Balloon Valvuloplasty Guidance For The Submission Of an IDE Application and a PMA Application (Text Only)

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BALLOON VALVULOPLASTY GUIDANCE FOR THE SUBMISSION OF AN INVESTIGATIONAL DEVICE EXEMPTIONS APPLICATION AND A PREMARKET APPROVAL APPLICATION

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BALLOON VALVULOPLASTY GUIDANCE DOCUMENT

This document describes the general framework to be followed in developing and testing a safe and effective percutaneous balloon valvuloplasty catheter (PBVC). The tests are grouped into (A) material biocompatibility and toxicity tests, (B) in vitro physical tests, (C) animal tests and (D) human clinical tests.

Please note that other elements of an investigational device exemptions (IDE) application (21 CFR Part 812) must be included for submission of an IDE to FDA.

A. Material Biocompatility and Toxicity Tests

For a material which has been tested and used previously in direct blood contacting devices, a sponsor may submit information available in publications or other legitimate sources which show that the material is non-toxic in tests which are identical or equivalent to the tests 1 through 5 listed below.

All new materials must pass tests 1 through 5 below to insure their safety for use in a PBVC. All materials (polymers, metals, radiopaques, color dyes and other leachable additives) in each component of the PBVC must be non-toxic to human tissue.

The effects of sterilization on device materials and potential

leachables, as well as toxic by-products resulting from sterilization, should be considered. Therefore, testing should be performed on the sterilized final product or representative samples therefrom. Specific chemical analyses of the sterilized final product and any leachable material from the sterilized final product must be performed before toxicity testing. The chemical analyses and toxicity data must be submitted to FDA for review. The tests and analyses for leachable materials must be conducted by choosing appropriate solvent systems which will yield a proper extraction of the leachables. Extraction temperature should be 50 C which is one of the three temperatures recommended in the current U.S.P. The required toxicity tests for a PBVC system are listed below. Additional tests are outlined in the Tripartite Biocompatibility Guidance for Hedical Devices dated September 1986. Both lists of tests are for guidance purposes. A manufacturer may substitute or omit tests with adequate justification.

1. U.S.P. Biological Tests for Class IV plastics. Extraction by solvents to be done at 50øC.

2. Sensitization assay: estimate the potential for sensitization of a material using a test such as the guinea pig maximization test.

3. Cytotoxicity test: determine the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by materials and extracts from the materials using cell culture techniques.

4. Thrombogenicity test: evaluate whether the blood contacting materials will accelerate the processes of intravascular thromboses. Describe test methodology and identify control materials.

5. Hemolysis: determine the degree of red cell lysis and the separation of hemoglobin caused by materials in vitro. Describe test methodology and identify control materials.

6. Genotoxicity test: apply the mammalian and non-mammalian cell culture techniques to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by materials and extracts from the materials. A battery of tests commonly accepted by the scientific community should be

used.

B. In Vitro Physical Tests

Before the device is tested in vivo, it must be tested in vitro to ensure that the design, specification, integrity, and other physical functions or characteristics of the device are sound and suitable for its intended purpose. The following physical tests must be done on samples of devices which have been put through the validated sterilization processes, because sterilization may affect the device properties.

1. Balloon Minimum Burst Strength Test. Conduct the test on balloons of each diameter and length. Test results must show statistically that, with at least 95X confidence, 99.9% of balloons will not burst at or below the maximum recommended burst pressure.

2. Balloon Distensibility (Compliance) Test. Show that the diameter of the balloons will not be significantly increased at increasingly higher pressures. A plot of balloon diameter against inflation pressure should be submitted.

3. Balloon Deflatability Test. Ensure that the balloons can be completely deflated by the recommended procedure when they are in an environment simulating transvalvular placement. Observe and describe any interference with balloon deflation.

4. Balloon Inflation and Deflation Times Test. Show that the inflation and deflation of the balloons using conventional techniques can be accomplished within a specified time and supply data.

5. Repeated Balloon Inflation (Balloon Fatigue) test. Test a randomly selected group of balloons to determine the repeatability of balloon inflation without failure using the recommended inflation pressure (not lower than 5 atmospheres even if the recommended inflation pressure is lower). At least 30 balloons should be tested, and there should be no failures after forty inflations of a given balloon. According to binomial distribution, 30 successes out of thirty tests would indicate

that, with 95% confidence, 90 to 100% of balloons in the same population would pass the test without failure.

6. Tip Pulling and Torquing Test. Show that the force required to break the joints and materials in the distal end of the catheter (such as spring tip and nose-cone tip made of metal, plastic or other materials) is suffiently large to guarantee the integrity of the tip during pulling, pushing, or torquing maneuvers.

7. Catheter Body Maximum Pressure Test. Determine the maximum pressure that the catheter body can withstand when one of the lumina (usually the inner lumen) is used for the power injection of contrast media.

8. Bonding Strength Test. Test the bonding strength at points where adhesives are used for bonding between parts (such as the proximal end and luer fitting) of the PBVC. Report the results and compare with specifications.

9. Pressure Waveform Test. Determine the natural frequency of the catheter for pressure measurement from the distal port. Damping of the wave form must be appropriate and provide accurate measurement.

10. Diameter and Profile Test. Determine the diameter of catheter shafts, profile of balloons, and inflated diameter of balloons to ensure that the actual diameters match the labeled diameters.

11. Radiopacity Test. Make sure that the radioopaque markers of the balloon are adequate to show the position of the balloon fluoroscopically. This can be done during animal testing.

12. Balloon Preparation Test. Test the ease of balloon preparation procedures, e.g., filling the balloon with contrast medium and expelling the air from the balloon lumen.

C. Animal Tests

The following tests should be carried out on normal animals, since there is no suitable animal model for valvular stenosis. Information from the following testing should be described in full in the

application.

1. The maneuverability or torquing characteristics of the guide wire must be tested to show that it can easily be steered to the valve of interest.

2. Test the maneuverability and ease of catheter movement over a guide wire of specific diameter. Test the ease and completeness of balloon inflation, deflation, and catheter withdrawal. The test should also ensure the physical integrity of the guide wire and catheter while in use.

3. Determine the balloon inflation and deflation times (visualized fluoroscopically), distal flow rate of contrast media with or without the guide wire in place, and the distal tip arterial pressure with or without the guide wire in the distal lumen.

D. Clinical Testing

PBVCs for pulmonary valve use are class II devices, and may be approved for marketing by premarket notification (510(k)) application after IDE approval has been obtained and a clinical study of 50 patients with two-month follow-up has been completed, FDA has examined the results, and declared the device to be substantially equivalent.

PBVCs for the aortic and mitral valves are class III devices and require a premarket approval (PMA) application. Under IDEs for aortic and mitral valvuloplasty, FDA usually grants permission for 20 investigators and 250 subjects.

Balloon valvuloplasty catheters should be evaluated in well organized clinical studies. Before a clinical study may begin, the sponsor must obtain approval from both FDA (via an IDE application) and an institutional review board (IRB). In addition to the requirements imposed by 21 CFR Part 812, the following items should be addressed in the IDE.

1. Patient selection and treatment should reflect the intended use and labeling claims for the device. Appropriate clinical assessment should be performed in order to make proper patient selection for the valvuloplasty procedure and studies should be

performed to evaluate the post-procedure results.

2. Current FDA policy for premarket approval requires that (a) for aortic valvuloplasty at least 100 patients who have had initially successful results be followed and (b) for mitral valvuloplasty at least 50 patients who have had initially successflul results should be followed. For either type of valvuloplasty, the required number of patients must be followed for a period of six months after the valvuloplasty procedure before a PMA application may be filed. In order to meet these criteria, the original number of patients entered in the study (including valvuloplasty failures) will need to be considerably larger. The study shall continue until the PMA is approved by FDA and all patients enrolled in the study shall be followed according to the study protocol while the PMA application is being reviewed. FDA will request post-approval follow-up to five years. Follow up studies should include 2D echo and Doppler at 3 months. Catheterization should be perfromed at 6 months unless it is felt inappropriate to the patient's condition. In such cases, ZD echo and Doppler may be substituted. If data from the six month follow-up are to be obtained by ultrasound techniquesl intraoperative ultrasound at the time of valvuloplasty should be performed in order to correlate ultrasound findings with pressure measurements.

3. Establish methods or techniques for preparing the balloon catheter, inserting and controlling the guide wire and the valvuloplasty catheter inside vessels, positioning the balloon at the appropriate valve, and dilating the balloon at proper pressures for suitable time periods.

4. Current literature indicates that the following list of indications, contraindications and special cautions for the use of the device should be considered.

   Indications for aortic balloon valvuloplasty

   1. symptomatic patients who represent a high risk for valve replacement and
   2. patients who have refused surgery.

   Contraindications for aortic balloon valvuloplasty

1. aortic regurgitation more than mild,
2. non-valvular aortic stenosis,
3. aortic valve area of over 1 square centimeter,
4. severe coronary artery disease - especially left main coronary artery disease, and
5. bacterial endocarditis.

Indications for mitral balloon valvuloplasty

1. mitral valve area of 1.3cm2 or less,
2. patients with mitral regurgitation 1+ or less,
3. symptomatic patients, and
4. no age or sex limitations.

Contraindications for mitral balloon valvuloplasty

1. mitral valve area greater than 1.5cm2,
2. patients with mitral regurgitation greater 2+,
3. asymptomatic patients,
4. aortic regurgitation greater than 2+,
5. bacterial endocarditis,
6. left atrial thrombus,
7. patients with severe subvalvular fibrosis documented by echocardiography, and
8. patients with severe mitral valve calcification.

(Patients who have severe mitral valve calcification and severe subvalvular fibrosis should be considered candidates for the procedure only if they are non-operative candidates.)

5. Patient records must include the model, size and length of the guide wires and valvuloplasty catheters, balloon inflation pressure, inflation time, the number of inflation cycles used in each valvuloplasty procedure and any evidence of balloon rupture.

6. Records of the study must be completed by each investigator. The record for each patient receiving valvuloplasty should include the date, ID number, pre-treatment symptons, functional class (NYHA), results of tests performed on the patient, the degree of

stenosis, success or failure of the procedure according to predetermined criteria, pre- and postoperative pressure gradients, patient's tolerance of the procedure, post-procedural condition, complications, medications required, and any other pertinent data. Evaluation criteria must be uniform among all investigators.

7. All patient data must be analyzed to determine the reasons for failed procedures and the causes of all complications.

8. If a patient dies during the valvuloplasty procedure or prior to hospital discharge, the cause of death must be documented. An autopsy should be performed where possible, and the findings reported to FDA. Information should include: a) at what point in the procedure the patient expired, b) whether another valvuloplasty catheter was used, and c)whether artificial valve replacement was attempted. An opinion should be expressed as to whether the death was caused by (1) problems with the investigational catheter, (2) the valvuloplasty procedure, or (3) other factors. Patients who die during the remainder of the follow-up period should have the circumstances explained as completely as possible, although this documentation will understandably be less complete than deaths occuring under medical surveillance.

9. Survival analysis methods should be used to analyze the study results. Follow-up data at three and six months should be used to construct actuarial life tables to show the estimated probabilities of freedom from each postoperative complication at the end of each follow-up period. A survival analysis should be conducted separately for aortic and mitral valvuloplasty and for fatal and non-fatal events, including both catheter and non-catheter related complications. The study results should be compared to controls, which may be the results of similar studies. Statistical methods, such as the Mantel-Haenszel, one-degree of freedom, chi-square test, should be used for any comparisons of life table results.

E. Clinical Testing Without Intent To Manufacture

FDA is aware that many physicians are using the Mansfield catheter

(presently marketed for pulmonary valvuloplast in children) for valvuloplasty of the aortic and mitral valves, although it has FDA approval for pulmonic valvuloplasty only. FDA has decided to abbreviate requirements for such investigators in order to expedite submission and approval of IDEs in a timely fashion.

The following items are required for such an IDE;

1. Report of Prior Investigations

    a. copies of all published and unpublished adverse information.

    b. written permission from Mansfield Scientific to reference any appropriate files within the agency.

        NOTE: If item b is not obtained, then the applicant must submit a report of prior clinical, animal and laboratory testing, a bibliography of all publications, a summary of all obtainable information, and a statement whether nonclinical tests comply with the GLP regulation.

2. Investigational Plan

    Submit the name and intended use of the device, the objectives of the investigation and the duration of the investigation.

3. Protocol

    Submit a written protocol describing the methodology and an analysis of the scientific soundness of the protocol.

4. Risk Analysis

    A description and analysis of all increased risks to subjects, the manner in which risks will be minimized, a justification for the investigation, and a description of the patient population in terms of number, age, sex, and condition.

5. Monitoring procedure

   Provide a written procedure for monitoring, and the name and address of the monitor.

6. Investigator Agreement

   Provide an example of investigator agreement, the name and address of investigators who have signed the agreement, a certification that all participating investigators will and have signed the agreement and that no investigator will be added until the agreement is signed.

7. IRB Information

   Provide the name, address and chairperson of each IRB, and the action taken by the IRB (i.e., approval-disapproval).

8. Sales Information

   Give the amount charged for the device,if sold, and give an explanation of why sale does not constitute commercialization.

9. Informed Consent Materials

   Submit all forms and informational materials to be presented to the patient. The informed consent should not contain exculpatory language and should comply with 21 CFR, Part 50.

10. Environmental Impact Assessment

    An environmental impact assessment describing the potential environmental impact of investigatin~ a device, and a claim for a categorical exclusion from this requirement should be submitted.

More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

Cross-Center Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm)

Office of Compliance Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm)

Office of the Center Director Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm)

Office of Communication and Education Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm)

Office of Device Evaluation Final Guidance 2010 - 2016
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm)

Office of Device Evaluation Final Guidance 1998 - 2009
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm)

Office of Device Evaluation Final Guidance 1976 - 1997
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm)

Office of In Vitro Diagnostics and Radiological Health Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm)

Office of Surveillance and Biometrics Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070275.htm)

Office of Science and Engineering Laboratories Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070277.htm)

Draft Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm407274.htm)

Radiation-Emitting Products Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283507.htm)

Withdrawn Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm425025.htm)