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AdvaMed

Advanced Medical Technology Association

July 7, 2000

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BY HAND

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857-1706

RE: Docket No. 99N-0035 - Reclassification of 38
Preamendments Class III Devices into Class II

Dear Sir or Madam:

The following comments are submitted on behalf of the Vascular Grafts Reclassification Task Force of the Health Industry Manufacturers Association ("HIMA Task Force" or "Task Force") in response to the above-referenced proposed rulemaking. (65 Fed. Reg. 20933, April 19, 2000).¹ The Task Force is comprised of C.R. Bard, Inc. and W.L. Gore, Inc.

The comments are particular to vascular grafts of less than 6 mm in diameter ("small diameter vascular grafts.") In addition to providing relevant background information, the following addresses three separate issues: (1) the need to amend the classification regulation defining vascular grafts subject to Class II special controls; (2) comments regarding the "Guidance Document for Vascular Prostheses 510(k) Submissions"; and (3) whether vascular grafts of animal origin, and instruments, tools and devices used by physicians to create vascular graft prostheses, should be reclassified to Class II.

I. Summary

The HIMA Task Force agrees with FDA's proposal to reclassify small diameter vascular grafts and appreciates the agency's efforts in this regard. With the exception of certain

¹ Effective June 21, 2000, HIMA changed its name to the Advanced Medical Technology Association ("AdvaMed"). In the text of this document, we have retained the term HIMA for consistency with the name that was used in our original petition to reclassify vascular grafts.

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clarifications, the Task Force concurs with FDA's "Guidance Document for Vascular Prostheses 510(k) Submissions". However, it is critical that the classification regulation appearing in the Code of Federal Regulations be amended to accurately reflect the type of grafts and indications covered by the reclassification. Amendment of the regulation is necessary because the "Guidance Document for Vascular Graft Prostheses 510(k) Submissions" -- which provides certain information identifying the grafts covered by the reclassification -- is not binding and is thus subject to change.

Comments were filed in response to FDA's proposed rulemaking by a company (not affiliated with the HIMA Task Force) requesting reclassification of vascular grafts of "other synthetic materials", grafts made of human and animal tissue, and "instruments, tools, and devices used by physicians to create vascular graft prosthesis". Grafts made of human and animal tissue should remain in Class III in that biologics grafts are excluded from the current classification regulation and, thus, cannot be subject to reclassification. "Instruments, tools and devices" used to create vascular grafts are also not subject to the classification regulation. In addition, the comments filed with the agency regarding biologics grafts and "instruments, tools and devices" do not provide sufficient information to meet the statutory standard for reclassification.

II. Relevant Background

A. Law

The Safe Medical Devices Act ("SMDA") added section 512(i) (21 U.S.C. § 360e(i)) to the Food, Drug and Cosmetic Act ("FDCA"). This section required FDA to issue an order requiring manufacturers of certain preamendments and postamendments devices to submit safety and effectiveness information regarding these devices. 21 U.S.C. § 360e(i)(1). The SMDA also directed FDA to revise the classification of these devices into Class I or Class II or retain them in Class III and, thereafter, require submission of a PMA. 21 U.S.C. §§ 360(e)(2); 360(e)(3).

B. Reclassification Petition

In response to the requirement for submission of safety and effectiveness information, the HIMA Task Force submitted a reclassification petition to FDA on August 14, 1997 which requested reclassification of small diameter vascular grafts from Class III to Class II.² The

² According to FDA's regulations, "a vascular graft prosthesis of less than 6 millimeters ("mm") diameter is a device used to replace sections of small arteries. This prosthesis is commonly constructed of woven or knitted materials such as polyethylene terephthalate and polytetrafluoroethylene and is not made of materials of animal origin, including human umbilical cords." 21 C.F.R. § 870.3450

reclassification petition specifically sought reclassification of small diameter polytetrafluoroethylene ("PTFE") and polyester grafts, as well as new materials that may be developed in the future (e.g., biologic or synthetic coatings). (The petition did not request any agency action regarding grafts made of animal origin, including human umbilical cords.) The reclassification petition specifically noted that reclassification was not requested for coronary artery bypass or cerebral revascularization indications, but that reclassification was sought for every indication other than those expressly excluded.

In addition, the reclassification petition discussed the fact that some vascular grafts, when used for vascular access, may have been considered by FDA to be Class III devices under 21 C.F.R. § 876.5540(b)(1) (blood access device and accessories). Considering this, the petition requested clarification that such vascular grafts used for vascular access are devices included within the classification regulations for vascular grafts (currently 21 C.F.R. §§ 870.3450 and 870.3460) and that they be considered to be part of the reclassification petition.

Per FDA's request, the Task Force's reclassification petition included information about large diameter vascular grafts since this information is relevant to evaluating small diameter grafts in that all synthetic grafts, regardless of diameter, are used for similar purposes, in similar tissue beds, with similar patient populations, etc. As discussed in the reclassification petition, the scientific literature, medical device reports ("MDRs") and complaints, and general clinical experience with small diameter vascular grafts since 1980 have demonstrated that small diameter vascular grafts are as safe and effective as Class II large diameter vascular grafts, and that the comparable risks presented by these products can be adequately addressed through a combination of general and special controls that were proposed in the reclassification petition.

Considering the above, the Task Force proposed that FDA promulgate a new classification regulation (to replace 21 C.F.R. §§ 870.3450 and 870.3460) that covers *both* small and large diameter grafts as follows:

§ 870. [] Vascular graft prosthesis. (a) *Identification*. A vascular graft prosthesis is an implanted device used to repair, replace, or bypass sections of native or artificial vessels and/or to provide vascular access. This prosthesis is commonly constructed of materials such as polyethylene terephthalate and polytetrafluoroethylene and may include biological or synthetic coatings (e.g., albumin or collagen). The graft structure itself is not made of materials of animal origin, including human umbilical cords. (b) *Classification*. Class II (special controls). Vascular grafts intended for coronary artery bypass or cerebral revascularization are Class III (premarket approval).

C. Proposed Rulemaking

In a March 15, 1999 Federal Register notice, FDA proposed to reclassify 38 preamendments Class III devices into Class II (special controls). 64 Fed. Reg. 12774. This proposal was based on new information regarding the devices. Id. at 12776. The 38 devices proposed for reclassification included small diameter vascular grafts.

As noted by FDA, the Federal Register notice “focuses on the special controls, explains the types of risks to health addressed by the special controls, and identifies the devices to which the special controls apply”. Id. Consistent with this description, the Federal Register notice specified three special controls that would be applicable to small diameter vascular grafts: biocompatibility guidance; sterility guidance; and a “Document for Special Controls for Vascular Prosthesis 510(k) Submissions” (“Special Controls Guidance Document” or “Guidance Document”).³ The Federal Register notice also proposed amending the § 870.3450 classification regulation to reflect Class II status and to list the three special controls documents noted above. The Federal Register notice did not include any other discussion regarding small diameter vascular grafts.

D. Guidance Document for Vascular Prostheses 510(k) Submissions

FDA issued the above-referenced Special Controls Guidance Document on November 26, 1999. The Guidance Document states that it is applicable to *both* small diameter vascular grafts and vascular graft prostheses of 6 millimeters and greater diameter. Guidance Document at p. 1. The Guidance Document also specifies that it is applicable to vascular grafts that are intended for vascular access, and that vascular grafts intended for coronary and neurovasculature uses are excluded. Id. The special controls document does not address the issue of what graft materials are subject to the Guidance, nor does it specify that all indications, but for those intended for coronary and neurovasculature use, are considered to be Class II indications.

The bulk of the Special Controls Guidance Document is the tabular summary of the risks associated with use of the device and the corresponding special controls that address each risk. Id. at pp. 3-10. In the context of this table of risks and corresponding controls, the Guidance Document notes that the risks associated with large and small diameter vascular grafts and vascular access grafts are generally the same and that most of the special and general controls apply equally to all vascular grafts. Id. at pg. 3.

Consistent with current FDA practice, it is noted that the Guidance Document:

is intended to provide guidance. It represents the Agency’s current thinking It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An

³ According to the Federal Register notice, the agency believes that the information contained in the Special Controls Guidance Document is adequate to address the identified risks to health and thus that it be a special control for small diameter vascular grafts. As noted in FDA’s April 19, 2000 Federal Register notice (which is discussed below), the proposed Special Controls Guidance Document relating to small diameter vascular grafts was not available for comment when the proposed rule was published. Pursuant to comments submitted by HIMA, the agency extended the comment period to July 18, 2000 for certain devices including small diameter grafts.

alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Id. at pg. 1.

E. Comments Submitted in Response to FDA's Proposed Rulemaking

On June 18, 1999, comments were submitted by Ramus Medical Technologies in response to FDA's March 15, 1999 Federal Register notice proposing reclassification of 38 preamendments Class III devices. The comments focused on small diameter vascular grafts, and proposed, among other things, to downclassify grafts made of human and animal tissue ("biologics grafts") that are "shown to be suitable" for vascular graft prostheses and "instruments, tools and other devices" that are used by physicians to create vascular graft prostheses.

F. Comment Period Reopened

FDA published a Federal Register notice on April 19, 2000 reopening the comment period regarding reclassification of several devices including small diameter vascular grafts.⁴

III. Discussion

A. The Classification Regulation Must be Amended

Consistent with the HIMA Task Force's reclassification petition, the "Guidance Document for Vascular Prostheses 510(k) Submissions" states, in the introductory paragraph, that the document is applicable to vascular grafts intended for vascular access and that vascular grafts intended for coronary and neurovasculature are excluded. While this descriptive

⁴ Note that FDA's April 19, 2000 Federal Register notice indicates, at one point, that the opportunity is given in order to submit comments regarding the various guidance documents. It is important to clarify here that the comment period has been reopened with regard to FDA's proposed rule to reclassify these devices (March 15, 1999 Federal Register notice) which includes, by reference, the special controls documents. (See letter (undated) from Linda Kahan, (Deputy Director for Policy, Center for Devices and Radiological Health) to Marlene K. Tandy, (Director Technology and Regulatory Affairs and Associate General Counsel, HIMA) confirming the above. See also June 14, 1999 letter from Marlene K. Tandy to Dockets Management Branch (Docket No. 99N-0035) reserving HIMA's right to comment on both the proposed rule to reclassify the six devices at issue and the guidance documents/special controls for these devices.

information is helpful in order to place the risks and accompanying special controls in the appropriate context, an accurate characterization of the type of devices that fall within the Class II designation is absent from the classification regulation itself -- where, as discussed below, it properly belongs.

1. The Distinction Between Regulations and Guidance Documents

Properly promulgated regulations have the force of law, and bind federal agencies as well as other affected persons. See e.g., Atkins v. Rivera, 477 U.S. 154, 163 (1986) (quoting Batterton v. Francis, 432 U.S. 416, 425-426) (regulations "supported by the plain language of the statute and adopted pursuant to the explicit grant of rulemaking authority" are "entitled to more than mere deference or weight" but, rather, are entitled to "legislative effect.") In contrast to regulations, FDA's "Good Guidance Practices" document notes that:⁵

[t]he purposes of guidance documents are to: (1) Provide assistance to the regulated industry by clarifying requirements that have been imposed by Congress or issued in regulations by FDA and by explaining how industry may comply with those statutory and regulatory requirements and (2) provide specific review and enforcement approaches to help ensure that FDA's employees implement the agency's mandate in an effective, fair, and consistent manner.... Other [guidance documents] explain FDA's view on how one may comply with the relevant statutes and regulations.... Id. at 8967.... [Guidance documents] explain how the agency believes the statutes and regulations apply to certain regulated activities. Id.

Guidance documents do not themselves establish legally enforceable rights or responsibilities and are not legally binding on the public or the agency. Id.

If a member of the public wishes to propose one or more topics for new guidance or guidance revisions or to propose one or more draft guidance documents for adoption by FDA, that person should submit the proposal to the Centers or Offices with responsibility

⁵ FDA published a document entitled "Good Guidance Practices" ("GGPs") on February 27, 1997. 62 Fed. Reg. 8961, 8967-72. This GGP document sets forth the agency's policies and procedures for the development, issuance, and use of guidance documents.

for overseeing the regulatory activity to which the guidance document would apply. *Id.* at 8967-68.⁶

Based on the above, it seems clear that the "Guidance Document for Vascular Prostheses 510(k) Submissions" should not independently set forth critical information characterizing Class II devices that should, instead, be established by regulation. Also, while it is true that special controls guidance documents -- including the one for vascular grafts -- should be subject to updating or other revisions, characterization of the *type of device* that is subject to reclassification to Class II should not, and cannot, be a "moving target" that would be subject to "comments and suggestions" made regarding the guidance document.⁷ Rather, such characterization must be accurately portrayed in a classification regulation that would be changed only by rulemaking under circumstances where there is new information sufficient to meet the statutory standard for reclassification.

2. The Amended Classification Regulation Must Identify the Type of Device That Meets the Statutory Criteria for Class II.

Section 515(i)(2) of the FDCA provides that "in determining whether to revise the classification of [a] device ... the Secretary shall apply the criteria set forth in section 513(a)". 21 U.S.C. § 360e(i)(2). In relevant part, Section 513(a) states that a Class II device is one "for which there is sufficient information to establish special controls to provide [reasonable assurance of the safety and effectiveness of the device] including the ... development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with Section 510(k))...." 21 U.S.C. § 360c(a)(1)(B).

FDA's March 15, 1999 Federal Register proposed rulemaking states that the agency's proposal to reclassify small diameter vascular grafts is based on "new information."⁸ We assume that this "new information" reflects the very comprehensive data and analysis submitted by the

⁶ The above theme is reiterated in FDA's March 15, 1999 Federal Register notice of proposed rulemaking which notes that FDA guidances are periodically updated as new information becomes available. 64 Fed. Reg. at 12777.

⁷ Note that the "Preface" to the "Guidance Document for Vascular Prostheses 510(k) Submissions" states that "Comments and suggestions may be submitted at any time for Agency consideration.... Comments may not be acted upon by the Agency until the document is next revised or updated."

⁸ As noted in FDA's August 14, 1995 Federal Register notice ("Order for Certain Class III Devices; Submission of Safety and Effectiveness Information") information provided by companies in response to FDA's order for submission of safety and effectiveness will enable FDA to promptly "begin the process established by Section 515(i) of the act to either revise or sustain the current classification of these devices." 60 Fed. Reg. 41985.

HIMA Task Force in its reclassification petition.⁹ Considering the statutory mandate that a device can only be downclassified where there is sufficient information to establish special controls to provide reasonable assurance of the device's safety and effectiveness, and assuming that the agency's reclassification decision is based on information in the HIMA Task Force's reclassification petition, the classification regulation *must* reflect the device characteristics and indications discussed in that reclassification petition.

3. How and Why the Classification Regulation Should be Amended

As noted above, the HIMA Task Force's reclassification petition proposed a new classification regulation covering small and large diameter vascular grafts that would replace 21 C.F.R. §§ 870.3450 and 870.3460. That language reads as follows:

§ 870. [] Vascular graft prosthesis. (a) *Identification*. A vascular graft prosthesis is an implanted device used to repair, replace, or bypass sections of native or artificial vessels and/or to provide vascular access. This prosthesis is commonly constructed of materials such as polyethylene terephthalate and polytetrafluoroethylene and may include biological or synthetic coatings (e.g., albumin or collagen). The graft structure itself is not made of materials of animal origin, including human umbilical cords. (b) *Classification*. Class II (special controls). Vascular grafts intended for coronary artery bypass or cerebral revascularization are Class III (premarket approval).

This proposed language should be adopted for several reasons:¹⁰ (1) it is incumbent upon FDA to revise the definition of small diameter vascular grafts to accurately reflect the type of device for which the agency has sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of that device; (2) FDA has already made the determination -- as set forth in the "Guidance Document for Vascular Prostheses 510(k) Submissions" -- that small and large diameter vascular grafts have the same risks and accompanying special controls; (3) if 21 C.F.R. § 870.3450 (small diameter vascular grafts) is amended and § 870.3460 (larger diameter vascular grafts) is not amended, there will be a confusing discrepancy between the two regulations; (4) there is nothing that should prohibit FDA

⁹ Per the administrative record, there were no other comments filed with the agency regarding small diameter vascular grafts prior to issuance of FDA's March 15, 1999 proposed rulemaking. The HIMA Task Force's reclassification petition was comprised of 12 volumes (volumes 3 through 12 included nearly 500 articles and abstracts regarding small and large diameter vascular grafts that were summarized in the body of the document).

¹⁰ For purposes of clarity, the HIMA Task Force proposes at this time to revise the above definition slightly by adding an example of a synthetic coating. The revised language would read as follows "... may include biological or synthetic coatings (e.g., albumin, collagen or silicone)."

from making a technical amendment to § 870.3460 in the course of this rulemaking;¹¹ and (5) FDA should take the given opportunity (particularly considering the arduous and slow nature of rulemaking) to revise the regulations at this time to accurately reflect the characteristics of vascular grafts subject to Class II controls.¹²

4. The Preamble of FDA's Final Rule Should Explain FDA's Decisionmaking.

According to FDA's General Administrative Procedures regulations, any final rule published in the Federal Register must have a preamble, including supplementary information about the regulation, that contains references to prior notices relating to the same matter and a summary of each type of comment submitted on the proposal and the Commissioner's conclusions with respect to each. 21 C.F.R. § 10.40(c)(3). The regulations further note that the preamble is to contain a thorough and comprehensive explanation of the reasons for FDA's decision on each issue. Id.

In light of this regulation, and the above comments, it is necessary for FDA to address various issues, including the following, in its final rulemaking document: the definition of vascular grafts subject to Class II special controls; the basis for FDA's decision if the classification regulation is not amended; the basis for FDA's decision if a definition other than that proposed by the petitioner is used; and clarification regarding any other important aspect of the reclassification (e.g., that reclassification applies to all indications other than those excluded.)

B. Specific Comments Regarding the Guidance Document for Vascular Prostheses 510(k) Submissions

The HIMA Task Force is in full agreement with the substance of the "Guidance Document for Vascular Prostheses 510(k) Submissions". There are, however, certain editorial

¹¹ This is particularly true because the "Guidance Document for Vascular Prostheses 510(k) Submission" -- which covers both small diameter and large diameter vascular grafts -- is referenced in the March 15, 1999 Federal Register proposed rulemaking document and the April 19, 2000 Federal Register notice reopening the comment period. This latter notice specifically states that an opportunity is being given in order to submit comments regarding the various guidance documents.

¹² One acceptable alternative would be to keep two separate regulations (§ 870.3450 and § 870.3460) but amend the language of each during the course of this rulemaking to accurately reflect the characteristics of vascular grafts subject to Class II controls. Another alternative (albeit not an expeditious one), would be for FDA to amend § 870.3450 in the current rulemaking and amend the regulation for large diameter vascular grafts (§ 870.3460) in a separate, later rulemaking to make the language consistent with § 870.3450 and the information that is in the "Guidance Document for Vascular Prostheses 510(k) Submissions."

changes to the Guidance document that the HIMA Task Force suggests be made. See Attachment A (“redlined” version of the tabular summary of risks and special controls showing proposed changes.)

In addition, the HIMA Task Force proposes that the following language (in bold) be added to the “Introduction” section of the Guidance Document for Vascular Prostheses 510(k) Submissions in order to clarify the type of vascular grafts and indications that are covered by the guidance document:

“It also applies to vascular graft prosthesis of 6 millimeter and greater diameter. (21 C.F.R. § 870.3460). **Vascular grafts subject to this guidance are commonly constructed of materials such as polyethylene terephthalate and polytetrafluorethylene and may include biological or synthetic coatings (e.g., albumin, collagen or silicone). The graft structure itself is not made of materials of animal origin, including human umbilical cords.** It includes vascular grafts that are intended for vascular access. It excludes vascular grafts intended for coronary and neurovasculature. **This guidance is applicable to all other indications.**”

C. Comments Submitted by Ramus Medical Technology

Ramus Medical Technology (“Ramus”) submitted comments on June 18, 1999 in response to FDA’s March 15, 1999 Federal Register notice proposing reclassification of small diameter vascular grafts. Among other things, Ramus requested reclassification of biologics grafts and “instruments, tools and other devices” that are used by physicians to create vascular graft prostheses.

The current regulation for small diameter vascular grafts explicitly excludes biologics grafts i.e., “This prosthesis is commonly constructed of woven or knitted materials such as polyethylene terephthalate and polytetrafluoroethylene and is not made of materials of animal origin, including human umbilical cords.” 21 C.F.R. § 870.3450 (emphasis added). Because biologics grafts are not subject to the classification regulation, they cannot be *reclassified*. Similarly, instruments, tools and other devices used by physicians to create vascular prostheses are not subject to the classification regulation.

Also, as discussed previously, the statutory standard for reclassification to Class II requires that there be sufficient information to establish special controls to provide a reasonable assurance of safety and effectiveness of the device. 21 U.S.C. § 360c(a)(1)(B).¹³ The comments

¹³ In order to determine whether such “sufficient information” was available, FDA required that Class III manufacturers (who believed that existing information would support reclassification of their device into Class I or II) submit certain information to

submitted by Ramus Medical Technologies are brief, and do not meet this statutory standard. In addition, since there is longstanding FDA policy that accessories to devices are generally subject to the same classification as the "parent" device, "instruments, tools and other devices" used to create vascular prostheses may not even be relevant to this reclassification proceeding.

IV. Conclusion

Summarizing the above, the HIMA Task Force respectfully requests the following with regard to reclassification of small diameter vascular grafts:

- the classification regulation be amended to accurately characterize the type of devices that fall within the Class II designation for small diameter vascular grafts;
- the classification definition read as follows:

§ 870. [] Vascular graft prosthesis. (a) *Identification*. A vascular graft prosthesis is an implanted device used to repair, replace, or bypass sections of native or artificial vessels and/or to provide vascular access. This prosthesis is commonly constructed of materials such as polyethylene terephthalate and polytetrafluoroethylene and may include biological or synthetic coatings (e.g., albumin, collagen or silicone). The graft structure itself is not made of materials of animal origin, including human umbilical cords. (b) *Classification*. Class II (special controls). Vascular grafts intended for coronary artery bypass or cerebral revascularization are Class III (premarket approval).

- the preamble of FDA's final rule should explain FDA's decisionmaking;
- the Guidance Document should be revised per Attachment A to these comments; and

the agency including: device description; a summary of adverse safety and effectiveness information; identification of the risks presented by the device and the mechanisms/procedures to control these risks; and a summary of valid scientific evidence upon which the recommendation is based. 60 Fed. Reg. 41984, 41985-86 (August 14, 1995).

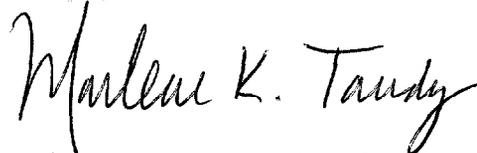
- the "Introduction" section of the Guidance Document should be revised as follows (revisions in bold):

"It also applies to vascular graft prosthesis of 6 millimeter and greater diameter. (21 C.F.R. § 870.3460). **Vascular grafts subject to this guidance are commonly constructed of materials such as polyethylene terephthalate and polytetrafluorethylene and may include biological or synthetic coatings (e.g., albumin, collagen or silicone). The graft structure itself is not made of materials of animal origin, including human umbilical cords.** It includes vascular grafts that are intended for vascular access. It excludes vascular grafts intended for coronary and neurovasculature. **This guidance is applicable to all other indications.**"

* * *

Thank you for your time and consideration of the above comments.

Sincerely,



Marlene K. Tandy, M.D., J.D.
Director Technology and Regulatory Affairs,
and Associate General Counsel

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Guidance for Industry and FDA Staff

**Guidance Document for Vascular
Prostheses 510(k) Submissions**

Document issued on: November 26, 1999



**U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Circulatory Support and Prosthetic Devices Branch
Division of Cardiovascular, Respiratory and Neurological Devices
Office of Device Evaluation**

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Dorothy B. Abel, Center for Devices and Radiological Health, HFZ-450, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Dorothy B. Abel at (301) 443-8262, extension 165 or by electronic mail at dba@cdrh.fda.gov.

Additional Copies

World Wide Web/CDRH/ home page: <http://www.fda.gov/cdrh/ode/1357.pdf>, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 1357 when prompted for the document shelf number.

Guidance¹ Document for Vascular Prostheses 510(k) Submissions

Introduction

This guidance document describes a means by which vascular graft prostheses devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate vascular graft prostheses device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

This guidance was developed as a special control to support the reclassification from class III to class II for vascular graft prostheses of less than 6 millimeters in diameter. (21 C.F.R. § 870.3450). It also applies to vascular graft prostheses of 6 millimeter and greater diameter. (21 C.F.R. § 870.3460.) It includes vascular grafts that are intended for vascular access. It excludes vascular grafts intended for coronary and neurovasculature. It includes a tabular summary of the risks associated with the use of the device and the corresponding special controls to address these risks. All manufacturers must comply with the Quality Systems Regulations; (QSR) set forth in the Code of Federal Regulations at 21 C.F.R. Part 820. QSR issues of particular significance

¹ This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

to manufacturers of permanently implantable medical devices, such as vascular grafts, include but are not limited to the following:

Overall Controls

- Management responsibility
- Design controls
- Document controls
- Purchasing controls
- Identification
- Traceability of finished and in-process devices
- Production and process controls
- Inspection, measuring and test equipment

Process Validation

- Acceptance activities
- Raw materials
- In-process and finished device acceptance
- Non-conforming product
- Corrective and preventative action
- Labeling and packaging control
- Handling and storage
- Distribution and records

It is further recommended that vascular graft manufacturers utilize relevant provisions of ANSI/AAMI VP20-1994, Cardiovascular Implants-Vascular Prostheses, where appropriate.

TABLE OF RISKS AND CORRESPONDING CONTROLS²

RISK	CONTROLS
1. Thrombosis Embolitic Events Occlusion Stenosis	<p align="center">510(k)</p> <p>Characterize the graft material in accordance with ANSI/AAMI VP20-1994, <i>Cardiovascular implants - Vascular prostheses</i> (ANSI/AAMI VP20-1994), Section 4.3 (Materials and Construction).</p>
	<p>Address the issue of biological safety in accordance with FDA guidance document Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (FDA biocompatibility guidance) and ANSI/AAMI VP20-1994, Section 4.4 (Biocompatibility and Biostability).</p>
	<p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p>
	<p>Provide a characterization of kink radius in accordance with ANSI/AAMI VP20-1994, Section 5.9 (Kink Diameter/Radius).</p>
	<p>Address the adequacy of attachment of the <u>external</u> support such that normal handling and implantation forces should not disrupt the external support, for those devices that incorporate permanent or removable external support.</p>
	<p>Address removal of the external support such that removal should not impair device integrity, for those devices that incorporate removable external support.</p>
	<p align="center">Labeling - Instructions for Use</p> <p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p>
	<p>Indicate that thrombosis, embolic events, occlusion, and stenosis are potential complications associated with the use of vascular grafts.</p>

² Because the risks associated with large and small diameter vascular grafts and vascular access grafts are generally the same, most of these special and general controls apply equally to all vascular grafts. Some special controls, such as strength testing after repeated puncture, apply solely to grafts intended for vascular access.

RISK	CONTROLS
1. Thrombosis Embolic Events Occlusion Stenosis continued	<p style="text-align: center;">Labeling - Instructions for Use</p> <p>Recommend techniques for implanting the vascular graft, e.g., tunneling (with consideration for external support, if appropriate), and methods to avoid kinking, where appropriate.</p> <p>Provide instructions, where appropriate, on how to safely perform a revision procedure in the case of occlusion.</p> <p>State that the physician should consider the need for intraoperative and postoperative patient anticoagulation therapy.</p> <p>Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p> <p style="text-align: center;">510(k)</p> <p>Conduct all appropriate tests specified in ANSI/AAMI VP20-1994, Section 5.2 (Porosity, Water Permeability, Integral Water Permeability/Leakage, and/or Water Entry Pressure).</p> <p>Conduct preclinical and/or clinical (in vivo) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through in vitro testing.</p>
2. Leakage (a) Hematoma (b) Hemorrhage (c) Blood Leakage (from failure to clot)	<p style="text-align: center;">510(k)</p> <p>Conduct all appropriate tests specified in ANSI/AAMI VP20-1994, Section 5.2 (Porosity, Water Permeability, Integral Water Permeability/Leakage, and/or Water Entry Pressure).</p>
	<p>Conduct preclinical (<i>in vivo</i>) and/or clinical evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through in vitro testing.</p>
2. Leakage (a) Hematoma (b) Hemorrhage (c) Blood Leakage (from failure to clot)	<p style="text-align: center;">Labeling - Instructions for Use</p> <p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p> <p>Provide instructions for proper pre-clotting of the graft (if applicable) and use of hemostatic agents (if applicable).</p>

State that potential complications associated with vascular grafts include leakage (which may occur in conjunction with hematoma, hemorrhage, and blood leakage from failure to clot).

Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).

RISK	CONTROLS
3. Biocompatibility Allergic Reaction	<p style="text-align: center;">510(k)</p> <p>Address the issue of biological safety in accordance with FDA biocompatibility guidance and ANSI/AAMI VP20-1994, Section 4.4 (Biocompatibility and Biostability).</p> <hr/> <p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p> <hr/> <p style="text-align: center;">Labeling - Instructions for Use</p> <p>Contraindicate device use for patients with known sensitivity to device material.</p> <hr/> <p>Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p>
4. Graft Disruption: Axillary Anastomotic Suture Line dehiscence	<p style="text-align: center;">510(k)</p> <p>Conduct testing in accordance with ANSI/AAMI VP20-1994, Sections 5.3 (Strength) and 5.8 (Suture Retention Strength).</p> <hr/> <p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p> <hr/> <p style="text-align: center;">Labeling - Instructions for Use</p> <p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p>

Discuss implantation techniques relating to product sizing; product placement; tunneling (with consideration for external support, if appropriate); and methods to avoid unduly stressing the axillary or femoral anastomoses.

Indicate that the health care provider is responsible for instructing the patient as to proper postoperative care, including limiting movement of the affected area during the convalescent period.

Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).

RISK	CONTROLS
<p>5. Seroma</p>	<p>510(k)</p> <p>Conduct all appropriate tests specified in ANSI/AAMI VP20-1994, <i>Cardiovascular implants - Vascular prostheses</i>, Section 5.2 (Porosity, Water Permeability, Integral Water Permeability/Leakage, and/or Water Entry Pressure).</p>
	<p>Labeling - Instructions for Use</p> <p>Provide adequate labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p>
	<p>State that seroma is a potential risk associated with the use of vascular grafts.</p>
	<p>Address techniques for graft handling and instrument manipulation (e.g., clamping).</p>
	<p>Provide instructions for proper implant techniques, such as tunneling (with consideration for external support, if appropriate).</p>
<p>6. False Aneurysm/ Pseudoaneurysm</p>	<p>510(k)</p> <p>Conduct testing in accordance with ANSI/AAMI VP20-1994, Section 5.8 (Suture Retention Strength).</p>
	<p>Conduct testing in accordance with ANSI/AAMI VP20-1994, Section 8.3.4 (Method for Determination of Strength After Repeated Puncture), if the indications for use include vascular access.</p>
	<p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p>
	<p>Labeling - Instructions for Use</p> <p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p>

RISK	CONTROLS
<p>6. False Aneurysm/ Pseudoaneurysm continued</p>	<p style="text-align: center;">Labeling - Instructions for Use</p> <p>Recommend product-specific techniques for implanting and revising the vascular graft, if appropriate, and <u>should</u> should indicate that care should be taken when cannulating the graft for dialysis access (e.g., avoidance of external support during cannulation, proper rotation of cannulation sites, post cannulation care such as proper compression to achieve hemostasis, etc).</p> <p>Provide appropriate instructions for graft handling and sizing (with consideration for external support, if appropriate, and potential arterial steal syndrome, if appropriate).</p> <p>Indicate that the health care provider is responsible for instructing the patient as to proper postoperative care.</p> <p>Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p>
<p>7. True Aneurysm/ Dilatation</p>	<p style="text-align: center;">510(k)</p> <p>Conduct testing in accordance with ANSI/AAMI VP20-1994, Section 4.4.2 (Biostability), 5.8 (Suture Retention Strength), Section 5.6 (Pressurized internal diameter), and Section 5.3 (Strength).</p> <p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p> <p style="text-align: center;">Labeling -- Instructions for Use</p> <p>Provide adequate labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p> <p>Recommend product-specific techniques for implanting and revising the vascular graft, if appropriate, and should indicate that care should be taken when cannulating the graft for dialysis access (e.g., avoidance of external support during cannulation, proper rotation of cannulation sites, post cannulation care such as proper compression to achieve hemostasis, etc.).</p>

RISK	CONTROLS
7. True Aneurysm/ Dilatation continued	<p data-bbox="794 314 1219 346" style="text-align: center;">Labeling -- Instructions for Use</p> <p data-bbox="525 389 1146 421">Provide instructions for graft handling and sizing.</p> <p data-bbox="525 449 1471 517">Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p>
8. Infection/Sterility	<p data-bbox="963 544 1050 576" style="text-align: center;">510(k)</p> <p data-bbox="525 612 1483 889">Perform a sterilization validation to ensure that the sterilization process is capable of providing the Sterility Assurance Limit (SAL) of 10^{-6}, in accordance with suitable guidance (e.g., ANSI/AAMI VP20-1994, Section 4.5 (Sterility), ANSI/AAMI/ISO 11134-1993, ANSI, AAMI/ISO 11135-1994, and ANSI/AAMI/ISO 11137-1994). Alternate sterilization methods should be validated to an appropriate SAL. If resterilization is indicated, manufacturers should also perform a validation of the resterilization method in accordance with suitable guidance.</p> <p data-bbox="525 917 1493 1229">Describe the sterilization method that will be used; the method that <u>will be used</u> to validate the sterilization cycle, and the SAL. Describe how the packaging serves to maintain the device sterility. For ETO sterilization, state the maximum levels of residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol. State whether the product is non-pyrogenic, and describe the method used to make that determination. For radiation sterilization; state the radiation dose used. See also, <u>Sterility Review Guidance, and Revision of 11/18/90 #K90-1.</u></p> <p data-bbox="525 1257 1483 1432">Conduct preclinical (<i>in vivo</i>) and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo Preclinical and Clinical Evaluation</u>); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p> <p data-bbox="525 1459 1496 1559">Provide a statement that biological testing (including pyrogen and bioburden testing) will be or has been performed to assess acceptable limits of biological contaminants.</p> <p data-bbox="525 1587 1506 1832">Provide a statement that package shelf life validation (including package integrity/distribution testing, accelerated aging, microbial challenge testing, and real time follow-up) will be or has been performed, in accordance with ANSI/AAMI VP20-1994, Section 4.5.1 (Shelf life), to determine that the device and package will maintain their integrity for the period of time specified on the device label, or should provide a justification as to why such validation is not necessary.</p>

RISK	CONTROLS
<p>8. Infection/Sterility continued</p>	<p style="text-align: center;">Labeling - Instructions for Use</p> <p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p> <p>State that the product is supplied sterile on the product package label and in the Instructions for Use, <u>if applicable</u>.</p> <p>Provide instructions for opening the vascular grafts package.</p> <p style="text-align: center;">Labeling - Instructions for Use</p> <p>Instruct the user that sterility cannot be assured if the graft packaging has been opened or damaged.</p> <p>State that the health care provider is responsible for instructing the patient as to proper postoperative care.</p> <p>State that the health care provider must observe aseptic technique during implantation and postoperatively.</p> <p>Address resterilization, where resterilization is an <u>indicated</u>.</p> <p>State that infection is a potential complication associated with the use of vascular grafts.</p> <p>Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p>
<p>9. Performance</p>	<p style="text-align: center;">510(k)</p> <p>Conduct testing on finished devices in accordance with ANSI/AAMI VP20-1994, Sections 4.4.2 (Biostability), 5.2 (Porosity, Water Permeability, Integral Water Permeability/Leakage, and Water Entry Pressure), 5.3 (Strength), 5.4 (Length), 5.5 (Relaxed Internal Diameter), 5.6 (Pressurized Internal Diameter), 5.7 (Wall Thickness), 5.8 (Suture Retention Strength), and 5.9 (Kink Diameter/Radius). Manufacturers should also address applicable requirements specified in ANSI/AAMI VP20-1994, Section 5 (Introduction).</p> <p>Assure that subjecting prostheses to the maximum number of sterilization cycles recommended, (where resterilization is indicated) does not adversely affect the properties of the device, in accordance with ANSI/AAMI VP20-1994, Section 4.5 (Sterility).</p>

RISK	CONTROLS
9. Performance (continued)	510(k)
	<p>Address the adequacy of attachment of the support such that normal handling and implantation forces should not disrupt the external support, for those devices that incorporate permanent or removable external support.</p>
	<p>Address removal of the external support such that removal should not impair device integrity, for those devices that incorporate removable external support.</p>
	<p>Address shelf life testing, for new or substantially modified materials, in accordance with ANSI/AAMI VP20-1994, Section 4.5.1 (Shelf Life).</p>
	<p>Conduct testing in accordance with ANSI/AAMI VP20-1994, Section 5.3, paragraphs 3 and 4 (Strength after Repeated Puncture), if the indications for use include vascular access.</p>
	<p>Conduct (<i>in vivo</i>) preclinical and/or clinical (<i>in vivo</i>) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for <u>In Vivo</u> Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through <u>in vitro</u> testing.</p>
	Labeling - Instructions for Use
	<p>Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).</p>
	<p>Recommend product-specific techniques for implanting the vascular graft, (e.g., tunneling with consideration for external support, where appropriate, and methods to avoid kinking, where appropriate); and revising the vascular graft, if appropriate; and should indicate that care should be taken when cannulating the graft for dialysis access (e.g., avoidance of external support during cannulation, proper rotation of cannulation sites, post cannulation care such as proper compression to achieve hemostasis, etc).</p>
	<p>Provide appropriate instructions for graft handling and sizing (with consideration for external support, if appropriate, and potential arterial steal syndrome, if appropriate).</p>
<p>State that the health care provider is responsible for instructing the patient as to proper postoperative care.</p>	
<p>Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).</p>	