Implanted Blood Access Devices for Hemodialysis

Guidance for Industry and Food and Drug Administration Staff

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Center for Devices and Radiological Health
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Preface

Public Comment

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Implanted Blood Access Devices for Hemodialysis

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance document provides recommendations for complying with special controls issued as part of the reclassification of Implanted Blood Access Devices for Hemodialysis into class II (special controls).[1] The devices are intended to provide access to a patient's blood for hemodialysis.

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.

II. Background

FDA has issued a final order reclassifying implanted blood access devices for hemodialysis, which were preamendments Class III devices, into Class II (special controls) and subject to premarket notification. FDA finalized the reclassification under the Federal Food, Drug and Cosmetic Act (FD&C Act) based on new information pertaining to the device. This guidance is intended to provide recommendations on how to comply with the special controls codified in 21 CFR 876.5540(b)(1) and indicate what information is recommended for submission to FDA in a 510(k) to demonstrate that the special controls have been met. Throughout the guidance, requirements per the special controls are noted in *italic* font for clarity.

[1] 79 FR 43241, July 25, 2014

This document supplements other FDA documents regarding the specific content requirements of a premarket notification [510(k)] submission. You should also refer to 21 CFR 807.87 and FDA's guidance, "Format for Traditional and Abbreviated 510(k)s" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm).

III. 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:

Product Code	Name
FIQ	A-V shunt cannula
FKW	vessel tip
LFJ	subclavian catheter
MSD	implanted hemodialysis catheter
NYU	implanted coated hemodialysis catheter
PKI	fully subcutaneous implanted hemodialysis catheter

Implanted blood access devices outside of this aspect of this subpart of the classification regulation are not within the scope of this guidance.

IV. 510(k) Submission Recommendations

The sections below provide recommendations on information to include in a 510(k) submission for implanted blood access devices for hemodialysis. These recommendations include recommendations for compliance with special controls.

A. 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. 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.

As defined in 21 CFR § 876.5540(a)(1), the implanted blood access device is a prescription device and consists of various flexible or rigid tubes, such as catheters, or cannulae, 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 various catheters, shunts, and connectors specifically designed to provide access to blood. Examples include single and double lumen catheters with cuff(s), fully subcutaneous port-catheter systems, and A-V shunt cannulae (with vessel tips). The implanted blood access device may also contain coatings or additives, which may provide additional functionality to the device.

We recommend that you identify your device by the regulation and product code described in Section III. "Scope." Per 21 CFR 807.87 you must also identify the common name of your device (e.g., double lumen hemodialysis catheter) as well as the trade or proprietary name. We recommend you also provide the following information:

a. classification name (e.g., blood access device);

b. a listing of all model numbers (if known);

c. a clear description of the proposed device's intended use

d. 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, connectors[2], extension lengths, hole diameters and positions) 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 for use with such a hemodialysis catheter system 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 device, commonly referred to as the 'predicate' device.[3] FDA recommends that all comparisons be

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[2] The currently FDA recognized versions of the following standards may apply to connectors for implanted blood access devices: ISO 80369: Small-bore connectors for liquids and gases in healthcare applications and ISO 594: Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment - Part 1: General requirements.

FDA's currently recognized version of standards and the extent of recognition can be located via FDA's standards database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm)

[3] A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that (i) was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required; *or* (ii) has been reclassified from Class III to Class II or I; *or* (iii) has been found SE through the 510(k) process. The legally marketed device for purposes of determining substantial equivalence is commonly referred to as the "predicate device."

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 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 to which the proposed device is compared. The 510(k) should provide as much information as possible regarding the predicate device, such as, the proprietary and common name, manufacturer, model number, 510(k) reference number, preamendments status[4] (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 predicate device (21 CFR 807.87(f)). Side by side comparisons, whenever possible, are desirable.

The comparison between the proposed and predicate device should include, at a minimum, the following information:

a. Intended Use/Indications for use to include, as appropriate:

    1. general purpose of device (e.g., blood access for hemodialysis treatment)
    2. location of use (e.g., internal jugular, femoral, subclavian, transhepatic, translumbar);
    3. lengths and diameters of the catheters;
    4. duration of use (e.g., long-term [>30days]; and
    5. 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, when applicable, 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.

Section 513(i) of the FD&C Act states that for a new device to be considered substantially equivalent to a predicate device, the new device must have the same intended use as the (primary) predicate device **and** the same technological characteristics or different technological characteristics that do not raise different questions of safety and effectiveness than the predicate device.

[4] *See* Preamendment Status (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ComplianceActivities/ucm072746.htm)

c. Performance specifications

d. Design parameters, including:

1. catheter type;
2. number of cuffs;
3. outer and inner diameters;
4. length; and
6. tunneler information.

B. Device Materials

FDA has established a special control that requires that *material names and specific designation numbers must be provided (21 CFR 876.5540(b)(1)(i)).*

Recommendation: As specified in Section A. "Device Description" above, in the 510(k), you should provide the 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, additives, or coatings (as further discussed in section I. "Special Considerations – Coatings"). We recommend you group these materials according to whether they have direct or indirect contact with the circulating blood. As also discussed in Section A. "Device Description," you should provide a detailed comparison of your materials to those of the predicate device.

C. Biocompatibility

FDA has established a special control that requires that *components of the device that come into human contact must be demonstrated to be biocompatible (21 CFR 876.5540(b)(1)(i)).*

Recommendation: For all patient contacting materials, you should provide appropriate biocompatibility testing on finished, sterilized device(s) as recommended in the ODE General Program Memorandum #G95-1 (1995), entitled "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm). Hemodialysis catheters are considered "External communicating devices," "Circulating blood," "Permanent contact duration – (Category C)."

If you are unable to identify a legally marketed predicate device with similar location/duration of contact and intended use that uses the same materials as used in your device, we recommend you conduct and provide a biocompatibility risk assessment. The assessment should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and identify any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks. Unless otherwise mitigated, the following biocompatibility evaluations should be conducted:

- Cytotoxicity
- Sensitization (Guinea pig maximization with polar and non-polar extracts)
- Irritation or intracutaneous reactivity
- Systemic toxicity (acute)
- Sub-chronic toxicity
- Implantation[5]
- Hemocompatibility
- Genotoxicity

D. Performance Testing - Bench

FDA has established a special control that requires that *performance data must demonstrate that the device performs as intended under anticipated conditions of use (21 CFR 876.5540(b)(1)(ii)).*

Recommendation: The 510(k) should include adequate information describing the performance characteristics of the device. At a minimum, this should include functional testing.

The performance testing outlined below should be conducted on a minimum of three (3) devices of each model. If you choose to test one or more models to represent subsets of the product portfolio, you should provide a sample selection rationale detailing why this is appropriate. The special controls established the following requirements for testing and performance characteristics.

a. *Pressure versus flow rates for both arterial and venous lumens, from the minimum flow rate to the maximum flow rate in 100 ml/min increments, must be established. The fluid and its viscosity used during testing must be stated (21 CFR 876.5540(b)(1)(ii)(A)).*

   Recommendation: In order to provide pressure versus flow rate characterization data that is representative of clinical use of the device, a fluid with a viscosity analogous to that of blood (viscosity = 3.2 – 3.8 cP) should be used during the testing. This is consistent with current practice for most manufacturers. The test results should be compared to the predicate device (preferably in tabular format). The predicate device should be tested concurrently with the subject device using the same methodology and test fluid.

b. *Recirculation rates for both forward and reverse flow configurations must be established, along with the protocol used to perform the assay, which must be provided (21 CFR 876.5540(b)(1)(ii)(B)).*

   Recommendation: The recirculation rates should be compared with the predicate device (preferably in tabular format). The predicate device should be tested concurrently with the proposed device using the same methodology.

[5] Patients are exposed to hemodialysis catheter and shunt materials over a long period of time, and potentially with repeated use. A long-term (90 to 120 days) implantation study with histopathology may replace sub-chronic toxicity.

c. *Priming volumes[6] must be established (21 CFR 876.5540(b)(1)(ii)(C)).*

d. *Tensile testing of joints and materials must be conducted. The minimum acceptance criteria must be adequate for its intended use (21 CFR 876.5540(b)(1)(ii)(D)).*

Recommendation: 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 joints and polyurethane materials that comprise the main lumens of the catheter excluding the catheter tip (due to the more frequent handling of hemodialysis catheters compared to general catheters). Testing should be completed as specified in the FDA currently recognized version of consensus standard ISO 10555-1, Sterile, single-use intravascular catheters – Part 1: General requirements.[7]

e. *Air leakage testing and liquid leakage testing must be conducted (21 CFR 876.5540(b)(1)(ii)(E)).*

Recommendation: Testing should be completed as specified in the FDA recognized version of consensus standard ISO 10555-1 Annex D and Liquid leakage testing as specified in ISO 10555-1 Annex C.

f. *Testing of the repeated clamping of the extensions of the catheter that simulates use over the life of the catheter must be conducted, and retested for leakage (21 CFR 876.5540(b)(1)(ii)(F)).*

Recommendation: Assuming that five clampings are done at each treatment, with an average of three treatments per week, an average catheter life of 26 weeks, and a three times safety factor, repeatedly clamping at least 1,200 times, followed by tensile strength and leakage testing, as described in "d" and "e" above, should provide assurance of extension durability.

g. *Mechanical hemolysis testing must be conducted for new or altered device designs which affect the blood flow pattern (21 CFR 876.5540(b)(1)(ii)(G)).*

Recommendation: In vitro mechanical hemolysis testing should be conducted for new hemodialysis catheter designs. Devices consisting of alterations to a previous design (e.g., catheters with an added coating) should also undergo *in vitro* hemolysis testing if the blood flow pattern or surface characteristics of the device are affected. Hemolysis testing should be performed on shelf-life aged devices (which would include sterilization and thermal cycling from exposure to simulated shipping and storage conditions). However, testing on sterilized, non-aged devices is acceptable if justification is provided that shows that the chemical and physical properties of the blood contacting surfaces do not change over the shelf-life of the device. The hemolysis data for the proposed device

[6] The priming volume is the amount of fluid required to fill the inside of the catheter from the hubs to the tip.
[7] FDA's currently recognized version of standards and the extent of recognition can be located via FDA's standards database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm)

should be compared to that of the predicate device and demonstrate that no more red blood cell lysis occurs with the proposed design in comparison to the predicate device. The testing should utilize the maximum labeled blood flow rate for the proposed device (see also Appendix A for considerations for testing). For a family of catheters, hemolysis testing should be performed on the model with the greatest expected hemolysis potential (e.g., smallest internal diameter and longest length).

h. *Chemical tolerance of the device to repeated exposure to commonly used disinfection agents must be established (21 CFR 876.5540(b)(1)(ii)(H)).*

   Recommendation: FDA considers the following to be commonly used disinfection agents[8]: chlorhexidine, sodium hypochlorite, povidone-iodine (ointment and solution), 70% alcohol, mupirocin, polysporin or triple antibiotic ointment, hydrogen peroxide, and gentamycin. At a minimum, testing should include these, but additional agents should also be tested if the manufacturer recommends alternative specific agents. Test conditions should simulate the intended clinical use.

Results of performance testing for the proposed device should be compared to those obtained for the predicate device. If test results for the proposed device are outside the range of the predicate device, the 510(k) should include an explanation of why this difference supports the substantial equivalence of the proposed device. The variances should be noted and any significant deviations from those of the predicate device should be justified in the 510(k) submission.

E. Sterility and Shelf-Life

FDA has established special controls that require *performance data must demonstrate sterility of the device and must support the shelf-life of the device for continued sterility, package integrity, and functionality over the requested shelf life, that must include tensile, repeated clamping and leakage testing (21 CFR 876.5540(b)(1)(iii) and (21 CFR 876.5540(b)(1)(iv)).*

Recommendation: FDA's guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile," (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm109897.pdf) provides basic information on sterility issues. All sterile devices intended for internal use are generally expected 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. For ethylene oxide residuals, you may refer to the FDA currently recognized version of the

[8] Patel PR, Coutts K, Sauer AG, Shugart A, Melville AM, Arduino MJ, Thompson ND, Kallen A. 2012 National Survey of Hemodialysis Infection Prevention and Vascular Access Practices. #SA-OR044 Presented at American Society of Nephrology (ASN) Kidney Week; 2013 Nov 9, Atlanta, GA.

consensus standard ANSI/AAMI/ISO 10993-7: Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals);**Error! Bookmark not defined.**

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);

e. a description of the packaging system, and

f. testing to demonstrate that the package and its contents remain sterile.

FDA has established a special control that requires that *labeling of implanted blood access devices for hemodialysis catheters must specify an expiration date* and, as stated above, that *performance data must support the shelf life of the device (21 CFR 876.5540(b)(1)(v)(D) and (21 CFR 876.5540(b)(1)(iv))*.

Recommendation: The following test results or an appropriate rationale should be provided to substantiate the validity of the specified expiration date:

a. performance testing on aged samples to include, at a minimum, the performance testing as described in Section D. "Performance Testing – Bench" for tensile, repeated clamping, and leakage; and

b. package integrity testing (to demonstrate sterility and non-pyrogenicity over the labeled shelf life) as specified in the FDA currently recognized version of ASTM F1980-7: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.[7]

For devices with established materials and designs, accelerated conditions for establishing an expiration date or an acceptable scientific rationale may be used to support a 510(k). In such cases, it is typically acceptable to provide accelerated aging results for an initial time point such as "6-months equivalent" within a submission. Coatings or additives may make accelerated aging inappropriate. The labeled shelf life should reflect the initial test results provided in the 510(k), but may be increased by the manufacturer as subsequent accelerated aging results conducted under a protocol that FDA has found acceptable, which represent longer time points, become available.[9] In addition, a scientific rationale should be provided to support the chosen conditions for the accelerated testing. Real-time testing results should be included in the device history file for subsequent review by FDA.[10]

[9] For more information on deciding when a change to the device or labeling requires submission of a new 510(k) submission, please see FDA's guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080235.htm)
[10] 21 CFR 820.30 Device History File

F. Labeling

The 510(k) submission must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following recommendations are provided to assist you in preparing labeling that satisfies the requirements of 21 CFR Part 801 and the special controls for this device type.

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, and any relevant hazards, contraindications, side effects and precautions. (21 CFR 801.109(d)).

Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use (21 CFR 807.87(e)) must be provided. In addition, a specific intended use statement and any warnings, contraindications, or limitations should be clearly displayed.

Under 21 CFR 801.109, the instructions for use must include indications for use, and warnings, precautions, and contraindications associated with the use of the device. The instructions for use should also include principle of operation, device description, features and/or accessories, directions for device use, implantation procedures, and troubleshooting. Detailed instructions on catheter care should be provided, for example cleaning, site care, and disinfection.

The device label affixed to the device packaging must include the name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1). The label should also include the device name, U.S. point of contact, storage conditions, priming volume, sterility status and method, lot number, and expiration date.

In addition to the general labeling recommendations and provisions above, we recommend the following labeling considerations specific to hemodialysis catheters:

a. The intended use statement should include the specific indications and intended patient population.

b. Device labeling for the hemodialysis catheter should address the following potential complications of the device related to insertion location:

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

        i. language to specify the placement site such as “Catheters greater than 40 cm are intended for femoral vein insertion”;
        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;
    ii. potential complications specific to subclavian placement, including pneumothorax and hemothorax;
    iii. a caution statement related to the risk of subclavian vein stenosis if the subclavian vein site is used; and
    iv. a caution statement which states that subclavian access should only be used when no other upper-extremity or chest-wall options are available.

c. If applicable, the labeling should summarize the results of clinical performance data needed to demonstrate substantial equivalence.

FDA has established a special control that requires that the labeling for use of the implanted blood access devices for hemodialysis, include the following:

a. Labeling must provide arterial and venous pressure versus flow rates, either in tabular or graphical format. The fluid and its viscosity used during testing must be stated (21 CFR 876.5540(b)(1)(v)(A)).

b. Labeling must specify the forward and reverse recirculation rates (21 CFR 876.5540(b)(1)(v)(B)).

Recommendation: It is recommended that catheters with greater than 50% recirculation in the reverse direction should include a caution in the labeling listing the percent reverse recirculation.

c. Labeling must provide the arterial and venous priming volumes (21 CFR 876.5540(b)(1)(v)(C)).

Recommendation: If possible, these should be printed directly on the catheter.

d. Labeling must specify an expiration date (21 CFR 876.5540(b)(1)(v)(D)).

Recommendation: For additional details, please see Section E "Sterility and Shelf Life."

e. Labeling must identify any disinfecting agents that cannot be used to clean any components of the device (21 CFR 876.5540(b)(1)(v)(E)).

f. Any contraindicated disinfecting agents due to material incompatibility must be identified by printing a warning on the catheter. Alternatively, contraindicated disinfecting agents must be identified by a label affixed to the patient's medical record and with written instructions provided directly to the patient (21 CFR 876.5540(b)(1)(v)(F)).

g. Labeling must include a patient implant card (21 CFR 876.5540(b)(1)(v)(G)).

Recommendation: The implant card should be provided to the patient at the time of implantation and should include the name and model number (or serial number/unique device identifier as applicable) of the device, the name and contact information of the company, a reference to the complete instructions for use, and a blank space to be filled in with the name and contact information for the implanting physician. Additional information may be recommended for unique circumstances such as contraindicated disinfection agents, MRI compatibility, or other specific instructions.

h. The labeling must contain comprehensive instructions for the following (21 CFR 876.5540(b)(1)(v)(H)(1-6)):

1. *preparation and insertion of the device, including recommended site of insertion, method of insertion, and a reference on the proper location for tip placement;*
2. *proper care and maintenance of the device and device exit-site;*
3. *removal of the device;*
4. *anticoagulation;*
5. *management of obstruction and thrombus formation;*
6. *qualifications for clinical providers performing the insertion, maintenance, and removal of the devices.*

G. Animal and Clinical Testing

Implanted blood access devices for hemodialysis will generally not be subject to animal or clinical testing if they are similar to legally marketed implanted blood access devices in design and technology except as noted in Section H (Special Considerations). However, modifications in the indication for use or significantly different technological characteristics may warrant animal or clinical testing in addition to nonclinical performance testing to demonstrate substantial equivalence.

(1) Performance Testing – Animal

Testing performed in animals may be used to support substantial equivalence. Some areas that animal testing has been useful are for demonstrating anti-thrombotic properties, or testing for adequate flow. Such testing must comply with 21 CFR Part 58, which prescribes Good Laboratory Practices for nonclinical studies.

(2) Performance Testing – Clinical

Clinical evidence is generally not warranted for implanted blood access devices for hemodialysis except as noted in Section H (Special Considerations); however, such testing may be requested in situations such as the following:

a. indications for use dissimilar from legally marketed devices of the same type;

b. different 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

c. 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.

Any labeling claims about performance of the device *in vivo* should be supported with appropriate bench testing, in addition to either animal and/or clinical testing.

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). Hence, 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. 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). Also, FDA's "Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators" (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf) provides recommendations to assist clinical investigators and sponsors in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54.

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 that may be expected with implanted blood access devices. FDA encourages that you utilize the opportunity to seek advice on prospective IDE clinical studies prior to the submission of an IDE application. FDA's guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf) outlines the recommended procedures for seeking feedback from FDA on a clinical study design.

H. Special Considerations

(1) Subcutaneous Catheters

Subcutaneous catheters refer to those catheters that 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 than described above in order to resolve issues of infection rates, adequacy of dialysis, maintenance of blood flow, and long-term patency.

In addition to the aforementioned considerations, in accordance with the established special controls, implanted blood access devices that include subcutaneous ports must include the following:

a. *Labeling must include the recommended type of needle for access as well as detailed instructions for care and maintenance of the port, subcutaneous pocket, and skin overlying the port (21 CFR 876.5540(b)(1)(vi)(A)).*

b. *Performance testing must include results on repeated use of the ports that simulates use over the intended life of the device (21 CFR 876.5540(b)(1)(vi)(B)).*

c. *Clinical performance testing must demonstrate safe and effective use and capture any adverse events observed during clinical use (21 CFR 876.5540(b)(1)(vi)(C)).*

   Recommendation: The clinical performance data should demonstrate that the device is as safe and as effective as currently marketed hemodialysis vascular access devices such as implanted hemodialysis catheters.

(2) Coatings

Implanted blood access devices for hemodialysis may include coatings, additives, or have material properties that impart antithrombotic, antimicrobial, or other novel properties to the device.

In accordance with the established special controls, in addition to the aforementioned requirements for implanted blood access devices for hemodialysis, implanted blood access devices with coatings or additives must include the following:

a. *A description and material characterization of the coating or additive material, the purpose of the coating or additive, duration of effectiveness, and how and where the coating is applied (21 CFR 876.5540(b)(1)(vii)(A)).*

b. *An identification in the labeling of any coatings or additives and a summary of the results of performance testing for any coating or material with special characteristics, such as decreased thrombus formation or antimicrobial properties (21 CFR 876.5540(b)(1)(vii)(B)).*

c. *A Warning Statement in the labeling for potential allergic reactions including anaphylaxis if the coating or additive contains known allergens (21 CFR 876.5540(b)(1)(vii)(C)).*

d. *Performance data must demonstrate efficacy of the coating or additive and the duration of effectiveness (21 CFR 876.5540(b)(1)(vii)(D)).*

Recommendation: If there is a clinical benefit for such coatings, FDA recommends that the results of a clinical study be provided in the labeling in support of these benefits.

Antimicrobial coatings generally require a clinical study to demonstrate a clinically and statistically significant decrease in the rate of infection or microbial colonization compared to an uncoated catheter. Coatings identical to previously cleared coatings for similar indications may not need new supportive clinical data. 510(k) submissions should include at a minimum, a comparison of the chemical entity, concentration, physical specifications (particle size, surface texture, etc.), elution profile, and manufacturing method.

Antimicrobial coatings may lead to the development of microorganisms that are resistant to the antimicrobial in the coating as well as other antimicrobial products. The 510(k) submission should address the potential for the coating to lead to antimicrobial resistance, and if necessary, include testing to demonstrate that the coating does not lead to the induction of resistant microorganisms.

Inclusion of a coating with a new drug entity or a coating that is released from the catheter may 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 device, we would strongly encourage the submission of a pre-submission.

(3) Arteriovenous (A-V) shunt cannulae (with vessel tips)

The arteriovenous (A-V) shunt cannula (with vessel tips) was the first vascular access used for hemodialysis, but has not been used in clinical practice in the US since the early 1980s with the advent of newer implanted blood accesses which have lower rates of complications; however, it remains a part of the Implanted Blood Access Devices for Hemodialysis regulatory classification. Compared with contemporary implanted blood access devices such as implanted hemodialysis catheters, A-V shunt cannulae have a higher risk of hemorrhage and have unique risks of arterial stenosis, arterial thrombosis and vascular access steal syndrome given that the device accesses the arterial circulation.

In addition to the aforementioned requirements for implanted blood access devices for hemodialysis (except for performance testing and labeling related to recirculation rates and priming volumes, which are not applicable) (21 CFR 876.5540(b)(1)(viii)(A)), in accordance with the special controls for this device type, the following requirements must be met:

a. *Labeling must include Warning Statements to address the potential for vascular access steal syndrome, arterial stenosis, arterial thrombosis, and hemorrhage including exsanguination given that the device accesses the arterial circulation (21 CFR 876.5540(b)(1)(viii)(B)).*

b. *Clinical performance testing must demonstrate safe and effective use and capture any adverse events observed during clinical use (21 CFR 876.5540(b)(1)(viii)(C)).*

Recommendation: The clinical performance data should demonstrate that the device is as safe and as effective as currently marketed hemodialysis vascular access devices such as implanted hemodialysis catheters or arteriovenous grafts (21 CFR 870.3450).

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 in this Appendix 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.[11,12,13,14,15] 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.[11] 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 should be 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

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[11] ASTM F1830-97: Standard practice for selection of blood for *in vitro* evaluation of blood pumps. American Society for Testing and Materials (ASTM) International, West Conshohocken, PA.

[12] ASTM F1841-97: Standard practice for assessment of hemolysis in continuous flow blood pumps. American Society for Testing and Materials (ASTM) International, West Conshohocken, PA.

[13] Guidance for cardiopulmonarybypass oxygenators 510(k) submissions; Final guidance for industry and FDA staff (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073668.htm)

[14] Mueller, MR, Schima, H, et al. *In vitro* hematological testing of rotary blood pumps: Remarks on standardization and data interpretation. Artificial Organs, 17(2): 103-110, 1993.

[15] Malinauskas, R. Plasma hemoglobin measurement techniques for the *in vitro* evaluation of blood damage caused by medical devices. Artificial Organs, 21(12): 1255-67, 1997.

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 under appropriate clinical arterial and venous pressure conditions, and a reservoir made of a hemocompatible material (which can be heated to physiologically relevant temperatures 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 User's Manual, carefully check the occlusion setting of the blood pumps prior to the testing. The blood flow rate through the pump should be calibrated under appropriate clinical arterial and venous pressure conditions.

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 such that all of the inlet and exit ports of the catheters are completely submerged and 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 five devices for each cohort. The testing should be performed at the maximum labeled blood flow rate for the proposed device. For a family of catheters, hemolysis testing should be performed on the model with the greatest expected hemolysis potential (e.g. smallest internal diameter, longest length, greatest pressure loss, and highest blood flow rate).

Performing the test:

6. Prior to testing with blood, buffered saline should be circulated through the loop for five minutes to rinse the surfaces.

7. The blood should be warmed and maintained at a physiological temperature (35– 38ºC) prior to and during the testing, while avoiding exposing the blood to temperatures (e.g., from a water bath) in excess of 39ºC. The saline from the loop should be drained, the warmed blood should be introduced, and air bubbles should be cleared from the mock circuit. The blood should be allowed to circulate in the loop for approximately three minutes before taking a baseline sample (time = 0). The baseline sample should be evaluated for blood hematocrit, total blood hemoglobin concentration, and the plasma hemoglobin concentration. A validated method should be used to assess the critical measurement parameter, the plasma hemoglobin concentration.[15]

8. The *in vitro* testing with blood is usually conducted for as long as the device will be labeled for a clinical treatment. For a four 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 that needle-less syringes be used. Clear the port first by drawing out some fresh blood (1 mL) into a needle-less syringe. Then, a new syringe should be used 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 prevent pressure or velocity-induced hemolysis.

10. The arterial and venous catheter pressures, the blood temperatures, and the blood flow rates in each loop should be measured and recorded 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 documented in the final report.

12. Data from individual experiments should be provided in both tabular and graphical format. The plasma hemoglobin should 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, a least squares fit to the data for each of the individual test circuits can be calculated. The slope of the least fit line is the rate of plasma hemoglobin generation.

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

14. Using paired statistical testing between the matched individual test circuits, the rate of plasma hemoglobin generation between the new and the predicate catheters can be compared.