

**FDA Executive Summary**

Prepared for the **June 27, 2013**  
meeting of the Gastroenterology and Urology Devices Panel

Classification of Implanted Blood Access Devices for Hemodialysis  
**(21 CFR 876.5540(b)(1))**

Division of Reproductive, Gastro-Renal, and Urological Devices  
Office of Device Evaluation  
Center for Devices and Radiological Health  
Food and Drug Administration

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## 1 Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), on June 27, 2013, the Food and Drug Administration (FDA) is convening the Gastroenterology and Urology Devices Advisory Panel (the panel) for the purpose of obtaining recommendations regarding reclassification of implanted blood access devices for hemodialysis (21 CFR 876.5540(b)(1)) that were subject to orders under Section 515(i). This section of the Act requires FDA to order manufacturers of preamendments Class III devices for which no final regulation has been issued requiring the submission of premarket applications (PMAs) to submit to the FDA a summary of, and a citation to, any information known or otherwise available to them respecting such devices, including adverse safety and effectiveness information that has not been submitted under other sections of the Act.

Implanted blood access devices for hemodialysis are one of the remaining preamendments Class III medical devices currently cleared for marketing through the 510(k) pathway.

The panel will be asked to provide input on the risks to health and benefits of implanted blood access devices for hemodialysis. The panel will also be asked to discuss the FDA's proposed reclassification strategy for implanted blood access devices for hemodialysis based upon the available safety and effectiveness information. FDA believes that these devices can be reclassified into class II (Special Controls) because special controls, in addition to general controls, can be established to provide reasonable assurance of the safety and effectiveness of these devices. If the panel believes that Class II is appropriate for implanted blood access devices for hemodialysis, the panel will also be asked to specifically comment on the adequacy of the proposed special controls to mitigate the identified risks to health.

## 2 Device Description

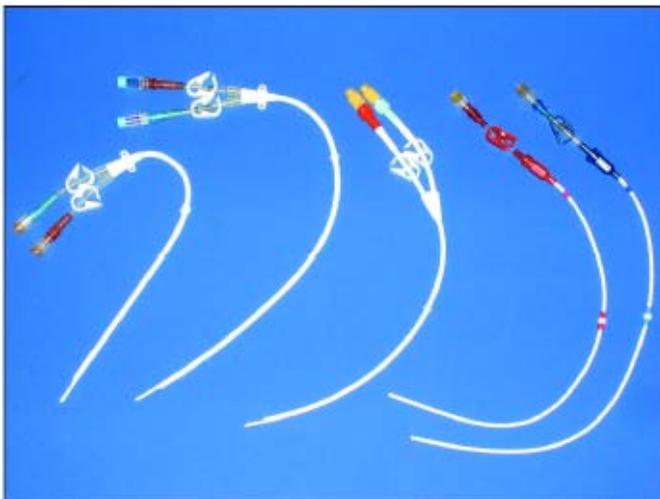
As currently defined in 21 CFR 876.5540

(a) *Identification.* A blood access device and accessories is 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. The device includes implanted blood access devices, nonimplanted blood access devices, and accessories for both the implanted and nonimplanted blood access devices.

**(1) The implanted blood access device consists of various flexible or rigid tubes, 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 shunts and connectors specifically designed to provide access to blood, such as the arteriovenous (A-V) shunt cannula and vessel tip.**

- (2) The nonimplanted blood access device consists of various flexible or rigid tubes, such as catheters, cannulae or hollow needles, which are inserted into appropriate blood vessels or a vascular graft prosthesis (870.3450 and 870.3460), and are intended to remain in the body for less than 30 days. This generic type of device includes fistula needles, the single needle dialysis set (coaxial flow needle), and the single needle dialysis set (alternating flow needle).
- (3) Accessories common to either type include the shunt adaptor, cannula clamp, shunt connector, shunt stabilizer, vessel dilator, disconnect forceps, shunt guard, crimp plier, tube plier, crimp ring, joint ring, fistula adaptor, and declotting tray (including contents).

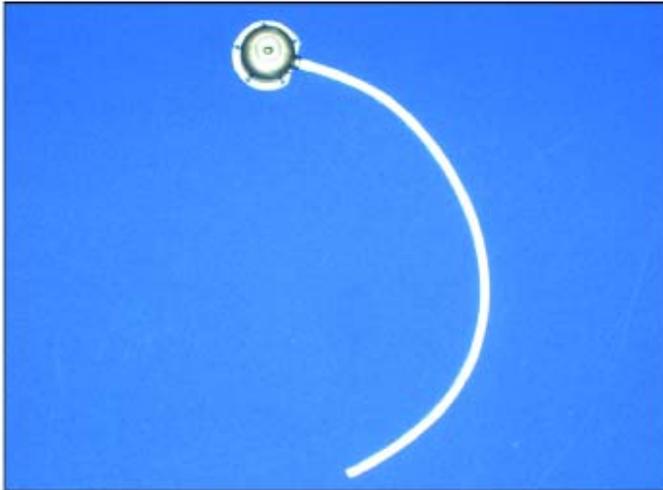
The scope of the device description for today's panel discussion will be on part (a)(1) of the identification of the classification regulation. Implanted hemodialysis catheters (Figure 1) are soft, blunt-tipped plastic catheters that have a subcutaneous "cuff" for tissue ingrowth and exit the skin through a subcutaneous "tunnel." They are generally placed in a central vein (internal jugular, subclavian, or femoral) to allow blood access. Chronic hemodialysis catheters serve as conduits for the removal of blood from the patient, delivery to a hemodialysis machine for filtering, and return of filtered blood to the patient. They have no moving parts, consisting, essentially, of flexible tubing terminating in rigid Luer lock connectors for attachment to a dialysis machine. As seen in Figure 1, there are variations in catheter design and many also include the addition of antimicrobial or antithrombotic coatings. Currently cleared implanted catheter coatings include heparin and/or silver.



**Figure 1: Examples of Implanted Hemodialysis Catheters**

Reproduced with permission from Nephrology Nursing Journal (*Ball LK. Forty years of vascular access. Nephrol Nurs J. 2009 Mar-Apr; 36(2):119-23.*)

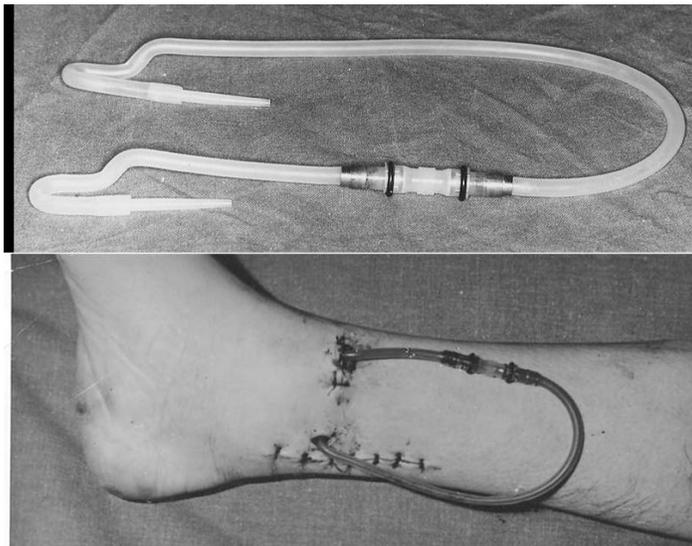
Subcutaneous catheters (Figure 2) provide a similar functionality in that they also provide access to the blood, but are totally implanted below the skin surface with no external communication.



**Figure 2: Example of a Subcutaneous Implanted Hemodialysis Catheter**

Reproduced with permission from Nephrology Nursing Journal (*Ball LK. Forty years of vascular access. Nephrol Nurs J. 2009 Mar-Apr;36(2):119-23.*)

AV Shunts and Vessel Tips (Figure 3) are tubing with tapered tips that are inserted into the artery and vein. The tubing is attached to the roughened or etched outer surface of the tip. These also provide a similar functionality in that they provide access to the blood, but the tubing is external to the skin and is accessed with needles.



**Figure 3: Example of an Arteriovenous (A-V) Shunt Cannula with Vessel Tips**

Reproduced with permission from InTech (*Ivica Maleta, Božidar Vujičić, Iva Mesaroš Devčić and Sanjin Rački (2012). Vascular Access for Hemodialysis, Aneurysm, Dr. Yasuo Murai (Ed.), ISBN: 978-953-51-0730-9, InTech, DOI: 10.5772/48787.*) Available from:

[http://www.intechopen.com/books/aneurysm/vascular\\_access\\_for\\_hemodialysis](http://www.intechopen.com/books/aneurysm/vascular_access_for_hemodialysis)

**Table 1: Current Product codes assigned to implanted blood access devices for hemodialysis.**

<b>Product Code</b>	<b>Name</b>
<b>FIQ</b>	A-V Shunt Cannula
<b>FKW</b>	Vessel Tip
<b>LFJ*</b>	Subclavian Catheter
<b>MSD</b>	Implanted Hemodialysis Catheter
<b>NYU</b>	Implanted Coated Hemodialysis Catheter

*\*Note: Product codes for implanted catheters were initially based on insertion site. The first marketed catheters were inserted into the subclavian vein, although this insertion site later fell out of favor when it was discovered that the internal jugular insertion site was associated with fewer complications. FDA started using a product code (MSD) that was not site-specific around 1997.*

### **3 Current Classification**

As currently defined in 21 CFR 876.5540

- (b) **Classification. (1) Class III (premarket approval) for the implanted blood access device.**
- (2) Class II (performance standards) for the nonimplanted blood access device.
- (3) Class II (performance standards) for accessories for both the implanted and the nonimplanted blood access devices not listed in paragraph (b)(4) of this section.
- (4) Class I for the cannula clamp, disconnect forceps, crimp plier, tube plier, crimp ring, and joint ring, accessories for both the implanted and nonimplanted blood access device. The devices subject to this paragraph (b)(4) are exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in 876.9.

It should be noted that this classification regulation is currently split between Class I, Class II and Class III depending upon the technological aspects. The focus of this panel is on 876.5540(b)(1) of the classification regulation.

### **4 Classification and Regulatory History for 21 CFR §876.5540**

A brief summary of the regulatory history for implanted blood access devices for hemodialysis is provided within this section.

Following the classification panel meeting, FDA published a proposed rule on January 23, 1981 (46 FR 7616) for blood access devices and accessories. In the preamble to the proposed rule (46 FR 7616), the Gastroenterology-Urology Devices Panel recommended that both implanted and nonimplanted blood access devices be classified into class II. Although FDA agreed with the panel recommendation for nonimplanted blood access devices, FDA disagreed with the panel's recommendation for implanted blood access devices and proposed that implanted blood access devices be classified into class III because FDA believed that these devices presented a potential unreasonable risk of illness or injury to the patient if there were not adequate data to assure the safe and effective use

of these devices. FDA also noted that implanted blood access devices are part of a life-supporting and life-sustaining system and that general controls and performance standards were insufficient to provide reasonable assurance of the safety and effectiveness of implanted blood access devices.

In 1983, FDA classified implanted blood access devices into class III, but the accessories to these devices were classified into class II (48 FR 53023, November 23, 1983). In 1987, FDA published a clarification by inserting language in the codified language stating that no effective date had been established for the requirement for premarket approval for implanted blood access devices (52 FR 17732 May 11, 1987).

In 2009, FDA published an order for the submission of information on implanted blood access devices (74 FR 16214, April 9, 2009). In response to that order, FDA received information in support of reclassification from 15 device manufacturers who all recommended that implanted blood access devices be reclassified to class II. The manufacturers stated that safety and effectiveness of these devices may be assured by bench testing, biocompatibility testing, sterility testing, expiration date testing, labeling, and appropriate utilization of standards.

On June 20, 2012, FDA published a proposed rule proposing the reclassification of implanted blood access devices for hemodialysis from class III to class II (77 FR 36951) and announced the availability of a draft Special Controls Guidance Document that, when finalized, would serve as a special control, if FDA reclassified these devices. FDA believed that the special controls as described in the guidance document "Class II Special Controls Guidance Document: Implanted Blood Access Devices for Hemodialysis" would be sufficient to mitigate the risks to health associated with implanted blood access devices for hemodialysis.

The proposed rule provided for a comment period that was open until September 18, 2012. FDA received 3 comments which suggested modifications to the proposed Special Controls Guidance Document. These were considered by FDA. Comments included:

1. Expanding the product code list to include implanted blood access devices of mammalian origin and polytetrafluoroethylene ("PTFE") grafts.  
FDA response: These devices are outside the scope of this regulatory classification and are therefore not included in this guidance.
2. Distinguishing between cuffed and un-cuffed catheters.  
FDA response: Our intent is to revise the guidance to clarify that it is applicable for cuffed catheters regulated under 21 CFR 876.5540(b)(1).
3. Subclavian catheters should not be mentioned due to their potential risks.  
FDA response: Since these catheters are still legally marketed and included as part of the scope of this portion of the classification regulation, FDA is proposing to consider these as part of the downclassification into Class II, subject to special controls.

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted, which amended the device reclassification procedures under Sections 513

and 515 of the Food, Drug and Cosmetic Act (FD&C Act), changing the process for taking final administrative action for these devices. Now the, FDA must use an administrative order process instead of using rulemaking. Under the new requirements, FDA must issue proposed and final orders to reclassify a device, hold a device classification panel meeting to consider the classification of this device, and consider comments submitted by the public.

FDA intends to issue a proposed administrative order to comply with the new procedural requirement created by FDASIA when reclassifying a preamendments class III device. Further, FDA intends to codify the proposed special controls within the 21 CFR 876.5540(b)(1) classification regulation itself rather than through guidance.

## **5 Indications for Use**

According to 21 CFR 876.5540, blood access devices are intended to provide access to a patient's blood for hemodialysis or other chronic uses.

Implanted hemodialysis catheters are generally indicated for use in attaining long-term vascular access for hemodialysis and apheresis. They may be implanted percutaneously and are primarily placed in the internal jugular or subclavian vein of an adult patient. Catheters greater than 40 cm are intended for femoral vein insertion.

Additional variations in Indications for Use Statements exist for other implanted blood access device designs such as those for the fully subcutaneous catheters, coated catheters, or the A-V shunt cannulae.

## **6 Summary of Clinical Evidence**

### **6.1 Systematic Literature Review**

#### **6.1.1 Methods**

The aim of the systematic literature review was to summarize the safety and effectiveness outcomes from the use of implanted hemodialysis catheters (IHCs) reported in the literature since the year 2000. Although IHCs have been widely used since the 1980s, there has been an evolution of materials, technology, and clinical practices over time. Starting at the year 2000 gives a relative framework for current catheter use, as older data would be less relevant to currently marketed catheters.

A search of the PubMed database was conducted on March 5, 2013, to retrieve articles on IHC use. Results were limited to human studies published in English from January 1, 2000. A total of 57 original articles reporting safety and effectiveness outcomes with IHC use were retrieved for epidemiological data extraction, qualitative data synthesis and analysis. (References in Section 10).

Twenty-seven single-arm studies evaluated safety and effectiveness of various brands of IHC use. All studies were observational. A total of 3,175 patients were evaluated in these studies. The performance of various IHCs was compared in 9 studies. The comparative studies had limited power to detect statistically significant differences between catheter groups due to the relatively small number of patients in each catheter group, and the results are not discussed in depth. A total of 15 case series and reports were published

since 2000. A fully subcutaneous venous access device that was specifically designed to overcome the limitations of standard hemodialysis catheters and deliver high flow rates with a low incidence of adverse events was examined separately.

## 6.1.2 Safety and Effectiveness: Implanted Hemodialysis Catheters (IHCs)

### Effectiveness:

#### *Non-comparative studies*

The main effectiveness endpoints evaluated were technical success (the establishment of hemodialysis access via the access vein with adequate catheter function), blood flow rate and catheter patency rate. In 10 papers that reported technical success of catheter placement, a rate of 100% was achieved in 8 studies<sup>1, 6, 16, 18, 34, 46, 52, 55</sup>, with the remaining two studies reporting 92.9%<sup>7</sup> and 88%<sup>17</sup> of technical success respectively. Five studies<sup>6, 11, 13, 18, 34</sup> reported a mean blood flow rate of 250ml/min-303 ml/min, as summarized in Table 2.

**Table 2: Mean Blood Flow Rate with the Use of IHCs**

Reference *	Study Location	Sample Size	Mean Blood Flow Rate (ml/min)
Conz et al., 2001	Italy	5	250±50
Di Iorio et al., 2001	Italy	88	272±38
Gallieni et al., 2002	Italy	28	303±20
Falk et al., 2007	US	33	>300
Bertoli et al., 2010	Italy	25	270±17
Power et al., 2010	UK	26	300±3

\* All studies were observational

Catheter patency was reported in 6 studies, as summarized in Table 3. The primary patency rates (from catheter insertion to intervention) were 44%-96% at 1-month<sup>16-18, 52</sup>, 29% at 2-month<sup>16</sup>, 19%-64% at 3-month<sup>16, 52</sup>, 4%-71% at 6-month<sup>6, 16, 17, 52</sup>, 25%-73% at 12-month<sup>6, 17, 34</sup>, 33% at 24-month<sup>34</sup> and 28% at 36-month<sup>34</sup>. The secondary patency rates (from insertion to exchange or removal) were 85%-100% at 6-month<sup>6, 17</sup> and 65%-70% at 12-month<sup>6, 17</sup>.

**Table 3: Primary Patency Rate with the Use of IHCs**

Reference *	Study Location	Sample Size	Primary Patency Rate						
			1M	2M	3M	6M	12M	24M	36M
Funaki et al., 2001	US	24	90%	NR	NR	71%	25%	NR	NR
Falk et al., 2007	US	33	44%	29%	19%	4%	NR	NR	NR
Van Ha et al., 2007	US	97	86%	NR	64%	39%	NR	NR	NR
Bertoli et al., 2010	Italy	25	NR	NR	NR	67%	54%	NR	NR
Power et al., 2010	UK	26	NR	NR	NR	NR	73%	33%	28%

\* All studies were observational

NR – Not Reported

### **Safety:**

Device-related infection, thrombosis, malfunction and device survival were the most common safety endpoints evaluated and reported in the studies. Two US studies<sup>3, 46</sup> reported a total complication rate of 3.65 and 7 per 1,000 catheter-days respectively.

### ***Infection***

Catheter-related infection occurred in all study populations except two studied in Italy<sup>11, 18</sup> which reported no infections in 5 and 28 patients evaluated. Six studies<sup>3, 13, 22, 29, 50, 56</sup> reported a total of 10.2% to 50% of treated patients with catheter-related infections. As shown in Table 4, the overall infection rates resulting from IHC insertion were reported in 11 studies<sup>1, 3, 7, 12, 15, 17, 31, 34, 46, 52, 53</sup>, with the rate between 0.6 and 3.0 per 1,000 catheter-days. The rates of bacteremia were reported in 8 studies<sup>6, 12, 29, 31, 34, 46, 49, 52</sup> with the range from 0.3 to 1.77 per 1,000 catheter-days. One study in Ireland<sup>28</sup> reported that 27.5% of the 336 patients implanted with IHCs experienced catheter-related sepsis (CRS), with a rate of 1.3 per 1,000 catheter-days and 4 patients died from CRS. In a study from Israel<sup>50</sup>, 38% of the 29 patients became severely infected requiring catheter removal and ended in 6 deaths.

**Table 4: Catheter-related Infection and Bacteremia Rate with the Use of IHCs**

<b>Reference *</b>	<b>Study Location</b>	<b>Sample Size</b>	<b>Infection Rate **</b>	<b>Bacteremia Rate **</b>
Funaki et al., 2001	US	24	0.6	NR
Ewing et al., 2002	UK	88	2.4	NR
Gallieni et al., 2002	Italy	28	0	NR
Cetinkaya et al., 2003	Turkey	85	0.82	NR
Develter et al., 2005	Belgium	157	2.31	1.71
Wang et al., 2006	US	200	1.3	NR
Alomari et al., 2007	US	207	3.0	NR
Van Ha et al., 2007	US	97	1.4	1.0
Spector et al., 2008	US	85	1.4	0.3
Mojibian et al., 2009	US	57	1.12	0.56
Bertoli et al., 2010	Italy	25	N/A	1.77
Power et al., 2010	UK	26	2.84	0.82
Thomson et al., 2010	UK	365	N/A	1.77
Adeb et al., 2012	US	120	1.8	NR
Martin-Pena et al., 2012	Spain	123	N/A	0.34

\* All studies were observational; \*\* per 1,000 catheter-days NR – Not Reported

### ***Thrombosis***

Catheter thrombosis is another common complication of IHC. Five studies<sup>7, 13, 15, 30, 56</sup> reported a total of 10.2% to 26% of treated patients with catheter thrombosis. Two studies in UK<sup>15</sup> and Belgium<sup>12</sup> reported thrombosis rates of 1.16 and 1.94 per 1,000 catheter-days respectively. Two other studies in Italy<sup>11, 18</sup> reported no thrombosis in 5 and 28 patients evaluated.

### ***Other complications***

The catheter malfunction rates were reported in 4 studies<sup>1, 3, 47, 53</sup>, with the rate between 1.7 and 7.4 per 1,000 catheter-days. Besides catheter-related infections and thrombosis, some other low frequency complications reported were fibrin sheath formation<sup>46, 53, 57</sup>, bleeding<sup>1, 13, 15, 16, 57</sup>, broken catheter<sup>13</sup>, kinked or pinched catheters<sup>57</sup>, catheter dislocation<sup>13, 34</sup>, pneumothorax<sup>55</sup>, hemothorax<sup>55</sup>, carotid artery puncture<sup>15</sup> and air embolism<sup>1, 15</sup>.

### ***Device survival***

Device survival was evaluated in 13 studies. The Kaplan-Meier (KM) catheter survival rates were reported in 5 studies. The KM survival rates were 62%-78% at 1-month<sup>1, 15</sup>, 54% at 3-month<sup>15</sup>, 25%-65% at 6-month<sup>1, 7, 15, 53</sup>, 13%-42% at 12-month<sup>1, 7, 33, 53</sup>, 28.6% at 24-month<sup>53</sup>, 19.5% at 36-month<sup>53</sup> and 15.6% at 48-month<sup>53</sup>. One study in Italy<sup>13</sup> reported a device survival rate of 88.6% during 84-month of follow-up, while in another study conducted in Ireland<sup>29</sup>, only 21.8% of the catheters were still functioning at the end of the 3-year study. Catheter survival time was reported in 7 studies<sup>7, 12, 15, 28, 31, 46, 53</sup>, with the mean survival time between 105 and 289 days per catheter.

A few studies evaluated catheter removal due to complications. In two studies<sup>31, 34</sup>, 10.5% and 23.1% of the IHCs were removed during the study period due to malfunction. One US study<sup>16</sup> reported that 27% of catheters were removed due to poor blood flow. In another US study<sup>53</sup>, 27.4% of the catheters were removed due to infection or malfunction. The catheter exchange rate was 13% for catheters inserted within one year and 52% for catheters inserted for more than one year.

### **Assessment and Critique:**

#### ***Non-comparative studies***

There were various brands of IHCs evaluated in the literatures since 2000. The major limitations of the studies include lack of controls, small sample size, single center experience, missing information due to retrospective design, wide range of follow-up duration, different patient population and different techniques in catheter placement, and some missing or inconsistencies in the definition of study endpoints. Nevertheless, data published since 2000 continue to indicate similar safety and effectiveness profile for IHCs as compared to pre-2000 data. While the placement of IHCs is a technically successful procedure in all ages and appropriate blood flow rate can be achieved at the time of catheter insertion, the catheter patency rate and device survival decrease significantly over time due to catheter-related complications. Infections and thrombosis remain the most common complications with IHC use. A few deaths resulting from catheter-related bacteremia/sepsis were reported in two European countries<sup>28, 50</sup>.

#### ***Comparative studies***

The performance of various IHCs was compared in 9 studies published since 2000. The studies were limited in terms of power to detect statistically significant differences between catheter groups due to the relatively small number of patients in each catheter group. In addition, in two prospective and four retrospective studies, the differences in patient selection and other uncontrolled factors between catheter groups due to the non-randomized design may have influenced the study findings. In the three RCTs comparing

Ash-Split with other IHCs, the randomization was suboptimal in one study as the catheters were placed in revolving order<sup>37</sup>, one study had a relative short follow-up time<sup>32</sup>, and blinding was not applied in at least one other study<sup>51</sup>. Although no significant differences were indicated in the mean blood flow rate and catheter-related infection, catheter survival was significantly higher in the Ash-Split group than the Opti-flow group in one RCT<sup>51</sup>.

The significant difference in infection rate was reported in only one study<sup>47</sup> where the rate was significantly higher in catheters with side holes than catheters without side holes. Only a single manufacturer's catheter was evaluated in this retrospective study. In all studies, the reported infection rates for different IHCs were comparable to the rates reported in the non-comparative studies. In a retrospective study comparing two IHCs with different antimicrobial coating, the rate of thrombosis for Hemo-Split BioBloc IHC was significantly higher than Tal Palindrome Ruby IHC. Several observational studies also reported significant differences in catheter patency and device survival between catheter groups.

### **6.1.3 Safety and Effectiveness: A Fully Subcutaneous Venous Access Device**

#### **Overview of Studies**

A fully subcutaneous venous access device was specifically designed to overcome the limitations of standard hemodialysis catheters and deliver high flow rates with a low incidence of adverse events. The system consists of an access valve and silicone cannula which is typically implanted below the clavicle and tunneled to the right internal jugular vein. There are a total of 6 papers published since 2000, involving 5 original studies. One multi-center study<sup>39, 42</sup> conducted in US compared the efficacy and safety of the device with Tesio-Cath IHC in a hybrid study design. A randomized prospective design was utilized for Phase 1 of the study, with 36 patients enrolled in the device group where 0.2% sodium oxychlorosene was used as an antimicrobial solution and 34 patients enrolled in the Tesio-Cath group. Phase 2 of the study followed 34 non-randomized patients implanted with the device where a 70% isopropyl alcohol was used as an antimicrobial solution. The other 4 studies<sup>5, 23, 35, 40</sup> evaluated a total of 100 patients implanted with the device in US, Canada and Germany.

#### **Effectiveness**

The mean blood flow rate was 245±42 ml/min in the German study<sup>23</sup>, 358.7 and 384.7 ml/min in 2 US studies<sup>5, 42</sup>. In the multi-center RCT<sup>43</sup>, the blood flow rates were significantly higher for the device (358.7 ml/min) compared to Tesio-Cath IHC (331.8 ml/min).

The venous pressure was 223.2±60.3 mmHg in one of the US studies<sup>5</sup>. In phase 2 of the US multi-center study<sup>39</sup>, venous pressures were significantly lower in the device group (223 mmHg) compared to the Tesio-Cath group (242 mmHg) at a blood flow rate of 400 ml/min.

One US study<sup>35</sup> reported a primary and secondary patency rate of 62% and 87% at 8 months with the device.

## **Safety**

### ***Infection***

The device-related infection rates with device use were 1.3-4.8 per 1,000 catheter-days in the 5 studies. One study<sup>41</sup> reported a high infection rate of 4.8 per 1000 patient-catheter days. This study describes 7 patients who all have a history of access failure and limited options for dialysis. Five patients (71%) developed device-related infection and in only one patient the infection was cured without removal of the device. In the study conducted in US and Canada<sup>5</sup>, device-related infection occurred in 52.2% of the cases, resulting in valve removal in all cases. One US study<sup>35</sup> reported that at least 2 patients died from catheter-related sepsis. The German study<sup>23</sup> also indicated that 2 deaths seemed to be related to device infection. In the US multi-center study<sup>39, 42</sup>, fewer device-related infections were observed for the device when used with 70% isopropyl alcohol than for Tesio-Cath at both 6-month (1.3 vs. 3.3 per 1,000 catheter-days) and 12-month of follow-up (1.9 vs. 3.4 per 1,000 catheter-days).

### ***Thrombosis***

Thrombosis is another common complication with IHC use. In 3 studies<sup>23, 35, 39, 42</sup> the reported rates of thrombolytic infusions or occlusions were between 1.4 and 2.3 per 1,000 catheter-days. In the multi-center study<sup>39, 42</sup>, the device with alcohol group required significant fewer thrombolytic infusions compared to the Tesio-Cath group at both 6-month (2.3 vs. 8.8 per 1,000 catheter-days) and 12-month of follow-up (1.6 vs. 6.6 per 1,000 catheter-days).

### ***Device survival***

The Kaplan-Meier device survival rates with the device were 84.9% in the German study<sup>23</sup> and 89.9% in the multi-center US study<sup>42</sup> at 6-months, 55.2% in the German study<sup>23</sup> and 74% in one US study<sup>39</sup> at 12-months, and 55.2% in the German study<sup>23</sup> at 24-months. In the multi-center US study<sup>39, 42</sup> the Kaplan-Meier device survival was significantly higher in the device with alcohol group compared with the Tesio-Cath group at both 6-month (89.9% vs. 69.1%) and 12-month follow-up (74% vs. 48%). In the initial study conducted in US and Canada<sup>8</sup>, the mean duration of device survival for the device was 6.8±0.97 months. In one US study<sup>35</sup>, 18 patients (49%) underwent device removal due to infection or thrombosis.

## **Assessment and Critique:**

Five studies evaluating the safety and effectiveness of the fully subcutaneous venous access system were published between 2000 and 2006. The four observational studies were conducted either retrospectively or with very small sample size (23 and 7 subjects in each of the two prospective studies). The only RCT<sup>39, 42</sup> changed an antimicrobial solution in the device group during the course of the study when the device was compared with Tesio-Cath IHC, which resulted in non-randomized patient enrollment in phase 2 of the study. Therefore it is difficult to draw any conclusions from the study although better device survival and fewer device-related infections and required thrombotic infusions were observed for the device. Overall, the device-related infections and device survival with the device are comparable to other IHCs in the published studies. The device's subcutaneous nature may delay the diagnosis of infection until sepsis develops and result in death.<sup>35</sup>

## 6.1.4 Case Series and Case Reports

### Overview

A total of 15 case series and reports were published since 2000. One article<sup>4</sup> identified 71 patients referred to a dialysis access center in US primarily for a broken clamp or cracked extension tube. There were 11 brands of IHCs involved in this case series. The remaining 14 papers reported 18 patients with various complications including catheter fracture or rupture causing adhesion, perforation, migration or embolization<sup>8, 14, 36, 41, 44, 54</sup> (n=8), catheter leak causing prolonged bleeding<sup>25</sup> (n=2), catheter dislocation<sup>19</sup> (n=1), bacteremia<sup>9, 21</sup> (n=2), stuck catheter due to stenosis and thrombosis in central veins that needs to be removed by median sternotomy<sup>2</sup> (n=2), catheter caused central venous injury with massive hemothorax requiring thoracotomy<sup>48</sup> (n=1), esophageal varices due to superior vena cava obstruction<sup>24</sup> (n=1). One paper<sup>20</sup> reported a large squamous cell carcinoma in situ at the exit site of prior IHC in a liver transplant patient with end-stage renal disease, probably due to the patient's immunosuppression condition and the scar at the exit site of the IHC. Fifteen of the 18 cases reported were women. All complications were resolved without significant consequences.

### Assessment and Critique:

Most of the complications presented in the case series and reports resulted from catheter malfunction or catheter-related infection. While case reports provided detailed information of often uncommon complications related with device use, no rates can be estimated and the results cannot be generalized beyond the context of the case to a larger population of patients.

## 6.1.5 Conclusions

Studies published since 2000 indicated that although the placement of IHC is generally a technically successful procedure in all ages and appropriate blood flow rate can be achieved at the time of catheter insertion, the catheter patency rate and device survival decrease significantly over time due to catheter-related complications. Catheter-related infections, thrombosis and device malfunction remain the most common complications with IHC use.

This literature review has some limitations. First, the review does not include relevant data published before 2000. Second, as we restricted our evaluation to the data presented in the papers, the publication bias and bias arising from selective reporting of study findings in a publication cannot be ruled out from the review. Finally, we did not attempt a meta-analysis to develop estimates based on the aggregation of poolable study data.

## 6.2 Adverse Events Associated with Implanted Blood Access Devices

### 6.2.1 FDA MAUDE Search Methodology

Medical Device Reporting (MDR) is the mechanism for the FDA to receive significant medical device adverse events from manufacturers, importers and user facilities. Information is gathered via the use of prespecified codes (patient or device problem codes) as well as a user narrative of the event. This search was conducted to identify the types of adverse events reported for implanted blood access devices. Multiple queries were created to identify all relevant MDRs from the Manufacturer and User Facility Device Experience (MAUDE) Database. The searches were run by product code and date entered. The search was limited to reports received between January 1, 1998 and March

24, 2013 in order to have 15 years of MDR data to assess any trends over time, especially since the clinical use of some of the implanted blood access devices has declined in more recent years. Additionally, FDA changed product code practices in 1998, using primarily “MSD” instead of insertion-site specific product codes.

A total of 4,796 unique MDRs were found related to the product codes associated with implanted blood access devices, as shown in Table 5. The reports are separated by product codes. These searches resulted in 18 reports under FIQ, 1,413 reports under LFJ, 3,339 reports under MSD, and 26 reports under NYU. No reports were found for procodes FKW during the 1998 to 2013 time period.

**Table 5: Product codes assigned to implanted blood access devices for hemodialysis.**

<b>Product Code</b>	<b>Name</b>
<b>FIQ</b>	A-V Shunt Cannula
<b>FKW</b>	Vessel Tip
<b>LFJ*</b>	Subclavian Catheter
<b>MSD</b>	Implanted Hemodialysis Catheter
<b>NYU</b>	Implanted Coated Hemodialysis Catheter

*\*Note: Product codes for implanted catheters were initially based on insertion site. The first marketed catheters were inserted into the subclavian vein, although this insertion site later fell out of favor when it was discovered that the internal jugular insertion site was associated with fewer complications. FDA started using a product code (MSD) that was not site-specific around 1997.*

## **6.2.2 Results: Adverse Event Information**

As shown in Table 6, the majority of reports over the 1998 to 2013 time period were reported under procodes MSD and LFJ. The NYU procode consists of two catheters which were cleared by FDA in 2006 and 2011. From 2006 to 2013 only 26 reports on NYU devices have been received by FDA. Since these two catheters have been on the market for seven and just two years, respectively, and due to the limited number of reports received so far, little insight can be offered regarding long term trends associated with the use of Implanted Coated Hemodialysis catheters.

The FIQ procode encompasses A-V shunt cannulas and the last report received under this procode was in 2008. The market for these devices has declined with the development of new catheters covered under procode MSD as well as the more frequent use of arteriovenous grafts and arteriovenous fistulae. Therefore, the relevance of the MDR data for this procode to the proposal for down-classification of implanted blood access devices for hemodialysis, is minimal.

Key patient problem codes associated with FDA’s described risks to health were identified and included the following: thrombus / thrombosis, bleeding, blood loss, exsanguination and hemorrhage. It should also be noted that the numbers presented below are based on the MDRs individually reviewed which represents approximately a 15% sample of the reports under MSD and LFJ. The results are summarized in Table 6.

**Table 6: Summary of 10 Adverse Event Categories based on the “Risks to Health” identified in Section 7 and the number of MDRs associated with each group per product code**

Group	Risk to Health	MSD*	LFJ*	NYU	FIQ
		Catheter, Hemodialysis, Implanted	Catheter, Subclavian	Catheter, Hemodialysis, Implanted, Coated	A-V Shunt Cannula
1. Thrombosis	1. Thrombosis in Patient and Catheter	7	6	1	3
2. Allergy	2. Adverse Tissue Reaction	1	0	0	2
3. Infection	3. Infection and Pyrogen Reactions	58	4	0	3
4. Break	4. Device Failure	120	98	15	1
5. Leak		115	49	6	5
6. Vascular Injury	5. Cardiac Arrhythmia, Hemorrhage, Embolism, Nerve Injury, Vessel Perforation	12	10	0	0
7. Placement		26	5	0	0
8. Hemolysis	6. Hemolysis	0	0	0	0
9. Dislodgement	7. Accidental Withdrawal or Catheter Migration	80	35	4	0
10. Other		49	14	0	4
<b>TOTAL</b>		468	221	26	18

*\*Note: The number of MDRs represents the total number of MDRs in each procode for the 1998 to 2013 time period. For procodes MSD and LFJ, it is restated that an approximate 15% sampling of MDRs was reviewed for these products.*

For several of the risks identified, there were notable trends in the data while others were relatively flat. For thrombosis, the majority of the reports involved thrombosis within the catheter as opposed to the vasculature. A minimal number of reports were observed in the 15% sampling and no peaks were present in the adverse event profile. Regarding infection, following 2002, the number of infection reports experienced a sharp drop-off. This is likely related to “best practices” identified by clinical practice guidelines as well as other national initiatives and surveillance efforts established as efforts to prevent intravascular catheter-related infections.

Adverse events falling under the risk to health of “device failure” are the substantial contributor to the increased volume of malfunction reports since 2007 observed under the MSD procode, as shown in Figure 4. These events are further broken down into breaks, dislodgement, and leaks. The number of breaks reported under MSD in recent years is similar to the number reported in the early 2000’s. Based on the 15% sampling, the number of breaks reported under LFJ experienced a substantial drop-off following 2000. The number of adverse events relating to dislodgement peaked in the 1998 to 1999 time period and decreased in the early 2000’s. While the number of reports under LFJ remained minimal, the number of reports under MSD almost quadrupled from 2008 to 2012. Upon further investigation into this increase, it was noted that the devices were returned to the manufacturers, but 81% of the time the complaint could not be confirmed. For leaks, again, the adverse event profiles differed between the MSD and LFJ devices. The number of leaks reported in the 15% sampling under MSD was found to increase from 2007 (3

reports) to 2012 (25 reports) whereas under LFJ, the number of reports remained at eight or less for the entire 15 year time period.

While a number of reports are still being received by FDA under MSD regarding the device failures described above, the data suggests that several manufacturers have reacted to the reports of these failures by implementing corrective actions and/or recalls to improve the safety and effectiveness of the affected devices in the post-market environment. The review of the reports and the Recall Enterprise Database demonstrated that the majority of the 13 recalls under MSD have occurred since 2008 and were identified as either Class II or Class III recalls. These classes of recalls are less severe, and indicate that use of the product may cause temporary or medically reversible adverse health consequences or the probability of serious adverse health consequences is remote (Class II) or that use of the product is not likely to cause adverse health consequences (Class III). These recalls addressed reported issues of detached catheter cuffs, tunneler sleeve breakages, tip breakages, and luer connector separations as well as other packaging and labeling issues associated with the use of these devices. There was a single Class I recall in 2011 which addressed breakages and/or separations of the stylet within the catheter. Class I recalls are more serious and reflect a situation in which there is a reasonable probability that the use of, or exposure to, the product will cause serious adverse health consequences or death.

While the reports relating to “vascular injury” were minimal compared to the numbers reported under the “device failure” risk to health category, these reports were typically associated with serious injuries or deaths.

The overall volume of reports received under the MSD procode has not decreased over the 1998 to 2013 time period. This can be seen in Figure 4(A). While the number of injury reports has substantially decreased since the early 2000’s, the number of malfunctions has increased. Early in the time period, top patient problem codes included surgical procedures, mainly device explants/removals, and infections. The increased number of malfunctions in the last 3-4 years (2009-2012) is characterized by three major device failures: breaks, dislodgements, and leaks. Therefore, although the seriousness of the events has declined, these results do not clearly demonstrate an overall change in the number of adverse events reported over the past 15 years.

The LFJ product code demonstrated a different adverse event report profile over the 1998 to 2013 time period. This can be seen in Figure 4(B). For this procode, the volume of reports has decreased since the early 2000’s and has remained less than 40 reports per year for the past 5 years. However, this decrease could have been influenced by factors other than a decrease in adverse events, such as changes in market conditions or shifting in hospital practices to devices included under MSD.

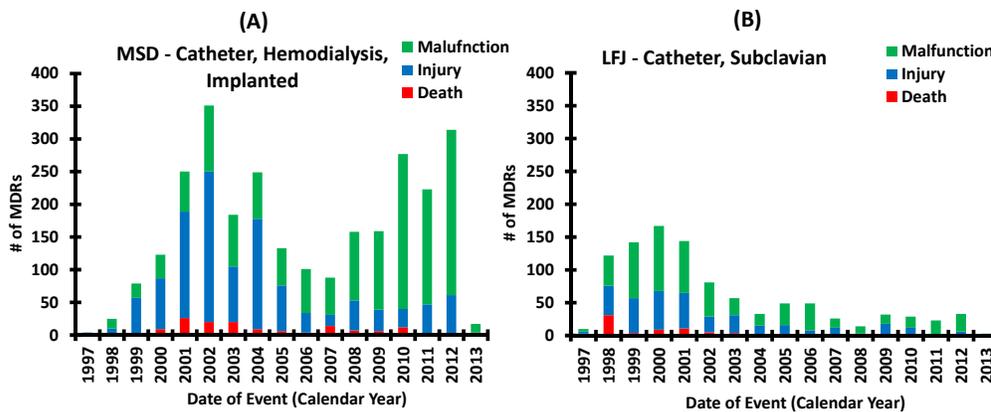


Figure 4: Number of adverse events per year under the procodes MSD (A) and LFJ (B).

### 6.2.3 Results: Summary

From 2006 to 2013, only 26 reports on NYU devices have been received by FDA. Since the two devices cleared under this product code have been on the market for seven and just two years, respectively, and due to the limited number of reports received so far, no conclusions regarding their long-term behavior can be made. Similarly, the FIQ procode encompasses the A-V shunt cannulas, and the last report received in MAUDE under this procode was in 2008. The market for these devices has declined with the development of new catheters covered under procode MSD.

The majority of adverse event reports received by FDA over the 1998 to 2013 time period were reported under procodes MSD and LFJ. The small number of reports received under NYU and FIQ provide minimal insight into the long-term behavior of implanted blood access devices for hemodialysis because devices under NYU are relatively new to the market and there has been a decline in clinical use of devices under FIQ. The overall volume of reports received under the LFJ procode has substantially decreased since 2000. Reasons for this include less frequent use of the subclavian vein insertion site over time by clinicians and the development of product codes by the FDA that were not insertion-site specific in the late 1990s. While the volume of reports received under the MSD procode still remains around the same level as it did in 2000, and warrants continued monitoring for any assignable causes detected by the manufacturer(s), and/or FDA through its various enforcement and surveillance mechanisms, the severity associated with the reports has substantially decreased. The increase in malfunction reports are attributed to device breaks, dislodgements and leaks that fall under the device failure risk to health group. While these events have some potential for patient injury, the experiences reflected in the reports received to date have shown the actual impact to be very limited. Individual review of the adverse event reports demonstrated that in relation to certain reported events, manufacturers have identified causes of the reported device problems and have taken actions and/or recalls intended to address device malfunctions.

Therefore, review of the MDR data does not seem to raise any new areas of concern associated with the use of these devices which has not been captured in the “Risk to Health” categories as summarized in Section 7. Further, FDA believes that these risks to health can be appropriately mitigated by the special controls proposed by FDA as

discussed in Section 8. There does not appear to be any basis identified through a systematic review of the MDR database against the down-classification from Class III to Class II (special controls) of implanted blood access devices for hemodialysis.

### 6.3 Clinical Summary

Hemodialysis is a treatment for kidney failure or end-stage renal disease (ESRD). When the kidneys have failed or are no longer working effectively, toxins, fluid, and metabolic wastes can build up in the blood. Hemodialysis can be used to remove these substances from the blood, but requires the presence of a vascular access so that circulating blood can be removed, filtered, and returned to the body.

There are three main types of vascular access for hemodialysis: the arteriovenous fistula (AVF), the arteriovenous graft (AVG), and the central venous catheter (CVC). The AVF and AVG are both formed by the surgical creation of a direct connection of a patient's artery and vein. The AVF uses a patient's native vein to make this connection, and the AVG uses a prosthetic conduit. An AVF has no implanted device component and is not regulated by FDA. AVGs (vascular graft prostheses) are not subject to this proposed reclassification, and are currently regulated as Class II (special controls) medical devices under 21 CFR 870.3450. CVCs used for hemodialysis have many variations, but are basically hollow plastic tubes which are placed into a large central vein. Nonimplanted (short-term) CVCs for hemodialysis are currently regulated under 21 CFR 876.5540(b)(2) as Class II, and implanted (long-term) CVCs are the subject of this proposed reclassification.

Each type of vascular access for hemodialysis has advantages and disadvantages, but current clinical practice guidelines recommend the use of an AVF, given that they last longer and have a lower complication rate than other types of vascular access. Use of catheters as the first choice for long-term vascular access is discouraged because of infection, susceptibility to thrombosis, and inconsistent delivery of blood flow.<sup>58</sup> Because of the risks associated with CVCs, there has been an increased use of AVF in recent years with 67% and 20% of prevalent hemodialysis using an AVF or AVG, respectively as of 2011.<sup>59</sup>

While current clinical practice guidelines recommend avoiding long-term catheters if possible, they are still a necessary treatment option, and are used in a significant number of hemodialysis patients. Using data collected by the ESRD Networks, 79,590 patients used a CVC for their initial vascular access for hemodialysis, which is 81% of all patients who started on dialysis in 2011. Additionally, among the 376,957 prevalent hemodialysis patients for which data were available, 20% of patients used a catheter for dialysis and 7.6% had been using a CVC for  $\geq 90$  days.<sup>59</sup>

While the risks are frequently cited, there are many advantages of CVCs, which leads to their relatively frequent use as described above. In many cases, vascular access for hemodialysis is needed urgently, and AVG and AVF require weeks and months, respectively, before they can be used. CVCs are frequently used as the immediate hemodialysis vascular access and also as a bridge to a more permanent vascular access. Additionally, some patients may have inadequate vascular anatomy to establish a more permanent vascular access and may require continued CVC use.

Of note, the arteriovenous (A-V) shunt cannula (with vessel tips), while rarely used in clinical practice in the US, remains a part of the regulatory classification under review by this advisory panel. Interestingly, the A-V shunt was the first vascular access used for hemodialysis, and was first described in 1960.<sup>60</sup> Like CVCs, A-V Shunts were prone to thrombosis, infection, and dislodgement, and their use became less frequent in the late 1970s and early 1980s as CVCs came into favor for temporary hemodialysis access.<sup>61</sup> FDA believes that the well-described risks to health associated with implanted CVCs are also relevant for the A-V shunt cannulae. While the last MDR adverse event reported for an A-V Shunt cannula was received in 2008, the types of adverse events for A-V shunt cannulae are similar to other implanted blood access devices as seen in Table 6 (Section 6.2.2). Because the risk categories are similar, FDA believes that the proposed Special Controls would be relevant for A-V shunt cannulae, and could be used to help provide a reasonable assurance of safety and effectiveness in the unlikely event that there was resurgence in their clinical use.

In summary, while implanted blood access devices are not the optimal vascular access for hemodialysis, they are still a necessary treatment option and are used in a significant number of hemodialysis patients. The risks associated with these devices are well-described in the medical literature. FDA believes that the proposed Special Controls would be sufficient to mitigate these risks and proposes the reclassification of implanted blood access devices for hemodialysis from class III to class II.

## 7 Discussion of Risks to Health

FDA has identified the following risks to health for implanted blood access devices for hemodialysis [as included within 21 CFR 876.5540(a)(1)] based on the input of the original classification panel on January 23, 1981, review of industry responses to the April 9, 2009 515(i) order and the June 20, 2012 proposed rule, review of marketing applications, the Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review:

- Thrombosis in patient and catheter, catheter occlusion, or central venous stenosis. Inadequate blood compatibility of the materials used in this device, blood pooling between dialysis sessions, or turbulent blood pathways could lead to potentially debilitating or fatal thromboembolism.
- Adverse tissue reaction. Inadequate tissue compatibility of the materials used in this device could cause an immune reaction.
- Infection and pyrogen reactions. An improperly sterilized device could cause a skin or bloodstream infection.
- Device failure. Weakness of connections or materials could lead to blood loss or device fragment embolization.
- Cardiac arrhythmia, hemorrhage, embolism, nerve injury, or vessel perforation. Improper placement into the heart or blood vessel could damage tissues and result in injuries.
- Hemolysis. Turbulence or high pressure created by narrow openings or changes in blood flow paths could cause the destruction of red blood cells.

- Accidental withdrawal or catheter migration. A catheter's cuff may not allow adequate ingrowth from the surrounding subcutaneous tissue, which could cause the device to dislodge or fall out with subsequent blood loss.

It should be noted that there are some modifications to the risks to health that are identified as part of this Summary in comparison to those previously identified as part of the proposed rule (77 FR 36951). The updated list presents a more comprehensive list.

*The panel will specifically be requested to comment on the risks to health identified by FDA and whether these risks are appropriate, and/or whether there are additional risks to health that should be considered for these devices.*

## **8 Mitigation of Risks to Health/Proposed Special Controls**

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified in Section 7 above, and provide reasonable assurance of the safety and effectiveness of implanted blood access devices for hemodialysis.

When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health. Hence, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness of implantable blood access devices for hemodialysis:

- (1) Components of the device that come into human contact must be demonstrated to be biocompatible. Material names and specific designation numbers must be provided.
- (2) Performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
  - 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.
  - 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.
  - c. Priming volumes must be established.
  - d. Tensile testing of joints and materials must be conducted. The minimum acceptance criteria must be adequate for its intended use.
  - e. Air leakage testing and liquid leakage testing must be conducted.

- 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.
  - g. Mechanical hemolysis testing must be conducted.
  - h. Chemical tolerance of the catheter to repeated exposure to commonly used disinfection agents must be established.
- (3) Performance data must demonstrate the sterility of the device.
- (4) Performance data 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.
- (5) Labeling must bear all information required for the safe and effective use of implanted blood access devices for hemodialysis including the following:
- a. Labeling must provide arterial and venous pressure versus flow rates, either in tabular or graphical format.
  - b. Labeling must provide the arterial and venous priming volumes.
  - c. Labeling must specify the forward and reverse recirculation rates.
  - d. Labeling must specify an expiration date.
  - e. Labeling must identify any disinfecting agents that cannot be used to clean any components of the device.
  - f. Any contraindicated disinfecting agents due to material incompatibility must be identified by printing a warning on the catheter. Alternatively a label can be provided that can be affixed to the patient's medical record with this information.
  - g. The labeling must contain the following information: comprehensive instructions for the preparation and insertion of the hemodialysis catheter, including recommended site of insertion, method of insertion, a reference on the proper location for tip placement, a method for removal of the catheter, anticoagulation, guidance for management of obstruction and thrombus formation, and site care.
  - h. The labeling must identify any coatings or additives and summarize the results of performance testing for any coating or material with special characteristics, such as decreased thrombus formation or antimicrobial properties.
- (6) For subcutaneous devices, the recommended type of needle for access must be described, stated in the labeling, and test results on repeated use of the ports must be provided.

- (7) Coated devices must include a description of the coating or additive material, duration of effectiveness, how the coating is applied, and testing to adequately demonstrate the performance of the coating.

*If the panel believes that Class II is appropriate for implantable blood access devices for hemodialysis, the panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.*

## 9 Device Classification

For the purposes of classification (see the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. the persons for whose use the device is represented or intended;
2. the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. the reliability of the device.

Part (g)(1) of this regulation further states that it “is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III.”

### **Reasonable Assurance of Safety**

According to 21 CFR 860.7(d)(1), “There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.”

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury.

### **Reasonable Assurance of Effectiveness**

According to 21 CFR 860.7(e)(1), “There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

### **Summary**

FDA believes that the available evidence supports a reasonable assurance of safety and effectiveness, the proposed special controls, in addition to general controls, would be sufficient to provide such assurance, and there is not an unreasonable risk of illness or injury for implanted blood access devices.

Consequently, FDA recommends that implanted blood access devices for hemodialysis under regulation 21 CFR 876.5540 subpart (a)(1) be reclassified to Class II (Special Controls).

***The panel will be asked to discuss the proposed device classification as well as discuss whether the proposed Special Controls are adequate to support downclassification of implanted blood access devices for hemodialysis from Class III to Class II.***

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