

Guidance for Industry and CDRH Reviewers

# **Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzers**

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This document supersedes document, "Guidelines for Premarket Testing of New Conventional Hemodialyzers, High Permeability Hemodialyzers, and Hemofilters" dated March 1, 1982



**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**

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# Preface

## Public Comment

Comments and suggestions 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. For questions regarding the use or interpretation of this guidance contact Miriam C. Provost, Ph.D. at (301) 594-1220 or [mxp@cdrh.fda.gov](mailto:mxp@cdrh.fda.gov).

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## **Guidance for the Industry and CDRH Reviewers on the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzers**

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This guidance document represents the FDA's current thinking on the content of premarket notification submissions for conventional and high permeability hemodialyzers. 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), 4) the Safe Medical Devices Act of 1990, 5) 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 legally marketed in the United States.

A **conventional** hemodialyzer is described in the FDA regulation, 21 CFR 876.5820. Generally, a conventional hemodialyzer is a device that allows a transfer of water and solutes between the blood and the dialysate through a semipermeable membrane. The semipermeable membrane of the conventional hemodialyzer has a sufficiently low permeability to water that an ultrafiltration controller is not required to prevent excessive loss of water from the patient's blood. FDA believes that the *in vitro* ultrafiltration coefficient ( $k_{UF}$ ) for a conventional hemodialyzer would be equal to or less than 12 ml/hour/mm Hg.

A **high permeability** hemodialyzer is described in the FDA regulation, 21 CFR 876.5860. Generally, a high permeability hemodialyzer is a device that has a semipermeable membrane that is more permeable to water than the semipermeable membrane of the conventional hemodialyzer. This highly permeable, semipermeable membrane may also permit greater loss of higher molecular weight substances from the

blood. The dialysate delivery system for these high permeability hemodialyzers requires the use of an ultrafiltration controller to regulate the rate of removal of water from the patient's blood. FDA believes that the *in vitro* ultrafiltration coefficient ( $k_{UF}$ ) for high permeability hemodialyzers would be greater than 12 ml/hour/mm Hg.

The primary reference for the information required in a premarket notification (510(k)) for a medical device is found in 21 CFR 807.87. Substantial equivalence to a 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. Additional guidance on the required elements for a premarket notification submission can be obtained by referring to the "DRAERD Premarket Notification [510(k)] Screening Checklist" and "DRAERD Draft Guidance for the Content of Premarket Notifications." A copy of each of these 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 at their internet address: <http://www.fda.gov/cdrh/dsmamain.htm#contents>.

Whether a hemodialyzer is intended for single or multiple use, this information should appear prominently on the device label. If a hemodialyzer is intended for multiple use, the submission should also include all information described in the "Guidance for Hemodialyzer Reuse Labeling (October 6, 1995)" which can be obtained from DSMA at the telephone number listed above.

To expedite review of your 510(k) submission, please provide the information described in this document. FDA recommends that your 510(k) submission include numbered pages, a table of contents and clearly titled sections.

## **I. DEVICE NAME**

Provide the name of the device, including:

- A. Classification name (i.e., conventional hemodialyzer or high permeability hemodialyzer);
- B. Common name (i.e., hemodialyzer);
- C. Trade or proprietary name;
- D. Intended use.

## **II. MANUFACTURER INFORMATION**

Provide the following information about your company:

- A. Establishment registration number;
- B. Address of manufacturing site;
- C. Name, title and telephone and fax number of contact person.

## **III. DEVICE CLASSIFICATION**

Provide the CFR classification regulation number for the device and any components or accessories.

## **IV. DEVICE DESCRIPTION**

Provide a detailed description of the hemodialyzer. The description should include a labeled diagram and the specifications (i.e., length, width, height, diameter, weight, number of hollow fibers/blood layer sheets, etc.) for each model included in the submission.

## **V. COMPARISON WITH PREDICATE DEVICE**

The hemodialyzer 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 date of the Medical Devices Amendments), or one which has been cleared for marketing in the United States under Section 510(k) of the Food, Drug and Cosmetic Act (the Act). The comparison should include, at a minimum, the following:

- A. Intended use
- B. Materials, specifically:
  - 1. Potting resin for fibers, where applicable;
  - 2. Blood and dialysate port caps;
  - 3. End molds , where applicable;
  - 4. Headers;

5. Jacket/Housing; and
6. "O" rings, if applicable.

C. Membranes

1. For hollow fiber type, provide:
  - a. Chemical composition;
  - b. Inner diameter [ID] (measured average);
  - c. Wall thickness;
  - d. Number of fibers; and
  - e. Effective fiber length.
2. For flat plate type, provide:
  - a. Chemical composition;
  - b. Membrane thickness; and
  - c. Number of blood layer sheets.

D. Effective membrane surface area

E. Configuration (i.e., overall casing length, width, dimension and geometry, including ports)

F. Total blood volume (priming volume)

G. Sterilization method as described in Section IX

H. Regulatory status of the predicate hemodialyzer (i.e., 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])

FDA recommends that all comparisons be provided in a manner that is clear and comprehensible, such as in tabular form.

## VI. DEVICE MATERIALS AND BIOCOMPATIBILITY

- A. An exact identification of all materials used to fabricate all components of the hemodialyzer, including any colorants (inks, dyes, markings, etc.), plasticizers or additives should be provided. Materials should be separated according to whether they have direct or indirect body contact and according to the duration of contact.
- B. Biocompatibility data, as recommended by Blue Book memorandum, G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" should be provided. Due to the large disparity in surface area between the hollow fiber membrane and the rest of the device components, the FDA does not recommend that extractions be performed on the complete, finished device. The large surface area of the membrane may dilute the extract of another small component which could be highly toxic, making the results difficult to interpret. Instead, FDA recommends that manufacturers separate the membrane from the rest of the device and extract it separately. Two extracts should therefore be tested - the membrane and the rest of the device components (i.e., casing, potting material, end caps, etc.). FDA believes that this approach will provide scientifically meaningful results while minimizing the number of tests to be performed. Alternatively, manufacturers may perform finished device testing, provided the extraction conditions (i.e., volume of solvent used per surface area of product) are more rigorous than those recommended in ISO-10993.

Hemodialyzers are considered external communicating devices, circulating blood, prolonged contact (category B). For the purposes of this document, a membrane material will be considered **new** if it contains a membrane, filler yarn or spacer material that is new to this intended use in the United States or if the membrane fiber has been chemically modified or altered from previously legally marketed fibers for a similar intended use. In contrast, for the purposes of this document, **predicate** materials are those that have been well characterized chemically and physically in the published literature, and have a long history of safety in products with a similar intended use. Materials should be similar in the complete formulation (including plasticizers, additives and colorants) to be considered **predicate** materials. For predicate materials, the FDA will accept adequate justification for not conducting some or all of the following suggested tests.

- Cytotoxicity
- Sensitization (Guinea pig maximization with polar and non-polar extracts)
- Irritation or intracutaneous reactivity
- Systemic toxicity (acute)
- Implantation\*
- Genotoxicity\*\*
- Hemocompatibility (hemolysis)\*\*\*
- Chronic toxicity\*
- Carcinogenicity\*\*\*\*
- Chemical analysis of potential leachables for membrane or other blood contacting materials

\* Patients are exposed the hemodialyzer materials repeatedly over a long period of time. A long term implantation study with histopathology may replace implantation and chronic toxicity.

\*\* Suggested Genotoxicity test battery should include:

1. Bacterial cell reverse mutation assay employing specific TA tester strains of *S. Typhimurium* and WP2 tested strains of *E. coli*:
  - (a) TA98 and (b)TA100 and (c)TA1535 and (d) TA1537 or TA97 or TA97a and (e) TA102 or WP2uvrA or WP2uvrA(pKM101)
2. Mammalian cell in vitro assay
  - (a) mouse lymphoma cell L5178Y/TK<sup>(+/-)</sup> mutagenesis assay with large and small colony analysis or
  - (b) Chinese hamster ovary cell (CHO) or
  - (c) CHO cell or lung (V79) cell/hyposanthine-guanine phosphoribosyl transferase (HGPRT) assay plus the CHO AS52 cell/GPT assay or
  - (d) CHO or V79/HGPRT plus an in vitro assay for chromosome aberrations in CHO cells (or human peripheral blood lymphocytes)
3. In vivo cytogenetics assay in rodents (usually mice) for detection of:
  - (a) bone marrow micronuclei, or

- (b) peripheral blood erythrocytes, or
- (c) bone marrow chromosomal aberrations

\*\*\* For **new** materials, thrombus formation and the potential for complement activation should be evaluated in a clinical study.

\*\*\*\* Adequate justification for not performing carcinogenicity testing on **new** materials should consist of:

- (1) Information from genotoxicity testing (including the *in vivo* assay described above), and
- (2) Information from the chemical analysis of the leachables, described above, and
- (3) Risk assessment based on the carcinogenic potential of the expected leachables obtained from referenced literature.

## VII. PERFORMANCE TESTING - BENCH

Bench testing of hemodialyzers is needed to establish substantial equivalence. The following tests should be performed on a minimum of three (3) hemodialyzers of each model:

- A. For conventional (low flux, Class II) hemodialyzers, the ultrafiltration rate should be measured at transmembrane pressures (TMPs) of 0, 100, 300, 500, and maximum TMP (when different from these TMPs) and the ultrafiltration coefficient [ $k_{UF}$ ] (ml/hr/mm Hg) should be calculated. For high permeability (high flux, Class III) hemodialyzers,  $k_{UF}$  data should be computed by measuring the slope of the ultrafiltration rate versus TMP at ultrafiltration rates between 600 and 1800 ml/hr using a minimum of four data points. The  $k_{uf}$  data should be measured using either bovine or expired human blood (specify hematocrit).
- B. The pressure drop (resistance to flow) across the blood side of the hemodialyzer membrane should be measured for blood flow rates ( $Q_b$ ) of 200 ml/min, 300 ml/min, 400 ml/min, 500 ml/min, and maximum rate, when different from these rates. The pressure drop (resistance to flow) across the dialysate side of the membrane should be measured for dialysate flow rates ( $Q_d$ ) of 500 ml/min, 600 ml/min, 700 ml/min, 800 ml/min and maximum rate, when different from these rates.

- C. Clearances should be measured for urea, creatinine, and Vitamin B<sub>12</sub> or inulin at blood flow rates ( $Q_b$ ) of 200 ml/min, 300 ml/min, 400 ml/min, 500 ml/min, and maximum rate, when different from these rates. For conventional hemodialyzers, clearance data should be collected at 0 and maximum TMP. For high permeability hemodialyzers, the ultrafiltration rate should be specified.
- D. Hemocompatibility (i.e., mechanical hemolysis) data should be provided for a new/altered hemodialyzer design affecting the blood flow pattern or for maximum blood flow rates that differ significantly from those recommended for the predicate devices. The data should demonstrate that this design does not cause excessive lysis of red blood cells. The testing should utilize the maximum recommended blood flow rates.

## VIII. PERFORMANCE TESTING - CLINICAL

- A. For hemodialyzers labeled “single use only”, clinical data on a minimum of 12 patients selected by the submitter should be provided to clarify the relationship between the ultrafiltration data obtained from the *in vitro* tests and the expected clinical performance of the hemodialyzer. The testing should be performed using at least one model of each family. For the purposes of this document, a **family** is considered to be a group of dialyzers for which the chemical composition and the method of processing of the membrane are identical. *In vivo* ultrafiltration coefficients should be provided for hemodialyzers during the first use. A summary of this data should be provided in the instructions for use and compared to the ultrafiltration coefficients measured in the *in vitro* tests. For hemodialyzers labeled for multiple use, additional clinical data requirements are described in the “Guidance for Hemodialyzer Reuse Labeling” which can be obtained from DSMA at the telephone numbers listed above. The FDA considers clinical studies of hemodialyzers with predicate materials to be non-significant risk.

Existing clinical data (e.g., studies published in the scientific literature or data collected from foreign sites), may be submitted instead of the clinical data described above. However, such data must have been collected under conditions reflecting current hemodialysis practice in the United States, especially with regard to blood flow rates and dialysis times. In general, a minimum blood flow rate of 350 ml/min is needed.

- B. For both single or multiple use hemodialyzers, if the membrane material is considered **new** or the design of the hemodialyzer is significantly different from the predicate device, more extensive clinical data than that described in part A above or in the “Guidance for Hemodialyzer Reuse

Labeling”, will be needed. The FDA recommends that the data be collected on a minimum of 12 patients for a minimum of 36 treatments. *In vivo* ultrafiltration coefficients ( $k_{uf}$ ) and extent of removal of urea, albumin and  $\beta_2$ -microglobulin should be provided for hemodialyzers during the first use from blood samples taken pre- and post-dialysis. In addition, the submission should include a summary of any adverse events and data on complement activation and thrombus formation (discussed in section VI.B above). If applicable, these data may be collected in conjunction with the clinical data requirements described in the “Guidance for Hemodialyzer Reuse Labeling.” Since the membrane material is new, the FDA considers this to be a significant risk study, therefore, clinical studies in the United States must be conducted under an IDE. The FDA recommends that manufacturers contact us before submitting a 510(k) or IDE to discuss these issues if appropriate.

As in part A, existing clinical data (e.g., studies published in the scientific literature or data collected from foreign sites), may be submitted instead of the clinical data described above. However, such data should be collected under conditions reflecting current hemodialysis practice in the United States, especially with regard to blood flow rates and dialysis times. In general, a minimum blood flow rate of 350 ml/min will be needed.

## IX. STERILITY

Guidance on sterility issues is described in ODE Bluebook Memorandum #K90-1, "Sterility Review Guidance (2/12/90)". A copy can be obtained from DSMA at the telephone number listed above. All sterile devices are generally required to meet the sterility assurance level (SAL) of  $10^{-6}$ . Your submission should include the following information:

- A. Sterilization method
- B. Validation method and SAL
- C. Description of packaging method
- D. Radiation dose or the maximum levels of residuals of ethylene oxide, ethylene chlorohydrin, and ethylene glycol which remain on the finished sterilized device, whichever is applicable.
- E. For device labeling that includes pyrogenicity information, provide a description of the method (Limulus Amebocyte Lysate or Rabbit test) and the sensitivity of the method.

## X. EXPIRATION DATE TESTING

- A. All labels for hemodialyzers should include an expiration date. The following test results should be provided to substantiate the validity of the proposed expiration date:
1. Performance testing, to include fiber leak integrity, ultrafiltration coefficients and clearance of small and large molecules; and
  2. Biocompatibility testing of hemodialyzer extracts, to include:
    - a. All testing described in Part VI.B above, or
    - b. Cytotoxicity testing and extraction and chemical analysis of leachables from the membrane and other blood contacting materials along with a risk assessment of the potential toxicity of the leachables;
- and
3. Package Integrity testing (to demonstrate sterility and non-pyrogenicity).
- B. Data should be collected from samples stored during real-time at conditions that are 110% of the recommended storage conditions (e.g., temperature, relative humidity). Accelerated conditions may be used to support a marketing application, however, real-time testing should be initiated at the time of submission of the marketing application. The real-time results should be included in the device master record for subsequent review by FDA field personnel. In addition, a scientific rationale should be provided to support the chosen conditions for the accelerated testing.

## XI. PROPOSED LABELING

A device label is defined as any identification on the hemodialyzer and/or on the package in which it is stored and shipped. Guidance on labeling issues is described in Bluebook Memo G91-1 "Device Labeling Guidance (3/8/91)". A copy may be obtained from DSMA at the telephone number listed above. Proposed labels, labeling, and advertisements sufficient to describe the hemodialyzer, its intended use, and the directions for use should be provided

with 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 label of the device 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."

The device label affixed to the hemodialyzer should include, at a minimum, the device name, U.S. point of contact, corporation name, address, and phone number, storage conditions, priming volume, sterility status and method, sterilization date, effective membrane surface area, lot number, expiration date and an indication whether the device is for single or multiple use.

In addition, device labeling for the hemodialyzer should address the following:

- A. The intended use statement should include specific indications and intended patient population.
- B. Contraindications, Warnings, and Precautions should be included in the labeling of the device. High permeability hemodialyzers should contain a Warning that they are to be used only with hemodialysis delivery machines with ultrafiltration controllers.
- C. The directions for use should contain at a minimum the following:
  - 1. Comprehensive instructions for the preparation of the hemodialyzer, initiation of dialysis, troubleshooting, and discontinuance of dialysis;
  - 2. A summary of the *in vitro* performance data described in section VII above, provided in tabular form;
  - 3. A listing of the surface area, priming (blood) volume, maximum TMP, maximum blood flow and maximum dialysate flow for each model;
  - 4. A summary of the clinical data described in Section VIII above,
  - 5. Instructions for reprocessing the hemodialyzer and additional labeling, as described in the "Guidance for Hemodialyzer Reuse Labeling", where applicable.
  - 6. Any claims made in the labeling for clinical benefit of the hemodialyzer will need to be supported with the appropriate performance data.

Advertisements or promotional literature for the hemodialyzer should be provided, if available. Literature or labeling may not imply approval by FDA in any manner or extend the intended use beyond those cleared in the 510(k).

## **XII. 510(k) SUMMARY OR STATEMENT**

The Safe Medical Devices Act of 1990 (SMDA) requires all persons submitting a premarket notification to include either:

- A. A summary of the safety and effectiveness information in the premarket notification, or
- B. The following statement: *I certify that, in my capacity as (provide title) of (provide name of firm), I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential information, as defined in 21 CFR 20.61.*

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. The 510(k) statement (part B above) must be signed and dated.

## **XIII. CERTIFICATION OF TRUTHFULNESS AND ACCURACY**

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).

#### **XIV. INDICATIONS FOR USE**

The indications for use should be provided on a separate sheet and they should agree exactly with the indications provided in the device labeling.