This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer 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. This guidance will be updated in the next revision to include the standard elements of GGP's.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

MAY 1 1 1990

Dear Vascular Graft Manufacturer, Developer, or Representative:

This letter is intended to notify you of the Food and Drug Administration's (FDA) policy on prosthetic vascular grafts, greater than or equal to 6mm in diameter, and to provide general guidance for the preparation of market clearance applications. This policy has evolved in response to the changes in technology in this field and our experience in evaluating new vascular graft devices. As you are aware, FDA has classified preamendment synthetic vascular grafts of 6mm and greater diameter into Class II. FDA has determined that the preamendment grafts covered by this classification regulation are limited to woven, knitted, or extruded polytetrafluoroethylene (PTFE) or polyethylene terephthalate (PET) grafts. Therefore, synthetic vascular grafts ($\geq$ 6mm in diameter) that can be considered for marketing through the premarket notification (510(k)) process are limited to those that are very similar in technological characteristics (i.e., material, design, fabrication), preimplant treatment (e.g., preclotting), and indications for use, to the predicate grafts defined above.

The 510(k) process for vascular grafts can accommodate some differences with the predicate device when there is a clear, simple, and direct relationship of the effect of the difference on the expected performance of the device. However, it must be recognized that vascular grafts are critical implant devices. New technological characteristics such as a new material or a coating can alter the many physical and physiological host/implant interactions in ways that are interdependent and unpredictable. When no singular accepted scientific method exists for assessing the effects of the new technological characteristic(s), the pathway for market clearance is through the evaluation of safety and effectiveness data via the premarket approval (PMA) process. The attached table shows that FDA is, therefore, reserving the 510(k) market clearance process for those devices made of PET or PTFE only.

When a 510(k) application is submitted for a PET or PTFE graft, it is expected that the applicant will provide full descriptive information to demonstrate the equivalence of the device to its predicate. As a minimum, the information in Table I must be provided.

If there are variations in the manufacturing, design, or material characteristics, additional performance data to demonstrate that the device performs at least as well as its predicate must be provided. As a minimum, the information in Table II must be provided.

If the vascular graft is intended for vascular access, then additional performance data to demonstrate that the device performs at least as well as its predicate must be provided. As a minimum, the information in Table III must be provided. The information must demonstrate that the expected fatigue life of the product under in-service use conditions (worst case pulsatile loading and puncture) equals or exceeds its predicate.

If the material is not a PET or PTFE vascular graft, the attached outline for vascular graft guidance should be consulted as well as contacting the Division of Cardiovascular Devices and/or the Division of Gastroenterology-Urology Devices.

If there are questions or comments regarding this policy, please contact Arthur A. Ciarkowski at (301) 427-1200.

Sincerely yours,

Abhijit Acharya, Ph.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

6mm Grafts, Straight or Bifurcated

IF	AND	AND	THEN
PET* or PTFE**	No Coating or Surface Treatment	Peripheral Use	510(k) -use Table I
		Access	510(k) -use Table I & III
	Atypical Material Properties or Radially Supported	Peripheral Use	510(k) -use Table II -possible animal studies required
		Access	510(k) -meet peripheral use requirements plus Table III
	Glow Discharge TFE*** on PET	Peripheral Use	510(k) -use Table I -also animal study
		Access	510(k) -use Table I & III -also animal study
	Coating or Composite		IDE/PMA -consult outline -contact FDA for clinical data requirements
All Other Materials			

Polyethylene terephthalate
Polytetrafluoroethylene
*... Tetrafluoroethylene

Table I

I.	Labeling:	includes all indication for use statements, warnings, and precautions; brochures; and literature provided to a user	
II.	Description:	Sizes	- length - diameter - wall thickness
		Material	- PET or PTFE - source and acceptance criteria - additives
		Markings	- color strips, etc.
III.	Properties:	Fabrication	- extruded - knitted or woven - ply - velouring - denier - No. of filaments
		Structure	- configuration - external reinforcement - extruded - internodal distance - knitted or woven - course per inch - wales per inch - crimps per inch - pile height
		Characteristics	- burst strength - tensile strength - compliance - suture hole elongation - suture retention strength - knitted or woven - water permeability - extruded - water entry pressure
IV.	Acceptance Criteria:		- dimensions - physical attributes - residuals/toxicity/pyrogenicity - sterility

References

"Blue Book" - Tripartite Biocompatibility Guidance
"Blue Book" - 510(k) Sterility Review Guidance
Voluntary Standards - AAMI** Standard for Vascular Graft Prostheses (Proposed)

* Contact Carl DeMarco at (301) 427-1072 for copies.
** Association for the Advancement of Medical Instrumentation

Table II

I. Table I requirements

II. Properties: - kink resistance
- compression resistance

III. Durability/Fatigue Life: Purpose - To Show Durability, Dimensional Stability, and Estimated Life

Material Testing	- classic S/N analysis, or zero default/critical crack growth analysis - creep
Stress Analysis	- nominal loading - worst case loading
Estimated Life	- static and dynamic loading
In-vitro Pulsatile Testing and Critical Device Evaluation	- conditions - 20 x 10^6 (1/2 year) cyclic testing - 80 to 120 mmHg - >60, <140 bpm - physiological saline

IV. Radial Support: - S/N for support material or crack growth analysis
- tensile adhesion for support material
- radial adhesion for support material
- residual stress of support material
- estimated life with and without support

V. Animal Studies: At least 8 animals must complete at least a 20 week period with complete explant analysis.*

* See attached guidance.

Table III

I. Item III from Table II

II. Puncture Test: - from stress analysis determine worst case physiologic load

- puncture fabric with 16 gauge needle for:
  (a) 150 (approximately 0.5 years)
  (b) 300 (approximately 1 year)
  (c) 900 (approximately 1.5 years)

- conduct S/N where S = worst case physiologic load

- calculate fatigue life

Puncture	Estimated Life -New-	Estimated Life -Predicate-
150	a	a_1
300	b	b_1
450	c	c_1

III. "Mock dialysis" treatments should be carried our for the purpose of demonstrating that the access graft is capable of supporting blood flows of 300 - 500 cc/min without collapsing and for the purpose of determining the effects of blood being returned at that rate - it is not uncommon to see some hyperplasia at the venous end.

IN VIVO TESTING

Purpose: The purpose of animal studies is to (1) evaluate the degree of risk that an implant will present when used in human trials, or (2) to provide information that cannot be obtained from a human trial (e.g., the pattern of biologic response to the device at intermittent time periods through explant analysis). In either case, the experience in animals may not translate directly to the performance of the device in humans. The inquiry can, however, compare the pattern of response in an animal model to what is known about the pattern of response of comparable marketed implants in the animal model selected. The best way to achieve this comparison is through a well controlled animal study in which the animal model selected is well understood by the investigator.

Summary of Literature: Summarize the results of animal studies published in scientific journals using the device proposed for marketing clearance or similar devices. Discuss definitive findings from these studies and questions posed by the results that require further investigation.

Summary of Prototype Studies: Describe the animal tests that were done to develop your prototype model and subsequent studies leading to your final design.

Protocol: Results from a scientific animal study of the final clinical design is expected to accompany the application for marketing clearance. This *in vivo* testing is expected to demonstrate both acute safety and performance of the device as a complement to *in vitro* testing. The following are minimum protocol expectations for this study:

- Provide standardized procedures and data collection techniques.
- Discuss the rationale for the choice of animal(s) selected in the study.
- Provide the rationale for the number of animals to be studied and the duration of the studies (a minimum of 8 animals for 20 weeks is expected).
- Describe and justify the control graft.
- Describe the implant techniques and the postoperative care procedures.
- Describe and evaluate all of the device related and non-device related adverse events.
- Provide an evaluation of the explanted device and the control (see attached draft explant analysis).

Revised
November 1989

ANALYSIS OF EXPLANTED VASCULAR GRAFTS

Purpose

The evaluation of explanted vascular grafts in order to assess tissue and blood biomaterials interactions, graft integrity and related pathology.

Implant Retrieval

In situ gross photographs are taken following tissue dissection. The surgeon excises the vascular graft, ideally including the anastomoses with approximately 1 cm of native vessel and the outer capsule, and rinses residual blood from the graft surfaces by gentle agitation in sterile Ringer's lactate solution. The proximal and distal ends of the graft are differentiated by placing one or two sutures through the vessel or graft wall, respectively. If the entire graft is not excised, appropriately label the retrieved segment (e.g., proximal, middle, distal).

The excised graft is then placed in an appropriate container containing 4% formaldehyde-1% glutaraldehyde in 0.1M phosphate buffer, pH 7.4.

A brief explant record including: type of graft; implantation site; estimate of length and diameter; implantation date; explant date; duration of implantation; surgical pathology or autopsy number; patient history; reason for reoperation; and, a brief gross description, especially if only a portion of the graft is retrieved for study.

Gross Examination

In addition to gross visual examination, the graft is examined completely submerged in fixative with the aid of a dissecting microscopy and findings photographed as indicated. Radiographic studies are conducted to assess the extent of graft calcification using routine methods.

Histologic Examination

Representative samples are taken from the native vessel, both anastomoses, the proximal, middle and distal regions of the graft, and other sites as indicated by gross and macroscopic examination. These specimens are then divided equally and processed for light microscopic and ultrastructural studies. Wet specimens and blocks retained for future studies as required.

Light microscopy: Glycol methacrylate duplicate sections (1 micron) stained with hematoxylin and eosin, alkaline toluidine blue and von Kossa (calcium phosphate).

Paraffin duplicate sections (6 micron) stained using phosphotungstic acid hematoxylin, Verhoeff's elastica, Masson's trichrome, Movat's pentachrome, alcian blue-PAS and special stains for bacteria/fungi.

Electron microscopy:

Transmission:	Epon duplicate sections stained using uranyl acetate and lead citrate; duplicate unstained grids retained for additional studies (e.g., energy dispersive x-ray analysis).
Scanning:	The specimen is critical point dried and sputter coated using routine methods.

Textile Studies

The tissue components of the graft, when appropriate, will be removed (boiling 5 minutes in 5% sodium bicarbonate) in order to examine the underlying graft fabric by means of light or scanning electron microscopy.

Special Studies

Special studies will be conducted, as required, to quantitate the area of the graft luminal surface covered by endothelial cells and/or thrombus; anti-Factor VIII, Ulex Europaeus lectin binding for the identification of endothelial cells; and, freshly harvested unfixed tissue assayed for prostacyclin and plasminogen activator activity.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date

From Chief, Prosthetic and Monitoring Devices Branch

Subject Development of FDA Guidance for Vascular Grafts

To Developers, Researchers, and Users of Vascular Grafts

Over the last few years, I have observed a change in vascular graft technology that will result in innovative products being distributed. To facilitate the information that is needed to obtain market clearance from FDA, my staff and I are preparing a document that will provide guidance for the type of information that will be needed to substantiate claims of safety and effectivenss.

Rather than wait until a complete guidance document has been prepared, we are releasing a detailed outline of information requirements that FDA will need to make a determination of whether a vascular graft is safe and effective. Over time, it is our intent to expand this outline into a guidance document. To accomplish this and make the document useful to manufacturers, clinical investigators, and FDA, we are seeking input from professionals who are actively engaged in the development and use of vascular grafts.

We would appreciate your comments, thoughts and suggestions on preparing this guidance document. You may send your information to us either by telephone, in writing, or electronically through our electronic bulletin board service (BBS).

The BBS contains this outline and other guidance documents. These files may be downloaded from the BBS to your computer, or you may choose to leave messages or comments on the BBS. To contact the BBS, you will need to set your modem to 1200 Baud, No Parity, 8 Data Bits, and 1 Stop Bit. The X-Modem protocol is the most common protocol that is used to transfer documents although other software protocols have worked as well. You may contact the BBS via your computer at (301) 443-7496.

If there are comments or questions, please contact me at (301) 427-7594.

Sincerely yours,

Arthur A. Ciarkowski

Arthur A. Ciarkowski
Branch Chief
Prosthetic & Monitoring
Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

OUTLINE FOR VASCULAR GRAFT GUIDANCE 9/20/88

Dorothy Abel
Lisa Kennell
Art Ciarkowski

DRAFT

1.0 DESCRIPTION OF THE DEVICE

1.1 COMPOSITE GRAFTS

1.1.1 Base Graft

1.1.1.1 Dacron

(1) Fabrication
- (a) Warp Yarn
  - (i) Ply
  - (ii) Velouring
  - (iii) Denier
  - (iv) No. of filaments
- (b) Weft Yarn
  - (i) Ply
  - (ii) Velouring
  - (iii) Denier
  - (iv) No. of filaments

(2) Structure
- (a) Knitted or Woven
  - (i) Course per inch
  - (ii) Wales per inch
- (b) Crimps per inch
- (c) Pile height
- (d) Configuration

(3) Characteristics
- (a) Water permeability
- (b) Burst strength
- (c) Tensile strength
- (d) Compliance
- (e) Wall thickness

1.1.1.2 Teflon

(1) Fabrication

(2) Structure
- (a) Expanded polymer
- (b) External reinforcement
- (c) Configuration

(3) Characteristics
- (a) Water permeability
- (b) Internodal distance
- (c) Burst strength
- (d) Tensile strength
- (e) Compliance
- (f) Wall thickness

1.1.1.3 Other Synthetics: see section 1.2

1.1.2 Coating

1.1.2.1 Biologic/Non-Cellular (21 CFR Part 610)
- (1) Source
  - (a) If human origin, must be licensed biologic
- (2) Characterization
  - (a) Characterization of soluble components
  - (b) Extractability of protein
  - (c) Morphologic assessment
- (3) Purity (e.g., the following)
  - (a) Amino acid analysis
  - (b) Total lipid analysis
  - (c) Heavy metal content
  - (d) Protein content
  - (e) Glycoaminoglycan content
  - (f) Molecular weight distribution
- (4) Physical characteristics
  - (a) Certification
    - (i) Percent solids
    - (ii) pH
    - (iii) Content
    - (iv) Microscopic examination
    - (v) Shrink temperature
    - (vi) Shipping temperature

1.1.2.2 Biologic/Cellular, e.g., endothelial cells (21 CFR Part 610)
- (1) Reagents
- (2) Components
- (3) Operating principle

1.1.2.3 Dacron or Teflon
- (1) Type

1.1.2.4 Other Coatings and Treatments
- (1) Polymers: see section 1.2.1 (3)
- (2) Others are handled on a case by case basis

1.1.3 Raw Materials Used in Manufacturing
- (1) Grade
- (2) Specifications

1.1.4 Complete Device

1.1.4.1 Synthetic or biologic coating
- (1) Characteristics
  - (a) Wall thickness
  - (b) Nominal internal diameter
  - (c) Usable length
  - (d) Water permeability

(e) Burst strength
(f) Tensile strength
(g) Compliance
(h) Amount of coating (%)
(i) Surface morphology
(scanning electron microscopy)
(j) Contact angle measurements

1.2 SYNTHETICS OTHER THAN DACRON OR TEFLON

1.2.1 Polymer

(1) Fabrication
(2) Structure
(a) Configuration
(3) Characterization of the polymer
(a) Density
(b) Specific gravity
(c) Particle size
(d) Molecular weight
(e) Melting point
(f) Peak temperature
(g) Degree of crystallinity
(h) Contact angle measurements
(4) Characteristics
(a) Water permeability
(b) Internodal distance
(c) Burst strength
(d) Tensile strength
(e) Compliance
(f) Surface morphology
(scanning electron microscopy)
(g) Nominal internal diameter
(h) Diameter under physiological pressure
(i) Usable length (at implant)
(j) Wall thickness

1.2.2 Raw Materials Used in Manufacturing

(1) Grade
(2) Specifications

1.3 BIOPROSTHESES

1.3.1 Mandrel Grown, Allograft, or Xenograft

(1) Source
(2) Fabrication
(a) Type of treatment
(i) Crosslinking
(ii) Support structures

(b) Cell viability
(3) Configuration
(4) Characterization
(a) Water content
(b) Collagen content
(c) Morphologic evaluation
(d) Shrink temperature
(e) Wall thickness
(f) Nominal internal diameter
(g) Diameter under physiological pressure
(h) Usable length
(i) Water permeability
(j) Burst strength
(k) Compliance

1.3.2 Raw Materials Used in Manufacturing
(1) Grade
(2) Specifications

2.0 IN-VITRO TESTING

2.1 COMPOSITE GRAFTS

2.1.1 Base Graft (for comparison purposes)

2.1.1.1 Dacron
(1) Water permeability
(2) Burst Strength
(3) Tensile strength
(4) Suture retention
(5) Suture hole elongation
(6) Compliance
(7) Scanning electron microscopy

2.1.1.2 Teflon: same as section 2.1.1.1

2.1.1.3 Other synthetics: see section 2.2

2.1.2 Coating

2.1.2.1 Biologic/Non-cellular
(1) Characterization: see section 1.1.2.1 (2)
(2) Purity: see section 1.1.2.1 (3)
(3) Physical Characteristics: see section 1.1.2.1 (4)
(4) Shelf life (see section 8.0)
(5) Biocompatibility
(a) Pyrogenicity
(b) Bioburden

2.1.2.2 Endothelial cells/cellular

2.1.2.3 Dacron or Teflon

2.1.2.4 Other coatings and treatments

2.1.3 Complete device

2.1.3.1 Biologic coating
- (1) Water permeability
- (2) Burst strength
- (3) Tensile strength
- (4) Suture retention
- (5) Suture hole elongation
- (6) Compliance
- (7) Kinkability
- (8) Mechanical pumping challenge
- (9) Content
- (10) Strength of bonding
- (11) Residual chemicals
- (12) Shrink temperature
- (13) Morphologic characterization
- (14) Shelf life (see section 8.0)
- (15) Biocompatibility
  - (a) Pyrogenicity
  - (b) Bioburden
  - (c) USP Class VI Biologic tests
  - (d) Ames Mutagenicity test
  - (e) Sterility

2.1.3.2 Synthetic coating: same as section 2.1.3.1 with the exception of shrink temperature

2.2 NEW SYNTHETICS

2.2.1 Polymer
- (1) Characterization of the polymer: see section 1.2.1 (3)
- (2) Water permeability
- (3) Burst strength
- (4) Tensile strength
- (5) Suture retention
- (6) Suture hole elongation
- (7) Compliance
- (8) Residual chemicals
- (9) Kinkability
- (10) Mechanical pumping challenge
- (11) Leachables
- (12) Morphologic characterization
- (13) Shelf life (see section 8.0)

(14) Biocompatibility
  (a) Pyrogenicity
  (b) Bioburden
  (c) USP Class VI Biologic tests
  (d) Ames Mutagenicity test
  (e) Sterility
(15) Materials characterization vs accelerated wear, including chemical/molecular degredation of polymer

2.3 BIOPROSTHESES

2.3.1 Mandrel Grown, Allograft, or Xenograft

(1) Water permeability
(2) Burst strength
(3) Tensile strength
(4) Suture retention
(5) Suture hole elongation
(6) Compliance
(7) Leak rate test
(8) Mechanical pumping challenge
(9) Kinkability
(10) Branch ligature strength
(11) Integrity of seams
(12) Materials/surface characterization (e.g. the following)
  (a) Critical surface tension
  (b) Infrared spectroscopy
  (c) Contact angle measurements
  (d) Energy dispersive X-ray analysis
  (e) Routine heavy metal analysis
(13) Residual chemicals
(14) Cell viability
(15) Content
(16) Shrink temperature
(17) Mesh show through
(18) Morphologic characterization
(19) Shelf life (see section 8.0)
(20) Biocompatibility
  (a) Pyrogenicity
  (b) Bioburden
  (c) USP Class VI Biologic tests
  (d) Ames Mutagenicity test
  (e) Sterility

3.0 IN-VIVO TESTING

3.1 COMPOSITE GRAFTS/SYNTHETIC/BIOPROSTHETIC

.1.1 Protocol
(1) Choice of animal model
(2) Duration of study
(3) Purpose (e.g., the following)
(a) Thrombogenicity
(b) Healing pattern
(c) Embolization
(d) Morphology
(e) Hemolysis
(f) Leak rate
(g) Ease of handling and suturability
(h) Resorption (coated grafts)

DR.

4.0 CLINICAL STUDIES

4.1 COMPOSITE GRAFTS

4.1.1 Complete Device

4.1.1.1 Investigational Plan
(1) Name and intended use of the device
(a) Special instructions for use
(b) Contraindications for use in the study
(2) Purpose/Study Objectives (e.g., the following)
(a) To assess leakage through the graft at implant
(b) To assess leakage through the graft post implant
(c) To assess complication rates such as immunological complications, survival, thrombosis/occlusion, infection as they compare to a reference/control group
(d) To assess healing of the graft and histology in explanted grafts
(e) To assess the ease of handling of the graft
(f) To assess thrombogenicity in endothelial seeded grafts
(g) To substantiate all labeling claims
(3) Duration of the investigation
(a) Expected enrollment period
(b) Proposed follow-up period (minimum of 1 year)
(4) Study size
(a) Number of patients (minimum 100, maximum 300)
(b) Investigators (minimum 3, maximum 6)

4.1.1.2 Protocol

(1) Procedures to be followed (standarized for all centers)
    (a) patient inclusion/exclusion criteria
(2) Data collection formats (e.g., timing of follow-ups, type of tests to be performed, including those that are specific to the graft under investigation, e.g.
    (a) Palpation
    (b) Doppler (imaging and velocity)
    (c) Platelet deposition
    (d) Arteriogram
    (e) Immunological studies
    (f) Blood cultures (infection)
(3) Definition of complications and adverse reactions as applied in the study, to include device-related episodes as well as non-device-related episodes
(4) Case Report Forms (CRFs)
    (a) Preperative form
        (i) Risk factors
        (ii) Other factors that could affect healing or complication rates
    (b) Operative form
        (i) Reassess factors affecting healing and complication rates
        (ii) Complication type, severity, duration, onset and relatedness to graft
        (iii) Drug type and dosage
        (iv) Complication definitions
        (v) Device tracking data (model, serial number, size, length implanted)
        (vi) Other operative information, as necessary (such as implant location)
    (c) Follow-up form
        (i) Information as detailed in 4.1.1.2(4)(b), i, ii, iii, iv, and v
        (ii) Results of diagnostic tests
    (d) Adverse reaction form
        (i) Information about deaths and complications, such as cause, relatedness and rationale for relatedness to the graft, diagnosis (if not on Follow-up form), and outcome of any intervention
        (ii) Copies of autopsy or explant pathology reports
        or explant reports available at the investigational center

4.1.1.3 Risk Analysis

(1) Peripheral use must precede coronary use

4.1.1.4 Monitoring procedures
- (1) Written procedure for monitoring the study
  - (a) Frequency of CRF data audit for accuracy and completeness
  - (b) Frequency of site visits and information to be obtained
  - (c) Frequency of analysis of data
  - (d) Auditing procedures (at the investigational center and at the sponsor location)
- (2) Name and address of sponsor or contracting facility

4.1.1.5 Data analysis
- (1) Simple percentage rates for complications occurring under 30 days of implant
- (2) Linearized rates for complications occurring after 30 days of implant
- (3) Actuarial rates for deaths and complications (occlusion, infection, thromboembolism, leakage, etc.)
- (4) A discussion about how complications will be analyzed (which events will be entered into analyses)

4.2 NEW SYNTHETICS (additional elements added to section 4.1)

4.2.1.1 Investigational Plan
- (1) Purpose/Study objectives (e.g., the following)
  - (a) To assess immunological affects of new material
  - (b) To assess leakage, complications, healing, and handling, as in 4.1.1.1(2)
  - (c) To assess long term degradation

4.3 BIOPROSTHESES (additional elements added to section 4.1)

4.3.1.1 Investigational Plan
- (1) Purpose/study objectives (e.g, the following)
  - (a) To assess leakage, complications, healing, and handling, as in 4.1.1.1(2)
  - (b) To assess vessel wall integrity (e.g., aneurysm, dissection)
  - (c) To assess immunological reactions

4.3.1.2 Protocol
- (1) Data collection formats (timing of follow-ups, type of test performed) e.g.
  - (a) Blood titer studies for immunological reactions

5.0. MANUFACTURING

5.1 Location of manufacturing facility

5.2 Organization of the firm

5.3 Description of the physical plant(s)
(include environmental controls having an effect on the device)

5.4 Description of the manufacturing equipment

5.5 Description of control system for components

- 5.5.1 Raw materials (sampling and testing)
- 5.5.2 Non-labeling packaging components (sampling and testing)
- 5.5.3 Labeling packaging components (sampling and testing)

Manufacturing process and quality control procedures

- 5.6.1 Description of all manufacturing steps
(from basic maerials to finished device)
- 5.6.2 Flowchart
- 5.6.3 Production Procedures
- 5.6.4 Quality control tests

5.7 Packaging, sterilization, and labeling controls

- 5.7.1 Packaging (specification and inspection)
- 5.7.2 Sterilization (specification and validation)
- 5.7.3 Pyrogen testing
- 5.7.4 Labeling (control system)
- 5.7.5 Temperature indicators for biologic products

5 Holding, distribution, and installation controls

- 5.8.1 Product storage
- 5.8.2 Stock rotation
- 5.8.3 Packing slips
- 5.8.4 Routing

5.9 Finished device inspection procedures

- 5.9.1 Finished packaged products (sterile)
- 5.9.2 Synthetic product release
- 5.9.3 Finished products (pre and post sterilization)
- 5.9.4 Pyrogen testing
- 5.9.5 Bioburden testing

5.10 Description and location of device records

6 PROCESS VALIDATION

7.0 LABELING

7.1 Manufacturing information

- 7.1.1 Name and address of manufacturer, distributor, or packer
- 7.1.2 Listing of contents
- 7.1.3 Sterile lot number
- 7.1.4 Expiration date

7.2 Cautionary statements

- 7.2.1 Investigational device caution per 21 CFR 812.5(a)
- 7.2.2 Other cautions, as appropriate

7. arning statements

7.3.1 Use of graft for other locations or sizes than approved under the IDE for the device, e.g.
(1) Coronary bypass
(2) A-V fistula use
(3) Smaller diameters

7.4 Indication for use

7.4.1 Indicate for all uses approved or proposed in the IDE

7.4.2 No indication for use or indication that the device is safe or effective for use in the investigational application(s)

7.4.3 No false or misleading language

7.5 Contraindications for use, e.g.

7.5.1 In patients with Dacron sensitivity

7.5.2 In patients with bovine collagen sensitivity

7 Interfering devices or substances

7.7 Instructions for use

7.7.1 Implantation procedures, including any recommended suture techniques and rinse procedures

7.7.2 Recommended antiplatelet/anticoagulation therapies

7.7.3 Recommended sterilization/resterilization procedures, maximum number of resterilizations, including any accessories

7.8 Bibliography/references

7.9 Warranties

8.0 Shelf Life

8.0.1 Must relate to both the product and package

8.0.2 Testing must include handling, shipment, and storage conditions

8.1 Product

8.1.1 Actual conditions of shipment, handling, and storage
(1) Describe environments shipped to

8.1.2 Simulated conditions of shipment, handling, and storage
(1) Relate all conditions simulated to real life experience anticipated for the device (worst case)
(2) Simulate all possible conditions (e.g., temperature extremes and temperature shock, humidity extremes, atmospheric pressure differentials, etc.)
(3) Materials may be accelerated aged if rationale and protocol are acceptable
(4) Rejected materials may be acceptable for testing

8.2 Package

8.2.1 Actual conditions of shipment, handling and storage
(1) Describe environments shipped to

8.2.2 Simulated conditions of shipment, handling, and storage
(1) Relate all conditions simulated to real life experience anticipated for the package (worst case)
(2) Simulate all possible conditions (e.g., temperature extremes, and temperature shock, humidity extremes, atmospheric pressure differentials, microbial onslought, etc.)
(3) Package assembly must be the same as the final package assembly for the graft

8.2.3 Studies performed after aging
(1) Submit protocol for all tests proposed
(2) Must minimally include burst strength, tensile strength, suture retention, porosity, compliance, SEM and residual sterilant/storage solution after aging, compared to un-aged samples
(3) Aerosol or dust chamber type of microbial onslought study of the package, followed by sterility testing of the product
(4) Provide rationale for sample size proposed for each test

9.0 **APPENDICES** (e.g., definitions, explant pathology protocol, process validation protocol)