Guidance for Industry and CDRH Reviewers

# Guidance for the Content of Premarket Notifications for Hemodialysis Delivery Systems

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**U.S. Department Of Health And Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**

**Gastroenterology and Renal Devices Branch**
**Division of Reproductive, Abdominal, Ear, Nose and Throat**
**and Radiological Devices**
**Office of Device Evaluation**

# Preface

## Public Comment

Comments and suggestions on this draft document may be submitted at any time for Agency consideration to Carolyn Y. Neuland, Ph.D., Chief, Gastroenterology and Renal Devices Branch, Office of Device Evaluation, 9200 Corporate Boulevard, HFZ-470, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Elias Mallis at (301) 594-1220 or by electronic mail to eym@cdrh.fda.gov.

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# GUIDANCE FOR INDUSTRY AND CDRH REVIEWERS ON THE CONTENT OF PREMARKET NOTIFICATIONS FOR HEMODIALYSIS DELIVERY SYSTEMS

## I. BACKGROUND

This guidance document represents the FDA's current thinking on the content of premarket notifications for hemodialysis delivery machines. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance 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, the FDA Modernization Act of 1997, 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. Comments and suggestions on this draft document are welcomed and should be submitted to Carolyn Y. Neuland, Ph.D., Chief, Gastroenterology and Renal Devices Branch, Office of Device Evaluation, 9200 Corporate Boulevard, HFZ-470, Rockville, MD, 20850. Comments should be submitted within 90 days of the date of issue of this document to receive consideration for the next revision.

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 is necessary before the FDA can clear a device for marketing. The submission must provide evidence that the device is safe, effective, and substantially equivalent to a predicate device that is currently legally marketed in the United States.

Hemodialysis delivery systems are described and classified in two sections of the FDA regulation. Under 21 CFR §876.5820, a conventional hemodialysis delivery system is defined as a system that "**consists of mechanisms that monitor and control the temperature, conductivity, flow rate, and pressure of the dialysate and circulates dialysate through the dialysate compartment of the dialyzer**." This system "includes the dialysate concentrate for hemodialysis (liquid or powder) and alarms to indicate abnormal dialysate conditions."

Under 21 CFR §876.5860, a high permeability hemodialysis delivery system is defined as a machine that **contains an ultrafiltration controller and mechanisms that monitor and/or control the system temperature, dialysate conductivity, fluid (e.g.,**

**blood, dialysate, effluent) flow rate, pressure, fluid balance, proportioning of the dialysate, pumps, air foam (bubble detectors), alarms, computer interfaces, and patient treatment parameters (e.g., blood pressure, hematocrit, urea, oxygen saturation, etc.).** This includes those components that are incorporated into the machine, such as heparin pumps, monitors, etc. (Note that this definition is based on the proposed reclassification of this section and is subject to change.).

The systems described in the above classifications are generally part of the hemodialysis system that also contains the hemodialyzer, extracorporeal and associated tubing lines, water treatment systems, and patient access devices.

For the purpose of this document, a hemodialysis delivery system will refer to both classifications listed above. In addition, you may refer to this guidance when preparing a submission for devices that perform hemoconcentration, hemofiltration, and other related extracorporeal therapies. In addition, a separate section is included in this guidance document that specifically addresses the use of devices that perform on-line hemodiafiltration.

In addition, for the purpose of this document, a "hemodialysis delivery system," "dialysis system," and "hemodialysis system" may be interchanged and generally refer to either the proposed (new) or predicate (currently legally marketed) device.

Recommendations for hemodialyzers may be found in these separate guidance documents: "Guidance for Hemodialyzer Reuse Labeling," and "Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzers." Each of these guidances is available from the Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at 1(800) 638-2041 or at the internet address: **http://www.fda.gov/cdrh/dsma/dsmamain.html**.

The primary reference for the information required to be included in a 510(k) for a medical device is set forth in 21 CFR §807.87. The purpose of this section is to inform the submitter of the information necessary for FDA to determine substantial equivalence of a proposed device to a device in commercial distribution. Substantial equivalence to a currently legally marketed device is to be established with respect to, but not limited to, intended use, design, energy used/delivered, materials, performance, safety, effectiveness, labeling, and other applicable characteristics.

FDA recommends that each 510(k) for a hemodialysis delivery system include the information in this guidance document in order to ensure that the submission is adequate to permit a determination of substantial equivalence to a predicate hemodialysis delivery system.

Additional guidance on the required elements for a 510(k) submission can be obtained by referring to the "DRAERD Premarket Notification [510(k)] Screening Checklist." A copy may be obtained from DSMA.

## II. SCOPE OF GUIDANCE

This guidance document is intended to aid in the preparation of 510(k) applications for devices with either of the following classifications:

| Device Group | Class | CFR Section | Panel/Product Code |
|---|---|---|---|
| conventional | II | §876.5820 | 78 FKP |
| high permeability | III* | §876.5860 | 78 KDI |

*subject to change pending reclassification of §876.5860

The 510(k) should include the appropriate CFR classification regulation number, class, panel, and product code for the proposed device. This is a comprehensive guidance that describes the type of information generally needed for the submission of a new hemodialysis delivery system. However, you should also follow this guidance for the submission of modifications to currently legally marketed hemodialysis systems.

## III. PROPOSED DEVICE

The 510(k) should include both the trade/proprietary name of the device, including specific model, and the common/usual, name for the particular type.

## IV. PREDICATE DEVICE

The 510(k) should include an identification of the currently legally marketed device(s) to which the proposed device will be compared. Be as specific as possible, e.g., include the proprietary and common name, manufacturer, model number, 510(k) reference number, pre-Amendments status (i.e., marketed in the United States prior to May 28, 1976), etc. The 510(k) should include a tabbed section with product literature (description, specifications, labels and labeling, etc.) for the predicate device.

## V. APPLICANT INFORMATION

The 510(k) should include the following information about the applicant:

- establishment registration number;
- address of manufacturing site; and
- name, title, telephone and FAX numbers, and address of contact person.

## VI. INTENDED USE/INDICATIONS FOR USE

The 510(k) should include a clear description of the proposed device's intended use/indications for use. This description should identify, at a minimum, the following:

- the modalities under which the dialysis system may be operated (e.g., low flux hemodialysis, high flux hemodialysis, ultrafiltration, hemofiltration); and

- the environment in which the machine may be used (e.g., chronic dialysis facility, (acute) intensive care unit, etc.).

## VII. DEVICE DESCRIPTION

The 510(k) should include a detailed device description that describes the safe and effective features of the dialysis system, which includes a description of the following: (a) physical and/or electronic components, (b) system features/functions, (c) materials and biocompatibility, and (d) software. Each of these areas is described in more detail below.

### A. PHYSICAL AND/OR ELECTRONIC DESCRIPTION

1. Provide a description of the overall device system. We recommend that the information be provided in the form of a block diagram that identifies the interconnection between the various sub-systems, system components, user interfaces, and networks.

2. Provide a functional description (including specifications, if applicable) of the individual components of the dialysis system, which generally includes the following:

    a. pumps (e.g., type of pump)
    b. valves
    c. ultrafiltration controller mechanism
    d. air detector systems
    e. blood leak detectors
    f. heat exchangers
    g. other safety features

3. Provide a diagram (in color, if possible) that identifies the fluid paths (e.g., blood, dialysate, effluent) and indicate how each path interacts with the various components of the dialysis system.

4. Provide a description of the dialysate that is used with the dialysis system (e.g., concentrate that is prepared on-line, pre-mixed).

   a. If the dialysis solution is prepared on-line during the dialysis treatment, provide the following:

      (1) the ratio of the mixture of concentrates and water used;

      (2) the minimum quality of water that is to be mixed with the dialysate (e.g., AAMI quality); and

      (3) an identification of the type of concentrates that may be used (i.e., acid and bicarbonate, acetate).

   b. If the dialysis solution is not prepared on-line, provide a complete description of the type of solution that may be used, how it is prepared for and stored prior to use, and how it is delivered into the fluid path system.

5. Provide a description of all possible configurations (e.g., single-needle, double needle) for which the delivery system may be used, and explain which features of the system are used for each configuration.

6. Identify the accessories that may be used within the delivery system (e.g., patient data card, network interface, non-invasive blood pressure (NIBP) monitor, or ECG). If the system incorporates a device component for which there is a specific guidance document issued by FDA (e.g., NIBP monitor), you should follow the recommendations outlined in that document.

7. Any accessory device that is identified for use with the dialysis system should be currently legally marketed or be included as part of the dialysis system 510(k) (with adequate information on the accessory device to allow a determination of substantial equivalence).

8. Identify the tubing set(s) compatible with your device. This is particularly needed for dialysis systems with complex, multi-pump designs and configurations unique to their systems. This information should also be included in the device labeling, so that the user of the dialysis system is informed of the tubing set(s) needed to safely operate the system. Where applicable, the functional testing described in Section VIII (1) should be conducted with the (or one of the) tubing set(s) designated as compatible with your device.

B. SYSTEM FEATURES/FUNCTIONS

1. Provide a listing of the performance specifications for the various features of the dialysis system, giving both the range of allowable values and the default. This information should be provided, at a minimum, for these parameters:

   a. flow rate that each pump can deliver;
   b. transmembrane pressure;
   c. ultrafiltration rate;
   d. dialysate temperature
   e. dialysate conductivity; and
   f. arterial and venous pressure.

   Each of these values should be compared to those for the predicate device. If the proposed device has a range outside of the range for the predicate device, explain why this difference does not affect the safety or effectiveness of the proposed device.

2. Provide a listing of the alarms included in the dialysis system For each alarm, provide a description of the alarm (e.g., whether it is audible, visible, etc.) and describe:

   a. the hazard condition that triggers the alarm;
   b. how the machine user must respond to and resolve the alarm; and
   c. how the machine responds to the alarm condition (e.g., system shut down).

   Note that this information should be included, at a minimum, in the troubleshooting section of the operator's manual for the dialysis system.

3. Due to their inherent design and operational properties, a dialysis machine should include several key design features and associated alarms and fail-safe responses. As a result, we expect you to incorporate and validate the following:

   a. disinfection, cleaning, and reprocessing method(s) (see Item 5 below);
   b. dialysate conductivity monitor;
   c. pH sensor;
   d. ultrafiltration controller;
   e. air detector system;
   f. blood leak detector;
   g. temperature monitor; and
   h. fail-safe design feature in the event of power failure.

4. Provide a description of all prescription profiling features (e.g., dialysate, ultrafiltration, sodium) that may be used within the dialysis treatment. This should include an identification of the possible profiles that may be selected, how the operator selects a particular profile, and how the dialysis system reacts to a particular profile during machine use. If applicable, clarify whether a profile has precedence over another in the event that they require different operating conditions/parameters.

5. Provide a description of the complete system disinfection and/or reprocessing methods that are required for the dialysis system. This should include a complete description of the disinfection protocol and the steps the operator must follow in order to complete machine disinfection, including methods for determining disinfectant residuals. If you identify a disinfection method or protocol that has not previously been cleared or is not used in a currently legally marketed device, then validation of this method is needed. We encourage you to contact FDA prior to the submission of a 510(k) with a new disinfection method or protocol.

## C. MATERIALS/BIOCOMPATIBILITY

Provide an identification of the machine components (and the corresponding materials) that are either patient- or patient-fluid contacting. For the purpose of this guidance, a machine component in the dialysate fluid path is considered patient-fluid contacting.

For each of these materials, either identify a currently legally marketed device that uses the identical material for a similar intended use, or provide appropriate biocompatibility testing as recommended in the current FDA guidance on biocompatibility.

Alternatively, you may conduct leach testing that identifies and characterizes the potential leachables using appropriate chemical analyses for patient-fluid contacting materials. In addition, you should conduct a risk assessment of the toxic potential of these leachables obtained from referenced literature.

## D. SOFTWARE

The requirements for software-controlled medical devices and for the use of off-the-shelf software are described in guidance documents issued by the Office of Device Evaluation. Contact DSMA for the latest version of these guidance documents.

In general, your documentation on the software of the device should be partitioned into the following sections:

1. structure chart of flow chart describing software architecture;

2. summary of software development procedures, including changes made to the software

3. software requirements specification with traceability back to the hazard analysis;

4. verification and validation test plan, including pass/fail criteria and traceability back to the requirements;

5. system level test results; and

6. current software version number and date of latest revision.

## VIII. DEVICE PERFORMANCE

The 510(k) should include adequate information describing the performance characteristics of the dialysis system. At a minimum, this should include the following:

A. functional testing that demonstrates that the device performs as designed and expected;

B. a system-level hazard analysis that confirms that the device does not perform in an unexpected and/or unsafe manner;

C. electrical safety testing (in lieu of providing the results of this testing, a declaration of conformity with IEC 60601-1 is adequate); and

D. electromagnetic compatibility (EMC) testing (in lieu of providing the results of this testing, a declaration of conformity with IEC 60601-2 is adequate. However, if the dialysis system is intended for use in a home environment, we expect you to conduct testing that addresses the potential hazards in the home environment).

## IX. CLINICAL DATA

Due to changes in technology that may have a significant impact on safety and effectiveness of dialysis, clinical data may be needed to support a marketing application. Please contact FDA for guidance on whether clinical data is needed for your application.

## X. HEMODIAFILTRATION

For the purpose of this guidance document, an on-line hemodiafiltration system is a system that receives non-sterile solution, processes it, and delivers it as a sterile replacement priming or rinseback solution to the patient. Further, the phrases "replacement fluid" and "fluid for priming or rinseback on-line" may be used interchangeably in terms of the requirements listed below.

For those devices that either perform on-line hemodiafiltration or produce fluid for priming and rinseback on-line, you should provide the information listed in this section in addition to the other information described elsewhere in this guidance document.

### A. DEVICE DESCRIPTION

1. Identify the components that are considered part of the replacement fluid path, from the point of entry into the system until the point where the fluid is delivered to the patient. Clarify whether the fluid is pre-treated (e.g., with a reverse osmosis system) prior to entering the system. Identify whether the components are single-use or multiple-use. If multiple-use, identify the number of times the component may be used, or the maximum volume of fluid that can be processed by the component before it should be replaced used.

2. Describe the specific sterilization process that is used to produce the fluid for priming or rinseback on-line and identify the design features that address potential failures of this process.

3. For filtration-sterilization systems:

    a. Redundancy should be built into the design, so that safety is assured in the event of a component failure during treatment.

    b. The system should include pressure gauges or some other means of determining when a filter leak has occurred or when the filters are clogged and need to be replaced.

    c. If the disinfection process differs from the process described in Section VII(B)(5), provide a description of the recommended disinfection process that is needed to reprocess the filters, and identify the steps the operator must follow in order to complete the disinfection process. If you identify a disinfection process that has not been previously cleared for marketing, or is not used in a currently legally marketed device, then validation of this method is needed.

B. BENCH TESTING

1. Provide test data to demonstrate that the replacement fluid meets the standard for USP Sterile Water for Injection <1231>. The test should be performed by challenging the system with large numbers of appropriate water-borne organisms (e.g., *Brevundimonas diminuta* and *Mycobacterium abscessus* for filtration-sterilization systems), as well as endotoxin to demonstrate that the system continues to produce USP sterile water for injection after the challenge.

2. Testing should be performed to address the potential for the formation of biofilms. Data should demonstrate that biofilm formation will not occur in the replacement fluid path when the device is operated and maintained according to the instructions provided in the labeling.

3. For filtration-sterilization systems:

   a. If the filters are intended for multiple use, provide data to demonstrate that the recommended disinfection process does not adversely affect the performance of the filters.

   b. The bench tests described above should be performed at the beginning and at the end of the useful life of the filter. For the purpose of the device label, the tests should incorporate a safety factor.

C. LABELING

1. The labeling should include instructions for the user on how to conduct microbiological testing and surveillance of the system, and guidance on how to establish a quality control (QC) program. This QC program should recommend a minimum frequency of testing, pass/fail criteria, procedures for resolution of problems, etc.

2. The labeling should specify disinfection procedures (e.g., disinfectant, contact time, rinse procedures, measurement of residuals) and should recommend a minimum frequency for disinfection of the system.

3. The labeling should state that only AAMI quality water and AAMI quality dialysate must be used, as specified in ANSI/AAMI RD5-1992, parts 3.2.1.1 and 3.2.1.2. The labeling should provide the minimum requirements for the water purification system that is to be used in conjunction with the on-line hemodiafiltration device. For example, FDA believes that the water purification system should include a reverse osmosis (RO) unit equipped with a system shut-down or divert-to-drain

feature in the event of a water quality alarm. In addition, the system should not include RO bypass, nor should it include a deionizer (DI) system unless the DI is also equipped with a system shut-down or divert-to-drain feature. More information on FDA recommendations for water purification systems may be found in the "Guidance for Premarket Notification Submission for Water Purification Components and Systems for Hemodialysis." A copy of this guidance may be obtained from the FDA website or by contacting DSMA.

4. The labeling should include a warning that preventive maintenance must be performed and should describe the consequences if maintenance is not performed (e.g., contamination leading to pyrogen reaction, infection, other adverse events).

5. For filtration-sterilization systems:

   a. The labeling should advise the user on when to change the filters for both routine replacement based on usage/time and replacement due to failure of the filter to meet the minimum performance specifications (as defined e.g., by a pressure leak test). Note that recommendations for the routine replacement should be validated by the bench testing described above and should incorporate a safety factor.

   b. The filter label should (1) include a place where the user can write the date it was installed in the system, and (2) identify when it should be replaced (e.g., replace within 1 month of initial use, or due to poor performance with a recommended test method). As noted above, the replacement schedule should reflect the safe use life of the filter that incorporates a safety factor.

## D. CLINICAL DATA

Clinical data is needed to demonstrate the safety of the on-line production of fluid under actual use conditions. We believe that such data should be collected in a multi-center clinical study that reflects current hemodialysis practice in the United States. FDA considers this to be a significant risk study; therefore, clinical studies in the United States must be conducted under an investigation device exemption (IDE). FDA recommends that you contact us before submitting a 510(k) or IDE to discuss clinical data requirements unique to each system.

In general, the study should track adverse events (AEs) (e.g., fluid imbalance, infection, pyrogen reaction, etc.) and compare the AE rates with the new system to those of patients receiving standard dialysis in the United States. Microbiological surveillance of the system will also be needed to demonstrate

that the system continues to produce USP Sterile Water for Injection under actual use conditions.

## XI. COMPARISON TABLE

The 510(k) should include a comparison of the proposed device to a predicate device. This comparison may be done in a table that lists the similarities and differences between the proposed device and predicate device(s) in terms of intended use, design features, performance specifications, and other important safety and/or effectiveness information.

## XII. DEVICE LABELING

The 510(k) should include the device labeling for dialysis machines, which generally consists of the operator's manual, promotional advertising, and labels affixed directly to the machine.

This labeling should include a specific intended use statement and any warnings, contraindications, or limitations clearly displayed as described in 21 CFR §807.87(e). This may be provided in draft form. The device labeling must bear the caution statement as outlined in 21 CFR §801.109(b)(1): "CAUTION: Federal law restricts this device to sale by or on the order of a physician." Guidance on labeling issues is described in Bluebook Memo G91-1 "Device Labeling Guidance (3/8/91)." A copy of this guidance may be obtained from DSMA at the telephone number listed above.

The operator's manual should provide detailed information regarding the safe use of the dialysis machine. In general, the manual should include these sections:

A. Therapy Background - This section should provide an overview of the therapy(ies) that may be performed with the system, the target population, and general principle of operation. Identify indications, contraindications, warnings, cautions, and precautions.

B. Device Description - This section should provide an overall description of the device and individual components. Describe the safety-related components included in the system (e.g., ultrafiltration controller, arterial and venous pressure sensors, etc.). Describe the accessories (extracorporeal tubing, replacement fluids, etc.) that need to be used with the system. The manual should recommend that the dialysate solution should be prescribed by a physician and conform to the AAMI Standard RD-5. Identify operational parameters, such as flow rates, monitoring pressure, and, where appropriate, the accuracy of such parameters. Identify the model number and current software version of the machine.

C. Device Operation - This section should describe the pre-treatment, performance, and post-treatment steps needed to safely perform each therapy mode (if more than one may be performed). If the machine may be used with different configurations (e.g., single-needle vs. double needle), the instructions should be clear enough to distinguish them.

D. Alarms and Troubleshooting - This section should clearly identify the alarms included in the system, the format in which it appears (e.g., visual, audible alarm), the suspected cause of the alarm condition, and how the user must respond to the alarm.

E. Cleaning, Disinfection, and Preventative Maintenance - This section should provide detailed instructions for the user to properly clean, disinfect, and maintain the dialysis machine. The disinfection information should be consistent with the information requested in Section VII(B)(5) of this guidance.

While certain aspects of the operator's manual may be specific to the design of a particular hemodialysis delivery machine, we believe that several critical user-related aspects should be included in all manuals. This includes the following:

- a caution regarding the possible susceptibility to EMI and possible electrical hazards associated with the use of the hemodialysis delivery machine;

- instructions for the user to properly use, monitor, and verify the conductivity and temperature of the dialysate used in the hemodialysis delivery machine;

- instructions for the user to properly monitor and adjust the patient's dialysis treatment to ensure proper fluid balance, and to use high-permeability dialyzers with UF-controller hemodialysis machines; and

- a caution that the user should not over-ride or bypass the air embolism/foam detector during treatment.

## XIII. MODIFICATIONS TO CURRENTLY LEGALLY MARKETED DEVICE

For modifications to a currently legally marketed dialysis machine, refer to the CDRH guidance titled "Deciding When to Submit a 510(k) for a Change to an Existing Device" on whether a 510(k) is required for this proposed change. In general, a modification that affects the safe and effective use of the dialysis machines (e.g., change in alarm features, performance specifications) requires a 510(k) submission. In addition, a 510(k) should be submitted if the modification is correcting problems or failures associated with one or more components of the machine.

If you submit a 510(k) for a modification to a legally marketed dialysis delivery system, clarify the regulatory status of this device (identify the 510(k) number if known), and clearly describe the differences between the new device and legally marketed dialysis delivery system.

## XIV. ADMINISTRATIVE INFORMATION

As required by FDA regulation, several documents are needed to complete the administrative record for a 510(k).

### A. TRUTHFUL AND ACCURATE STATEMENT

The 510(k) should 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).

### B. INDICATIONS FOR USE STATEMENT

The 510(k) should include the indications for use for the hemodialysis delivery machine should be provided on a separate page. Note that (1) you should identify the specific device name (including model number, if applicable) on this statement and (2) the indications should agree exactly with the indications for use statement in the device labeling.

C. 510(K) SUMMARY/510(K) STATEMENT

The 510(k) should contain either a 510(k) Summary or 510(k) Statement. Refer to 21 CFR §807.92 and §807.93 for the content and format of these documents. The 510(k) Summary should not include any trade secret information or patient identifiers.

D. PREMARKET NOTIFICATION CLASS III CERTIFICATION AND SUMMARY*

If your device is a Class III device, you should provide the Premarket Notification Class III Certification and Summary as required by 21 CFR §807.94(p)(q).

* Note that this may no longer be needed, pending reclassification of §876.5860 from Class III to Class II.