Draft Guidance for Industry and Food and Drug Administration Staff

Class II Special Controls Guidance Document: Implanted Blood Access Devices for Hemodialysis

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: June 20, 2012

You should submit comments and suggestions regarding this draft document within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments should with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document, contact Jeffrey Cooper, DVM at (301) 796-5590 or via email at jeffrey.cooper@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Reproductive, Gastro-Renal, and Urological Devices
Gastroenterology and Renal Devices Branch
Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number 1781 to identify the guidance you are requesting.
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1. Introduction

This draft guidance document was developed as a special control guidance to support the reclassification of the Implanted Blood Access Devices for Hemodialysis into class II (special controls). The device, as proposed, is intended to provide access to a patient’s blood for hemodialysis. This draft guidance will be issued in conjunction with a Federal Register notice announcing the proposal to reclassify this device type. This guidance is issued for comment purposes only. If a final rule to reclassify this device type is not issued, this guidance document will not be issued as a special control.

When finalized, designation of a guidance document as a special control means that any firm currently marketing, or intending to market, Implanted Blood Access Devices for Hemodialysis will need to address the issues covered in the special controls guidance. The firm will need to show that its device addresses the issues of safety and effectiveness identified in the guidance, either by meeting the recommendations of the guidance or by some other means that provides equivalent assurances of safety and effectiveness.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of Implanted Blood Access Devices for Hemodialysis. Thus, a manufacturer who intends to market a device of this generic type must (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the FD&C Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with Implanted Blood Access Devices for Hemodialysis identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special controls guidance document identifies the classification regulation and product code for Implanted Blood Access Devices for Hemodialysis (Please refer to Section 3. Scope). In addition, other sections of this special controls guidance document list the risks to health identified by FDA and
describe measures that, if followed by manufacturers and combined with the general controls, will
generally address the risks associated with Implanted Blood Access Devices for Hemodialysis and
lead to timely 510(k) review. 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 the section of
CDRH’s Device Advice, *Premarket Notification Submission 510(k).*²

As described in the guidance entitled, *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). Manufacturers considering certain modifications to their own cleared devices may lessen the
regulatory burden by submitting a Special 510(k).

3. Scope

The scope of this document is limited to the implanted blood access devices for hemodialysis
regulated under 21 CFR § 876.5540(a)(1) and with product codes listed in the table below:

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIQ</td>
<td>A-V shunt cannula</td>
</tr>
<tr>
<td>FKW</td>
<td>vessel tip</td>
</tr>
<tr>
<td>LBW</td>
<td>single needle (co-axial flow) dialysis set</td>
</tr>
<tr>
<td>LFJ</td>
<td>subclavian catheter</td>
</tr>
<tr>
<td>MSD</td>
<td>implanted hemodialysis catheter</td>
</tr>
<tr>
<td>NIF</td>
<td>implanted triple-lumen hemodialysis catheter</td>
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<tr>
<td>NYU</td>
<td>implanted coated hemodialysis catheter</td>
</tr>
</tbody>
</table>

4. Device Description

The implanted blood access device for hemodialysis is described in 21 CFR § 876.5540 as a device
intended to provide access to a patient’s blood for hemodialysis or other chronic uses for 30 days or
more. When used in hemodialysis, it is part of an artificial kidney system for the treatment of
patients with renal failure or toxemic conditions and provides access to a patient’s blood for
hemodialysis.

The implanted blood access devices for hemodialysis consist of various flexible or rigid tubes, such
as catheters or cannula, which are surgically implanted in appropriate blood vessels, may come
through the skin, and are intended to remain in the body for 30 days or more. This generic type of
device includes single, double and triple lumen catheters with cuffs, subcutaneous ports with

¹ [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm)
² [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm)
³ [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm)
catheters, shunts, cannula, vessel tips, and connectors specifically designed to provide access to blood.

We recommend that you identify your device, by the regulation and product code described in Section 3. Scope. We recommend you also provide:

- classification name (e.g., blood access device);
- common name (e.g., double lumen hemodialysis catheter);
- trade or proprietary name, including a listing of all model numbers;
- a clear description of the proposed device's intended use; and
- the CFR classification regulation number under which you believe the device and any components/accessories are regulated.

The device description should include a labeled diagram and the specifications (e.g., lengths, inner and outer diameters, French size, cuff positions, extension lengths, hole diameters and positions, etc.) for each model included in the submission. The physical description should include:

a. a description of the overall device system including accessories, pictures, samples (if practical), and engineering diagrams;

b. a functional description (including specifications, if applicable) of the individual components of the catheter system; and

c. a description of the accessories that may be used to place the catheter or shunt. Any accessory device that is labeled for use with the proposed catheter system should either be currently legally marketed or submitted as part of the 510(k) submission for the proposed catheter system. Information on the accessory device to allow a determination of substantial equivalence should be provided.

The 510(k) should include a comparison of the proposed device to a legally marketed predicate device. FDA recommends that all comparisons be provided in a manner that is clear and comprehensible, such as in tabular form that lists the similarities and differences between the proposed and predicate device(s) in terms of intended use, technological features, performance specifications, and other important information necessary to determine substantial equivalence between the proposed and predicate device.

The 510(k) should identify the predicate device(s) to which the proposed device will be compared. Provide as much information as possible regarding the predicate device(s), such as, 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.

You should provide information to describe how your device is similar to and different from the legally marketed predicate device (“predicate device”) 21 CFR 807.87(f). Side by side comparisons, whenever possible, are desirable.

The comparison between the proposed and predicate device(s) should include, at a minimum, the following information:
a. Intended Use/Indications for use to include, as appropriate:
   1. mechanism of action (e.g., blood access for hemodialysis treatment)
   2. location of use (e.g., internal jugular, femoral, subclavian, transhepatic, translumbar);
   3. duration of use (e.g., long-term [>30 days]; short-term [<30 days]; and
   4. conditions of use (e.g., acute renal failure, chronic renal failure).

b. Materials used, including the supplier, the material name, and the material designation numbers, for each device component, including:
   1. Catheter lumens and extensions;
   2. Clamps;
   3. Cuffs;
   4. Luer Adapters (bloodline connectors);
   5. Hub;
   6. Suture wing;
   7. Caps;
   8. Coatings;
   9. Adhesives; and
   10. Colorants or inks.

c. Performance specifications; and

d. Design parameters, including:
   1. Catheter type
   2. Number of cuffs
   3. Outer diameter
   4. Length
   5. Biocompatibility
   6. Tunneler information
   7. Restrictions of implantation site (not common but some may be restricted)
   8. Insertion technique(s)
   9. Contraindications for use (e.g., thrombosed vessel)

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the devices addressed in this document. The measures recommended to mitigate these identified risks are provided in the table below. We recommend that you identify any other risks specific to your device and include the results of your risk analysis in your 510(k). If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks in addition

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4 A material designation number is a unique number assigned to a unique material or component. An example is polyurethane 2360-80A.
to those identified in this document, then you should provide sufficient detail to support the approach you have used to address that risk.

<table>
<thead>
<tr>
<th>Identified Risk</th>
<th>FDA Recommended Mitigation Measures</th>
</tr>
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<tbody>
<tr>
<td>Thrombosis in patient, catheter occlusion, or central venous stenosis</td>
<td>Section 7. Bench testing</td>
</tr>
<tr>
<td></td>
<td>Section 8. Sterility</td>
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<tr>
<td></td>
<td>Section 10. Animal testing</td>
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<tr>
<td></td>
<td>Section 11. Clinical testing</td>
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<tr>
<td></td>
<td>Section 14. Coatings</td>
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<tr>
<td></td>
<td>Section 15. Labeling</td>
</tr>
<tr>
<td>Adverse tissue reaction, pain, infiltration, or extravasation</td>
<td>Section 6. Biocompatibility</td>
</tr>
<tr>
<td></td>
<td>Section 8. Sterility</td>
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<tr>
<td></td>
<td>Section 9. Expiration date testing</td>
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<tr>
<td></td>
<td>Section 11. Clinical testing</td>
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<tr>
<td></td>
<td>Section 15. Labeling</td>
</tr>
<tr>
<td>Infection (exit site or catheter-related blood stream infection) or pyrogen reactions</td>
<td>Section 7. Bench testing</td>
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<tr>
<td></td>
<td>Section 8. Sterility</td>
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<tr>
<td></td>
<td>Section 9. Expiration date testing</td>
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<tr>
<td></td>
<td>Section 11. Clinical testing</td>
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<td></td>
<td>Section 13. Subcutaneous Catheters</td>
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<td></td>
<td>Section 14. Coatings</td>
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<tr>
<td></td>
<td>Section 15. Labeling</td>
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<tr>
<td>Device malfunction</td>
<td>Section 7. Bench testing</td>
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<tr>
<td></td>
<td>Section 9. Expiration date testing</td>
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<td></td>
<td>Section 11. Clinical testing</td>
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<td></td>
<td>Section 12. Co-Axial Flow Needles</td>
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<td></td>
<td>Section 13. Subcutaneous Catheters</td>
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<td></td>
<td>Section 15. Labeling</td>
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<tr>
<td>Cardiac arrhythmia, hemorrhage, embolism, nerve injury, or vessel perforation</td>
<td>Section 7. Bench testing</td>
</tr>
<tr>
<td></td>
<td>Section 15. Labeling</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Section 6. Biocompatibility</td>
</tr>
<tr>
<td></td>
<td>Section 7. Bench testing</td>
</tr>
<tr>
<td>Accidental withdrawal or catheter migration</td>
<td>Section 7. Bench Testing</td>
</tr>
<tr>
<td></td>
<td>Section 15. Labeling</td>
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</tbody>
</table>

### 6. Device Materials and Biocompatibility

Please provide an exact identification of all materials used to fabricate all components of the hemodialysis catheter, including any colorants (inks, dyes, markings, etc.), plasticizers (including di-(2-Ethylhexyl) phthalate or DEHP), lubricants, mold release agents, or additives. Provide material names and specific designation numbers. 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 for each material that uses the identical materials, additives, release agents, and manufacturing methods for a similar intended use, or;
b. For patient contacting materials, provide appropriate biocompatibility testing on a finished, sterilized device as recommended in the current FDA guidance on biocompatibility testing, Office of Device Evaluation (ODE) Blue Book memorandum, G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". Hemodialysis catheters are considered “External communicating devices,” “Circulating blood,” “Permanent contact – (Category C).”

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
- Systemic toxicity (acute)
- Sub-chronic toxicity
- Implantation
- Hemocompatibility
- Genotoxicity

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5 [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071380.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071380.htm)

6 Patients are exposed to hemodialysis catheter and shunt materials over a long period of time. A long-term (90 to 120 days) implantation study with histopathology may replace sub-chronic toxicity.
7. **Performance Testing - Bench**

The 510(k) should include adequate information describing the performance characteristics of the device. At a minimum, this should include functional testing demonstrating that the device performs as designed and expected.

The following performance characteristics should be tested on a minimum of three (3) hemodialysis catheters of each model:

a. a range of appropriate blood flows during use of the device, as stated in product labeling. Pressure versus flow rates for both arterial and venous lines, from 100 ml/min to the maximum flow rate in 100 ml/min increments. The fluid and its viscosity used during testing should be stated;

b. recirculation rates for both forward and reverse flow configurations compared to the predicate device.

c. priming volumes;

d. tensile testing of joints and materials as specified in ISO 10555-1. The minimum acceptance criteria should be at least equal to the predicate device. We recommend the minimum force at break should be 10 pounds for polyurethane catheters (due to the more frequent handling of hemodialysis catheters compared to general catheters.)

e. air leakage as specified in ISO 10555-1 Annex D and Liquid leakage as specified in ISO 10555-1 Annex C;

f. repeated clamping of the extensions of the catheter. This simulates use over the life of the catheter. Assuming that three clampings are done at each treatment, with a maximum of 6 treatments per week, and a catheter life of 3 years, repeatedly clamping at least 3000 times should provide assurance of extension durability;

g. mechanical hemolysis (recommended for a new/ altered hemodialysis catheter design affecting the blood flow pattern). The data should demonstrate that the catheter tip design does not cause excessive lysis of red blood cells. The testing should utilize the maximum recommended blood flow rates (see Appendix A for considerations for testing); and,

h. chemical tolerance of the catheter to repeated exposure to commonly used disinfection agents.

Results of performance testing should be compared to those obtained for the predicate device(s). If test results for the proposed device exceed the range for the predicate device, explain why this difference supports the substantial equivalence of the proposed device. The variances should be

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7 The priming volume is the amount of fluid required to fill the inside of the catheter from the hubs to the tip.
noted and any changes from those of the predicate device should be justified.

8. Sterility

Guidance on sterility issues is described in Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA(8/30/2002)\(^8\). 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. radiation dose or the maximum residual levels of ethylene oxide and ethylene chlorohydrin that remain on the finished sterilized device, whichever is applicable. FDA recognizes the consensus standard ANSI/AAMI/ISO 10993-7:1995 and 2008 *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals,* for ethylene oxide residuals;

c. validation method for the sterilization cycle and Sterilization Assurance Level (SAL);

d. since the product should be labeled "non-pyrogenic," a description of the method used to make the determination, e.g., limulus amebocyte lysate (LAL) and the sensitivity of the method in Endotoxin Units per milliliter (EU/mL); and

e. a description of the packaging system.

9. Expiration Date Testing

All labels for hemodialysis catheters should include an expiration date. The following test results should be provided to substantiate the validity of the proposed expiration date:

a. performance testing on aged samples to include at a minimum the testing listed in Part 7 for d, e, and f; and

b. package integrity testing (to demonstrate sterility and non-pyrogenicity) as specified in ASTM F1980-7

Accelerated conditions may be used to support a 510(k); however, real-time testing should be initiated at the time of submission of the 510(k). The real-time results should be included in the device history record for subsequent review by FDA\(^9\). In addition, a scientific rationale should be provided to support the chosen conditions for the accelerated testing.

10. Performance Testing – Animal

Testing performed in animals may be needed to establish substantial equivalence. Some areas that

\(^8\) [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm)

\(^9\) 21 CFR 820.184 Device History Record
animal testing has been useful are for demonstrating anti-thrombotic properties, testing for adequate flow, and looking for infection potential. Such testing must comply with 21 CFR Part 58, which prescribes Good Laboratory Practices for nonclinical studies.

11. Performance Testing – Clinical

Clinical evidence is generally unnecessary for most implanted blood access devices for hemodialysis; however, such testing may be requested in situations such as the following:

- indications for use dissimilar from legally marketed devices of the same type;
- new technology, i.e., technology different from that used in legally marketed devices of the same type, yet does not raise different questions of safety or effectiveness; or
- cases where engineering and/or animal testing raise issues that warrant further evaluation with clinical evidence.

FDA will consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

For hemodialysis catheters and shunts, any labeling claims about performance of the device in vivo should be supported with appropriate bench, in addition to either animal and/or clinical, testing.

If a prospective clinical study is needed to demonstrate substantial equivalence, the study must be approved by FDA and conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812, if conducted in the United States. FDA believes that implanted blood access devices for hemodialysis addressed in this guidance document are considered significant risk as defined in 21 CFR 812.3(m)(4). In addition to the requirements of 21 CFR 812, sponsors of such studies must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

A clinical study for implanted blood access devices should include endpoints that address both the safety and effectiveness of the proposed device that supports its substantial equivalence to the predicate device(s). Effectiveness endpoints should focus on the ability of the device to properly function over a long period of time such as 180 days. Safety should focus on an evaluation of the adverse events listed in Section 5 that may be expected with blood access devices. FDA encourages the opportunity to provide advice on prospective IDE clinical studies prior to the submission of an IDE application.

12. Co-Axial Flow Needles

A co-axial flow dual flow single needle consists of a formed stainless steel needle housing containing two lumens with a center septum. This device is designed to access an arteriovenous graft or fistula.

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10 See [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm)
For any anti-needle stick feature, the guidance on Medical Device Sharps Injury Prevention Features\textsuperscript{11} should also be followed.

Features that should be considered regarding the substantial equivalence of co-axial flow needles include:

\begin{itemize}
  \item Blood recirculation
  \item Blood flow parameters
  \item Hemolysis
  \item Visual inspection for sharpness and lack of metal burrs
\end{itemize}

\section*{13. Subcutaneous Catheters}

Subcutaneous catheters are completely implanted below the skin surface and have no part of the device exposed to the outside of the body. Subcutaneous catheters warrant more testing to resolve issues of infection rates, adequacy of dialysis, maintenance of blood flow, and long-term patency. The recommended type of needle should be described (e.g., non-coring). Test results on repeated use of any ports should be provided. Clinical data is necessary to establish the substantial equivalence of this type of device.

\section*{14. Coatings}

Implanted blood access devices for hemodialysis are sometimes coated with agents for lubricity or antithrombotics. If a clinical benefit is claimed for such coatings, results of a clinical study should be provided to support the labeling claim. Labeling claims will be limited to the testing performed on the coated device.

Coatings and claims for infection control generally require a clinical study to demonstrate that ability. Coatings identical to previously cleared coatings may not need to provide new supportive clinical data, depending upon the specific claims.\textsuperscript{12}

Coating information should include:

\begin{itemize}
  \item A description of the coating material;
  \item The duration of effectiveness;
  \item How the coating is applied; and
  \item Testing to show how well the coating performs.
\end{itemize}

\textsuperscript{11} See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm

\textsuperscript{12} CDRH has issued draft guidance on Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents. When finalized, this guidance will represent the Center's current thinking on this topic. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071380.htm.
Keep in mind that inclusion of a coating with a new drug entity will usually either change the intended use or raise different questions of safety and effectiveness. An antimicrobial coating could create a combination product. In situations where you are proposing inclusion of a drug that is not included on a predicate, we would strongly encourage the submission of a pre-IDE.

15. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are provided to assist you in preparing labeling that satisfies the requirements of 21 CFR Part 801.13

Directions for Use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Labeling must, however, include adequate information for practitioner use of the device, including indications, effects, routes, methods, frequency and duration of administration and any relevant hazards, contraindications, side effects and precautions. (21 CFR 801.109(d)). Proposed labels, labeling, and advertisements sufficient to describe the hemodialysis catheter, 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).

The operator's manual should include, at a minimum, the indications for use, principle of operation, device description, features, and/or accessories, instructions for use, troubleshooting, warnings, precautions, and contraindications associated with the use of the catheter. Detailed instructions on catheter care should be provided.

The device label affixed to the hemodialysis catheter packaging 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, lot number, and expiration date.

In addition, device labeling for the hemodialysis catheter 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.

1. If a femoral catheter is indicated, the labeling should include:

13 Final labeling must comply with the requirements of 21 CFR Part 801 and 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.
i. Language to specify the placement site such as “Catheters greater than 40 cm are intended for femoral vein insertion”; and

ii. Potential complications specific to femoral placement (femoral artery bleed, femoral nerve damage, retroperitoneal bleed, and venous stenosis).

iii. Suggestions to avoid infections such as tunneling the catheter to a pelvic area rather than an inguinal area; and

iv. A caution that increased infections are a possibility;

2. If a trans-lumbar catheter is indicated, the labeling should include:

i. Language to specify the placement site; and

ii. Potential complications specific to trans-lumbar placement, including migration of the catheter tip into subcutaneous tissues, retroperitoneum or iliac veins (causing hematoma or frank bleeding).

3. If a subclavian catheter is indicated, the labeling should include:

i. Language to specify the placement site; and

ii. Potential complications specific to subclavian placement, including pneumothorax and hemothorax.

c. An arterial and venous pressure vs. flow rate table and graph, identification of the recommended flow rate and pressure range;

d. Arterial and venous priming volumes printed on the catheter;

e. Forward and reverse recirculation rates. Catheters with greater than 50% recirculation in the reverse direction should include a caution in the labeling listing the percent reverse recirculation;

f. Identification of any contraindicated disinfecting agents due to material incompatibility by printing a warning on the catheter or a label that can be affixed to the patient’s medical record.

g. The directions for use should contain at a minimum the following:

1. Comprehensive instructions for the preparation and insertion of the hemodialysis catheter, including recommended site of insertion, method of insertion, a reference in the English language on the proper location for tip placement, method for removal of the catheter, anticoagulation, guidance for management of obstruction and thrombus formation, and site care.

2. Any claims made in the labeling for clinical benefit of the hemodialysis catheters will need to be supported with the appropriate performance data.
Appendix A

Mechanical Hemolysis Testing of Hemodialysis Catheters

To evaluate the potential for hemodialysis catheters to cause blood damage, in vitro testing simulating clinical use is usually conducted using animal blood. As animal blood is tested in an artificial in vitro environment and is more resilient to physical damage than the blood of hemodialysis patients, extrapolating the results of the bench testing to the clinical environment has limited value. However, by performing paired testing using blood from the same animal source, a relative comparison between a new and a predicate device can be made.

The references included at the end of this document address many of the issues related to in vitro hemolysis testing, represent FDA’s current state of knowledge for performing this type of testing, and can be used as guides for the testing of hemodialysis catheters (1-5). The testing is composed of three sections: setting up the test, performing the test, and reporting and interpreting the results.

**Setting up the test:**

1. Standardized guidelines for the collection and preparation of blood to be used in the in vitro assessment of blood damage caused by a medical device under dynamic test conditions have been previously described (reference #1). Briefly, the blood should be obtained from a healthy animal and immediately mixed with an appropriate anticoagulant (e.g., 4000-6000 USP units of heparin per liter of collected blood). If not used immediately, the blood can be refrigerated at 2 to 8º C, but should be used within 48 hours of drawing. Prior to testing, the blood is filtered and the hematocrit adjusted to a standard level (e.g., 35 +/- 2%).

2. For performing paired testing, two separate and identical mock circulation blood loops should be assembled; one for the predicate device and one for the new device. The components of the flow loops should include a blood pump, hemodialysis tubing with a side-port for drawing blood samples, luer connectors to attach the catheters, a system for measuring the pressure in both the arterial and venous catheter components, a calibrated method to measure blood flow rate, and a reservoir made of a hemocompatible material (which can be heated) to hold the blood. Due to the inherent variability in the blood from different animals, on each test date, the blood should be used from the same blood pool in both mock loops in a paired test configuration (operating under the same flow conditions and at the same time).

3. Blood pumps used in hemodialysis are positive-displacement roller-occlusive pumps. Following the manufacturer’s guidelines, carefully check the occlusion setting of the blood pumps prior to the testing. Investigators should also consider operating a third loop (i.e., a control blank circuit) concurrently with the test and the predicate device circuits to determine the baseline blood damage caused by the components of the recirculation circuit when the catheter is not present. To match the flow resistance of the arterial and venous components, compressive clamps can be placed on the tubing to gradually decrease the flow path so that hemolysis is minimized.

4. The total volume of blood in the two test circuits should be identical and minimized to increase the sensitivity of the testing. However, the blood volume in the reservoirs must be sufficient that all
of the inlet and exit ports of the catheters are completely submerged so that the blood is well-mixed, yet there is not significant mixing at the air-blood interface (e.g., cylindrical containers or blood bags should be considered for use as reservoirs).

5. Using the paired testing scheme described above, the new devices are typically compared to the predicate device using a sample size of 5 for each cohort. Testing should be performed at the maximum rated blood flow rate.

**Performing the test:**

6. Prior to testing with blood, circulate buffered saline through the loop for 5 minutes to rinse the surfaces.

7. The blood should be warmed and maintained at a physiological temperature (35–38°C) prior to and during the testing, while avoiding exposing the blood to temperatures (e.g., from a water bath) in excess of 39°C. Drain the saline from the loop, introduce the warmed blood, and clear air bubbles from the mock circuit. Let the blood circulate in the loop for approximately 3 minutes before taking a baseline sample (time = 0). The baseline sample will be evaluated for blood hematocrit, total blood hemoglobin concentration, and the plasma hemoglobin concentration. Use a validated method to assess the critical measurement parameter, the plasma hemoglobin concentration (5).

8. The *in vitro* testing with blood is usually conducted for as long as the device will be labeled for use. For a 4 hour test, blood samples can be taken at time = 0, 30, 60, 120, 180, and 240 minutes for plasma hemoglobin concentration analysis.

9. To insure a well-mixed blood sample, blood can be gently withdrawn from the tubing Luer side-port. As the use of small sampling needles may induce hemolysis, it is recommended to use needle-less syringes. Clear the port first by drawing out some fresh blood (1 mL) into a needle-less syringe. Then, use a new syringe to draw out a fresh sample for analysis. It is recommended that two samples be drawn at each time period. Avoid pulling the plunger of the syringe too rapidly, or pushing the collected blood forcefully into the blood sample collection tube, to avoid pressure or velocity-induced hemolysis.

10. The catheter pressures, the blood temperatures, and the blood flow rates in each loop should be measured periodically throughout the testing.

**Reporting the test results/interpretation:**

11. A detailed protocol for performing the blood damage testing should be provided along with a diagram of the *in vitro* test circuit. The date, time, and blood pool that were used in each testing circuit should be apparent in the final report.
12. The data should be provided in both tabular and graphical forms. The plasma hemoglobin can be reported as a concentration (mg/dL) that increases over time using overlaying line plots for each of the different test circuits. As these plots are generally linear over time, calculate the least squares fit for each of the test circuits. The slope of the least fit line is the rate of plasma hemoglobin generation.

13. Mean (+/- SD) results can also be tabulated and graphed for each of the different catheter groups and mock circuits.

14. Using paired statistical testing between the matched individual test circuits, compare the rate of plasma hemoglobin generation between the new and the predicate catheters. Paired comparisons can also be made to the control blank circuit (which did not utilize any catheters during the testing).

References:

Appendix B

Standards

The use of applicable standards is encouraged. These could include:
ISO 594: Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment - Part 1: General requirements

ISO 10555-1: Sterile, Single-use intravascular catheters - Part 1: General requirements (except for minimum force at break recommendation should be 10 pounds for polyurethane catheters due to the more frequent handling of hemodialysis catheters compared to general catheters, the great prevalence of polyurethane as the main material, and that polyurethane typically can support 50 lbs or more.)


ISO 14971:2007 Medical Devices – Application of risk management to medical devices