Draft Guidance for Industry and FDA Staff

Heart Valves - Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
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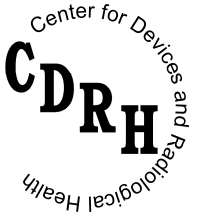

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Circulatory Support and Prosthetic Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation

Preface

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Draft Guidance for Industry and FDA Staff

Heart Valves - Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The guidance is intended to provide recommendations for the preparation of investigational device exemption (IDE) and premarket approval (PMA) applications for replacement heart valves that are not allograft heart valves or more than minimally manipulated allograft heart valves. This guidance[1] describes FDA's recommendations about manufacturing, preclinical *in vitro* bench testing, preclinical *in vivo* studies, clinical investigations, and labeling that are different from or in addition to the recommendations of the International Organization For Standardization (ISO), ISO 5840:2005, "Cardiovascular Implants - Cardiac Valve Prostheses" (ISO 5840).[2] Although the guidance provides information complementary to ISO 5840:2005,[3] the guidance can also be used with other methods equivalent to ISO 5840:2005.

This guidance is intended for use by members of industry and FDA staff who prepare or review replacement heart valve IDE and PMA applications. In this document, the terms "you" and

[1] FDA issued guidance on replacement heart valves in 1994 ("the 1994 draft"), before the FDA Good Guidance Practices were implemented in 2000 and before ISO 5840:2005 was published. FDA withdrew the 1994 draft in 2005 (70 FR 824, January 5, 2005) and is now issuing this draft guidance for public comment.

[2] Additional information on the CDRH standards program can be found at http://www.fda.gov/cdrh/stdsprog.html

[3] FDA has recognized only the 2005 version of ISO 5840, ISO 5840:2005 (71 FR 16313, March 31, 2006).

"your" refer to members of industry, also known as "sponsors" or "applicants," and the terms "we," "us," "our," and "Agency" refer to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. The use of the word *must* means that something is required.

II. Background

A replacement heart valve is a device intended to perform the function of any of the heart's natural valves. A replacement heart valve is a preamendment type device, that is, a device marketed prior to passage of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (the Act). A person may market a preamendments device that is class III by operation of law, through premarket notification procedures without submission of a premarket approval application (PMA), until FDA promulgates a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

On May 13, 1987 FDA issued a final rule (52 FR 18162) requiring a PMA or a notice of completion of a product development protocol (PDP) for any replacement heart valve that was in commercial distribution before May 28, 1976, or that on or before December 9, 1987, FDA had found to be substantially equivalent to a replacement heart valve that was in commercial distribution before May 28, 1976 (see 21 CFR 870.3925).

FDA refers to devices that were not in commercial distribution before May 28, 1976, as "postamendments devices." These device types are classified automatically by statute (section 513(f) of the act (21 U.S.C. 360c(f)) into class III without any FDA rulemaking process. Mechanical (product code LWR) and non-allograft tissue heart valves (product code LWQ) are postamendment device types that have been reviewed and approved as PMAs.

III. Scope

The heart valves addressed in this guidance are intended to perform the functions of any of the heart's natural valves. This guidance addresses valves constructed of prosthetic materials, biologic valves (e.g., porcine valves), or valves constructed of a combination of prosthetic and biologic materials.

Classification (21 CFR)	Class	Product Code	Description
870.3925	III	DYE	Replacement heart valve
†	III	LWQ	Heart valve, mechanical
†	III	LWR	Heart valve, non-allograft tissue

†Requires premarket approval application before marketing (see section 513(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(a))).

The recommendations in this document may also apply to new types of heart valves (e.g., tissue-engineered valves, polymer leaflet valves).

This guidance also applies to percutaneously delivered valves; however, different or additional *in vitro, in vivo* preclinical, and clinical studies may be appropriate for such devices, depending on the specific device design, the proposed indications for use, and the results of your risk analysis.[4] We recommend you contact the Circulatory and Prosthetics Devices Branch to discuss planned submissions for percutaneously delivered valves.

This guidance does not apply to valve-repair devices (e.g., annuloplasty rings (product code KRH, 870.3800)[5] or mitral valve repair devices (product code NKM)).

This guidance does not apply to allograft heart valves. Please contact FDA's Center for Biologics, Evaluation and Research (CBER) for information about the regulatory requirements for allograft heart valves.[6]

This guidance does not apply to more than minimally manipulated allograft heart valves (product code OHA), which require clearance of a 510(k) prior to marketing.

IV. Risk Analysis

Risk analysis is a formal procedure by which you estimate the probability and degree of harm a device represents, and plan appropriate investigations accordingly to mitigate those risks to the extent possible. We recommend that you perform a risk analysis as described in ISO 5840:2005 or its equivalent (e.g., hazard identification, associated failure modes, risk estimation, risk

[4] For recommendations that may be applicable to studies of delivery systems for percutaneously delivered valves, see the sections related to delivery system testing described in the FDA guidance, **Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems** at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071863.htm.

[5] See the FDA guidance, **Guidance for Annuloplasty Rings 510(k) Submissions** at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073644.htm.

[6] See http://www.fda.gov/cber/tiss.htm.

evaluation, risk control, and risk review). Your IDE applications should include your initial risk analysis for your device and your PMA should include an updated risk analysis.

V. The Pre-Submission Process

To use this guidance effectively, we encourage you to have frequent and early interaction with FDA reviewers. We also encourage you to use FDA's pre-submission procedure for this interaction. The purpose of a pre-submission interaction is to provide a mechanism for you and FDA to communicate informally about preclinical studies (i.e., bench and/or animal) before you conduct these studies, or about a clinical protocol before you submit an IDE application. Your pre-submission should include a description of the device, its intended use, and a risk analysis. Your pre-submission should also include summaries of your proposed test plan, protocols, and investigational plans. In addition, your pre-submission should contain clearly defined questions for discussion with FDA. You should include pictures, slides, videos, or samples, if you believe they are useful to understand your device.

VI. IDE and PMA Applications: General Considerations

Clinical studies conducted in the United States in support of a PMA approval must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[7] In addition to the requirement of having a FDA-approved IDE, sponsors must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

Your IDE application must include a complete report of prior investigations of the device including all prior clinical, animal and laboratory testing (21 CFR 812.20 (b)(2) and 812.27(a)). A complete report would include *in vitro* laboratory testing results, *in vivo* animal study testing results, and the protocols for the clinical investigations for prior investigations.

In general, we recommend that you complete *in vitro* testing of your replacement heart valve before you submit your IDE. It may be appropriate, however, to complete certain long-term *in vitro* tests while you conduct your clinical study. You should discuss your rationale for submission of any tests for which testing is not complete with the review branch before submitting your IDE. We believe that in all cases you should complete your accelerated wear testing before you submit your IDE.

Your PMA application must contain data and information in sufficient detail to permit FDA to approve or deny approval of the application, including the methods and protocols used in clinical investigations involving human subjects (21 CFR 814.20(b)(6)). You must provide the results from all preclinical *in vitro*, preclinical *in vivo*, and clinical testing you have conducted. Id.

[7] See http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

VII. Terms and Definitions

We recommend that you use the terms and definitions defined in ISO 5840:2005 when preparing IDEs and PMAs for replacement heart valves. In addition, FDA uses the following terms:

Replacement Heart Valve. Although ISO 5840:2005 uses the term "heart valve substitute" to mean a prosthetic heart valve, we use the term "replacement heart valve" in 21 CFR 870.3925 and in this guidance. We understand the term "replacement heart valve" to be equivalent to "heart valve substitute" (used in ISO 5840:2005) and equivalent to such terms as "prosthetic heart valve" and "heart valve implant" for purposes of this guidance.

Pressure Gradient. Although ISO 5840:2005 uses the terms "mean pressure difference" and "peak pressure difference," we use the term "mean pressure gradient" in this guidance instead of "mean pressure difference" and the term "peak pressure gradient" in this guidance instead of "peak pressure difference" because the term "pressure gradient" is used almost exclusively in the U.S. clinical arena and in the worldwide clinical heart valve literature. We recognize that the term "pressure gradient" has a very specific definition in engineering (i.e., pressure/distance) that is not consistent with the use of this term in this guidance.

Tissue Annulus Diameter. The tissue annulus diameter (TAD) is defined in ISO 5840:2005 as the diameter in millimeters at the smallest flow area within the patient's valve annulus. The valve size is now distinctly correlated with the TAD at its narrowest opening. As such, your designation of a replacement heart valve should indicate the TAD of the recipient in millimeters (i.e., TAD is now referred to as the designated valve size). We recommend that you follow this standardized definition to assure the correct sized valve is used.

If you use a term, definition or abbreviation that differs from any above or from those of ISO 5840:2005, we recommend that you include this information in your application.

VIII. Device Description

In your IDE and PMA application you must include a description of the device (21 CFR 812.25(d) and 21 CFR 814.20(b)(3)(ii)). We recommend that you provide the following descriptive information in your replacement heart valve IDE or PMA application.

Device Parameters

Your IDE and PMA application should include a description of each of the general device design parameters listed below. A tabular format is desirable, shown in the example following the list below.

- Implantation, including valve locations, annulus positions, and suture technique
- Leaflets/Occluder, indicating the number, material, and for rigid replacement heart valves, the fully opened angle, fully closed angle, and travel arc from opened to closed

- Radiopacity, identifying the radiopaque material and location of radiopaque material
- Housing/Stent, describing the leaflet articulation mechanism and stent material
- Sewing cuff, indicating whether the sewing cuff is rotatable and describing the attachment mechanism and material
- Coatings and treatments, if any, explaining the purpose (e.g., antibiotic, antithrombotic, anticalcific) and location
- Accessories, such as implantation tools (e.g., holder, rotator, leaflet probe, sizer).

Valve General Design Parameters Tabular Format Example

GENERAL DESIGN FEATURES		
PARAMETER		DESCRIPTION
Implantation:	Valve locations(s):	
	Annulus position(s):	
	Suture technique:	
Leaflets/ Occluder:	No. leaflets/occluders:	
	Fully opened angle*:	
	Fully closed angle*:	
	Travel arc from opened to closed*:	
	Material:	
Radiopacity:	Radiopaque material:	
	Location of radiopaque material:	
Housing/ Stent:	Leaflet articulation mechanism:	
	Material:	
Sewing cuff:	Rotatable/not:	
	Attachment mechanism:	
	Material:	
Coatings/ Treatments:	Purpose: (antibiotic, antithrombotic, anticalcific, etc.)	
	Location:	
Accessories:		Implantation tools (holder, rotator, leaflet probe, sizer).
Other:		

*Applicable only to rigid replacement heart valves.

Your IDE and PMA application should also include a description of each of the dimensional design parameters listed below for each size you plan to market.

- Tissue Annulus Diameter (TAD) (mm)
- Valve Outer Diameter (OD) (dictated by cuff OD) (mm)

- Valve Inner Diameter (ID) (dictated by housing ID) (mm)
- Geometric Orifice Area (mm^2)
- Profile Height(s) (mm).

Packaging Information

Your IDE and PMA application must include a description of the packing methods used (21 CFR 812.20(b)(3) and 21 CFR 814.20(b)(4)(v)). We recommend you include packaging design and performance information as described below. A tabular format is desirable, as shown in the example at the end of this section.

1. Package Design

We recommend that you describe the package design and include mass and volume (for purposes of calculating load density for sterilization validation), all components, and any feature that indicates whether the package has been opened. Your description should include sealing parameters, such as time, temperature, and lid closure torque. Your description should also include performance specifications for the sterilization cycles, lid, seal, vacuum leak resistance, and any sealing tape or temperature indicators.

2. Temperature Sensor

For valves that contain biological tissue, such as porcine, bovine, or equine valves, we recommend that you use a temperature sensor. We also recommend that you include information about how you validate the sensitivity of the sensor.

3. Storage for Valves that Contain Biological Tissue

We recommend that you provide a list of the components of the storage solution. We also recommend that you indicate the amount of the residual storage solution left on the valve tissue and in the used rinse solution after the valve has been rinsed according to the procedure specified in your labeling.

Package Information – Tabular Format Example

Package Information		
Package mass and volume	for purposes of calculating load density for sterilization validation	
Package components	i.e., container (jar), holder, lid and seal components (sealing tape), components or feature that indicates if the package has been opened	
Storage solution	amount of the residual storage solution left on the valve tissue and in the used rinse solution after the valve has been rinsed according to the procedure specified in your labeling	
Sealing parameters	PARAMETER	SPECIFICATION (average, min)
	Seal time, temperature, and pressure	
	Lid closure torque	

Performance specifications	Maximum no. of sterilization cycles		
	Sealing tape	Tensile strength	
		Shrinkage	
	Seal	Minimum seal width	
		Peel force	
		Burst strength	
	Lid removal torque		
	Vacuum leak resistance		
	Storage solution	Composition	
		pH	
	Temperature indicators		

IX. Pyrogenicity

You must establish and maintain procedures for acceptance activities (21 CFR 820.80). You must establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria (21 CFR 820.80(d)). A replacement heart valve is an implanted device; therefore we recommend that you test your device for pyrogenicity (specifically for endotoxins). We recommend that you provide:

- description of the method used to make the determination, e.g., Limulus amebocyte lysate (LAL)
- identification of the testing endpoint reached and rationale for selecting that endpoint
- description of the extraction technique used to obtain the test fluid from the test device, showing that all clinically relevant contact surfaces of the test device were assessed
- identification of the reference method used, e.g., United States Pharmacopeia (USP), ANSI/AAMI ST 72:2002, Bacterial endotoxins - Test methodologies, routine monitoring, and alternatives to batch testing or FDA guidance.

X. Sterilization

We recommend that you follow the sterilization methods described in ISO 5840:2005, or equivalent measures.

1. Non-Sterile Devices

If you intend to supply your device non-sterile, we recommend that you explain your rationale. You should indicate prominently on your labeling that the device is supplied non-sterile and provide instructions for acceptable use parameters, such as temperature, pressure, dwell times for the initial sterilization. Additionally, you should include in your

labeling whether re-sterilization, using these parameters, is appropriate. The determination whether re-sterilization is appropriate should be based on the validation testing for the stated parameters, and the number of resterilizations.

2. Resterilization

Your labeling should provide instructions for acceptable parameters to be used, such as temperature, pressure, dwell times, based on validations done to validate these parameters and numbers of resterilizations. If your labeling indicates your device is resterilizable (i.e., for packages that are "open but unused"), we recommend that your application include:

- a rationale supporting the safe and effective performance of your device after resterilization
- a description that differentiates between sterilization conducted at the manufacturing facility and sterilization performed by hospital staff
- validation of the effect of resterilization on the valve. (Validation should demonstrate that the maximum number of resterilizations recommended in your labeling does not affect the safe and effective performance of the valve.)

3. Validation Study

Where the results of a process cannot be fully verified by subsequent inspection and test, as with finished device sterilization, the process must be validated with a high degree of assurance (21 CFR 820.75). We recommend that you submit results of a validation study to show that the sterilization process provides a sterility assurance level (SAL) of at least 10^{-6}, i.e., the probability of finding an unsterilized device is one in one million. The validation should include use of inoculated product or indicators (biological or other types) placed in the location of the device that is most difficult to sterilize, and within the sterilization chamber. Viable spore count on biological indicators should be verified before each use. The organism chosen as the indicator should represent the worst case organism for the particular type of sterilization method chosen. All equipment used during the process to monitor conditions (thermocouples, gauges, etc.) should have been recently calibrated. Demonstrate and document that the validation methods chosen are compatible with the device and packaging materials thus establishing the high degree of assurance.

4. Controls

The environmental conditions of your facility can reasonably be expected to have an adverse effect on product quality. You must establish and maintain procedures to adequately control these environmental conditions (21 CFR 820.70(c) and 21 CFR 820.70(e)). We recommend that you include information on the controls used to ensure that the bioburden on the device is low (e.g., the cleaning schedule for the floors and other surfaces, disinfection procedures, management of water and air systems, laminar

flow hoods, sterilizers). We also recommend that you specify the warning and action limits for bioburden.

5. Package Integrity

You must ensure that device packages are designed and constructed to protect the device from alteration or damage, including the contamination of sterile devices (21 CFR 820.130). Testing should include an assessment of package integrity (via use of a physical method, such as a leak test, or a microbial challenge followed by sterility assessment of the contents). We recommend that you test the final whole package after simulated or real-time aging, shipment, handling and environmental stressing. Testing the final whole package is preferred over assessing package components separately, or only assessing sealed areas.

XI. Preclinical *In Vitro* Assessment

Based on your risk analysis, we recommend that you perform preclinical *in vitro* testing on your replacement heart valve following the methods described in ISO 5840:2005 or equivalent methods. We also recommend that you provide explanations for any *in vitro* testing you omit. Your IDE and PMA applications should include the test conditions, sample selection, and test reports for the following:

- material property testing
- biological safety
- hydrodynamic performance
- structural performance
- device durability
- component fatigue assessments
- device specific testing.

For each test, we recommend that your test report include the protocol, acceptance criteria and results (either as data or pass/fail). Your protocol should include sample size, environmental conditions, test parameters, and test duration. A tabular format is desirable, see the example table at the end of this section.

In addition, design controls apply to all heart valves. You must establish and maintain procedures in order to ensure that specified design requirements are met (21 CFR 820.30(a)). These procedures must include design validation procedures. Design validation must ensure that devices conform to defined user needs and intended uses and must include testing of production units under actual or simulated use conditions. (See 21 CFR 820.30(g)). Accordingly, we recommend that you include the information described below in your IDE or PMA application.

A. Valve Samples

We recommend that you perform all *in vitro* tests on finished valves, of the final design, exposed to the maximum number of recommended sterilization cycles.

B. Reference Valves

For any test that does not have validated pass/fail criteria, we recommend that you include the use of a legally marketed reference heart valve of similar composition as the valve you are testing.

C. Biocompatibility

FDA recommends that you conduct biocompatibility testing as described in the FDA guidance, **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**,[8] for blood-contacting, long-term implanted devices. If you follow a voluntary standard that is relevant to any aspect of the safety or effectiveness of the device that is known, or that should reasonably be known, to you, you must explain any deviation from such standard (21 CFR 814.20 (b)(5)(ii)). Material-mediated pyrogenicity testing using the rabbit pyrogen test should be performed as part of the biocompatibility battery of testing. A tabular format is desirable, as shown below.

Biocompatibility Information – Tabular Format Example

TEST PERFORMED/ LAB REPORT # (literature citation, standard reference)	EXTRACT(S) IF USED (polar, non-polar), or animal model/cell line	EXTRACT CONDITIONS (time, temperature, area or mass to volume ratio compared to in-use conditions)	TEST AND CONTROL(S) USED	RESULTS/COMMENTS (include units when appropriate, and include descriptions for all deviations from the standard/protocol
Cytotoxicity				
Sensitization				
Irritation / Intracutaneous Toxicity				
Systemic toxicity				
Sub-chronic toxicity				
Genotoxicity				
gene mutation				
chromosome aberration				
DNA damage				
In vivo assay				
Implantation				

[8] This guidance document can be obtained at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm

Hemocompatibility				
hemolysis				
complement activation				
in vivo thrombogenicity*				
Pyrogenicity				
Chronic toxicity				
Carcinogenicity				
Biodegradation				
Reproductive or Developmental toxicity				

*You may assess thrombogenicity in animal studies in place of this test.

D. Valve Durability Testing

We recommend that you assess the durability of replacement heart valves using accelerated wear testing (AWT) methods discussed in ISO 5840:2005 or equivalent methods. AWT should continue for 600 million cycles for rigid valves and 200 million cycles for flexible valves, using a back pressure between 125 and 150 mmHg, to test the durability of the components under pulsatile flow and physiologic loading. We recommend that you fully describe all conditions during AWT, including rationale for the conditions chosen, for the following:

- the fluid used
- the flow rates through the valves
- the pressure loading including back pressure.

E. Component Fatigue Testing

Components of rigid replacement heart valves and the load bearing, non-biological components of flexible replacement heart valves (e.g., stent wire) should be individually fatigue tested to 600 million cycles.

F. Dynamic Failure Mode Testing

We recommend that you subject a selection of valves that have survived the AWT to additional tests to determine the mode in which the valves will fail. We recommend that you provide qualitative and quantitative assessments of the failure modes and high stress areas in the valve (i.e., mode and location of the failure). We also recommend that you use these results to support any analytical validation or computational modeling of stress analyses of the components.

G. Cavitation

We recommend that you perform cavitation testing of rigid heart valves as described in Appendix B.

H. Corrosion Resistance

We recommend that you determine the corrosion resistance of the metallic materials by testing the final finished device in a physiological environment and, if appropriate, under stress. If you perform testing under cyclic loading, we recommend that you conduct tests under the same type of loading at a frequency that will not mask localized attack. We recommend that you perform corrosion testing both before and after your fatigue testing. Weight loss methods should not be used to evaluate localized attack (e.g., pitting) unless you are able to establish that your experimental technique is sufficiently sensitive. We recommend that you conduct all corrosion testing on final finished product.

I. Flammability of Valved Conduits

If your labeling recommends using an electrocautery device to cut the conduit material, you should assess the flammability of the conduit.

J. Hemodynamic Performance - Verification of the Bernoulli Relationship

We recommend that you assess the clinical hemodynamic performance by Doppler ultrasound, using the Bernoulli relationship,

$$\Delta P = K(V_d^2 - V_p^2)$$

where:

K is a constant

ΔP is the pressure gradient

V_d is the distal velocity measured by continuous wave Doppler

V_p is the proximal velocity measured by pulsed Doppler

The value of the constant K can vary depending on valve type. See **Appendix C. Bernoulli Verification** for additional recommendations.

K. Magnetic Resonance (MR) Safety Testing

For information regarding Magnetic Resonance (MR) safety testing, please see FDA guidance document entitled, "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment."[9]

See also **XVI. Professional Labeling**.

[9] This guidance document can be obtained at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm for guidance on MR safety testing of your device.

L. Shelf Life

We recommend that you perform the shelf life studies described in Appendix A of this guidance.

XII. Preclinical Animal Studies

FDA recommends that animal studies be conducted to evaluate most new replacement heart valve designs and that these studies marry best practices of biomedical research, including observance of 3R principles (i.e., reduce, refine, or replace), whenever it will not compromise the investigation of safety.[10] Therefore, we recommend that you perform *in vivo* animal testing on your replacement heart valve following the methods described in ISO 5840:2005 and ISO 10993:2006 or equivalent methods. If you use different endpoints or deviate from the testing described in this guidance or a standard you follow, we recommend that you explain why your approach is scientifically valid. We also recommend that you provide explanations for any *in vivo* animal testing you omit. Prior to performing animal studies, you may want to obtain FDA input on your animal study protocol via the pre-submission process. Your nonclinical laboratory studies must be conducted in accordance with 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. We refer you to those regulations for comprehensive regulation of Good Laboratory Practice, but discuss several aspects of animal studies here.

A. Methods

If technically feasible, we recommend chronic assessment of your replacement heart valve in all anatomical positions reflected in the indications for use. We also recommend that you explain your rationale for the animal model you have selected. ISO 5840:2005 generally recommends using only the same species, and suggests using animals of the same gender and age in animal studies; however, we believe this may not be adequate to evaluate all acute and chronic studies of a new valve design. Therefore, we may recommend additional animal testing beyond that described in ISO 5840:2005.

B. Study Design

We recommend that you evaluate the final finished product in your animal studies. We recommend that you assess the animal and the device immediately after implantation (acute hemodynamic performance; implantation handling characteristics) and at 20 weeks (chronic hemodynamic performance; explant pathology). We may, however, recommend that your chronic study continue more than 20 weeks, if the risk assessment of your device indicates that a greater duration is appropriate. We also recommend that your studies consist of a

[10] See Public Health Service Policy on Humane Care and Use of Laboratory Animals. http://grants.nih.gov/grants/olaw/references/phspol.htm#Health%20Research%20Extension%20Act%20of%201985

prospectively-defined number of animals for the acute, chronic and controls arms of your study. We recommend that a rationale for selection of the number of animals be provided.

Our Good Laboratory Practice regulations require that, for each study, you must have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study (21 CFR 58.120(a)).

We also recommend assessment of acute and chronic hemodynamic performance, valve-related pathology in either an orthotopic or non-orthotopic position, and chronic performance of anticalcification treatments (if applicable). In addition, we recommend 20 or more weeks of follow-up for chronic implantation.

C. Data Collection

We recommend that you collect the data listed below.

1. Study of Acute Hemodynamic Performance

In your acute study, we recommend that you collect:

- ease of handling and surgical implantation
- hemodynamic performance (catheter data as well as echocardiography)
- leaflet motion (by echocardiography and angiography)
- presence of stenosis or regurgitation.

2. Study of Chronic Hemodynamic Performance

In your chronic study, we recommend that you collect:

- ease of handling and surgical implantation
- hemodynamic performance (catheter data as well as echocardiography)
- leaflet motion (by echocardiography and angiography)
- presence of stenosis or regurgitation
- blood studies, imaging studies of leaflet motion and regurgitation
- *in situ* photos of inflow and outflow regions and valve surfaces
- necropsy and gross pathology
- explanted valve analysis (including histology of the valve and surrounding tissue).

3. Hemodynamic Performance Assessment

For the hemodynamic performance assessment, we recommend that you include:

- peak and mean pressure gradient
- effective orifice area (EOA) regurgitation
- a description of instrumentation and test methods.

4. Laboratory Results

Complete blood count (CBC) and chemistry analysis should include:

- red blood cell count
- white blood cell count (with differential)
- hematocrit
- free hemoglobin
- serum lactate dehydrogenase
- haptoglobin
- reticulocyte count
- platelet count.

For flexible leaflet valves, in addition to the tests listed above, you should include:

- serum calcium
- serum phosphorous
- leaflet calcium
- phosphate.

D. Data Analysis

In addition to the information described in ISO 5840:2005, your test report should include:

- appendices with clinical and hematological laboratory results
- hemodynamic findings
- the final pathology report (including gross pathology with macroscopic photographs, radiographs, structural integrity assessment for rigid and percutaneous delivered valves, and histopathology with representative micrographs)

E. Final Report of Animal Study

You must prepare a final report for each nonclinical laboratory study (21 CFR 58.185). Among other things, your final report must identify and describe the test and control device you used in the animal studies (21 CFR 58.185(a)(4)).

You must also include the numbers of animals used to obtain these data (21 CFR 58.185(a)(7)).

To meet the final report requirements, the report must include:

- valve model(s)
- valve size(s)
- whether the device was sterile or non-sterile
- whether the device was aged before implantation

- control device
- implant location.

The final report should also describe animal follow up. The description should include frequency, duration, and evaluation method(s).

Your report should define failures (e.g., device failures such as leaflet tear, stent fracture, balloon rupture). You should indicate the total number of device failures and include a complete description for each. We also recommend that you explain any procedural failures such as valve misalignment, improper suturing, or size mismatch, and that you provide a complete description of each. The report should show the total number of failures, stratified by your definitions.

Your test report must include a description of all circumstances that may have affected the quality or integrity of the data, including a listing of all protocol deviations and their impact on study findings (21 CFR 58.185(a)(9)).

F. Submitting Animal Study Information to your IDE and PMA

You must submit your final report of all animal studies to your IDE and PMA (812.27(a), 814.20(b)(6)(i)). You should provide for each study:

- study dates
- endpoints
- failure and success criteria
- physiological responses tested (e.g., cardiac output (CO))
- any inotropic drug administered (and dose)
- animal model(s) employed
- number of animals used
- animal age and verification (if birth records are not available, we recommend using dental eruption time and morphological changes of the dental table)
- medications and doses given for pre-procedure, during procedure, and post-procedure.

We also recommend that you explain how the animal models and medications adequately represent the intended patient population and anticipated clinical experience.

If the device you intend to market differs from the version used in the animal studies, we recommend that you describe all changes in design and manufacturing following the studies and that you provide a rationale to support using a device that is different from the one that is intended to be marketed.

XIII. Clinical Investigations

Clinical studies are necessary to evaluate most new replacement heart valve designs. We recommend that you perform clinical investigations of your replacement heart valve following the methods described in ISO 5840:2005 or equivalent methods. Prior to submitting your IDE application, you may want to obtain FDA input on your clinical study protocol via the pre-submission process.

Please see Appendix D of this guidance for additional recommendations about echocardiography when used in the clinical evaluation of replacement heart valves. The protocol submitted in your IDE and the final clinical report submitted in your PMA applications should address the issues described below.

A. Data Safety Monitoring Board

Sponsors are responsible for ensuring proper monitoring of the investigation and must select monitors qualified by training and experience (21 CFR 812.40 and 21 CFR 812.43(d)). We recommend that you establish a Data Safety Monitoring Board (DSMB)[11] to review adverse events and recommend study termination if safety concerns warrant. The DSMB should establish criteria for recommending study termination for safety reasons before the study begins and should meet at least two times during the study to monitor adverse events. The DSMB should have members who are independent from the study sponsors and investigators. Two or more members should be physicians, including a cardiothoracic surgeon and a cardiologist. If the study includes statistical analyses, one member should be a statistician.

B. Clinical Events Committee

We recommend that you establish a Clinical Events Committee (CEC) for the clinical investigation in order to adjudicate adverse events as being valve-related or not, and to classify the severity of adverse events. The CEC should have members who are independent from the study sponsors and investigators.

C. Number of Investigators

If your study uses only one clinical investigator, we recommend that you provide your rationale to show why experience from this one clinical investigator is sufficient to demonstrate the safety and effectiveness of your device and to ensure reproducibility of test results across multiple device users.

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[11] See Guidance for clinical trial sponsors on *Establishment and Operation of Clinical Trial Data Monitoring Committees*, March 2006. http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm.

D. Investigational Sites

Investigational sites are all the centers implanting the valve in the United States, and all the foreign centers implanting the valve that submit data as part of the investigation. All subjects should be completely accounted for in the final clinical report. We recommend that you provide complete subject accounting on a per subject basis for each cohort. You should include the number of subjects expected for follow-up, discontinued because of death or device removal, and actually evaluated at each evaluation time point.

E. Data Collection

The sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, requirements in 21 CFR Part 812 or other applicable FDA regulations, or any conditions of approval imposed by the reviewing investigational review board or FDA is responsible for promptly securing the investigators compliance or discontinuing shipment of the device to the investigator and terminating the investigator's participation in the investigation (21 CFR 812.46(a)). Your protocol must ensure that the investigation is scientifically sound by ensuring consistency between the indication studied, and the subject inclusion and exclusion criteria (21 CFR 812.25(b)). In all study designs, you should ensure that investigators collect the appropriate information. Specifically, you should ensure that the clinical data collection forms used by the investigators and institutions are consistent with the clinical protocol. You should also ensure that informed consent document(s) are consistent with the clinical protocol.

F. Control Data

Based on our long history in the evaluation of heart valves and the extensive reporting in the literature, FDA believes that a single-arm study with literature-based controls is the least burdensome approach to clinical evaluation of a replacement heart valve. Your clinical study should include appropriate controls including literature-based objective performance criteria (OPCs) for safety data, and literature articles and reports for both safety and effectiveness data. The OPCs should be established from data generated for a similar type of replacement heart valve, and the articles and reports should address a similar type of replacement heart valve in the same valve position. The control data from literature articles and reports should be collected from studies published in peer-reviewed journals during the past 5 years. The literature control safety data should include early adverse event rate data, linearized late adverse event rate data, and actuarial (usually Kaplan-Meier) adverse event rate data. The literature control effectiveness data should include New York Heart Association (NYHA) functional classification[12] data and hemodynamic data. See also section **I. Follow-Up Data** below for recommendations on hemodynamic studies data.

[12] The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

For infants and young children receiving replacement valves or valved conduits (such as pulmonic valved conduits) in clinical studies, NYHA functional classification data are not appropriate. Obtaining NYHA functional classification data on infants and young children is generally not feasible because these subjects are too young to provide the symptom information necessary for such classification. For these subjects the evaluation of effectiveness is typically based solely on the hemodynamic data, which may be variously supplemented with other effectiveness data such as cardiac imaging data and exercise testing data.

FDA recommends the use of the OPCs as listed in Table R.1 of ISO 5840:2005 Annex R since these OPCs are based on an extensive literature-based review of many articles from different institutions. We do not recommend the use of the OPCs in Table R.2 of Annex R since these latter OPCs are based on only one series of subjects (albeit a large series) at one institution. However, if you wish to include a concurrent control group in your study, we recommend that you contact the Division of Cardiovascular Devices.

G. Sample Size and Follow-Up Effect on Complication Rate

1. Patient-Years

We recommend that you measure follow-up in "patient-years" instead of the "valve-years" because double valve replacement (DVR) subjects, whose follow-up is expressed in valve-years, are typically excluded from the main analyses of safety data and NYHA functional classification data. We also recommend that you exclude DVR subjects from the main analysis because adverse events and NYHA functional classification cannot be clearly adjudicated to a particular valve position in DVR subjects.

2. Duration of Follow-Up

In order to provide a clinically sufficient amount of data on the investigational replacement heart valve, we recommend that all subjects be followed for 1 year or more.

If your clinical investigation is for one valve position, we recommend that you follow 300 or more subjects for 1 year or more for a total of 800 patient-years of follow-up.[13]

If the study is for two valve positions (i.e., aortic and mitral), we recommend that you follow 150 subjects for one year or more for each valve position for a total of 400 patient-years of follow-up per valve position.

[13] The recommended follow-up of 800 patient-years is statistically derived as follows: Single sample one-sided hypothesis testing can be used to demonstrate that each of the complication rates associated with the investigational device is less than 2 times the OPC for that complication. The appropriate null hypothesis is that the true rate associated with the investigational device is 2 or more times its OPC. To reject this null hypothesis is to accept the alternative hypothesis that the true rate associated with the investigational device is less than 2 times its OPC.

We recommend that you conduct the clinical study at eight or more primary centers, with 30 or more subjects implanted at each center for a one-position study and 15 or more subjects implanted at each center for a two-position study. We believe that using fewer than eight primary centers can introduce bias into the study.

For both one position and two position studies, we recommend implanting 15 or more subjects for each size and each position for all valve sizes. In other words, if your study assesses both aortic and mitral replacements, your study should enroll 15 or more subjects at the aortic position and an additional 15 or more subjects at the mitral position, for each valve size. The 15 subjects implanted per size per position criterion is based on statistical calculations for echocardiographic effective orifice area (EOA) data. These calculations show that in order to assure a sufficiently narrow 95% confidence interval, the minimum number of subjects implanted with each valve size is 15. If you omit any sizes, we recommend that you explain how the data you collect are representative of all the sizes that you intend to market.

3. Complication Rates

Assuming the Poisson distribution and the true rate being equal to its OPC, and with probabilities of Type I error of 0.05 and Type II error of 0.20, the amount of data necessary to achieve the smallest OPC of 1.2% per patient-year (excluding the OPCs for valve thrombosis, major hemorrhage, and major perivalvular leak, which are all less than 1.2% per patient-year) is 800 patient-years (aortic and mitral positions combined).[13] The null hypothesis for a complication rate can be rejected at the one-sided significance level of 0.05 if the upper 95% confidence limit for the complication rate is less than 2 times the OPC for that complication.[14,15]

4. Complications

We recommend that the complication data include hemorrhages resulting from all causes (all-cause hemorrhage) rather than just hemorrhage related to anticoagulant therapy (anticoagulant-related hemorrhage). Additionally, we recommend that the complication data include all-cause reoperation, valve-related reoperation, explant, all-cause death, and valve-related death.

H. Pre-Operative Data

The diagnostic pre-operative data collected should include the normal ranges for the clinical laboratory blood tests that are evaluated, with the normal ranges being determined by the laboratories used.

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[14] Grunkemeier GL, Johnson DM, and Naftel DC, Sample size requirements for evaluating heart valves with constant risk events. *J Heart Valve Dis* 3:53-58, 1994.

[15] Edmunds LH, Jr, *et al.* Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg* 112:708-711, 1996.

I. Follow-Up Data

Each subject entered into the study should be followed according to the study protocol. Additionally, follow-up data should be collected for each subject until the entire study is terminated for all subjects. This follow-up data should be collected by office, clinic, or hospital visit; telephone follow-up should be used only to verify death or loss to follow-up. As this follow-up data should be collected until the entire study is terminated for all patients, the follow-up period may be significantly longer than stated in the study protocol for most patients. Accordingly, you must receive informed consent to such follow-up period from all subjects (21 CFR 50.25(a)(1)). Any subject not willing to fully participate in the study, including the follow-up period, should not be entered.[16]

Follow-up data should include the normal ranges for the clinical laboratory blood tests evaluated according to the normal ranges used by the laboratories that conducted the testing. Plasma free hemoglobin is preferable to serum lactate dehydrogenase, haptoglobin, and reticulocyte count for the evaluation for hemolysis because we believe plasma free hemoglobin has higher clinical sensitivity for the detection of hemolysis than the other three laboratory tests.

We recommend that you provide the following echocardiographic hemodynamic data, stratified by valve size:

- peak pressure gradient
- mean pressure gradient
- effective orifice area
- valvular regurgitation
- effective orifice area index[17]
- performance index
- cardiac output
- cardiac index.

[16] Often patients are followed by their personal cardiologist, not the surgeon; therefore, the investigator should work in conjunction with the physician responsible for following the patient to ensure that the investigator collects the appropriate data at the correct time periods. This may be better accomplished if either the investigator or the sponsor obtains contact information for the following physician, so he/she can be advised of the actual study protocol.

[17] For replacement pulmonic valves and pulmonic valved conduits, we do not recommend that you calculate the effective orifice area, since the cone shape of the right ventricular outflow tract makes echocardiographic measurement of the right ventricular outflow tract diameter difficult. This difficult measurement leads to potential inaccurate calculation of the pulmonic valve effective orifice area via the continuity equation method. Similarly, for replacement pulmonic valves and pulmonic valved conduits, we do not recommend that you calculate effective orifice area index and performance index data, which are calculated using effective orifice area data.

J. Clinical Laboratory Results in Children

Clinical laboratory collections are very stressful for infants and young children receiving replacement valves or valved conduits (e.g., pulmonic valved conduits). Therefore, it may be appropriate to omit clinical laboratory collections for hemolysis evaluation at hospital discharge and 3 months post-implant in these populations. However, we recommend that you still perform clinical laboratory collections at 6 months and 1 year post-implant, and annually thereafter as specified in your protocol. For infants and young children who are unable to have all of the clinical laboratory blood test collections according to the normal ranges used by the laboratories that conducted the testing, spot urine urobilinogen is an acceptable test for hemolysis evaluation.

K. Imaging Data

We recommend that the imaging data within the follow-up data include reports of:

- echocardiograms
- cardiac catheterizations
- any other cardiovascular imaging procedures, including CT and MR scans
- chest x-rays.

L. Additional Information

In accordance with 21 CFR 814.20(b)(3)(v)(B), your PMA must include a summary of the clinical investigations, including adverse reactions and complications. We recommend your summary specifically include:

- case summaries of each death with a determination of whether the death represents an early or a late death[18]; and
- the summary of subjects not completing study stratified by lost-to-follow up, death, or explant).

We recommend that you also include the following information, if available:

- locations of the investigational sites;
- comparison of preoperative and postoperative NYHA functional class (presented as the percentage of subjects in each class at baseline, at each follow-up time-point, and as the percentage of subjects at each follow-up time-point who improved, worsened, or did not change in class);
- the "pre-implant" effective orifice area of the replacement heart valve;

[18] FDA considers a death occurring within 30 days of implantation or during the initial hospitalization, whichever time period is longer, to be an early death. FDA considers all other deaths to be late deaths.

- numbers of implanted subjects stratified by investigational site, replacement valve position (e.g., aortic, mitral, or double valve replacement), and valve size;
- numbers of implanted subjects followed to 1 year post-implant stratified by investigational site, replacement valve position (e.g., aortic, mitral, or double valve replacement), and valve size;
- follow-up duration information (total and by valve position), including mean follow-up, standard deviation and range of follow-up, and cumulative follow-up in patient-years;
- confounding factors by hazard regression analysis applied to identify risk factors (e.g., gender, age at implant, pre-operative NYHA functional classification, previous valve surgery, concomitant coronary artery bypass surgery, implant position, and implant size), which might affect the incidence of reoperation, explant, and death;
- patient compliance data for follow-up visits, NYHA functional classification data, echocardiographic data, and clinical laboratory results;
- list of complications by patient identification number;
- summary of subject complaints received;
- case report forms for a 10% random sampling of the subject population;
- copies of case report forms for all subjects not completing the study;
- explant analysis in all cases when a valve is explanted or an autopsy is performed; and
- death reports including autopsy reports, when available, especially when the cause of death has been classified as non-valve related.

M. Database Closure

The clinical data in your PMA application should be current to within six months of the date of submission. You must also periodically update your pending application with new safety and effectiveness information learned from ongoing or completed studies (21 CFR 814.20(e))

N. Subject Compliance

Subject compliance should be calculated as the following four percentages: the number of subjects having completed follow-up visits, with NYHA functional classification data, with echocardiographic data, and with clinical laboratory results at each follow-up time-point, divided by the total number of implanted subjects available (i.e., who have not died or had their valve explanted) and eligible (i.e., who have reached the given time-point) for follow-up at that particular time-point. The total number of subjects having echocardiography exams should be the same as the total number of subjects with data for each specific echocardiographic hemodynamic parameter (i.e., peak pressure gradient, mean pressure

gradient, effective orifice area, effective orifice area index,[17] performance index, cardiac output, cardiac index, and valvular regurgitation).

O. Data Pooling

We believe that pooling data from more than one valve position, such as pooling the data from the aortic and mitral valve positions, masks potential differences in valve function and valve-related adverse events. Therefore, you should stratify the data by valve position instead of pooling these data.

P. Adverse Events and Complication Rates

Your PMA should include the actual number of adverse events. In addition, we recommend that you express early complication rates as the number of adverse events divided by the total number of subjects, as recommended by Edmunds *et al.*[15] We recommend that you include linearized late complication rates. Linearized late complication rates are calculated as the number of late adverse events divided by the total number of late patient-years.

Q. Foreign Data

Any foreign data submitted in support of your PMA application must comply with 21 CFR 814.15.

If you are relying solely on foreign data to support your PMA application for a replacement heart valve, we recommend you provide the usual one-year data as well as up-to-date information including annual follow-up (e.g., New York Heart Association (NYHA) heart failure classification scheme,[12] echocardiogram, and blood tests according to the normal ranges used by the laboratories that conducted the testing. Your data should demonstrate long-term performance and failure mode, and include autopsy or explant analyses, when available.

XIV. PMA Supplements

An approved PMA supplement is generally required prior to making a change affecting the safety or effectiveness of your device. (21 CFR 814.39).[19] Recommendations below address special considerations related to modifications of the sewing ring configuration and valved conduits.

[19] See **Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process**, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm.

A. Modifications to the Sewing Ring Configuration

Generally, clinical data may not be needed to establish the safety and effectiveness of alternate sewing ring configurations provided you have not altered the substructures of the valve. We recommend that you validate changes to your sewing ring configuration by conducting *in vitro* studies to clearly establish that the new sewing ring can support the physiological loading. We recommend that you compare the specific material (manufacturer, weave, etc.) with the material used in your approved PMA. We also recommend that you validate common, clinically-accepted sewing ring materials (polytetrafluoroethylene [PTFE], polyethylene terephthalate [PET]) with animal healing data supplemented with explant data. For any sewing ring materials other than PTFE and PET, however, we recommend that you validate the modification with clinical data.

B. Valved Conduits

We recommend that you conduct clinical investigations for replacement valved conduits. Clinical investigations may not be needed when both the valve and the conduit or graft are legally marketed. If both are legally marketed, *in vitro* investigations may be sufficient. Whether an *in vitro* investigation is appropriate depends on your risk assessment; e.g., the risk assessment for a modified design may indicate the ability of the valve/graft interface to withstand physiological loading is potentially different. In this case, *in vitro* studies may be appropriate to validate a change in the design of the valve/graft interface. Or, for instance, if you modify your device by using a coated graft, the risk assessment should address whether there are any potential adverse effects to the coating (e.g., loss of coating integrity leading to bleeding due to the manufacturing steps associated with sewing the valve into the graft).

XV. Professional Labeling

Labeling requirements for medical devices are described in 21 CFR Part 801.[20] In accordance with 21 CFR 814.20(b)(10), you must submit all proposed labeling in your PMA. We recommend that your labeling include the information found in Section 6.2.3 and Annex Q of ISO 5840:2005 or equivalent suggested for inclusion in labeling and instructions for use**.** In addition, your labeling should include the information described below.

A. Non-Sterile Devices

If you intend to market your device in non-sterile form, you should provide clear and adequate instructions for sterilization in your instructions for use with acceptable parameters to be used, such as temperature, pressure, dwell times, and whether or not re-sterilization using these parameters is appropriate, We also recommend that you prominently indicate in your package labeling and instructions for use that your device is provided non-sterile.

[20] See **CDRH Device Advice** available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm for additional information about device labeling requirements.

B. Resterilization

If the device can be resterilized, then the labeling should include the recommended sterilization method and parameters to use.

C. Magnetic Resonance Imaging (MRI)

For information regarding Magnetic Resonance (MR) safety testing, please see FDA guidance document entitled, "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment."[21]

XVI. Patient Labeling

If you propose to provide patient labeling, e.g., a patient manual or patient identification cards with your device, you must submit the proposed labeling in accordance with 21 CFR 814.20(b)(10). The patient manual should include a discussion of anticoagulation therapy and the importance of follow-up visits. See **Guidance on Medical Device Patient Labeling**[22] for more information about the contents of patient labeling.

The patient identification card should show the following:

- patient name
- date of implant
- name and contact information for the implanting physician, the following physician, and the device manufacturer
- emergency contact person
- device name, size, position and serial number
- any medications and dosages
- MR Safe or MR Conditional information[23].

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[21] This guidance document can be obtained at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm for guidance on MR safety testing of your device.

[22] This guidance document can be obtained at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm.

[23] For additional information, please see, "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment" at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm.

Appendix A. Shelf Life Validation

Your PMA application must include a technical section which shall contain data and information, including the results of the shelf life testing, in sufficient detail to permit FDA to determine whether to approve or deny your application (21 CFR 814.20(b)(6)(i)). You should validate your replacement heart valve and package over the shelf life of the device because of the potential for valve deterioration that is not readily visible to the surgeon, but that could subsequently manifest in the patient as premature valve failure. For all valves, we recommend that you conduct comparative performance testing of aged and unaged whole valves, as described below.

We recognize that some shelf life validation tests identified in this guidance are applicable to only certain valves. If you believe that a particular test does not apply to your device, we recommend that you provide your rationale for omitting the test.

For shelf life validation, we recommend that you explain how each of the following is clinically representative and in agreement with the operational specifications of the device:

- test parameters (systemic pressure, beat rate, stroke volume, cardiac output (CO), tissue compliance, etc.)
- test duration
- applicable performance specification.

A. Test Valve Selection

To establish a shelf life for your device, you should evaluate whole valves aged to the labeled shelf life and unaged whole valves in a side by side manner in order to make a comparison. We recommend that you evaluate:

- valves of the smallest, intermediate, and largest sizes
- valves sterilized to the maximum number of cycles in accordance with the established and validated sterilization process
- final finished product (i.e., subjected to all manufacturing processes, including an anti-calcification treatment, if applicable)
- valves subjected to simulated distribution and handling conditions.

B. Real-Time and Accelerated Aging

We generally recommend real-time aging of test valves. However, if you use accelerated aging techniques, we recommend that you describe how you validated your accelerated aging methods and provide the results of any validation studies conducted. We recommend aging of the whole valve, including the stent for those valves with stents, because the storage solution can have an impact on the integrity of the stent. However, the stent may be removed for testing. Aging studies, whether real-time or accelerated, should address the effects of:

- temperature

- humidity
- pressure
- light exposure
- shipping and handling.

C. Device Stability

We recommend that you evaluate the functional performance, structural integrity, tissue morphology, if applicable, and properties of the device at zero time and at the labeled shelf life. We recommend that you explain your rationale for each test method used.

1. Hydrodynamic Performance

To demonstrate hydrodynamic performance, we recommend comparing data from the following tests on aged and unaged devices:

- steady forward flow (ΔP, EOA)
- pulsatile forward flow (ΔP, EOA)
- pulsatile regurgitation
- anti-calcification effects, if applicable, (as determined by subcutaneous implantation in rats or rabbits).

2. Structural Integrity

To demonstrate structural integrity, we recommend comparing data from the following tests, if applicable, on aged and unaged devices:

- leaflet durability
- leaflet prolapse (as determined by steady backflow testing).
- sewing cuff integrity (pull testing)
- sewing ring integrity (pull testing)
- stent fatigue
- stent creep
- scanning electron microscopy (SEM) analyses
- polymeric stent chemical concentration analyses.

3. Tissue Morphology and Properties

To demonstrate that the shelf life storage does not adversely affect tissue morphology and properties, if applicable**,** we recommend comparing data from the following tests on aged and unaged devices:

- histology with staining

- fixation stability (via shrinkage temperature or differential scanning calorimetry)
- residuals in storage solution (e.g., aldehyde ppm)
- biomechanical properties (biaxial testing, creep testing).

4. Storage Solution

We recommend that you assess the storage solution as part of the shelf life validation. Changes in pH, chemical composition, polymerization or breakdown, as well as leakage may occur and should be evaluated. Prolonged degradation of the storage solution may have an effect on tissue quality. Your assessment of the storage solution should include an analysis of the residuals in the storage solution and analysis of package components leached into the storage solution at the labeled shelf life of the device.

5. Package Integrity

You must ensure that device packages are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution (21 CFR 820.130). We recommend that you evaluate the package integrity of the product packaging at zero time and at the labeled shelf life, preferably using a method that evaluates the whole package rather than only the seal area. The package should contain either the real product, or a simulated product that has similar mass and geometry. You should include your rationale for the test methods employed.

Shelf Life Validation Information – Tabular Format Example

PLANNED QUALIFICATION & VALIDATION STUDIES	SAMPLE SIZE [subject (control)]	SAMPLE PREPARATION				ACCEPTANCE CRITERIA
		Sterilization	Aging	Distribution & Handling	Other (e.g., treatments)	
Valve *in vitro* hydrodynamic performance:						
Steady forward flow (ΔP, EOA)						
Pulsatile forward flow (ΔP, EOA)						
Pulsatile regurgitation						
Anti-calcification effect (if applicable) determined by subcutaneous implantation in rats or rabbits						
Valve structural integrity:						
Leaflet durability						
Leaflet prolapse determined by steady backflow testing						

	Sewing cuff integrity (pull testing)						
	Sewing ring integrity (pull testing)						
	Stent fatigue						
	Stent creep						
	Stent SEM analyses						
	Polymeric stent chemical concentration analyses						
Valve tissue morphology & properties:							
	Histology (with staining)						
	Fixation stability (shrink temperature or differential scanning calorimetry)						
	Residuals in storage solution (e.g., aldehyde ppm)						
	Biomechanical properties (biaxial testing, creep, and corrosion)						
Storage solution:							
	Volume						
	Chemical composition						
	pH						
	Leaching analysis (of package components into storage solution, particularly if EtO sterilized)						
Package integrity:							
	Test method used						
	Real or simulated product						

Appendix B. Cavitation Testing for Rigid Heart Valves

Cavitation erosion (and in some cases, catastrophic structure failure) has occurred in some rigid replacement heart valve designs. Additionally, cavitation can be induced in most rigid heart valves *in vitro*. Thus, we recommend cavitation potential testing for rigid valves. Since no one test is sufficient to assess the cavitation potential of a new rigid replacement valve design, we recommend that you perform a preclinical *in vivo* study, simulated long term *in vitro* study (i.e., durability testing) to assess possible cavitation damage, and examine the animal study and clinical (if applicable) explanted valves for evidence of cavitation.

This appendix represents our understanding of *in vitro* cavitation test methods at the time this guidance was issued. You should review state of the art cavitation testing before implementing a protocol. Our general recommendations for test parameters are given below.

A. Test Valve Selection

We recommend that you test two of the smallest and two of the largest valve sizes.

B. Test Valve Mounting

For cavitation testing, the valves should be rigidly mounted in the mitral position of a heart simulator. If no mitral valve model is under evaluation, a test protocol for the aortic position should be developed.

C. Reference Valves

We recommend that you use two samples of an FDA-approved valve as reference valves.

D. Working Fluid

The working fluid should be physiological saline allowed to come to equilibrium with room atmosphere for 24 hours.

E. Atrial Chamber

The atrial chamber should be open, with a cross sectional area greater than 75 cm^2.

F. Atrial Pressure

The mean atrial pressure on the test valve should be less than 7 mmHg.

G. Cavitation Definition

FDA defines cavitation as at least one instance of bubble formation noted on valve closing out of every ten cycles studied.

H. Description of Detector

We recommend that you describe the cavitation detection system and indicate its sensitivity.

I. Pressure Profile

We recommend that you provide a profile of the pressure vs. time (averaged over ten consecutive systolic cycles) at 120 mmHg, and at any peak ventricular pressure at which cavitation is found for any valve, either subject or reference. We also recommend that you report the average pressure over systole.

J. Ventricular Pressure

Valves should be tested at 120 mmHg peak ventricular chamber pressure and at a maximum flow rate of 7.0 L/min. The systolic ratio should be set at 35 ± 2 %.

K. Maximum Ventricular Pressure

If cavitation is not observed in either the set of subject valves or the set of reference valves, the peak ventricular pressure should be increased until cavitation is seen in at least one set of the valves, or until peak ventricular pressure is equal to 200 mmHg. If you vary system parameters to achieve cavitation, we recommend that you describe the system parameters you changed.

Appendix C. Bernoulli Verification

Clinical hemodynamic evaluation of replacement heart valves in clinical trials typically includes measurement of the pressure gradient by Doppler ultrasound. Doppler velocity measurements are converted into pressure gradients using the Bernoulli equation, $\Delta P = K(V_d^2 - Vp^2)$. Theoretically, the constant K will equal 4, but valve-dependent deviations from this value have been reported.[24,25,26,27] We recommend that you determine, *in vitro*, whether the coefficient 4 is appropriate, by comparing ΔP measured by Doppler with that measured directly by a pair of pressure transducers.

Testing should include one of the largest, intermediate, and smallest samples for each valve type, as well as an appropriate (same size and type) legally marketed valve as reference.

We recommend that you plot the values of ΔP as measured by pressure transducers against (V_d^2 - V_p^2) as measured by Doppler, for flow rates that you used.

We recommend that you describe how the resulting experimentally measured constant K may affect clinical measurements of pressure gradients, for diagnosis and prognosis**.**

[24] Yamashita T, Moriyama Y, Sata N, et al. Discrepancy between Doppler and catheter measurements of pressure gradients across small-size prosthetic valve. Jpn J Thorac Cardiovasc Surg. 2005;53:64-8.

[25]Mascherbauer J, Schima H, Maurer G, Baumgartner H. Doppler assessment of mechanical aortic valve prostheses: effect of valve design and size of the aorta. J Heart Valve Dis. 2004;13:823-30.

[26]Stewart SF, Herman BA, Nell DM, Retta SM. Effects of valve characteristics on the accuracy of the Bernoulli equation: a survey of data submitted to the U.S. FDA. J Heart Valve Dis. 2004;13:461-6.

[27]Bech-Hanssen O, Caidahl K, Wallentin I, Brandberg J, Wranne B, Ask P. Aortic prosthetic valve design and size: relation to Doppler echocardiographic findings and pressure recovery- an *in vitro* study. J Am Soc Echocardiogr. 2000;13:39-50.

Appendix D. Echocardiography Protocol

You must submit your clinical protocols with your PMA application (21 CFR 814.20(b)(6)(ii)). For your IDE application, you must submit an accurate summary of your protocols, and we may request additional information concerning the investigation. 21 CFR 812.20(b)(2), (c)). This appendix describes FDA's recommendations for the echocardiographic evaluation of replacement heart valves in clinical studies. Information regarding the echocardiography protocol (recording studies, data collection, and core laboratory calculations and analysis) can be found in Annex H of ISO 5840:2005.

We recommend the following in addition to ISO 5840:2005 Annex H, subsection H.1. The recommendations and methodologies are applicable to all replacement heart valves regardless of implantation method.

An echocardiography core laboratory should perform the central review of all echocardiographic data. The core laboratory should have a supervising director who is an echocardiologist experienced in echocardiographic replacement valve evaluation. The core laboratory should use a written echocardiography protocol, followed by all sonographers and investigators involved in the clinical study. Interpretation of the echocardiograms by the core laboratory should be masked. If there are any differences between the study centers and the core laboratory in the interpretation of echocardiograms, then the core laboratory will take precedent in FDA's review of the echocardiograms.

We recommend that you stratify all echocardiographic hemodynamic data, including valvular regurgitation data, by valve position and valve size.

If you collect transesophageal echocardiography (TEE) data, we recommend using a multiplane TEE exams, rather than monoplane or biplane TEE exams. Many standard hemodynamic measurements, such as aortic valve pressure gradients, that are available with the use of transthoracic echocardiography (TTE) may not be available if you use TEE. Since it is important to use the same echocardiographic imaging modality at all follow-up time-points, and since TTE is the clinical standard and least invasive method of echocardiography, we recommend that you perform TTE exams at all follow-up time points. These time points should include "at hospital discharge" or a time point at 30 days or less post-implant if the subject has not been discharged.

A. Data Collected by the Study Center

If you follow ISO 5840:2005 Annex H, subsection H.3, we recommend the additions described below.

Data collected by the study center should include:

- peak pressure gradient
- mean pressure gradient

- effective orifice area (EOA or A_{EO})
- effective orifice area index (EOAI or $A_{EO}I$)
- performance index (PI)
- cardiac output (CO or O_C)
- cardiac index (CI).

The data should consist of subject numbers and mean (average), standard deviation, minimum values, and maximum values. We recommend that you stratify the data by valve position and valve size.

Although ISO 5840:2005 uses the terms "velocity integral" and "[diastolic] velocity integral (DVI)," the common U.S. clinical term is "velocity time integral (VTI)" or "time velocity integral (TVI)."

ISO 5840:2005 recommends averaging 5 heart beats when obtaining echocardiographic hemodynamic measurements in subjects with atrial fibrillation. These subjects may have a highly variable heart rate which may cause measurements that are either several minutes apart (such as LVOT and mitral valve measurements) or obtained over 5 or more beats. Such measurements may be erroneous because they are subject to both heart rate variation and respiratory alteration. In order to mitigate measurement errors, the echocardiographer should select beats that follow a physiologic preceding cycle length (e.g., 800 ± 80 ms or 75 ± 10 bpm) or beats with 10% variability in heart rate. Using either of these two approaches, the standard multiple beats (usually 3) can be measured and averaged regardless of the underlying rhythm.

Valvular regurgitation data should consist of the numbers and percentages of subjects for each grade of severity. We recommend that you stratify valvular regurgitation data by grade of regurgitation severity, valve position, and valve size.

We recommend that you document other data that are routinely obtained as part of a complete echocardiographic examination, including:

- non-study valve (native or other replacement) structure and function
- left and right atrial size
- left and right ventricular size
- left and right ventricular function
- ventricular septal and left ventricular posterior wall thickness
- cavitary thrombi or other masses
- pericardial abnormalities (such as effusion)
- aortic root diameter.

B. Calculations and Analysis by the Core Laboratory

1. Effective Orifice Area

We recommend that you perform echocardiographic studies as described in ISO 5840:2005 Annex H, subsection H.4 or its equivalent. In addition, we recommend that you perform the core laboratory calculations and analyses as described below.

For effective orifice area, A_{EO}, we recommend the continuity equation below.

For aortic valves: $$A_{EO} = \frac{A_{CS.LVOT} \times VTI_{LVOT}}{VTI_{AV}}$$

For mitral valves: $$A_{EO} = \frac{A_{CS.LVOT} \times VTI_{LVOT}}{VTI_{MV}}$$

where A_{EO} is the effective orifice area in cm^2

$A_{CS.LVOT}$ is the left ventricular outflow tract (LVOT) cross-sectional area in cm^2, calculated from the diameter assuming circular cross-section

VTI_{LVOT} is the LVOT velocity time integral (VTI) in cm, as measured by pulsed wave (PW) Doppler

VTI_{AV} is the aortic velocity time integral (VTI) in cm, as measured by continuous wave (CW) Doppler

VTI_{MV} is the mitral velocity time integral (VTI) in cm, as measured by CW Doppler

If significant aortic regurgitation is present, the continuity equation for mitral valves will likely overestimate the mitral valve effective orifice area, if you use the LVOT cross-sectional area and LVOT velocity time integral. In this case, we recommend that you substitute the LVOT cross-sectional area and LVOT velocity time integral in the continuity equation as follows. We recommend that you use the substitutions shown in the table below.

IN PLACE OF:	**USE:**
LVOT cross sectional area ($A_{CS.LVOT}$)	pulmonic annulus cross sectional area ($A_{CS.PV}$) in cm^2 (calculated from the pulmonic annulus diameter)
LVOT velocity time integral (VTI_{LVOT})	pulmonic valve velocity time integral (VTI_{PV}) in cm (as measured by CW Doppler)

The mitral valve effective orifice area may be calculated by the pressure half-time method instead of the continuity equation. If significant mitral regurgitation is present, the continuity equation for mitral valves will likely underestimate the mitral valve effective orifice area if the LVOT cross-sectional area and LVOT velocity time integral are used. In this case, we recommend that you use the pressure half-time method instead. The pressure half-time (PHT) is defined as the time (in milliseconds) for the maximum (peak) early diastolic transmitral pressure gradient to decrease by one-half or for the maximum (peak) velocity to decrease by $1/\sqrt{2}$ (= 1/1.4). The PHT is determined by CW Doppler.

For mitral valves:

$$A_{EO} = \frac{220}{PHT}$$

$$PHT = 0.29 \times DT$$

where PHT is the pressure half-time in ms

DT is the deceleration time in ms

Alternatively, PHT can also be graphically determined at the point where the half-time velocity (peak velocity/1.4) intersects the linear velocity slope on the CW Doppler spectral velocity trace.

We recommend that you indicate the method of calculation of the effective orifice area used for each valve position. We also recommend that you use the same method of calculation for each valve position for all follow-up time-points.

One reference cautions that the PHT overestimates the effective orifice area of normal replacement mitral valves, since the constant 220 was derived based on native mitral valve stenoses rather than replacement mitral valve stenoses.[28] Therefore, when there is no significant mitral regurgitation, the continuity equation may be a better method for determining the effective orifice area of replacement mitral valves.

Most normally-functioning replacement aortic and mitral valves have some restriction to flow due to varying degrees of inherent stenosis. Consequently, normally-functioning replacement mitral valves may have high initial velocities, but will have a rapid PHT, as compared to an obstructed replacement valve which will have a prolonged PHT.

[28] Oh JK, Seward JB, and Tajik AJ. The Echo Manual, 2nd ed. Lippincott-Raven Publishers, Philadelphia, PA, New York, NY, 1999.

The pressure half-time method is unreliable in situations in which the left ventricular (LV) diastolic pressure rises rapidly (due to restriction to filling) as with significant aortic regurgitation, LV diastolic noncompliance, or ischemia. In these situations the rapid rise in LV diastolic pressure results in rapid equilibration of the pressure difference between the left atrium and the left ventricle, and the PHT is shortened. The pressure half-time method is also unreliable in situations in which quality spectral Doppler wave forms are not obtained, such as in atrial tachycardia and first degree AV block (long PR interval) where the E wave and the A wave merge, and in atrial flutter where the flutter wave Doppler patterns may change the E wave decay pattern.[29] Subjects with abnormal myocardial relaxation have a prolonged PHT, but the peak E velocity is not increased and is usually lower than 1 m/s.[28]

It is appropriate to calculate the aortic valve effective orifice area by the continuity equation only if you have an accurate LVOT measurement. If you cannot obtain an accurate LVOT measurement, we recommend that you report the Doppler velocity index as a surrogate for the aortic valve effective orifice area. The Doppler velocity index (also called the dimensionless index) is the ratio V_{LVOT}/V_{AV}, where V_{LVOT} is the LVOT velocity and V_{AV} is the aortic velocity. A Doppler velocity index less than 0.20 for a mechanical replacement valve or less than 0.15 for a heterograft bioprosthetic valve is generally consistent with severe replacement aortic valve obstruction.[29]

For replacement pulmonic valves and pulmonic valved conduits, we do not recommend that you calculate the effective orifice area, since the cone shape of the right ventricular outflow tract makes echocardiographic measurement of the right ventricular outflow tract diameter difficult. This difficult measurement leads to potential inaccurate calculation of the pulmonic valve effective orifice area via the continuity equation method. Similarly, for replacement pulmonic valves and pulmonic valved conduits, we do not recommend that you calculate effective orifice area index and performance index data, which are calculated using effective orifice area data.

However, we still recommend that the pulmonic peak gradient and mean gradient be calculated, using CW Doppler, as done for other valve positions.

For aortic and mitral valves, we recommend that you index the effective orifice area to body surface area as shown below.

[29] Kerut EK, McIlwain EF, and Plotnick GD. Handbook of Echo-Doppler Interpretation. Futura Publishing Company, Inc., Armonk, NY, 1996.

For aortic and mitral valves:

$$A_{EO}I = \frac{A_{EO}}{A_{BS}}$$

where $A_{EO}I$ is the indexed effective orifice area in cm^2/m^2.

A_{BS} is the body surface area in m^2

2. Velocity Time Integral

The velocity time integral [or time velocity integral (TVI)] is defined according to the following equation:

$$VTI = V_{mean} \times t_{EJ} \times 10^{-5}$$

where VTI is the velocity time integral in cm

V_{mean} is the mean velocity of forward flow in m/s

t_{EJ} is the ejection time in ms

Alternatively, you may calculate the velocity time integral (VTI) by the built-in software of modern echocardiography ultrasound machines using the technician's planimetry (tracing) of the Doppler velocity signal.

3. Peak Pressure Gradient

We recommend that you calculate the peak pressure gradient across the replacement valve via the modified Bernoulli equation below. Alternatively, you may calculate the peak pressure gradient using modern echocardiography ultrasound machines with built-in software that uses the equation below.

$$Peak\ \Delta P = 4\left(V_2^2 - V_1^2\right)$$

where $Peak\ \Delta P$ is the peak pressure gradient in mm Hg

V_2 is the velocity distal to the valve in m/s (as measured by CW Doppler)

V_1 is the velocity proximal to the valve in m/s (as measured by PW Doppler), measured in the LVOT for an aortic prosthesis

4. Mean Pressure Gradient

We recommend that you calculate the mean pressure gradient across the replacement valve via the equation below. We recommend that you use the built-in software of modern echocardiography ultrasound machines that use planimetry (tracing) of the CW Doppler spectral velocity signal and the simplified Bernoulli equation ($\Delta P = 4V_2^2$) to obtain multiple instantaneous pressure gradients, which you should then average to derive the mean pressure gradient, as shown in the following equation.

$$Mean\ \Delta P = \frac{\Delta P_{i=1} + \Delta P_{i=2} + \ldots + \Delta P_{i=n}}{n}$$

where	$Mean\ \Delta P$	is the mean pressure gradient in mmHg
	$\Delta P_{i=1}$	is the 1st instantaneous pressure gradient in mmHg
	$\Delta P_{i=2}$	is the 2nd instantaneous pressure gradient in mmHg
	$\Delta P_{i=n}$	is n^{th} instantaneous pressure gradient in mmHg
	n	is the number of instantaneous pressure gradients

The simplified Bernoulli equation assumes negligible proximal velocity. In other words, it assumes V_1 is less than 1m/s. If this assumption is untrue, however, the equation above may overestimate the mean pressure gradient.

5. Transvalvular Flow

For aortic and mitral valves, we recommend that you calculate transvalvular flow as follows:

$$Flow = \frac{V_s}{t_{EJ}} \times 10^3$$

where	$Flow$	is the transvalvular flow in ml/s
	t_{EJ}	is the ejection time in ms
	V_S	is the stroke volume in ml, calculated using the following stroke volume equation:

$$\begin{aligned} V_S &= A_{CS} \times VTI \\ &= \left[\left(\frac{D}{2} \right)^2 \times \pi \right] \times VTI \\ &= D^2 \times 0.785 \times VTI \end{aligned}$$

where A_{CS} is the cross-sectional area of the LVOT in cm^2 for the aortic stroke volume calculation, or the cross-sectional area of the mitral valve annulus in cm^2 for the mitral stroke volume calculation

D is the diameter of the LVOT in cm for the aortic stroke volume calculation, or the diameter of the mitral valve annulus in cm for the mitral stroke volume calculation

VTI is the LVOT velocity time integral in cm for the aortic stroke volume calculation, or the mitral velocity time integral in cm for the mitral stroke volume calculation

6. Cardiac Index

We recommend that you calculate the cardiac index as follows:

$$CI = \frac{O_c}{A_{BS}}$$

where CI is the cardiac index in $l/min/m^2$

O_C is the cardiac output in l/min

A_{BS} is the body surface area in m^2

7. Performance Index

We recommend that you calculate the performance index as follows:

$$PI = \frac{in\ vivo\ A_{EO}}{IOA_{PV}}$$

where PI is the performance index, which has no dimensions

in vivo A_{EO} is the *in vivo* effective orifice area in cm^2

IOA_{PV} is the pre-implant internal orifice area of the replacement valve in cm^2, obtained from the replacement valve specifications

For replacement pulmonic valves and pulmonic valved conduits, we do not recommend that you calculate the performance index, which is calculated using effective orifice area data, since the cone shape of the right ventricular outflow tract makes echocardiographic measurement of the right ventricular outflow tract diameter difficult. This difficult

measurement leads to potential inaccurate calculation of the pulmonic valve effective orifice area via the continuity equation method.

C. Valvular Regurgitation

In addition to ISO 5840:2005, Section H.4, subsection H.4.7, we recommend that you include the information described below in your evaluation of valvular regurgitation.

We recommend that you identify each jet as perivalvular, transvalvular, both, or uncertain. We also recommend that you show the site of each perivalvular jet on the sewing ring, for example, as a "clock-face" diagram.

The evaluation of valvular regurgitation should involve an integrated approach in which you use multiple echocardiographic methods to assess regurgitation at each follow-up time-point. Since certain methods may not be available at every follow-up visit, this approach allows you to compare sequential results for the entire duration of follow-up, with the results obtained by the same method or methods. We recommend, however, that you submit all follow-up results, including those obtained by methods with missing time-points. Appropriate methods for evaluating regurgitation are summarized below and discussed in further detail in the literature.[30,31]

1. Aortic Regurgitation

We recommend that you grade aortic regurgitation by an integrated evaluation based on factors including:

- instrument setting
- jet width
- jet area
- jet depth
- the shape (contour) and the density of the continuous wave signal (e.g., the deceleration time and pressure half-time both decrease with increasing AR severity; increased signal density generally indicates more severe AR)
- the duration of the continuous wave signal (e.g., a brief diastolic duration usually indicates physiologic or mild AR)

[30] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, and Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 16:777-802, 2003.

[31] Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, and Weissman NJ. American Society of Echocardiography recommendations for use of echocardiography in clinical trials, J Am Soc Echocardiogr 17:1086-1119, 2004.

- the structure of the aortic valve
- the size and function of the left ventricle
- how far diastolic flow reversal can be visualized within the aorta.[32]

Of these grading factors, the width of the aortic jet as a proportion of the left ventricular outflow tract diameter is the most frequently used single measure.[33] However, jet width should be applied carefully for eccentric jets.

We recommend that you also grade aortic regurgitation by the appearance of the diastolic filling pattern in mitral inflow (e.g., severe aortic regurgitation results in a restrictive mitral filling pattern with high E velocity, low A velocity, increased E/A velocity ratio, and short deceleration time).

We also recommend that you calculate the regurgitant volume, regurgitant fraction, and effective regurgitant orifice, to obtain a more objective quantization of the severity of aortic regurgitation. The regurgitant volume, regurgitant fraction, and effective regurgitant orifice area can be calculated by the volumetric or proximal isovelocity surface area (PISA) methods. Normal regurgitation due to backflow should be distinguished from pathologic regurgitation. The usual distinguishing features of normal regurgitation are a uniform color pattern and small jets with normal regurgitation. The usual distinguishing features of pathologic regurgitation are a mosaic color pattern and larger jets.

2. Mitral Regurgitation

We recommend that you grade mitral regurgitation by an integrated evaluation based on factors, including:

- instrument setting
- jet width
- jet area
- jet depth
- jet eccentricity
- the shape (contour) and the density of the continuous wave signal (e.g., severe mitral regurgitation may result in a "cut-off sign" due to a large v wave; increased signal density generally indicates more severe MR)
- the peak velocity of the continuous wave signal (e.g., peak velocity decreases with increasing mitral regurgitation severity due to increased left atrial pressure)
- the duration of the continuous wave signal
- the structure of the mitral valve

[32] Simpson IA, De Belder MA, Kenny A, Martin M, and Nihoyannopoulos P, How to quantitated valve regurgitation by echo Doppler techniques, Brit Heart J 73(5 Suppl 2):1-9, 1995.
[33] Perry GJ, Helmcke F, Nanda NC, Byard C, and Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping, J Am Coll Cardiol 9:952-959, 1987.

- the size and function of the left ventricle
- the size of the left atrium
- impingement of the jet on the left atrial wall
- the direction of systolic flow in the pulmonary veins (e.g., severe mitral regurgitation may result in systolic flow reversal)
- the width of the vena contracta (the narrowest portion of the mitral regurgitation jet downstream from the orifice).

Mitral regurgitation may also be graded by the appearance of the diastolic filling pattern in mitral inflow (e.g., severe mitral regurgitation results in a restrictive filling pattern with high E velocity, low A velocity, increased E/A ratio, and short deceleration time).

We also recommend that you calculate the regurgitant volume, regurgitant fraction, and effective regurgitant orifice to obtain a more objective quantitation of the severity of mitral regurgitation. The regurgitant volume, regurgitant fraction, and effective regurgitant orifice can be calculated by the volumetric or PISA methods. Normal regurgitation due to backflow should be distinguished from pathologic regurgitation. The usual distinguishing features of normal regurgitation are a uniform color pattern and small jets with normal regurgitation. The usual distinguishing features of pathologic regurgitation are a mosaic color pattern and larger jets.