water contact materials. The FDA recommends a 6 minute EBCT for the removal of chlorine and a 10 minute EBCT for the removal of chloramine. It is also recommended that two tanks be installed in series, with the first tank providing the primary purification and the second tank serving as backup.

2. Provide a user's manual that includes instructions for installing, operating, maintaining, troubleshooting and rebedding the device. Provide instructions for back-washing the device, including the recommended back-washing frequency. The manual should include a warning to monitor the total chlorine or chloramine in the water exiting the units along with a recommended monitoring frequency. The manual should recommend the grade of replacement carbon. If the manufacturer intends to market carbon filtration tanks directly to dialysis facilities, the labeling should state that they are to be used only for pre-treatment of water prior to R.O. or D.I.

E. SEDIMENT AND CARTRIDGE FILTER

1. Provide a device description that includes the sizes, filtration capacity, flow rates and expected pressure drop for all units supplied. Identify all water-contact materials.

2. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device. The labeling should describe

the parameters used to determine the useful lifetime of the product. If the manufacturer intends to market these filters directly to dialysis facilities, the labeling should state that they are to be used only for pre-treatment of water prior to R.O. or D.I.

F. ULTRAFILTERS

1. Provide a physical description of the device including the flow rates, expected pressure drop and the materials of construction. Provide a diagram of the membrane cartridge. Describe any monitors or alarms that may be installed with this component.

2. Provide the specifications for rejection of bacteria and pyrogens and supply data to demonstrate that the membrane, as typically installed, meets the performance specifications.

3. If dialysate passes through the ultrafilter, data to demonstrate that the dialysate composition or hydrodynamics is not affected by the device should be provided.

4. List all water contact materials. For these materials, results of leach testing should be provided that identify and characterize the leachables using appropriate chemical analyses. If dialysate passes through the ultrafilter, leach testing will be required using dialysate as the extracting solvent.

5. If dialysate passes through the ultrafilter, biocompatibility testing of the device materials will be required as recommended by Blue Book Memorandum G95-1, "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." A copy of this guidance may be obtained by contacting DSMA at the telephone numbers listed above.

6. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device. The manual should list any cleaning, disinfection or maintenance procedures that must be performed along with the recommended frequency. Recommended cleaning and disinfection agents and procedures for monitoring residuals should also be provided. The manual should specify the expected useful life of the device. If the manufacturer intends to market ultrafilters directly to dialysis facilities, the labeling should state that they are to be used only

for post-treatment of R.O. or D.I. treated water and are not intended to provide primary purification.

G. ULTRAVIOLET (UV) DISINFECTION UNITS

1. Provide a device description that includes the materials of construction, the recommended feed flow rates, the UV intensity, and the effectiveness of the UV disinfection. A device diagram should be included. Describe all monitors, alarms or control systems used to detect loss of lamp radiant energy output.

2. Provide data to demonstrate that the unit meets the performance specifications, e.g., the effectiveness of the UV disinfection.

3. List all water contact materials. For these materials, results of leach testing should be provided that identify and characterize the leachables using appropriate chemical analyses.

4. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device. The manual should specify the frequency of cleaning/disinfection, monitoring and maintenance procedures (including lamp replacement). If the manufacturer intends to market UV disinfection units directly to dialysis facilities, the labeling should state that they are to be used only for post-treatment of R.O. or D.I. treated water and are not intended to provide primary purification.

H. WATER STORAGE TANKS

1. Provide a device description that includes the dimensions of the tank and a description of any level controllers and air filters. The FDA believes that submicron filters should be installed on the inlet air line to the tank to prevent bacterial contamination.

2. List all water contact materials. For these materials, results of leach testing should be provided that identify and characterize the leachables using appropriate chemical analyses.

3. Provide a user's manual that includes instructions for installing, operating, maintaining and troubleshooting the device. The manual should provide guidance on the proper placement of storage tanks in a water purification system, along with any associated precautions or warnings.

I. AUXILIARY COMPONENTS

Auxiliary components include tubing, valves, fittings, gauges, sensors, meters, monitors, detectors and pumps. The following information should be provided for each component:

1. Specify the materials of construction. If the auxiliary component is installed in the product water line (following R.O. or D.I.), results of leach testing should be provided that identify and characterize the leachables in any material contacting product water, using appropriate chemical analyses.

2. Certify the accuracy of all sensors, meters, monitors, gauges and detectors.

3. If the sensors utilize software, information should be provided as recommended in the "Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review." A copy of this guidance can be obtained from DSMA at the telephone numbers listed above.

4. Describe all associated alarms or monitoring systems.

10. ADDITIONAL REQUIREMENTS FOR SUPPLIERS AND MANUFACTURERS OF WATER PURIFICATION SYSTEMS

The information in section 9 should be provided for each component that could potentially be included in the water purification system. If a component has already been cleared for marketing through the premarket notification program, the 510(k) number may be provided in lieu of the information in section 9. Suppliers of water purification systems should also provide the information described below.

A. Provide a description of the decision-making process utilized to customize the systems to meet the needs of the user. The description should identify specific solutes or contaminants in the feed water and the ranges of these substances that will result in the recommendation of a particular purification step. This may be done by describing a system that includes all of the components that could possibly be supplied and then specifying the conditions under which certain components may be omitted. The description should also include a generic diagram of the water purification system.

B. Describe the consequences of failure of each component and the required corrective action.

C. In addition to the user's manuals for each component that are described in section 9, manufacturers of systems should also provide a guidance for the installation, start-up and maintenance of the system. A generic sample of the guidance for a system incorporating all of the components should be submitted. The guidance should include, at a minimum, daily start-up procedures; a list of solutes or contaminants that must be monitored off-line (such as chloramine or bacteria) and a recommended monitoring schedule; cleaning and disinfection procedures and schedules; and a troubleshooting guide.

D. Provide the results of leach testing that identify and characterize the leachables from the water contact materials of the entire water purification system. The tests should be performed using appropriate chemical analyses. Leach testing of the water contact materials in the complete system would satisfy the requirements for leach testing of individual components, discussed in Section 9.

E. Label each component in the system with the name and address of the manufacturer/supplier of the water purification system.

F. Certify that the water produced by each customized purification system will meet or exceed current industry standards and government regulations.

11. TRUTHFUL AND ACCURATE STATEMENT

Your submission must contain the following statement:

> *I certify in my capacity as (provide title) for (provide manufacturer's name), I believe, to the best of my knowledge, that all data and information submitted in this premarket notification are truthful and accurate and that no material fact has been omitted.*

The above statement must be signed and dated by a representative of the company (not by a regulatory consultant).

12. INDICATIONS FOR USE STATEMENT

The indications for use for the water purification component or system should be provided on a separate sheet. The indications should agree exactly with the indications for use provided in the device labeling.