Guidance for Annuloplasty Rings 510(k) Submissions; Final Guidance for Industry and FDA Staff

Document issued on: January 31, 2001

This document supersedes Guidance for Annuloplasty Rings 510(k) Submissions
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 and Respiratory Devices
Office of Device Evaluation

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Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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INTRODUCTION

This guidance document describes a means by which annuloplasty ring 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 annuloplasty ring 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 a change in classification from class III to class II for the annuloplasty ring. The annuloplasty ring is a rigid or flexible ring implanted around the mitral or tricuspid heart valve for reconstructive treatment of valvular insufficiency (21 CFR 870.3800(a). The issues to be addressed in submissions are identified below.

THE LEAST BURDENSOME APPROACH

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Controls to address identified risks:

Performance Testing:

- Biocompatibility testing
- Computational structural analysis
- Tensile testing
- Suture pull-out testing
- Sterilization validation
- Biological testing including bioburden and pyrogen testing
- Shelf-life validation

Labeling:

- Contraindications
  patients with evolving bacterial endocarditis

- Potential complications
  stenosis, thrombosis, thromboembolism
  hemolysis
  regurgitation
  ring fracture
  left ventricular outflow tract obstruction
  systolic anterior motion/low cardiac output
  ring dehiscence
  endocarditis
  bleeding related to anticoagulants
  heart block
  suture injury to coronary arteries

- Instructions for use
  sterility assurance, prophylactic antibiotics
  sizing
  implantation
  suturing
  providing and assessing anticoagulation therapy
  assessing regurgitation and systolic anterior motion by echocardiography

- Specific warnings of potential risks
  hemolysis due to regurgitation
  bleeding due to anticoagulants
  heart block, damage to coronary arteries

The table below provides a discussion of the risks to health, the causes and sequelae of these risks, and the performance testing and labeling that serve as controls to address these risks. This guidance also provides further information on performance or clinical testing recommended for submission in 510(k)s for these devices.

RISK:	CONTROL
Tissue and Blood Damage: **Materials** **Product variability** If the materials, surface finish, or cleanliness are inadequate, damage to blood and tissue may result.	**510(k)** Conduct biocompatibility testing, in accordance with the FDA biocompatibility guidance "Use of International Organization for Standardization (ISO) 10993 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.'
Thrombosis and Thromboembolism: **Materials** **Anticoagulant therapy** **Operative technique** **Product variability** Annuloplasty rings are usually constructed of or covered with polyester fabric, which is relatively thrombogenic compared to other common implant materials (e.g., PTFE [Teflon®]. Though polyester typically heals to form a nonthrombogenic surface, thrombus formation on an inadequately healed annuloplasty ring could be a potential source of thromboembolism. A thromboembolic event may be any new, focal, clinically manifested neurological deficit which	**510(k)** Conduct biocompatibility testing in accordance with the FDA biocompatibility guidance. **Labeling - Instructions for Use** <u>Recommend or provide</u>: Techniques for implanting and suturing the annuloplasty ring. Warnings against loose sutures or threads, which may be a source of thrombosis or thromboembolism. Examples of cases where valve repair is specifically contraindicated.

RISK:	CONTROL
Thrombosis and Thromboembolism: Continued occurs more than three days postoperatively, whether transient (resolved within 24 hours) or chronic (lasting longer than 24 hours). It may be minor (transitory sequelae) or major (causes permanent residual sequelae or requires significant treatment, such as surgery) and may be triggered by a number of events: exposure to cardiovascular surgical procedures or the implant of a cardiovascular device or pre-existing conditions such as atrial fibrillation.	**Labeling - Instructions for Use** Include the following statements: Thrombosis and thromboembolism are potential complications associated with annuloplasty rings. There is a possible need for the postoperative anticoagulant therapy. Only surgeons having received appropriate training in valve repair should use the device. Surgeons who use annuloplasty rings should be current on all anticoagulation regimes.
Dilation of the Heart: Dilation of the heart, leading to intractable heart failure is associated with residual regurgitation only after unsuccessful repair of the valve.	**Labeling – Instructions for Use** Recommend or provide: Techniques for implanting and suturing the annuloplasty ring, and for assessing regurgitation by echocardiography. Examples of cases in which valve repair is specifically contraindicated. Cautions and warnings against oversizing the annuloplasty ring. Specific sizing techniques and explain the importance of proper ring sizing. Include the following statements: Use an obturator or sizer with annuloplasty rings. Uncorrected or recurrent regurgitation is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair, including ring implant and sizing techniques, should use the device. Only surgeons who have adequate training to determine whether incompetent heart valves are capable of being repaired, or if replacement is indicated; should use the device.

RISK:	CONTROL
Hemolysis: **Materials** **Operative technique** **Product variability** Annuloplasty rings typically are constructed of materials with known biocompatibility and with a history of use in other cardiovascular devices e.g., heart valves, vascular grafts, and pacemakers. Materials used in annuloplasty rings include titanium, silicone, polyester sutures, and polyester graft material. These materials have undergone biocompatibility tests in accordance with the FDA biocompatibility guidance on ISO 10993-1, which include tests for hemocompatibility and hemolysis.	**510(k)** Conduct biocompatibility testing, in accordance with the FDA biocompatibility guidance on ISO 10993. **Labeling – Instructions for Use** Recommend or provide: Techniques for implanting and suturing the annuloplasty ring Warnings against loose sutures or threads that may be a source of hemolysis, Cautions and warnings against the presence of excessive regurgitation following the procedure. Examples of cases where valve repair is specifically contraindicated. Include the following statements: Hemolysis may occur even with mild regurgitation. Only surgeons having received appropriate training in valve repair should use the device. Only surgeons who have adequate training to determine whether incompetent heart valves are reparable, or if replacement is indicated should use the device.

RISK:	CONTROL
Regurgitation: **Operative technique** **Device variability** Regurgitation is often due to leaflet abnormalities, secondary to damage to supporting heart structures resulting from (i) degenerative diseases, (ii) rheumatic diseases, and (iii) ischemia or vascular diseases. Rarely, incomplete repair can result in residual regurgitation, requiring further repair or valve replacement; however, the amount of regurgitation (compared to the patient's preoperative condition) is almost always significantly	**Labeling – Instructions for Use** Recommend or provide: Examples of cases where valve repair is specifically contraindicated. Specific sizing techniques and explain the importance of proper ring sizing. Cautions and warnings against oversizing the annuloplasty ring. Techniques for implanting and suturing the annuloplasty ring, and for assessing regurgitation by echocardiography.

RISK:	CONTROL
Regurgitation: **Continued** reduced. Intraoperative diagnostic tools help the surgeon decide if the repair is adequate; if not, further repair or valve replacement can be performed. Reducing regurgitation to minimal levels helps a patient functionally (e.g., improved quality of life) and would be expected to slow the progression of cardiac dysfunction, including heart enlargement. Echocardiographic assessment of left ventricular ejection fraction and thickening of the heart wall can help predict survival following surgical repair of mitral regurgitation To decrease the late mortality of patients with left ventricular dysfunction and regurgitation, early surgical treatment is recommended before ventricular function continues to deteriorate; thus the repair effectiveness can be maximized.	**Labeling – Instructions for Use continued** Include the following statements: Uncorrected or recurrent regurgitation is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair, including ring implant and sizing techniques, should use the device. Only surgeons who have adequate training to determine whether incompetent heart valves are capable of being repaired, or if replacement is indicated; should use the device. Use an obturator or sizer with annuloplasty rings.
Stenosis: **Operative technique** **Device variability** Causes of stenosis include congenital and acquired diseases, such as rheumatic disease. Annuloplasty rings along with other repair techniques are commonly used to treat stenosis, but occasionally the repair is incomplete, resulting in continued stenosis. Stenosis may return just due to progression of the disease process. Stenosis can result in turbulent blood flow and significantly reduced cardiac output, and, if left untreated, may ultimately lead to fibrosis and calcification of the valve, further reducing heart efficiency. The literature demonstrates that the rate of annuloplasty ring-induced stenosis and corrective reoperation is relatively low. In most cases, minor stenosis is manageable and patients continue to exhibit clinical benefit.	**Labeling – Instructions for Use** Recommend or provide: Examples of cases where valve repair is specifically contraindicated. Techniques for implanting and suturing the annuloplasty ring. Specific sizing techniques and explain the importance of proper ring sizing. Cautions and warnings against undersizing the annuloplasty ring. Include the following statements: Stenosis is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair, including ring implant and sizing techniques, should use the device.

RISK:	CONTROL
Stenosis: **Continued** Severe stenosis may result from selecting an annuloplasty ring that is too small, or from disease conditions that progress following the procedure. Proper ring sizing using sizing obturators or templates provided by the manufacturer is critical. If the annuloplasty ring is undersized, the result may be a stenotic valve. If it is oversized, the result may be regurgitation. Either case may result in diminished patient outcome, or require reoperation.	**Labeling – Instructions for Use continued** Only surgeons who are adequately trained to determine whether a stenotic valve is capable of being repaired via annuloplasty, or if valve replacement is required; should use the device. Use an obturator or sizer with annuloplasty rings.
Ring Fracture: **Materials or design** **Operative technique** **Product variability** The manufacturer of the rings that fractured studied two explanted rings and reported patches of discoloration and corrosive material similar to rust, suggesting weakening of the ring. Ring fracture may have been promoted by overload and dilation of the right ventricle, secondary to severe left-sided disease. Surgical technique causing ring distortion may also have played a role. Right atrial enlargement, secondary to the endocarditis-induced mitral regurgitation, may have placed extra stress on the ring. Patients with ring fracture typically presented several months after surgery with late tricuspid regurgitation associated with enlargement of the right side of the heart (secondary to failure of left-side valvular surgery), or persistence of increased pulmonary vascular resistance. Radiography confirmed abnormal ring shape associated with ring fracture. All patients underwent reoperation for replacement of the annuloplasty ring and, in most cases, repair or replacement of valves in the left side of the heart.	**510(k)** Evaluate the structural integrity of an annuloplasty ring with a rigid core using Computational Structural Analysis (such as Finite Element Analysis). Conduct tensile testing to determine the overall strength of the annuloplasty ring and to ensure that structural failure will only occur at loads greater than those experienced *in vivo*. **Labeling – Instructions for Use** <u>Recommend or provide</u>: Examples of cases where valve repair is specifically contraindicated. Techniques for implanting and suturing the annuloplasty ring. <u>Include the following statements</u>: Ring fracture is a potential complication associated with use. Only surgeons having received appropriate training in valve repair should use the device. Caution do not to use cutting edge needles. Do not alter or deform the ring conform to the anatomy.

RISK:	CONTROL
Left Ventricular Outflow Tract Obstruction, LVTO: **Operative technique** **Product variability** LVOTO caused by systolic anterior motion, SAM. SAM and LVOTO are linked as potential complications of mitral valve repair. Depending on cause and severity, either may be treated intraoperatively. Severe SAM and LVOTO may require surgical correction of size, shape, and coaptation of the mitral valve leaflets. LVOTO can be detected by intra-operative echocardiography, on weaning from bypass. Sizing the annuloplasty ring can help limit reductions in the annulus.	**Labeling – Instructions for Use** Recommend or provide: Examples of cases where valve repair is specifically contraindicated. Sizing techniques and the importance of proper ring sizing. Caution against undersizing the annuloplasty ring. Include the following statements: Left ventricular outflow tract obstruction is a potential complication associated annuloplasty rings. Only surgeons having received appropriate training in valve repair should use the device. Use an obturator or sizer with annuloplasty rings.
Systolic Anterior Motion (SAM)/Low Cardiac Output Some researchers believe that a rigid annuloplasty ring impairs the reduction of the anteroposterior dimension of the mitral annulus during systole, and displaces the mitral apparatus downward and towards the outflow tract causing SAM . Others have reported flexible rings are also associated with SAM and LVOTO. Intraoperative echocardiography has simplified diagnosis, and postoperative medical treatments, such as intraoperative intravascular volume repletion and reduction or cessation of intravenous inotropic therapy, have reduced the number of reoperations and extended bypass periods. The "sliding leaflet" and other techniques for mitral valve repair apparently have reduced the number of cases of post-operative SAM. See LVOTO	**Labeling – Instructions for Use** Recommend or provide: Techniques for assessing SAM by echocardiography. Examples of cases where valve repair is specifically contraindicated Techniques for implanting and suturing the annuloplasty ring. Sizing techniques, and explain the importance of ring sizing. Caution against undersizing the annuloplasty ring. Include the following statements: Systolic anterior motion and low cardiac output are potential complications associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair should use the device. Use an obturator or sizer with annuloplasty rings.

RISK:	CONTROL
Ring Dehiscence: **Materials or design** **Operative technique** **Product variability** Dehiscence related to initial annuloplasty ring repair may be avoidable, and the incidence should diminish with experience. Friable tissue or other deterioration of the patient's annulus may play a role. Bacterial endocarditis caused ring dehiscence immediately postoperative in one patient of 172. Blunt chest trauma due to a automobile accident has also caused dehiscence of a ring. None of the papers reviewed attributed dehiscence to failure of the device's fabric sewing ring.	**510(k)** Perform suture pull-out tests to determine fabric strength in the annuloplasty ring and to ensure fabric sewing cuff is capable of retaining the suture in the heart annulus. Conduct tensile testing to determine the overall strength of the fabric used in the annuloplasty ring and to ensure that structural failure will only occur at loads greater than those experienced *in vivo*. **Labeling – Instructions for Use** <u>Recommend or provide</u>: Examples of cases where valve repair is specifically contraindicated. Techniques for implanting/suturing the device. <u>Include the following statements</u>: Ring dehiscence is a potential complication associated with use. Only surgeons having received appropriate training in valve repair and are adequately trained to determine whether a diseased valve is capable of being repaired via annuloplasty, or if valve replacement is required; should use the device.
Heart Block: **Operative technique** Damage to the conduction system may result from disease, or from improper surgical technique such as suture placement or needle puncture in the atrioventricular node. Heart block has a low incidence of occurrence associated with valve repair, and is attributable to the surgical technique or to the patient's condition, rather than to the annuloplasty ring itself. Heart block following valve repair can be managed with a pacemaker to restore sinus rhythm.	**Labeling – Instructions for Use** <u>Recommend or provide</u>: Examples of cases where valve repair is specifically contraindicated Techniques for implanting and suturing the annuloplasty ring <u>Include the following statements</u>: Heart block is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair should use the device Do not to place sutures in the atrial tissue, as impairment of cardiac conduction may occur.

RISK:	CONTROL
Endocarditis: **Materials** **Sterilization** **Operative technique** **Product sterility** Endocarditis is caused by various pathogens Diagnosis is based on customary clinical criteria: positive blood cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly, immunopathological lesions, systemic emboli) and/or histological findings. Endocarditis is a known risk for patients receiving open heart surgery. Patients with evolving bacterial endocarditis are contraindicated for placement of annuloplasty rings. Patients with endocarditis are often treated medically, including pharmacologic therapy directed at the causative pathogen. For example, treatment for *Aspergillus flavus* endocarditis involving an mitral valve annuloplasty ring was demonstrated with combined surgical and antifungal therapy. Treatment for endocarditis following repair can also include valve replacement.	**510(k)** Conduct biocompatibility testing in accordance with the FDA biocompatibility guidance on ISO 10993. Perform sterilization validation to ensure that the sterilization process is capable of providing a Sterility Assurance Limit (SAL) of 10^{-6}. Perform biological testing, pyrogen testing and bioburden to ensure acceptable limits of biological contaminants. Conduct sterilization, validation, and biological tests on the sizer set to ensure that the ring sizers can be cleaned and sterilized according to the parameters specified in the labeling. Validate the package shelf life to ensure that the device will remain sterile for the period of time specified on the label: • Simulated or real shipment and handling conditions - dropping, vibration, stacking, temperature, humidity, and atmospheric pressure extremes followed by device functionality testing • Real or accelerated aging - if accelerated aging is used, plan to conduct a real time follow up to verify the accelerated results • Package integrity and barrier property assessment -using validated physical or microbial-based methods

RISK:	CONTROL
	Labeling – Instructions for Use Recommend or provide: Examples of cases where valve repair is specifically contraindicated Instructions for the possible prophylactic use of antibiotics in patients receiving the device. Instructions for opening the annuloplasty ring package and maintaining the sterile field. A warning, if applicable, that the sizer set is not sterile, must be sterilized prior to use, and include specific parameters for cleaning and sterilizing the ring sizer set components.
Endocarditis: continued	**Labeling – Instructions for Use continued** Include the following statements: Endocarditis is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair should use the device Annuloplasty rings is contraindicated for evolving bacterial endocarditis. Inspect the packaging, ensuring that it has not been opened or damaged.

RISK:	CONTROL
Bleeding Related to Anticoagulants: Bleeding related to anticoagulants is a known complication of cardiac surgery. Valve repair with annuloplasty rings offers an advantage over valve replacement, in that long-term anticoagulant therapy may not be indicated. As a result, anticoagulant-related bleeding is rarely associated with annuloplasty rings. When it occurs, bleeding is the result of anticoagulant therapy. Proper management of the patient's anticoagulation therapy can reduce the risk of bleeding.	**Labeling – Instructions for Use** Recommend or provide: Examples of cases where valve repair is specifically contraindicated Careful monitoring of the patient's anticoagulation status, when postoperative anticoagulant therapy is used , and surgeons who use annuloplasty rings be current on anticoagulation regimes. Include the following statements: Anticoagulant-related hemorrhage is a potential complication associated with annuloplasty rings. Only surgeons having received appropriate training in valve repair should use the device
Suture Damage to the Coronary Arteries: Suture damage to the coronary artery may cause a clot to form, which may lead to myocardial infarction and death. This complication may also occur during valve replacement surgery, or any heart surgery near the coronary arteries.	**Labeling – Instructions for Use** Recommend or provide: Examples of cases in which valve repair is specifically contraindicated. Techniques for implanting and suturing the annuloplasty ring Include the following statements: Do not place sutures in the circumflex coronary artery or in the right coronary artery. Damage to coronary arteries is a potential complication associated with annuloplasty rings. Only surgeons who have received raining in valve repair should use the device.

PERFORMANCE TESTING OF ANNULOPLASTY RINGS

The following is a generic protocol for validating a new annuloplasty ring using *in vitro* testing. The tests are not all-inclusive, but are representative tests applicable to most annuloplasty ring designs. Each manufacturer is responsible for selecting tests that are appropriate for their specific design.

This guidance addresses *in vitro* tests only. Biocompatibility and sterility are addressed in FDA's guidance documents, "Use of International Organization for Standardization's (ISO) 10993 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' " and "510(k) Sterility Review Guidance K90-1," respectively. Other consensus standards and FDA guidance documents are available to

manufacturers to assist in designing appropriate tests to validate a new annuloplasty ring design. The consensus standards include specific American National Standards Institute, American Society for Testing and Materials, Association for Advancement of Medical Instrumentation, International Standards Organization standards.

***In Vitro* and Computational Testing** – Computational analysis, tensile testing, and suture pull-out testing should be provided.

Computational analysis is used to evaluate the structural integrity of a new annuloplasty ring design with a solid core. One popular method for computational studies is finite element analysis, although other methods can be used. Validation of the ring's structural integrity under *in vivo* conditions can provide assurance against structural failure. Computational analysis is also an effective method to establish the dynamic failure modes of the prosthesis. Such testing serves as a special control to address the risk of ring fracture.

Tensile testing is used to measure the overall strength of the annuloplasty ring, to ensure that structural failure will occur at loads greater than those experienced *in vivo*. Tensile testing also may be used to determine the weakest elements of the design. Tensile testing serves as a special control to address ring fracture and the failure of the sewing ring fabric.

Suture pull out testing is used to determine the strength of the fabric component of a new annuloplasty ring design, and to ensure that the fabric sewing cuff can retain the suture in the heart annulus. This test is performed by placing the suture through the fabric of the sewing cuff, and pulling the ring and suture to failure in a tensile test apparatus. This test is used to verify that the fabric can withstand forces experienced *in vivo*. Suture pull out tests are recommended as a special control to help prevent ring dehiscence.

Additional Tests –More extensive *in vitro* tests and computational studies, as well as animal and/or clinical studies may be recommended for annuloplasty rings that depend on significantly new technology. Examples of new technologies include new materials (e.g., polyurethanes susceptible to oxidative or hydrolytic degradation), new designs (e.g., substantially different in design from current models), new surgical and/or suturing technologies (e.g., intended for percutaneous or endoscopic implantation), etc. These will be considered on a case by case basis.