Guidance for Industry and FDA Staff

Hemodialysis Blood Tubing Sets - Premarket Notification [510(k)] Submissions

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This document supersedes "Hemodialysis Blood Tubing Sets - Premarket Notification [510(k)] Submissions" dated April 14, 2008.

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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
Reproductive, Abdominal, and Radiological Devices Division
Office of Device Evaluation

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document is intended to assist industry in preparing an Abbreviated premarket notification submission (510(k)) to establish that the device is substantially equivalent to a predicate hemodialysis blood tubing set for use as the extracorporeal blood circuit during hemodialysis treatment. This guidance document identifies specific recommendations for the content and format of an Abbreviated 510(k) submission for hemodialysis blood tubing sets. This version of the guidance is intended to clarify the April 14, 2008, guidance of the same title and is consistent with FDA's original approach to premarket notification (510(k)) submissions.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2. Background

A manufacturer who intends to market a device of this generic type must conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the act), including the premarket notification requirements described in 21 CFR 807 Subpart E, and obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.81 and 807.87.)

This guidance document identifies the classification regulation and product codes for hemodialysis blood tubing sets (refer to **Section 4. Scope**). Other sections of this guidance document provide additional information to manufacturers on addressing risks related to these devices in premarket notifications (510(k)s).

This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87, the guidance, **Format for Traditional and Abbreviated 510(k)s**,[1] and "Premarket Notification 510(k)**"** on CDRH Device Advice.[2]

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications**,"[3] a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document addressing that device. Manufacturers considering certain modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), we recommend that you include an abbreviated 510(k) summary report of appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g). The abbreviated 510(k) summary report should explain how this guidance document was used during the device development and testing, briefly describe the methods or tests used, and include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document and any other additional risks

[1] http://www.fda.gov/cdrh/ode/guidance/1567.html
[2] http://www.fda.gov/cdrh/devadvice/314.html
[3] http://www.fda.gov/cdrh/ode/parad510.html

specific to your device. This section suggests information to fulfill some of the requirements of section 21 CFR 807.87 and identifies other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

Proposed Labeling

Proposed labeling must be sufficient to describe the device, its intended use, and the directions for its use. (21 CFR 807.87(e).) (Please refer to **Section 11. Labeling** for specific information that should be included in the labeling for devices of the type covered by this guidance document.)

Abbreviated 510(k) Summary Report[4]

In accordance with 21 CFR 807.87, your abbreviated 510(k) summary report should contain the following:

Description of the device and its intended use

We recommend that you describe the device and include an explanation of how the device functions and the specific physical and performance characteristics of the device. (Please refer to **Section 5. Device Description** for specific information to include in the device description for devices of the type covered by this guidance document.) You should also submit an "indications for use" enclosure.[5]

Description of device design

Please include a brief description of the device design requirements. (21 CFR 807.87(f).)

Identification of the risk analysis method

We recommend that you identify the risk analysis method(s) you used to assess the risk profile, in general, as well as the risk profile of the specific device's design and the results of this analysis. Please refer to **Section 6. Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.

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[4] An abbreviated 510(k) summary report is intended to explain how a device-specific guidance document was used during development and testing of your device. This is not the 510(k) summary described in 21 CFR 807.92, which may be submitted to satisfy 21 CFR 807.87(h). For additional information on abbreviated 510(k) summary reports, see section 9 of **Format for Traditional and Abbreviated 510(k)s** at http://www.fda.gov/cdrh/ode/guidance/1567.html.

[5] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

Discussion of the device characteristics

We recommend that you discuss the device characteristics that address the risks identified in this guidance document and any additional risks identified in your risk analysis.

Description of the performance aspects

We recommend that you include a brief description of the nonclinical tests submitted, referenced, or relied on in your submission. See **Sections 7-10** of this guidance for specific performance aspects. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[6] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

Reliance on standards

If you choose to rely on a recognized standard for any part of the device design or testing, you may include either a:

- statement that testing will be conducted and meet specified acceptance criteria before the device is marketed; or
- declaration of conformity to the standard.[7]

Because a declaration of conformity is based on results from testing, you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations**.[8]

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess

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[6] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[7] See **Required Elements for a Declaration of Conformity to a Recognized Standard** (Screening Checklist for All Premarket Notification [510(k)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

[8] See http://www.fda.gov/cdrh/ode/guidance/1131.html

the adequacy of your acceptance criteria. Under 21 CFR 807.87(l), you must submit any additional information that is necessary to reach a determination regarding substantial equivalence.

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering certain modifications to their own cleared devices should consider submitting Special 510(k)s.

The following is a specific discussion of how you should apply this guidance document to a premarket notification submission for hemodialysis blood tubing sets.

4. Scope

The scope of this guidance document is limited to the device described below, 21 CFR 876.5820 and product codes FJK and KOC.

> **Section 876.5820 Hemodialysis system and accessories.**
>
> The extracorporeal blood system and accessories consists of tubing, pumps, pressure monitors, air foam or bubble detectors, and alarms to keep blood moving safely from the blood access device and accessories for hemodialysis (§ 876.5540) to the blood compartment of the dialyzer and back to the patient.

This generic type of device does not include any tubing or devices used for vascular access, such as hemodialysis catheters, or any tubing used for peritoneal dialysis.

5. Device Description

You must include the device name (21 CFR 807.87(a)), and you should provide the appropriate product code described in Section 4. You should provide the following information for your device:

- a description of the overall device system;
- a labeled diagram and the specifications for each model included in the submission, e.g., lengths, inner and outer diameters;
- functionality, including specifications (if applicable) of the individual components of the tubing system, e.g., heparin lines, infusion ports, drip chambers, infusion lines, priming sets, transducer protectors; and
- a description, such as might be found in labeling, of the hemodialysis delivery systems legally marketed in the United States that are compatible with the blood tubing set.

We recommend that you state whether the arterial and venous lines are sold separately or sold as a

set.

You must also provide a comparison of your device to a legally marketed predicate device. (21 CFR 807.87(f)) Please provide your comparison in a manner that is clear and comprehensible, e.g., in tabular form listing the similarities and differences between the proposed and predicate device in terms of intended use, design features, performance specifications, and other important safety and effectiveness information. We recommend you compare the blood tubing and any accessories, e.g., clamps, connectors, transducer protectors, between your device and the predicate device.

We recommend you include the following information when comparing your device and the marketed predicate device.

- indications for use;
- materials;
- biocompatibility;
- design specifications; and
- performance specifications.

6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the device addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device and include the results of this analysis. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, then you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures
Device malfunction	Section 7. Performance Testing Section 10. Expiration Date Testing
Potential infection	Section 9. Sterility
Adverse tissue reaction	Section 8. Biocompatibility Testing
Improper use	Section 11. Labeling
Pyrogen reaction	Section 9. Sterility

Hemolysis	Section 7. Performance Testing Section 10. Expiration Date Testing
Air embolism	Section 7. Performance Testing Section 10. Expiration Date Testing
Blood loss	Section 7. Performance Testing Section 10. Expiration Date Testing

7. Performance Testing

You should describe the performance characteristics of the blood tubing set and include functional testing demonstrating the device performs as you describe. Please compare the results of performance testing data to results obtained for the predicate device. (21 CFR 807.87(f)) If your device performance range falls outside of the range for the predicate device, explain why this difference does not affect the safety or effectiveness, and therefore, the substantial equivalence of your device.

We recommend you perform the following tests on three or more hemodialysis tubing sets of each model you intended to market:

- pressure leak testing demonstrating that the blood tubing can withstand pressures up to 1.5 times the maximum labeled positive and negative pressures;
- endurance testing of the pump segment at maximum labeled blood flow rates and pressures;
- endurance testing, under both positive and negative pressures, of any injection ports (if applicable), using the largest recommended gauge needle identified in the labeling;
- priming volume assessment;
- tensile testing of joints and materials of all tubing segments;
- the ability of pressure transducers to withstand leakage when subjected to pressures up to 2 times the maximum labeled pressure, e.g., “strikethrough”
- performance testing of the device’s clamps to demonstrate that they can successfully occlude the blood tubing;
- hemocompatibility (i.e., mechanical hemolysis) for a new or significantly altered hemodialysis tubing design that affects the pattern of blood flow; and
- performance testing to evaluate the ability of the tubing to resist kinking after repeated clamping, particularly in the post-pump tubing segment.

We also recommend you evaluate a blood tubing set on each hemodialysis delivery system(s) specified in your labeling and operator’s manual by operating the unit with a blood analog fluid

for four hours at 37 °C to demonstrate that tubing failure (i.e., tube kinking) does not occur. During this testing, we recommend that you inspect the tubing for kinks caused by excessive or undersized tubing, across the length of the tubing, using a variety of hemodialyzer sizes. We also recommend that you validate the diameter of the blood pump segment to ensure that the correct blood volume is being pumped by the hemodialysis delivery system. .

8. Device Materials and Biocompatibility

Please describe the materials used to fabricate all components of the hemodialysis tubing set (807.87(f)), including any colorants (e.g., inks, dyes, markings), plasticizers (including di-(2-Ethylhexyl) phthalate or DEHP) or additives. We recommend you group these materials according to whether they have direct or indirect contact with the circulating blood. For each of these materials, we recommend you:

- identify a current, legally marketed device that uses the identical materials and manufacturing methods for a similar intended use; or
- provide appropriate biocompatibility testing on a finished, sterilized device such as the testing recommended in the current FDA guidance on biocompatibility testing, Office of Device Evaluation (ODE) Blue Book memorandum, G95¬-1 "Use of International Standard ISO-10993 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'".

Hemodialysis blood tubing sets are considered externally communicating devices, contacting circulating blood, prolonged contact Class II (Category B). If you are unable to identify a legally marketed predicate device that uses the exact materials as described above, we recommend you conduct the following tests:

- cytotoxicity;
- sensitization (Guinea pig maximization with polar and non-polar extracts);
- irritation or intracutaneous reactivity;
- acute systemic toxicity;
- hemocompatibility, e.g., chemical and mechanical hemolysis; and
- genotoxicity.

Alternatively, you may provide a justification for not conducting any of the tests identified above.

9. Sterility

FDA recommends that you provide sterilization information, such as that described in the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**[9]. We recommend the device be sterile with a sterility assurance level (SAL) of 1×10^{-6}.

[9] http://www.fda.gov/cdrh/ode/guidance/361.html.

Blood tubing sets are in contact with circulating blood; therefore, we recommend you test the devices for pyrogenicity. We recommend you provide a:

- description of the method used to make the determination, e.g., limulus amebocyte lysate (LAL);
- identification of the testing endpoint reached and rationale for selecting that endpoint;
- description of the extraction technique used to obtain the test fluid from the test device, showing that all clinically relevant contact surfaces of the test device were assessed; and
- identification of the reference method used, e.g., United States Pharmacopoeia (USP), ANSI/AAMI ST 72:2002, Bacterial endotoxins - Test methodologies, routine monitoring, and alternatives to batch testing or FDA guidance.

10. Expiration Date Testing

We recommend all labels for hemodialysis blood tubing include an expiration date. We recommend you provide the following tests to substantiate the validity of the proposed expiration date on devices subjected to real-time or accelerated aging:

- biocompatibility testing of hemodialysis blood tubing sets including all testing described in **Section 8. Device Materials and Biocompatibility**;
- performance testing on aged samples including the testing listed in **Section 7. Performance Testing;** and
- package integrity testing to demonstrate sterility and non-pyrogenicity.

Accelerated conditions may be used to support the labeled expiration date, as long as you include an adequate scientific rationale supporting your accelerated testing. In addition, we recommend you initiate real-time testing when you submit your 510(k) and include the real-time results in your device master record.

11. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are intended to assist you in preparing labeling that satisfies the requirements of 21 CFR Part 801.[10]

[10] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

A. Directions for Use

As a prescription device under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, you must adequate information for use, including indications, effects, routes, methods, and frequency and duration of use and any relevant hazards, contraindications, side effects, and precautions. (801.109(d)) Instructions should encourage local and institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

B. Intended Use

You must state the intended use of your device and include the indications for use and the intended (target) population (e.g., pediatric patients). (801.109(c))

C. Description of the Device

We recommend the description of the device include:

- identification of the components in the package, e.g., arterial tubing, venous tubing, priming set;
- total length of the arterial and venous tubing sets;
- outer diameter (OD) of the pump segment;
- priming volume;
- identification of the hemodialysis delivery systems which are compatible with the blood tubing set;
- identification of the largest gauge needle that can be used with the injection port (if applicable);
- identification of the maximum operating pressures for the transducer protectors;
- a statement that the device is for single use only, and has a nontoxic and non-pyrogenic fluid path;
- a statement that the package is sterile, if the package is intact and undamaged, and protective caps are secure.

We also recommend you color code the device so that the patient and dialyzer connectors of the arterial blood tubing are red and the patient and dialyzer connectors of the venous blood tubing are blue.

D. Warnings

You must include a warning that significant hemolysis of red blood cells can occur in kinked blood tubing, especially in the post-pump, arterial tubing segment. (801.109(d))

As a precaution, you must include a warning indicating that the device is intended for single use only.

E. Outer Package Labeling

In addition to the requirements of 21 CFR 801, we recommend that the outer package labeling include:

- device name;
- U.S. point of contact;
- storage conditions;
- priming volume;
- sterility status and method;
- sterilization date;
- a non-pyrogenic statement;
- lot number; and
- expiration date.

Appendix I. Glossary of Terms

The terms here are defined for the purpose of this guidance document only, unless otherwise noted.

Arterial blood tubing. The portion of the tubing set that transports blood from the patient to the hemodialyzer inlet port.

Conventional hemodialysis delivery device. Under 21 CFR 876.5820(a)(3), 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. The dialysate delivery system includes the dialysate concentrate for hemodialysis (liquid or powder) and alarms to indicate abnormal dialysate conditions."

High permeability hemodialysis delivery device. Under 21 CFR 876.5860(a)(2), a high permeability hemodialysis delivery system is defined as a machine that "…is similar to the extracorporeal blood system and dialysate delivery system of the hemodialysis system and accessories (21 CFR 876.5820), with the addition of an ultrafiltration controller and mechanisms that monitor and/or control such parameters as fluid balance, dialysate composition, and patient treatment parameters (e.g., blood pressure, hematocrit, urea, etc.)."

Infusion port. A component of hemodialysis blood tubing allowing the injection of fluids through a septum.

Priming set. A segment of tubing specifically designed to prime the hemodialysis blood tubing.

Pump segment. The portion of the tubing upon which a peristaltic or rotary hemodialysis delivery pump acts.

Sorbent regenerated dialysate delivery system. Under 21 CFR 876.5600(a), "A sorbent regenerated dialysate delivery system for hemodialysis is a device that is part of an artificial kidney system for the treatment of patients with renal failure or toxemic conditions, and that consists of a sorbent cartridge and the means to circulate dialysate through this cartridge and the dialysate compartment of the dialyzer. The device is used with the extracorporeal blood system and the dialyzer of the hemodialysis system and accessories (876.5820). The device includes the means to maintain the temperature, conductivity, electrolyte balance, flow rate and pressure of the dialysate, and alarms to indicate abnormal dialysate conditions. The sorbent cartridge may include absorbent, ion exchange and catalytic materials."

Transducer protector. A component of hemodialysis blood tubing with a hydrophobic membrane designed to prevent blood contamination of the pressure transducers of a hemodialysis delivery system.

Venous blood tubing. The portion of the tubing set that transports blood from the hemodialyzer outlet port back to the patient.