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Cardiovascular implants and extracorporeal systems—
Cardiac valve prostheses—
Part 2: Surgical heart valve substitutes

ISO copyright office
Case postale 56 – CH-1211 Geneva 20
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
Email copyright@iso.org
Web www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 5840-2 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems.*

This document cancels and replaces ISO 5840:2005.

This part of ISO 5840 is to be used in conjunction with ISO 5840-1 and ISO 5840-3.

Introduction

This International Standard has been prepared for surgical heart valve substitutes with emphasis on specifying types of *in vitro* testing, preclinical *in vivo* and clinical evaluations, reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations and labelling and packaging of the device. This process is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent issues.

This part of ISO 5840 is to be used in conjunction with ISO 5840-1.

Cardiovascular implants and extracorporeal systems—Cardiac valve prostheses—Part 2: Surgically implanted heart valve substitutes

1 Scope

1.1 This International Standard is applicable to heart valve substitutes intended for implantation in human hearts, generally requiring cardiopulmonary bypass and generally with direct visualization.

1.2 This International Standard is applicable to both newly developed and modified surgical heart valve substitutes and to the accessories, packaging, and labeling required for their implantation and for determining the appropriate size of the surgical heart valve substitute to be implanted.

1.3 This International Standard outlines an approach for qualifying the design and manufacture of a surgical heart valve substitute through risk management. The selection of appropriate qualification tests and methods are derived from the risk assessment. The tests may include those to assess the physical, chemical, biological, and mechanical properties of surgical heart valve substitutes and of their materials and components. The tests may also include those for pre-clinical *in vivo* evaluation and clinical evaluation of the finished surgical heart valve substitute.

1.4 This International Standard defines operational conditions and performance requirements for surgical heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

1.5 For novel surgical heart valve substitutes (e.g., sutureless), the requirements of both this International Standard and ISO 5840-3 might be relevant and shall be considered as applicable to the specific device design and shall be based on the results of the risk analysis.

1.6 This International Standard excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

1.7 This International Standard excludes homografts.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5840-1:201x (in development), *Cardiovascular implants and extracorporeal systems – Cardiac valve prostheses – Part 1: General requirements*

ISO 10993-1, *Biological evaluation of medical devices—Part 1: Evaluation and testing*

ISO 10993-2, *Biological evaluation of medical devices—Part 2: Animal welfare requirements*

ISO 14155:2011, *Clinical investigation of medical devices for human subjects—Good clinical practice*

ISO 14630:2012, *Non-active surgical implants—General requirements*

ISO 14971, *Medical devices—Application of risk management to medical devices*

ISO 16061, *Instrumentation for use in association with non-active surgical implants -- General requirements*

ISO 17025, *General requirements for the competence of testing and calibration laboratories*

ISO 22442-1, *Animal tissues and their derivatives utilized in the manufacture of medical devices—Part 1: Analysis and management of risk*

ISO 22442-2, *Animal tissues and their derivatives utilized in the manufacture of medical devices—Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Animal tissues and their derivatives utilized in the manufacture of medical devices—Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents*

IEC 62366, *Medical Devices - Application of usability engineering to medical devices*

ASTM F2052*, Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment*

ASTM F2119, *Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants*

ASTM F2182, *Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging*

ASTM F2213, *Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment*

ASTM F2503*, Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
cumulative incidence
statistical technique where events other than death can be described by the occurrence of the event over time without including death of the subjects

NOTE 1 to entry: Cumulative incidence is also known as “actual” analysis.

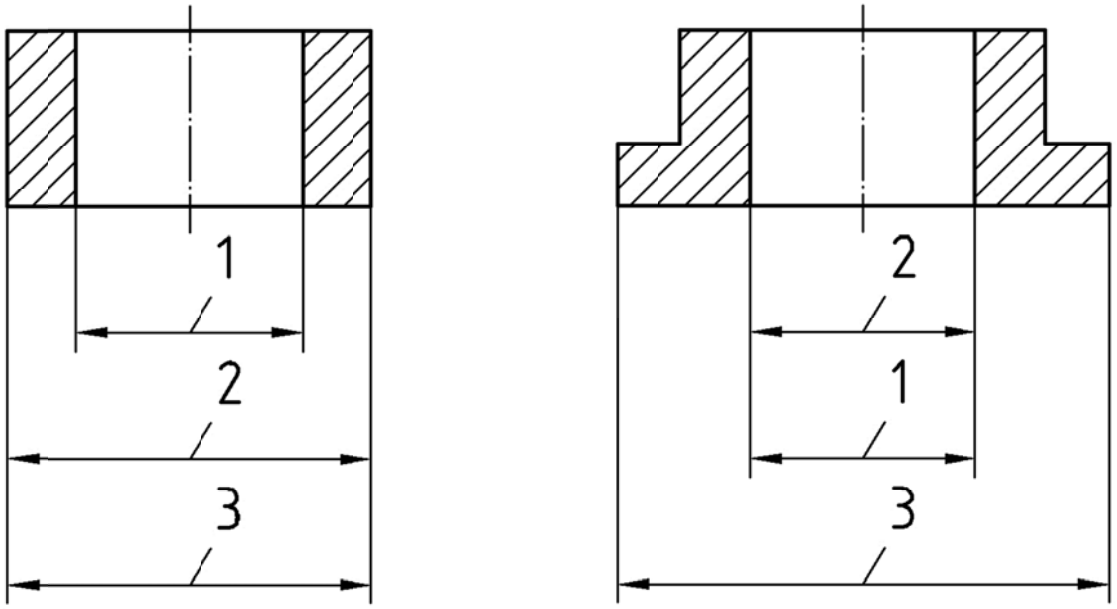
3.2
cycle rate
number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

3.3
internal orifice diameter
numerical indication of the minimum diameter within a surgical heart valve substitute through which blood flows

See Figure 1.

3.4
intra-annular sewing ring
sewing ring designed to secure the surgical heart valve wholly or mostly within the patient’s tissue annulus

See Figure 1. See also 3.3, 3.11, and 3.13.



Key
1 Internal Orifice Diameter
2 Tissue Annulus Diameter
3 External Sewing Ring Diameter

Figure 1—Designation of dimensions of surgical heart valve substitute sewing ring configurations

3.5
major bleeding
any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion

3.6
major paravalvular leak
paravalvular leakage leading to death or re-intervention, or causing heart failure requiring additional medication, or causing moderate or severe regurgitation or prosthesis 'rocking' on investigation even in the apparent absence of symptoms, or causing hemolytic anemia

3.7
nonstructural valve dysfunction
abnormality extrinsic to the heart valve substitute that results in stenosis, regurgitation and/or haemolytic anemia

3.8
prosthetic valve endocarditis
any infection involving a valve in which an operation has been performed, based on reoperation, autopsy or the Duke Criteria for Endocarditis

NOTE See Li et al. (2000).

3.9
structural valve deterioration
change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation

NOTE This definition excludes infection, or thrombosis of the heart valve substitute. It includes intrinsic changes such as wear, fatigue failure, stress fracture, occluder escape, suture line disruption of components of the prosthesis, calcification, cavitation erosion, leaflet tear and stent creep.

3.10
support structure
component of a heart valve substitute that houses the occluder(s), (e.g., stent, frame, housing)

3.11
supra-annular sewing ring
sewing ring designed to secure the valve wholly above the patient's tissue annulus

See Figure 1.

3.12
thromboembolism
any embolic event that occurs in the absence of infection after the immediate perioperative period. Thromboembolism may be manifested by a neurological event or a noncerebral embolic event

3.13
tissue annulus diameter
TAD
diameter in millimeters of the smallest flow area within the patient's valve annulus

3.14
valve size
manufacturer's designation of a surgical heart valve substitute which indicates the tissue annulus diameter (TAD in millimeters) of the patient into whom the surgical heart valve substitute is intended to be implanted (i.e., TAD = designated valve size)

NOTE This takes into consideration the manufacturer's recommended implant position relative to the annulus and the suture technique.

3.15
valve thrombosis
any thrombus not caused by infection attached to or near an operated valve that occluded part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.

NOTE See Akins, et. al. (2008).

4 Abbreviations

For the purposes of this document, the following abbreviations apply.

EOA Effective Orifice Area
CFD Computational Fluid Dynamics
FEA Finite Element Analysis
IFU Instructions For Use
OPC Objective Performance Criteria

5 Fundamental requirements

The manufacturer shall determine, at all stages of the product life cycle, the acceptability of the product for clinical use.

6 Device description

6.1 Intended use

The manufacturer shall identify the physiological condition(s) to be treated, the intended patient population, potential adverse events, and intended claims.

6.2 Design inputs

6.2.1 Operational specifications

The manufacturer shall define the operational specifications for the device, including the principles of operation, expected device lifetime, shelf life, shipping/storage limits, and the physiological environment in which it is intended to function. The manufacturer shall carefully define all relevant dimensional parameters that will be required to accurately select the size of device to be implanted. Tables 1 and 2 in ISO 5840-1 define the expected physiological parameters of the intended adult patient population for surgical heart valve substitutes for both normal and pathological patient conditions.

See pediatric annex of ISO 5840-1, Annex E.

6.2.2 Performance specifications

6.2.2.1 The manufacturer shall establish (define, document, and implement) the clinical performance requirements of the device and the corresponding device performance specifications for the intended use and device claims. The following list of desired clinical and device-based performance characteristics describe a safe and effective surgical heart valve substitute.

NOTE For novel devices portions of ISO 5840-3 may be applicable

6.2.2.2 Specifications shall be defined with respect to at least the following performance characteristics:

— the ability to allow forward flow with acceptably small mean pressure difference;

— the ability to prevent retrograde flow with acceptably small regurgitation;

— the ability to resist embolization;

— the ability to resist hemolysis;

— the ability to resist thrombus formation;

— is biocompatible;

— is compatible with *in vivo* diagnostic techniques;

— is deliverable and implantable in the target population;

— the ability to ensure effective fixation within the target implant site;

— has an acceptable noise level;

— has reproducible function;

— maintains structural and functional integrity during the expected lifetime of the device;

— maintains its functionality and sterility for a reasonable shelf life prior to implantation.

6.2.3 Packaging, labeling, and sterilization

The surgical heart valve substitute and accessories shall meet the requirements for packaging, labeling, and sterilization contained within ISO 5840-1 Annexes B, C, and D, respectively.

6.3 Design outputs

6.3.1 General

The manufacturer shall establish (i.e., define, document, and implement) a complete specification of the surgical heart valve substitute system, which includes component and assembly-level specifications, accessories, packaging, and labeling.

Annex E contains a listing of components and terms that may be used in describing various valve types.

6.4 Design transfer (manufacturing qualification)

6.4.1 The manufacturer shall generate a manufacturing flowchart identifying the manufacturing process operations and inspection steps. The input of all components and important manufacturing materials shall be indicated on the flowchart.

6.4.3 As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification activities necessary to demonstrate the acceptability of the process ranges chosen.

6.4.4 The manufacturer shall establish the adequacy of full-scale manufacturing by validation of the manufacturing process. The manufacturer shall document the results of the validation of all special processes and the validation of all process software.

NOTE See ISO 13485.

6.5 Risk management

The manufacturer shall define and implement a risk management program in accordance with ISO 14971.

Annex A contains a list of potential hazards specific to surgical heart valve substitutes that can serve as the basis for a risk analysis.

7 Design verification testing and analysis/Design validation

7.1 General requirements

The manufacturer shall perform verification testing in order to demonstrate that the device specifications result in a surgical heart valve substitute system that meets the design specifications (design output meets design input). The manufacturer shall establish those tests relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, set-up, equipment (specifications, calibration, etc.), test conditions (with a justification of appropriateness to anticipated *in vivo* operating conditions for the device), acceptance criteria, and sample quantities tested.

NOTE See ISO 16061.

For novel surgical heart valve substitutes (e.g., sutureless), the requirements of both this standard and ISO 5840-3 might be relevant and shall be considered if applicable to the specific device design and based on the results of the risk analysis.

The manufacturer shall validate the design of the surgical heart valve substitute, its packaging/labeling, and accessories.

7.2 *In vitro* assessment

7.2.1 Test conditions, sample selection, and reporting requirements

7.2.1.1 Test conditions and sample selection

Test specimens shall represent, as closely as possible, the finished product to be supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, process chemicals, and aging effects in accordance with all manufacturing procedures and Instructions for Use, where appropriate. Any deviations of the test specimens from the finished product shall be justified.

The specimens selected for testing shall fully represent the total implant size range. Depending on the particular test, testing might not necessarily have to be completed for each discrete valve size, but shall at least be completed for the smallest, intermediate and largest sizes. A rationale for device size selection shall be provided.

For all tests, the number of samples shall be justified based on the specific intent of the test (See ISO 5840-1 Annex F). Sampling shall ensure adequate representation of the expected variability in the manufacture of devices. Additional recommendations regarding sampling and sample conditioning are included within each test method defined herein, as appropriate.

Where simulation of in vivo conditions is applicable to the test method, consideration shall be given to those operational environments given in ISO 5840-1 Table 1 and Table 2 for the adult population. See ISO 5840-1 Annex

E for guidelines regarding suggested test conditions for the pediatric population. Where applicable, testing shall be performed using a test fluid of isotonic saline, blood, or a blood-equivalent fluid whose physical properties (e.g., specific gravity, viscosity at operating temperatures) are appropriate to the test being performed. The test fluid used shall be justified. Testing shall be performed at the intended operating temperature as appropriate,

Test methods for design verification testing shall be appropriately validated. Refer to applicable sections of ISO 17025.

7.2.1.2 Reporting requirements

Each test report shall include, at a minimum:

a) the rationale for the test;

b) identification and description of the sample(s) tested (e.g., batch number);

c) identification and description of the reference valve(s);

d) number of specimens tested, and sample size rationale;

e) detailed description of the test method including measurement accuracy and repeatability of the test system;

f) verification that appropriate quality assurance standards have been met (e.g., good laboratory practices);

g) test results and conclusions.

Statistical procedures such as described in ISO 5840-1 Annex F may be used to assist data analysis.

7.2.2 Material property assessment

7.2.2.1 General

Properties of surgical heart valve substitute system shall be evaluated as applicable to the specific design as determined by the risk assessment. The material requirements of ISO 14630 and ISO 16061 shall apply. Additional testing specific to certain materials shall be performed to determine the appropriateness of the material for use in the design.

7.2.2.2 Biological safety

The biocompatibility of the materials and components used in surgical heart valve substitutes shall be determined in accordance with ISO 10993-1. The test plan recorded in the risk management file shall comprise a biological safety evaluation program with a justification for the appropriateness and adequacy of the information obtained. The documentation shall include a rationale for the commission of any biological safety tests carried out to supplement information obtained from other sources, and for the omission of any tests identified by ISO 10993-1 but not performed. During the hazard identification stage of a biological safety evaluation, sufficient information shall be obtained to allow the identification of toxicological hazards and the potential for effects on relevant hematological characteristics. Where an identified hazard has the potential for significant clinical effects, the toxicological risk shall be characterized through evaluation of data on, for example, mode of action, dose-response, exposure level, biochemical interactions, and toxicokinetics.

For surgical heart valve substitutes using animal tissue or their derivatives, the risk associated with the use of these materials shall be evaluated in accordance with the ISO 22442 series.

7.2.2.3 Material and mechanical property testing

Material properties of all constituent materials comprising the surgical heart valve substitute shall be evaluated as applicable to the specific design. Scientific literature citations or previous characterization data from similar devices can be referenced; however, the applicability of the literature data to the surgical heart valve substitute shall be justified.

Mechanical properties shall be characterized at various stages of manufacture, as applicable. Environmental conditions that might affect device or component performance or durability shall be evaluated and included in testing protocols (e.g., shelf life testing). ISO 5840-1 Annex G provides potentially relevant physical, mechanical, and chemical properties by material class and components. ISO 5840-1 Annex H provides a list of standards that might be applicable to the testing of materials and components. ISO 5840-1 Annex I provides guidance on mechanical property characterization of raw and conditioned materials. ISO 5840-1Annex J provides guidance on corrosion assessment.

7.2.3 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid mechanical performance of the surgical heart valve substitute and provide indicators of valve performance in terms of load to the heart and potential for blood stasis and damage.

A guideline for the performing and reporting of hydrodynamic tests is given in Annex F.

Tests shall be carried out on at least three surgical heart valve substitutes of each size and on at least one reference valve of each of the smallest, medium, and largest sizes. A larger sample size may be required to ensure adequate representation of the expected variability in the manufacture of devices.

The *in vitro* test results shall meet or exceed the minimum performance requirements provided in Table 2, which are given as a function of valve size. The minimum performance requirements correspond to the following pulsatile-flow conditions: beat rate = 70 cycles/min, simulated cardiac output = 5,0 l/min, and systolic duration = 35 %, at normotensive conditions. The minimum performance requirements are based on values in the published scientific literature. The values in Table 1 and Table 2 of this 2014 version of the standard are applicable to new or modified heart valve substitutes which have not been clinically proven or evaluated under a previous version of this standard. The hemodynamic waveforms produced by the pulse duplicator shall reasonably simulate physiological conditions as shown in ISO 5840-1, Figure 3.

Table 1—Minimum device performance requirements, Aortic

Parameter	Valve size (mm)							
	17	19	21	23	25	27	29	31
EOA (cm^2) greater than or equal to	0,70	0,85	1,05	1,25	1,45	1,70	1,95	2,25
Total Regurgitant Fraction (% of forward flow volume) less than or equal to	10	10	10	10	15	15	≤ 20	≤ 20

Table 2—Minimum device performance requirements, Mitral

Parameter	Valve size (mm)					
	23	25	27	29	31	33
EOA (cm^2) greater than or equal to	1,05	1,25	1,45	1,65	1,90	2,15
Total Regurgitant Fraction (% of forward flow volume) less than or equal to	15	15	15	20	20	20

The total regurgitant fraction shall include closing volume, transvalvular leakage volume, and paravalvular leakage volume.

$$EOA = \frac{q_{v\,RMS}}{51{,}6 * \sqrt{\frac{\Delta p}{\rho}}}$$

Where:

EOA is the Effective Orifice Area (cm^2);

$q_{v\,RMS}$ is the root mean square forward flow (ml/s) during the positive differential pressure period;

Δp is the mean pressure difference (measured during the positive differential pressure period) (mmHg);

ρ is the density of the test fluid (g/cm^3).

NOTE 1 This equation is derived from a simplified version of the Bernoulli Equation and as such has limitations. The constant (51,6) is not dimensionless; thus this equation is only valid with the units shown.

NOTE 2 Defining the time interval for flow and pressure measurement as the positive differential pressure period of the forward flow interval for EOA computation provides repeatable and consistent results for comparison to the Table 1 and Table 2 reference values. It is recognized that this approach may not equate to the EOA computation approaches employed clinically. See 5840-1, Figure 2.

NOTE 3 The rationale for use of $q_{V_{RMS}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate, and it is the mean pressure difference that is required.

NOTE 4 See Yoganathan and Travis (2002).

NOTE 5 See Marquez et al. (2001).

NOTE 6 See Stewart (2002).

7.2.4 Structural performance assessment

7.2.4.1 General

An assessment of the ability of the surgical heart valve substitute to withstand the loads and/or deformations to which it will be subjected shall be performed in order to evaluate the risks associated with potential structural failure modes.

7.2.4.2 Device durability assessment

An assessment of the durability of the surgical heart valve substitute shall be performed in order to assess continued function over a reasonable lifetime. Unless the labeling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to demonstrate reasonable assurance that rigid surgical heart valve substitutes will remain functional for 400 million cycles and that flexible surgical heart valve substitutes will remain functional for 200 million cycles. For flexible surgical heart valve substitute materials without established clinical history as a valve leaflet material, testing durations greater than 200 million cycles shall be considered, and scientifically justified if not performed. If the labeling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to support the labeling claim. Testing shall be performed on at least three each of the largest, medium, and smallest sizes of the surgical heart valve. The risk assessment may identify the need for a larger sample size based on factors such as novel/new materials or non-traditional designs. One equivalent size reference valve shall be tested under identical conditions for each valve size tested.

Tests shall be performed at a defined differential pressure consistent with normotensive conditions specified in Table 1 or Table 2 of ISO 5840-1. See ISO 5840-1 Annex E for guidelines regarding suggested test conditions for the pediatric population. Each test valve shall experience the defined differential pressure across the closed valve for at least 5 % of each cycle during at least 95 % of the test cycles. If surgical heart valve substitutes identical in design are intended for implant in multiple valve positions, testing shall include the differential pressure conditions defined for the worst case valve position.

Cycle rates used for accelerated testing shall be justified. Consideration shall be given to the behavior of rate-dependent materials when selecting and justifying appropriate cycle rates.

Test valves shall experience the full range of occluder motion associated with normotensive conditions during testing (see ISO 5840-1, Table 1 and Table 2). Valves undergoing cycling in durability testers shall be observed at regular and frequent intervals (e.g., daily or weekly). Valves shall also be evaluated at least every 50 million cycles for flexible valves and 100 million cycles for rigid valves. A detailed description of the appearance of the heart valve and hydrodynamic performance shall be documented prior to testing, throughout the test at the established inspection intervals, and at the completion of test.

The durability assessment shall be performed by characterization of the test valve in terms of the observed damage and the extent of damage and by imposing pass/fail criteria for identified damage. An appropriate reference valve shall be used to further assess the durability test conditions being used to evaluate the surgical heart valve substitute. The failure modes to be considered and the pass/fail criteria for the test shall be determined by the risk assessment.

Potential modes of failure associated with structural valve deterioration shall be identified. Additional guidelines for durability testing, including dynamic failure mode evaluation, are given in Annex G.

7.2.4.3 Component fatigue assessment

An assessment of the fatigue performance of the surgical heart valve substitute structural components shall be conducted. Unless the labeling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to demonstrate reasonable assurance that the support structure will remain functional for a minimum of 400 million cycles. If the labeling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to support the labeling claim. Failure criteria for fatigue testing shall be justified by the manufacturer based on the results of the risk assessment.

The manufacturer shall identify and justify the appropriate *in vivo* loading and environmental conditions used. Fatigue test and analysis shall, at a minimum, use conditions consistent with pressures associated with moderate hypertensive conditions listed in Tables 1 and 2 of ISO 5840-1 and other relevant *in vivo* loading conditions. See ISO 5840-1 Annex E for guidelines regarding suggested test conditions for the paediatric population. In addition, dynamic effects imparted by leaflet/occluder motion on resulting stress/strain magnitudes during valve closure shall be addressed.

Test specimens shall represent, as closely as possible, the finished product as supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, process chemicals, aging effects, and any device handling steps in accordance with manufacturing procedure and IFU. Devices shall be tested at the intended operating temperatures and environmental conditions.

A validated stress/strain analysis of the structural components of the implant under simulated *in vivo* conditions shall be performed. Loading from all valve components shall be considered. For example, where analysis is only required for the support structure, it might be necessary to include reaction loads associated with dynamic effects of leaflet/occluder closure in the analysis in order to simulate *in vivo* loading realistically. An appropriate validated constitutive model for each material shall be used in the stress/strain analysis, including time-dependent, temperature-dependent and/or nonlinear models.

Fatigue characterization and lifetime assessment of the structural components under simulated *in vivo* conditions shall be performed in order to evaluate risks associated with fatigue-related failure modes. The manufacturer shall determine and justify the fatigue assessment approach and associated characterization technique adopted. Suggested guidelines are provided in Annex G and Annex I.

7.2.4.4 Component corrosion assessment

An assessment of the corrosion resistance of all constituent materials comprising the surgical heart valve substitute shall be conducted. It is well established that metal corrosion potential can be sensitive to variations in manufacturing processes (e.g., heat treatment, chemical etching, electropolishing). Therefore, the corrosion resistance shall be characterized using the finished component. ISO 5840-1 Annex J provides guidance on corrosion resistance characterization.

The manufacturer shall provide rationale for the selected test methods and justify that all corrosion mechanisms and conditions have been considered through testing or theoretical assessments.

7.2.4.5 Cavitation (rigid valves)

An assessment of the potential for cavitation as indicated by the formation of vapor bubbles during valve closure shall be considered for rigid valves. Assessment of cavitation damage shall be performed by a detailed examination of study valves used in the preclinical in vivo study and simulated long term *in vitro* study (i.e., durability testing). The in-vitro cavitation assessment shall be performed by characterization of the smallest and largest valve sizes in terms of any observed damage and the extent of damage compared to the appropriate reference valves.

7.2.5 Device MRI safety

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI per ASTM standards F2052, F2213, F2182, F2119, and F2503.

7.2.6 Additional implant design evaluation requirements

For novel surgical heart valve substitutes that require delivery systems for implantation, refer to applicable portions of ISO 5840-3. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific device design.

7.2.7 Design specific testing

In order to assess failure modes identified by the risk assessment that may not be related to durability or component fatigue, design specific testing may be necessary. In some cases, design specific testing may have direct implications for the overall structural lifetime of a component or valve, and additional tests may be required.
Examples of such design specific tests are provided in Annex H.

7.2.8 Simulated use

The ability to permit safe, consistent and accurate implantation of the surgical heart valve substitute within the intended implant position shall be evaluated using a model that simulates the intended use conditions. This assessment will include all elements of the surgical heart valve substitute. The model shall consider anatomical variation in intended patient population with respect to intended implant position, temperature effects, etc. Justification for critical parameters of the simulated use model shall be provided.

7.2.9 Human factors / Usability assessment

Simulated use shall be conducted as part of the required usability assessment (or "usability testing") per IEC 62366, *Medical Devices - Application of usability engineering to medical devices.* The main objective of the usability assessment is to validate that intended users of the device can use it safely and effectively to implant the device in the patient. Usability assessment performance measurements shall be based on use error analysis results. The assessment shall primarily focus on whether or not the design attributes of the device used to conduct the implant appropriately mitigate identified potential use errors that can occur. It is recommended that usability assessment is conducted throughout the design cycle.

7.3 Preclinical *in vivo* evaluation

7.3.1 Overall requirements

A preclinical *in vivo* test programme shall be conducted in order to address the surgical heart valve substitute safety and performance. The preclinical programme design shall be based on risk management assessment. This programme may involve the use of different species and implant durations to address the key issues identified in the risk management assessment.

For minor design modifications to clinically well documented surgical heart valve substitutes, the manufacturer shall justify omission of animal experimental evaluation.

The preclinical *in vivo* evaluation shall:

a) reflect the hemodynamic performance of the surgical heart valve substitute as assessed *in vitro*;

b) assess the surgical handling characteristics of the test surgical heart valve substitute and its accessories (if any);

c) assess the biological reaction to the surgical heart valve substitute. Consideration should be given but not limited to the following items, as relevant to the specific surgical heart valve substitute under evaluation:

   1) healing characteristics (pannus formation, tissue overgrowth);

   2) hemolysis;

   3) thrombus formation;

   4) embolization of material from the heart valve substitute;

   5) biological response (e.g. inflammation, rejection, etc.);

   6) calcification (flexible valves);

   7) acoustic characteristics (rigid valves), if the manufacturer is making specific acoustic claims;

   8) structural and/or non-structural dysfunction;

   9) cavitation (rigid valves);

d) mimic, as closely as possible, the condition of the finished product as intended for clinical use, including exposure to the maximum number of recommended sterilization cycles;

e) evaluate the test surgical heart valve substitute in all positions for which it is intended (aortic, mitral, etc.);

f) subject comparably sized reference surgical heart valve substitutes to identical test conditions as the test surgical heart valve substitute;

g) mimic, as closely as possible, the implantation technique for the placement of both the test and the reference surgical heart valve substitutes (e.g., suture technique and orientation);

h) be performed by appropriately experienced and knowledgeable test laboratories;

i) address animal welfare in accordance with the principles given in ISO 10993-2.

7.3.2 Methods

7.3.2.1 General requirements

Guidance on the conduct of *in vivo* preclinical evaluation and a series of tests which can be used to address the relevant issues are given in Annex C. The intent of these studies is to mimic as closely as possible the clinical use and haemodynamic performance of the surgical heart valve substitute. It is recognized that complications arising after valve implantation can be attributed to the implanted valve as well as the environment into which it is implanted—or the interaction between the two. Therefore, adverse clinical events arising during or after valve implantation shall be carefully analyzed and interpreted in order to identify the cause of the adverse event to the extent possible.

The investigator should seek to control as many variables as possible within each study arm (e.g. species, gender and age). The test surgical heart valve substitutes shall be assessed in a long term setting in anatomical positions for which it is intended to be used clinically. Animals suffering from perioperative complications (e.g. endocarditis) may be excluded from the group of study animals, but information about them shall be reported.

The number of animals used for implantation of test and control surgical heart valve substitutes shall be justified fully for each test based on the risk analysis.

For long term studies, the duration of the observation period of the animals must be specified according to the parameter(s) under investigation. The observation period shall be appropriately justified in each study protocol, but shall be no less than 90 days.

A macroscopic, radiographic and histological post-mortem examination shall be performed, focusing on device integrity and device- related pathology. The data shall include information from all animals that have been entered into the study.

The assessment shall provide at least the following:

a) any detectable pathological consequences involving the surgical heart valve substitute and/or the major organs, including but not limited to: post-implantation changes in shape or structural components; thrombo-embolic phenomena; pannus formation; and inflammatory responses;

b) any macro- or microscopic or radiographic detectable structural alterations in the surgical heart valve substitute (e.g. damage, support structure fracture, material degeneration, changes in shape or dimensions);

c) serial blood analyses performed pre-operatively, at appropriately justified intervals during the observation period, and at termination to assess hemolysis, abnormalities in hematology and clinical chemistry parameters;

d) implantation characteristics, including but not limited to ease of use, handling characteristics, and sizing technique;

e) haemodynamic performance over a range of cardiac indices (e.g., 2,5 to 6 L/min/m^2);

f) adverse clinical events, (e.g., myocardial infarction, significant cardiac arrhythmias, infection);

g) any other system or procedure related complication or events.

7.3.3 Test report

The test laboratory shall produce the test report, which shall include a summary assessment of the data generated during the course of the investigation. The test report shall include the complete study protocol. All data generated

from the preclinical *in vivo* evaluation must be incorporated into a comprehensive test report. The report should include the results generated by tests described in Annex C.

The test report shall include:

a) identification of each valve used (product description, serial number, and other appropriate valve identification);

b) detailed description of the animal model used and the rationale and justification for its use. The pre-procedural assessment of each animal shall include documentation of health status as well as gender, weight, and age of the animal;

c) description of the operative procedure, including implant technique, test surgical heart valve substitute orientation, valve position, and operative complications;

d) description of the pre-procedural and post-procedural clinical course of each animal including, clinical observations, medication(s) and interventions used to treat adverse clinical events. Describe anticoagulation or antiplatelet drug and regimen used as well as therapeutic level monitoring methods;

e) any significant deviations from the protocol or amendments to the protocol and their significance;

f) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with surgical heart valve substitute implantation and animal care;

g) interpretation of data, including a comparison of the results between test and reference animals, and a recommendation relative to the clinical safety and performance of the surgical heart valve substitute under investigation;

h) the study pathologist's report that includes gross and radiographic examination and histopathology findings for each explanted surgical heart valve substitute;

i) detailed full necropsy reports for each animal enrolled in the study. Reports should include an assessment of the entire body along with, and findings (e.g. thromboembolism) likely caused by the surgical heart valve substitute.

Further details of the test report depend on the defined test protocol.

Guidance on the composition of the test report is given in Annex C.

7.4 Clinical investigation

7.4.1 General

For new surgical heart valve designs, a prospective clinical investigation shall be carried out in accordance with this International Standard. For modification of an existing previously approved valve, a clinical investigation shall be considered, based on the risk analysis that evaluates the modification. Clinical investigations should be conducted for design changes that affect the safety and/or performance of the device (e.g., change in blood contacting materials, design changes that alter the flow characteristics or hemodynamics, and changes that affect the mechanical loading on the valve). These types of changes have historically affected the clinical safety of the valve. If a determination is made that clinical investigations are not required, justification shall be documented in the risk management file. The clinical investigation shall be conducted in accordance with ISO 14155.

Data are obtained on the safety and performance of a surgical heart valve substitute under normal conditions of use in humans; the side effects and related risks of surgical heart valve substitute implantation are documented. The clinical investigation shall include pre-operative, peri-operative, and follow-up data from a specified number of patients, each with a follow-up appropriate for the device and its intended use. The clinical data shall provide substantial evidence of acceptable performance and safety (i.e., freedom from unacceptable risk).

The study protocols should specify primary and secondary endpoints as well as specific study- related adverse events. The adverse event definitions of the outcome measures should be consistent with those employed in previous studies of heart valves, when appropriate. The study protocol shall include a data analysis plan and success criteria.

The manufacturer is responsible for ensuring collection of appropriate information. The design shall be consistent with the aims of the protocol. For a given study, data collection forms should be the same for each institution and investigator. The protocol shall ensure consistency between the study aims and the inclusion/exclusion criteria.

Studies should employ measures to minimize bias. The use of an independent clinical events adjudication committee to classify events against pre-established criteria, and core labs are recommended for outcome variables that might be prone to bias or inter-observer variability.

To ensure patient safety, adverse events shall be adjudicated and reviewed on a regular basis. For pre-market clinical studies, both safety data monitoring and adverse event adjudication shall be conducted by an independent committee(s) of qualified experts. Safety monitoring guidelines shall be established.

7.4.2 Statistical considerations

Study designs may vary depending on the purposes of the assessment (pre or post-market). Suggested methods of formal statistical evaluation of the clinical data are described in Annex J.

7.4.3 Distribution of subjects and investigators

Clinical investigations shall be designed to include enough subjects, clinicians and institutions to be reasonably representative of the intended user and patient populations to provide generalizable results applicable to the wider population in which the device is intended to be marketed. If the device is intended to be marketed in different patient populations and/or different geographical locations, which are not represented by the clinical investigation, additional clinical investigations shall be considered. The protocol shall specify and justify the planned number of institutions (including geographic distribution), the maximum number of subjects planned, and the maximum/minimum number of investigators planned per institution.

7.4.4 Sample size

The sample size should be sufficient to enable assessment of the clinical performance of the surgical heart valve substitutes as well as to quantify the associated risk. A minimum of 150 patients in each valve position is required. When appropriate to the study aims, standard statistical methods should be used to calculate the minimum sample size with prior specification of the Type 1 error rate, the statistical power, and effect sizes to be detected (see Annex J).

7.4.5 Entry criteria

The inclusion and exclusion criteria for patient selection shall be clearly established. Differences between the target population (i.e., those for whom the device is intended) and the accessible population (i.e., those who will enter the study) shall be specified. The study should only include patients who are willing and able to participate in the follow-up requirements.

7.4.6 Duration of the study

The protocol shall specify the duration of the study. The clinical investigation shall continue until the minimum number of recipients of each valve type have each been followed for a minimum of 1 year. There must be at least 400 patient-years of follow-up of each valve type (e.g., aortic or mitral). All implants shall be analyzed, including those patients not surviving through the first year, and including centers with enrollment below the intended minimum.

The protocol shall specify the duration of the study, including the appropriate follow-up intervals and the minimum overall patient-years in consideration of Annex J. The duration will depend on the risk assessment, the intended application and, if relevant, the type of device modification.

7.4.7 Clinical data requirements

7.4.7.1 General

Clinical data, including adverse events, shall be recorded for all patients in the study as required by ISO 14155. Critical aspects of the clinical study protocol shall be identical for all participating institutions, e.g., patient inclusion, patient exclusion and data collection requirements.

Where appropriate, the identified adverse event definitions used in the clinical protocol shall be consistent and aligned with the most applicable published guidelines, for example, the Guidelines for reporting mortality and morbidity after cardiac valve interventions (Akins et al 2008).

The investigational protocol shall include an explant pathology protocol with detailed instructions for the return of the explanted valves to the manufacturer or an independent laboratory for assessment. Whenever feasible, the explanted device shall be subjected to appropriate functional, imaging and histopathological investigations.

The following data shall be collected or a justification for not doing so shall be provided:

7.4.7.2 Baseline data

a) demographics (e.g., age, gender, race/ethnicity);

b) baseline information (e.g, weight, height, blood pressure);

c) Patient co-morbidities and co-existing medical conditions (e.g., liver, kidney, and lung disease, substance abuse, smoking history, diabetes, hypertension, history of cancer and history of endocarditis);

d) diagnosis (e.g., valvular lesion and etiology including degree of calcification) and cardiovascular comorbidities (e.g., congestive heart failure, cardiomyopathy, peripheral vascular disease, aneurysm, coronary artery disease, cardiac arrhythmia, previous myocardial infarction and previous history of thromboembolism);

e) functional status (e.g., New York Heart Association functional class). Quality of life measures and, exercise tolerance tests should also be considered;

f) clinical risk score and its components (e.g, Society of Thoracic Surgeons (STS) risk score or EuroSCORE II);

g) previous cardiovascular interventions (e.g., coronary artery bypass, coronary artery angioplasty, percutaneous valvuloplasty (position), operative valvuloplasty (position), annuloplasty (position), previous heart valve substitute replacement, peripheral vascular operations);

h) echocardiographic information and other relevant imaging data to provide cardiac hemodynamic, morphological, geometric, and functional information;

i) most recent blood studies sufficient to capture patient risk factors, according to the standard site practice.

7.4.7.3 Operative data

a) Any relevant intra-operative findings that modify the original diagnosis;

b) any concomitant interventions or procedures;

c) date of operation;

d) surgical heart valve substitute type, model, valve size (as labeled), and serial number;

e) tissue annulus diameter (TAD) of patient and how determined;

f) surgical approach (e.g., sternotomy, mini-sternotomy, thoracotomy and mini-thoracotomy);

g) details of procedure (e.g., cardiopulmonary bypass time, aortic cross clamp time, type myocardial preservation) and type of anesthesia;

h) suture technique, if applicable;

i) retention of all or part (specify) of native aortic/mitral valve structures (e.g., preservation of the mitral sub-valvular apparatus);

j) implant position (e.g., aortic or mitral), surgical heart valve substitute positioning in relation to tissue annulus (e.g., supra-annular, intra-annular) and device (disc/leaflet) orientation;

k) type of visualization (i.e., direct or indirect);

l) implant malfunction failure if applicable;

m) specified planned or unplanned treatment/interventions (e.g., cardioversion, renal support, blood transfusion);

n) echocardiography and/or relevant imaging and hemodynamic modalities intraoperatively or prior to discharge as appropriate (refer to Annex K in ISO 5840-1).

7.4.7.4 Early post-operative and follow-up data

Early post-operative and follow-up data shall be collected within 30 days, at least one specific timepoint ≥ 3 and ≤ 6 months after implantation of the surgical heart valve substitute, at one year and annually thereafter until the investigation is completed. The following evaluations should be performed for all patients at all follow-up assessments unless an adequate risk analysis justifies a less frequent interval. Depending on the trial design, additional data collection or follow-up timepoints might be appropriate.

The following data shall be collected or a justification for not doing so shall be provided:

a) date and method of follow-up (e.g., office, clinic, or hospital);

b) functional status (e.g., New York Heart Association functional class). Quality of life andor exercise tolerance tests should also be considered;

c) evaluation by echocardiography and/or relevant imaging and hemodynamic modalities intraoperatively or prior to discharge as appropriate);

NOTE If valve dysfunction is suspected, transesophageal echocardiography (TEE) is recommended.

d) appropriate blood studies including tests for hemolysis;

e) status of anticoagulant and/or antiplatelet therapy;

f) adverse events in accordance with Akins, 2008;

g) cardiac rate, conduction status and rhythm (12 lead EKG);

h) re-operation reports; if applicable

i) specified planned or unplanned treatment/interventions (e.g., in-hospital readmission, cardioversion, renal support, blood transfusion);

j) explant analysis when available; wherever feasible, the explanted test surgical heart valve substitute shall be subjected to appropriate functional, radiography, and histopathological investigations.

k) date and cause of death, if applicable;

l) autopsy report, if autopsy is performed.

NOTE Whenever feasible, autopsy is recommended to capture device related deaths and to ensure proper classification of adverse events.

7.4.8 Clinical investigation report

7.4.8.1 General

The clinical investigation report shall comply with ISO 14155. The report shall include the names of the investigators and institutions, the data collected in 7.4.7.1 and an analysis of the following, at a minimum:

a) demographics (e.g., age, gender, race/ethnicity);

b) patient co-morbidities (e.g., pre-operative diagnosis of valvular and co-existing disease, operative diagnoses);

c) implant procedures and techniques, implant position, type, model, valve size, tissue annulus diameter of patient, surgical heart valve substitute positioning in relation to the tissue annulus, disc/leaflet orientation;

d) pre-procedure versus post-procedure New York Heart Association functional class;

e) method and completeness of follow-up;

b) pre-procedural versus post-procedural haemodynamic and blood study results;

h) adverse events as specified in the study protocol;

i) summary of deaths and/or explants.

7.4.8.2 Analysis and reporting

The method of reporting shall conform to the *Guidelines for reporting morbidity and mortality after cardiac valve interventions*, Akins et al., 2008.

The clinical investigation report should include:

a) early adverse events shall be expressed as a percent of patients experiencing the event and shall be calculated for events occurring in the first 30 days. The numerator and denominator for each percentage shall be provided;

b) linearized rates shall be used for late adverse events, with other statistical models as appropriate. Late events are those occurring on or after the 31st day post implant;

c) analyses of survival rates and freedom from adverse events using an actuarial (e.g., Kaplan-Meier), or a cumulative incidence method or both;

NOTE For event rates at specific times, standard errors should be reported using Greenwood's algorithm or another statistically valid method. The standard error for hazard ratios should be calculated using standard statistical methods. See Andersen, et al.

d) specific analyses shall include:

1) overall survival;

2) occurrence of adverse events;

3) freedom from specific complications, including but not limited to valve thrombosis, embolism, anticoagulant-related hemorrhage, prosthetic valve endocarditis, structural deterioration of the surgical heart valve substitute, non-structural dysfunction of the surgical heart valve substitute, paravalvular leak, hemolysis, and re-operation;

e) the specific complications and deaths shall be stratified as follows:

1) all complications shall be stratified by valve position and size (TAD);

2) thromboembolism shall be stratified by anticoagulation therapy and cardiac rhythm;

3) non-structural dysfunction and structural valve deterioration shall be stratified by nature of dysfunction (e.g., thromboembolism, thrombosis, anticoagulant-related hemorrhage, prosthetic valve endocarditis, structural deterioration, non-structural dysfunction, paravalvular leak, hemolysis);

4) structural valve deterioration shall be stratified by valve size.

7.4.8.3 Post-market clinical follow-up

In addition to the one-year follow-up, a long- term follow-up evaluation shall be conducted according to the following principles:

a) ideally, the long-term cohort should include all patients in the pre-marketing studies. However, if this is not possible, the long-term cohort may include a clearly defined subset of the original patients, or additional patients who did not participate in any pre-marketing the study. The selection of the specific patients shall be justified so as to minimize selection bias;

b) the duration of the long-term study will depend on the risk assessment for the specific device design and/or device modification.

In addition to the follow-up of the original cohort of patients, post-market hypothesis- driven clinical studies shall be initiated when indicated on the basis of the risk analysis to gather data from a larger population. Objectives for post-market clinical follow-up studies include: a) to provide longer term safety and performance data to identify possible residual risks, and to determine if the data remain consistent with the OPCs, and b) to assess whether the results of the pre-market clinical investigation can be generalized to the post-market population of users and patients.

Annex A
(informative)

Heart valve substitute hazards, associated failure modes, and evaluation methods

A.1 Hazards, failure modes, and evaluation methods

A.1.1 General

Typical hazards, examples of their associated failure modes, and possible evaluation methods are given in Table A.1. This list is not intended to be all-inclusive but representative of hazards and failure modes that are applicable to surgical heart valve substitutes. For some novel designs, also refer to 5840-3 for applicable failure modes and possible evaluation methods.

Table A.1—Examples of Surgical heart valve substitute hazards, associated failure modes, and evaluation methods

Hazards	Possible failure mode(s)		Possible evaluation methods
	Rigid valve	Flexible valve	
Stenosis	Occluder binding, pannus overgrowth	Pannus overgrowth, leaflet mineralization, excessive stent deformation, stent fracture	Steady/pulsatile-flow pressure difference, stent creep testing, wear/durability testing, fatigue testing/analysis, pre-clinical animal evaluation with echo characterization
Regurgitation	Occluder binding, occluder escape, chipped occluder, chipped orifice, out-of-tolerance condition, anchoring frame deformation, paravalvular leakage	Leaflet tear, abrasion, delamination, or shrinkage, leaflet prolapse, excessive stent deformation, stent fracture, suture breakage/pull out, suture hole elongation, out-of-tolerance condition, anchoring frame deformation, paravalvular leakage	Steady/pulsatile-flow leakage, valve prolapse testing, material characterization, durability testing, fatigue testing/analysis, stent creep testing, device distribution testing, pre-clinical animal evaluation with echo characterization, *in vitro* flow visualization
Device Embolization	Occluder fracture, orifice fracture, occluder escape, sewing cuff separation, size mis-match	Leaflet tear, leaflet mineralization, sewing cuff separation, size mis-match	Material characterization, durability testing, fatigue testing/analysis, leaflet blowout/prolapse testing, leaflet escape testing, cavitation testing, device distribution testing, migration resistance evaluations
Hemolysis	Cavitation, elevated turbulence	Elevated turbulence	*In vitro* flow visualization, pre-clinical animal evaluation, clinical evaluation
Thrombosis, thromboembolism	Flow stasis, blood material interaction failure, improper anticoagulation regimen	Flow stasis, blood material interaction failure	Material characterization, *in vitro* flow visualization, blood material interaction characterization, pre-clinical animal evaluation, clinical evaluation
Bio-incompatibility	Local or systemic toxicity, inappropriate tissue response or effect on coagulation, material	Local or systemic toxicity, inappropriate tissue response or effect on coagulation, material	Biocompatibility safety evaluation, material characterization, blood material interaction characterization,

Hazards	Possible failure mode(s)		Possible evaluation methods
	Rigid valve	Flexible valve	
	degradation, leaching of component compounds	degradation, leaching of component compounds	biostability testing, corrosion testing, characterization of sterilization residuals, pre-clinical animal evaluation, clinical evaluation
Paravalvular leak	Sewing cuff non-compliant, sewing cuff tear, sewing cuff separation, suture breakage/pull out, support structure fatigue fracture, inadequate sealing skirt, valve improperly sized (i.e., too small for implant site), valve malposition	Sewing cuff non-compliant, sewing cuff tear, sewing cuff separation, suture breakage/pull out, support structure fatigue fracture, inadequate sealing skirt, valve improperly sized (i.e., too small for implant site), valve malposition	Needle penetration/suture drag characterization, sewing ring integrity testing, durability testing, wet labs, pre-clinical animal evaluation, *In vitro* models, *ex vivo* studies (e.g., cadaver hearts), hydrodynamic characterization
In vivo diagnostic incompatibility	Device migration, device heating, image distortion, poor device visualization	Device migration, device heating, image distortion, poor device visualization	Material characterization, MRI compatibility testing, radiographic evaluation
Endocarditis	Non-sterile device, non-sterile accessories	Non-sterile device, non-sterile accessories	Validation of sterility processes for device and accessories to a sterility assurance level of 10^{-6}, device package integrity testing
Inability to complete implant procedure; increased operative time	Failure of valve to rotate, improper sizing, valve damaged during handling, device not compatible with accessories, improper sizing, device not compatible with accessories	Failure of valve to rotate, improper sizing, valve damaged during handling, device not compatible with accessories, improper sizing, device not compatible with accessories	Design validation with device, packaging, accessories, and instructions for use; in-process inspections, pre-clinical animal evaluation, usability and clinical evaluations
Virus, BSE, or other transmissible agent	Tissue and/or tissue-derived source material contamination	Tissue and/or tissue-derived source material contamination	Demonstrated compliance with all parts of ISO 22442
Bleeding event	Improper anticoagulation regimen	Improper anticoagulation regimen	Design validation testing, pre-clinical *in vivo* evaluation, Clinical evaluation
Unintended anatomical interactions	Anterior mitral leaflet interference, coronary occlusion, conduction system interference, vascular or myocardial injury.	Anterior mitral leaflet interference, coronary occlusion, conduction system interference, vascular or myocardial injury.	*Ex vivo* evaluation (e,g, cadaver studies), pre-clinical *in vivo* evaluation, clinical evaluation

NOTE—This table is given as an example and is not all-inclusive.

A.1.2 Additional generic failure modes and causes

Additional generic failure modes and causes include (also refer to ISO 5840-3 as applicable to novel designs:

— sewing cuff defective;

— valve too noisy;

— valve holder broken;
— valve inverted on holder;
— valve cannot be removed from holder;
— instructions for use inadequate;
— inadequate labeling;
— inadequate warnings;
— use by unskilled personnel;
— packaging damaged during shipment;
— shelf life degradation;
— environmental damage during shipment and storage (excess heat or cold);
— improper re-use of device.

Annex B
(informative)

In vitro procedures for testing unstented or similar valves in compliant chambers

B.1 General

If the pressure difference and/or regurgitation is a function of the compliance of the vessel or chamber into which the valve is to be implanted (e.g., in the case of an unstented aortic valve), then the valve should be tested in compliant chambers as described in B.2. The protocols for pulsatile pressure difference, pulsatile regurgitation, and wear/durability should be amended as in B.3.

NOTE These values are for compliance of the aorta and are not annulus values.

See ISO 5840-1 Annex E for paediatric conditions.

B.2 Compliant chamber specifications

B.2.1 When testing valves in compliant chambers, consider using two compliant chambers:

— a low compliance chamber for simulating patients with a normal aorta;

— a high compliance chamber for simulating younger patients, or patients with a hypercompliant aorta.

B.2.3 Recommended values for the compliance of aortic chambers are:

— low compliance chamber: $C = \frac{0.68\%}{\text{kPa}} \left(= \frac{0.09\%}{\text{mmHg}} \right)$

— high compliance chamber: $C = \frac{2.40\%}{\text{kPa}} \left(= \frac{0.32\%}{\text{mmHg}} \right)$

Other values for compliance should be justified by the manufacturer.

B.2.4 Recommended pressure ranges over which the chamber compliance (without the valve present) should be characterized, and the valves tested, include the hypotensive, normotensive, and moderate hypertensive conditions defined in ISO 5840-1 Table 1 and Table 2 (see 6.2.1).

B.3 Test procedures using compliant chambers

B.3.1 Pulsatile-flow pressure difference

Test the valves in the low compliance chamber, under the hypo, normo and moderate hyper-tensive pressure conditions as defined in ISO 5840-1 Table 1 and Table 2 (see 6.2.1).

B.3.2 Pulsatile-flow regurgitation

B.3.2.1 Test the valves in the low compliance chamber under the hypo, normo, and moderate hyper-tensive pressure conditions as defined in ISO 5840-1, Table 1 and Table 2 (see 6.2.1).

B.3.2.2 Test the valves in the high compliance chamber, under the hypo and normo-tensive pressure conditions as defined in ISO 5840-1 Table 1 and Table 2 (see 6.2.1). Hypertensive conditions may be applicable for right-heart conditions.

B.3.3 Reference valves for hydrodynamics testing

One smallest and one largest currently marketed unstented valves should be used as reference valves in all testing using compliant chambers.

B.3.4 Wear/durability

The valves should be tested in the low compliance chamber.

Annex C
(informative)

Preclinical *in vivo* evaluation

C.1 General

Based on risk analysis and in order to predict the safety and performance of clinical use, the study should be designed to provide a sufficient number of animals implanted with the test and reference surgical heart valve substitute. The rationale for animal models and justification for the use of alternative implant positions and implantation methods should be provided.

Evaluations listed in this annex (Table C.1) are not intended as mandatory or all inclusive. Each of the described evaluations includes minimum parameters necessary to assess a specific issue. However, additional parameters might be relevant depending on specific study goals and/or manufacturer product claims.

Acute testing of surgical heart valve substitutes can be performed under nonsterile conditions.

Table C.1—Settings that can be evaluated

Issue	Acute	Chronic	Flexible	Rigid
Hemodynamic performance	X	X	X	X
Ease of surgical handling	X	X	X	X
Acoustic characteristics	X	X		X
Interference with adjacent anatomical structures	X	X	X	X
Haemolysis		X	X	X
Thrombo-embolic complications		X	X	X
Calcification/mineralization		X	X	
Pannus formation/tissue ingrowth/foreign body response		X	X	X
Structural valve dysfunction and non-structural dysfunction		X	X	X
Assessment of valve and non-valve related pathology		X	X	X
Cavitation		X		X

C.2 Disposition of evaluations

The evaluations listed in Table C.1 can be addressed as follows.

C.2.1 Hemodynamic performance

Transvalvular mean pressure differential and regurgitation should be performed, at minimum on the day of elective euthanasia, at cardiac indices across a range of cardiac indices (e.g., 2,5 L/min/m^2 to 6 L/min/m^2). Transvalvular regurgitation measurement should be performed using a continuous flow measurement technique or other methods which do not require crossing the valve with a catheter. Multiple measurements of pressure and flow should be obtained.

Measuring equipment used to assess haemodynamic performance should be described and its performance characteristics documented.

C.2.2 Ease of surgical implantation

The ease of surgical implantation should include a descriptive assessment of the surgical handling of the surgical heart valve substitute and accessories (if any), compared to a reference including any unique features.

C.2.3 Acoustic characteristics

The acoustic characteristics of rigid surgical heart valve substitutes should be evaluated in the intended implant position. One method of accomplishing this is to use intravascular/intracardiac pressure recordings with a micro-tip pressure transducer that has an upper frequency limit no lower than 20,000 Hz. Air transmitted sound should be recorded 10 cm above the beating heart in the open chest in accordance with IEC 60651. Alternatively, the valve loudness may be directly measured by applying the Zwicker loudness measurement in accordance with method B of ISO 532:1975 to valve sound recordings taken 5 cm to 10 cm above the closed chest. A technique similar to that described in e.g., Erickson, et al. could be used. The acoustic techniques are described in Nygaard, et al.

C.2.4 Interference with adjacent anatomical structures

Interference with coronary ostia, cardiac conduction system, mitral valve structures, etc. should be assessed and documented as appropriate.

C.2.5 Haemolysis

At minimum, the following laboratory analyses should be performed: red blood cell count, hematocrit, reticulocyte count, lactate dehydrogenase, haptoglobin, and plasma-free hemoglobin. Additional hematology and clinical chemistry analyses should also be conducted to assess inflammatory response, platelet consumption, liver and renal function.

C.2.6 Thrombo-embolic events

Thrombo-emboli should be evaluated in terms of macroscopic description, photographic documentation, and a histologic description of the thrombotic material. A full post-mortem exam should be performed to disclose peripheral thrombo-emboli both macro- and microscopically.

C.2.7 Calcification/Mineralization

Calcification/mineralization should be evaluated in terms of macroscopic description, photographic and radiographic documentation, and a histologic description of any mineral deposits. The results should be compared to a reference valve.

C.2.8 Pannus formation/tissue ingrowth

At minimum, the distribution and thickness of pannus formation/tissue ingrowth should be described using macroscopic and microscopic methods and photographic documentation. A description of any inflammatory response should also be included in the histologic description.

C.2.9 Structural valve deterioration and non-structural dysfunction

Structural valve deterioration and non-structural dysfunction should be macro- or microscopically documented and described. If deemed appropriate by the program sponsor and/or study director any unused portion of surgical heart valve substitute material should be retained in a suitable fixative for additional studies as needed.

C.2.10 Assessment of valve and non-valve related pathology

Assessment of other valve and non-valve related pathology should be macroscopically described, histologically evaluated (if appropriate), and photographically documented.

C.2.11 Cavitation

Macro- and microscopic assessment of any signs of erosion caused by cavitation should be documented.

Annex D
(informative)

Description of the surgical heart valve substitute

D.1 General

The description of the surgical heart valve substitute should include, at minimum, the information listed in Table D.1. The description should be supported by pictures or illustrations where appropriate. For novel surgical heart valve substitutes (e.g., sutureless), the requirements of both this International Standard and ISO 5840-3 might be relevant and shall be considered as applicable to the specific device design.

Table D.1—Information to be included in description of surgical heart valve substitute

Major class	Subclass	Component	Implant position	Annulus position	Orientability
Rigid	Bileaflet Tilting disc Caged ball Other	Orifice Occluder Connections to Annulus (e.g., Sewing cuff)	Aortic Mitral Tricuspid Pulmonic	Supra-annular Intra-annular	Rotatable Non-rotatable
Flexible	Stented Unstented subcoronary full root scalloped	Leaflets Support Structure (e.g., Stents) Connections to annulus (e.g., Sewing cuff)	Aortic Mitral Tricuspid Pulmonic	Supra-annular Intra-annular	Rotatable Non-rotatable

EXAMPLE 1 Rigid, tilting disc, Pyrolytic Carbon occluder with 6-4 titanium orifice, PET/PTFE sewing cuff, aortic and mitral, supra-annular, rotatable.

EXAMPLE 2 Flexible, stented, bovine pericardial, acetyl copolymer stent, PET/PTFE sewing cuff, aortic and mitral, supra-annular, non-rotatable.

D.2 Chemical treatments, surface modifications, or coatings

The description should include any chemical treatments, surface modifications, or coatings used, including primary fixation of tissue and any anti-calcification, anti-infection, or anti-thrombotic treatments.

For device-drug combination products, elements of ISO 12417 might be applicable.

D.3 Component description

Each of the components of the surgical heart valve substitute should be listed and the materials of construction should be documented. The components list should include packaging storage media (e.g., for tissue materials). An assembly sketch should be documented that includes all components, including joining materials, such as sutures.

D.3.1 Examples of components of some surgical heart valve substitutes

The following is a listing of examples of typical valve components of some surgical heart valve substitutes. The following listing is not meant to be exhaustive.

— coating: any thin-film material that is applied to an element of a surgical heart valve substitute in order to modify its physical or chemical properties;

— component-joining material: material, such as a suture, adhesive, or welding compound, used to assemble the components of a surgical heart valve substitute, thereby becoming part of the implant device (see Figures E.1, E.2, E.3, E.4, E.5, E.6, and E.7);

— covering: any element applied to enclose any other element of the surgical heart valve substitute (see Figures E.1, E.3, E.4, E.5, E.6, and E.8);

— occluder/leaflet: component that inhibits backflow (see Figures E.1, E.2, E.3, E .4, E.5, E.6, and E.8);

— occluder retention mechanism: component(s) of a surgical heart valve substitute which support(s) or retain(s) the occluder(s) (see Figures E.1 and E.2);

— orifice ring (also housing): component of a surgical heart valve substitute that houses the occluder(s) of a rigid surgical heart valve (see Figure E.1);

— sewing ring (also sewing cuff): component of a surgical heart valve substitute by which it can be attached to the heart (see Figure E.1);

— sewing-ring filler: any material within the confines of the sewing ring of the surgical heart valve substitute which provides it with bulk and shape (see Figure E.1);

— sewing-ring retaining material: material used to prevent separation of the sewing ring from the orifice ring or frame (see Figures E.1 and E.2);

— stent (also frame, body): component of a surgical heart valve substitute that houses the occluder(s) of a flexible leaflet device (see Figure E.5, E.6, and E.8);

— stiffening element: component which reduces deformation of the orifice ring or stent (see Figure E.1).

D.4 Implant position

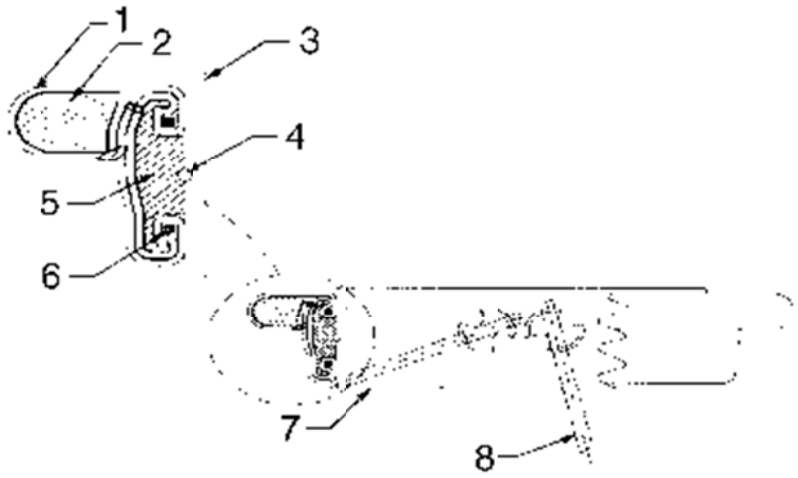
In addition to providing the implant position as listed in Table D.1, a brief description of the implant technique, including procedures for sizing the valve and the recommended implant technique, should be documented.

D.5 Accessories

Any accessories that are to be used in conjunction with the surgical heart valve substitute and its implantation (e.g., sizers, holders, loading tools, delivery systems) should be described and their materials of construction should be provided (see Figure E.7).

Annex E
(informative)

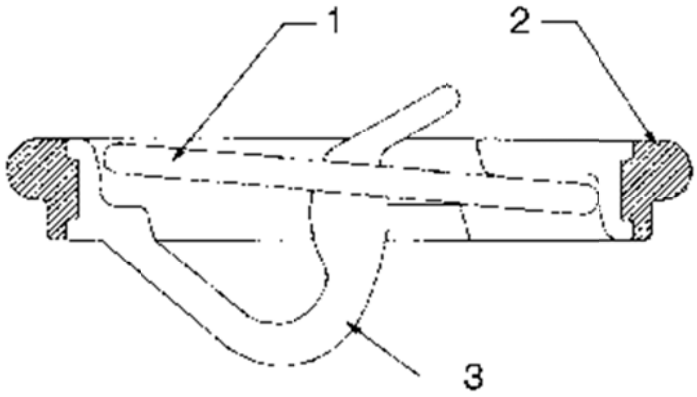
Examples of components of some surgical heart valve substitutes



Key

1 covering
2 sewing ring filler
3 orifice ring
4 component joining material
5 stiffening element
6 sewing ring retaining material
7 housing
8 occluder

Figure E.1—Generic bi-leaflet rigid surgical heart valve substitute



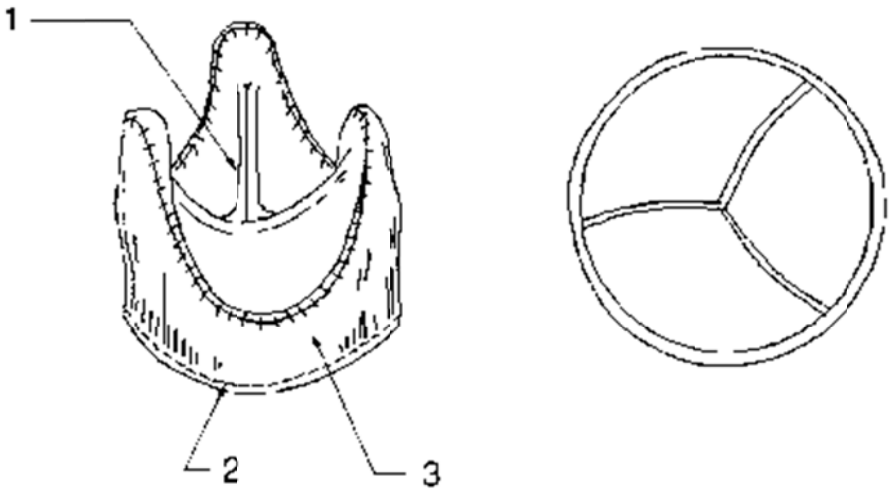
Key

1 occluder

2 sewing ring retaining material

3 occluder retention mechanism

Figure E.2—Generic mono-leaflet rigid surgical heart valve substitute



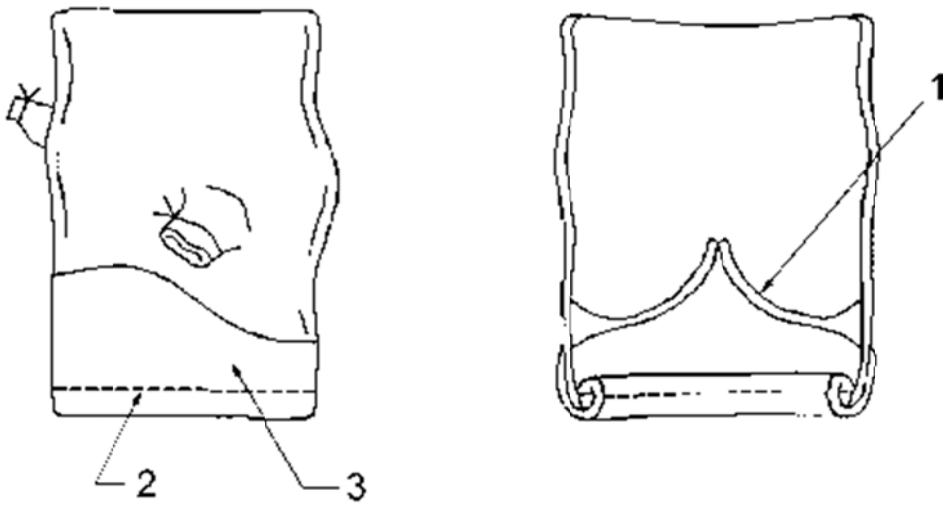
Key

1 leaflet

2 component joining material

3 covering

Figure E.3—Generic flexible surgical heart valve substitute (flexible, unstented, scalloped)



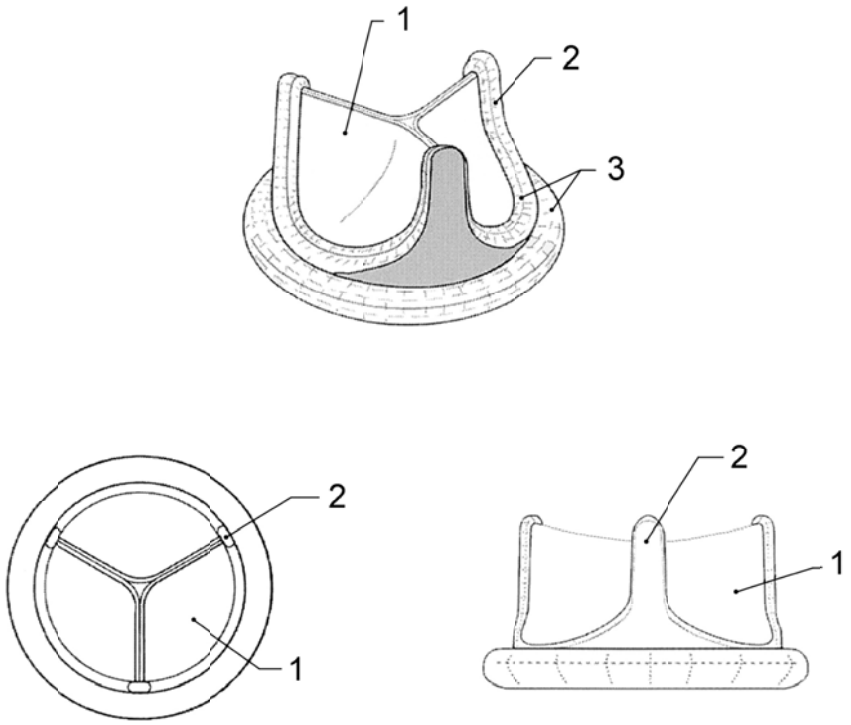
Key

1 leaflet

2 component joining material

3 covering

Figure E.4—Generic flexible surgical heart valve substitute (flexible, unstented, full root)



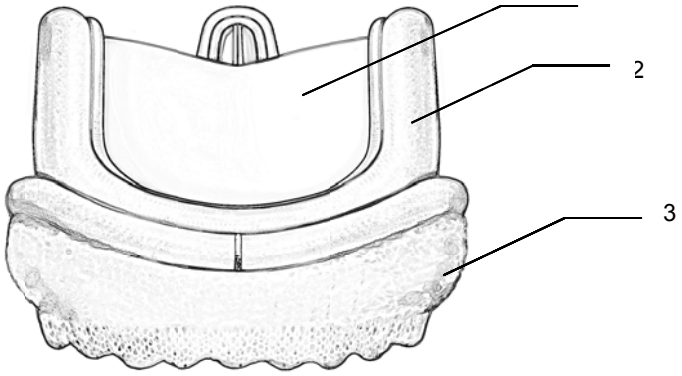
Key

1 leaflet

2 stent

3 covering

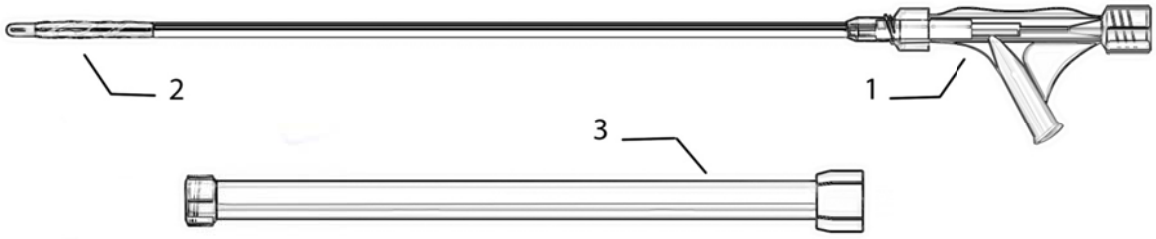
Figure E.5—Generic flexible stented surgical heart valve substitute



Key

1 leaflet
2 stent
3 anchoring stent

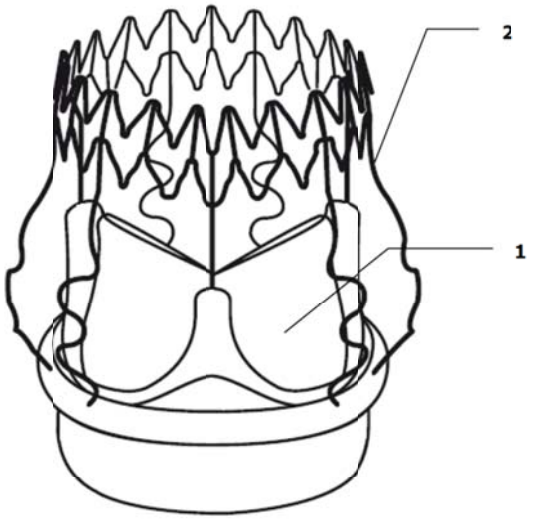
Figure E.6 – Generic Novel Surgical Valve Substitute, e.g., Sutureless



Key

1 delivery system
2 balloon
3 delivery sheath

Figure E.7—Generic balloon expandable rapid deployment surgical heart valve system



Key

1. leaflet
2 anchoring stent

Figure E.8—Generic self-expanding sutureless surgical heart valve

Annex F
(informative)

Guidelines for verification of hydrodynamic performance

F.1 General

This annex provides guidance on test equipment, test equipment validation, formulation of test protocols, and test methods for the hydrodynamic performance of surgical heart valves.

F.2 Steady forward-flow testing

F.2.1 Measuring equipment accuracy

F.2.1.1 Differential pressure measurement should have a measurement accuracy of at least ± 0,26 kPa (± 2 mm Hg).

F.2.1.2 All other measurement equipment should have a measurement accuracy of at least ± 5 % of the maximum intended test measurement (e.g., flow meter accuracy ± 1,5 l/min).

F.2.2 Test apparatus requirements

F.2.2.1 Steady flow testing for surgical heart valve substitutes should be conducted in a straight tube having an internal diameter of 35 mm.

F.2.2.2 The test system should be capable of generating flow rates of at least 30 l/min.

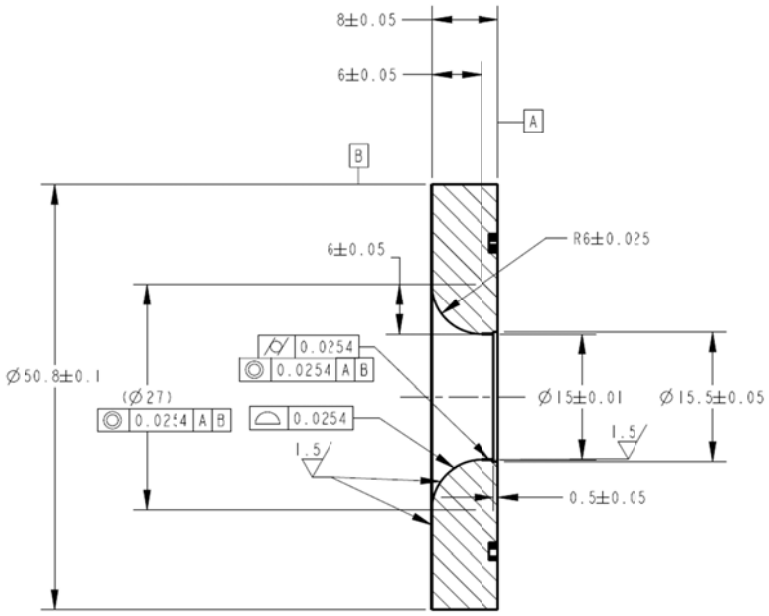
F.2.2.3 Flow entering the test chamber should be fully developed; this can be achieved by use of a flow straightener upstream of the surgical heart valve substitute.

F.2.2.4 Pressure taps should be located one tube diameter upstream and three tube diameters downstream from the midplane of the surgical heart valve substitute sewing ring. If sufficient data can be provided to demonstrate comparable results, other pressure tap configurations may be used.

F.2.2.5 Pressure taps should be flush with the inner wall of the tube.

F.2.2.6 A standard nozzle in accordance with Figure F.1 should be used to characterize the forward flow pressure and flow measuring equipment. A plot of expected values for the Forward Flow Standard Nozzle Gradients can be found in Figure F.2. When accounting for acceptable accuracy tolerances, measured values should agree with these data. See Marquez et al. (2001).

NOTE Based on physiologic saline with specific gravity of 1,005 g/ml and viscosity of 1,0 cP.



eters.

Figure F.1—Standard nozzle; forward flow

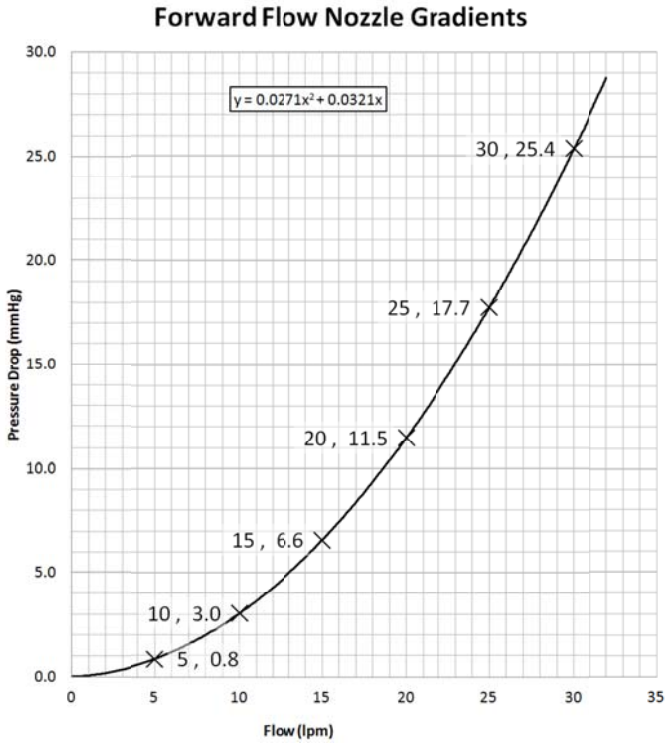


Figure F.2—Forward flow nozzle gradients

F.2.3 Test procedure

Measure the difference across the test valve and the standard nozzle over a flow rate range of 5 l/min to 30 l/min in 5 l/min increments.

F.2.4 Test report

The test report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity specific gravity;

b) a description of the steady flow apparatus;

c) details of the mean values and standard deviation of the following performance test variables at each simulated condition for each surgical heart valve substitute and standard nozzle should be presented in tabular and graphic form:

   1) steady flow rate;

   2) pressure differences;

   3) effective orifice area.

F.3 Steady back-flow leakage testing

F.3.1 Measuring equipment accuracy

F.3.1.1 Steady flow leakage flowrate should have a minimum measurement accuracy of ± 1 ml/s.

F.3.1.2 All other measurement equipment should have a measurement accuracy of at least ± 5 % of the maximum intended test measurement

F.3.2 Test apparatus requirements

F.3.2.1 The steady backflow leakage testing should be conducted in an apparatus that is capable of generating constant backpressures in the range of 5,2 kPa to 26 kPa (40 mm Hg to 200 mm Hg).

F.3.2.2 The surgical heart valve substitute should be mounted in such a manner as to minimize leakage around and through the sewing ring.

F.3.2.3 A standard nozzle in accordance with Figure F.3 should be used to characterize the backpressure, leakage volume flow rate, and pressure-measuring equipment. A plot of expected values for the Backflow Standard Nozzle Gradients can be found in Figure F.4. When accounting for acceptable accuracy tolerances, measured values should agree with these data.

NOTE Results when using Physiologic saline with specific gravity of 1,005 g/ml and viscosity of 1,0 cP.

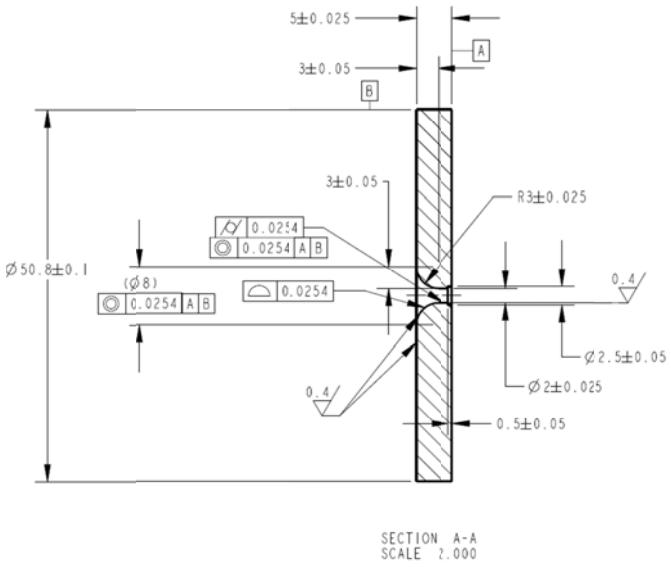


Figure F.3—Standard nozzle; back flow

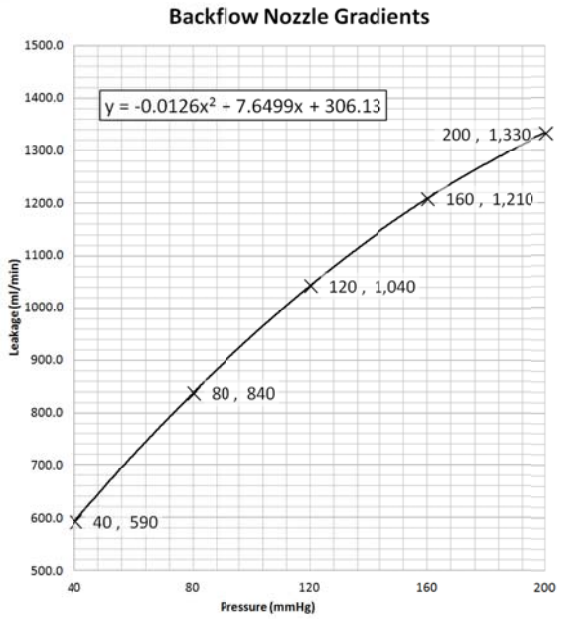


Figure F.4—Back flow nozzle gradients

F.3.2.4 The repeatability of the test system should be evaluated and documented.

F.3.3 Test procedure

Measure the static leakage across the surgical heart valve substitute and the standard nozzle at five equidistant back pressures in the range of 5,2 kPa to 26 kPa (40 mm Hg to 200 mm Hg). Collect at least five measurements at each back pressure.

F.3.4 Test report

The steady backflow test report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity, and specific gravity under the test conditions;

b) a description of the steady backflow apparatus;

c) details of the mean, range, and standard deviation of the performance test variables, at each simulated condition for each surgical heart valve substitute and standard nozzle, presented in tabular and graphic form; i.e., static leakage volume flow rate, expressed in l/min, as a function of back pressure.

F.4 Pulsatile-flow testing

F.4.1 Measuring equipment accuracy

F.4.1.1 The pressure measurement system should have an upper frequency limit (-3 dB cut-off) of at least 30 Hz and a differential measurement accuracy of at least ± 0,26 kPa (± 2 mm Hg). The flow meter should have an upper frequency limit (-3 dB cut-off) of at least 30 Hz.

F.4.1.2 Regurgitant volume measurements should have a measurement accuracy of at least ± 2 ml.

F.4.1.3 All other measurement equipment should have a measurement accuracy of at least ± 5 % of the maximum intended test measurement.

F.4.2 Test apparatus requirements

F.4.2.1 Pulsatile-flow testing should be conducted in a pulse duplicator that produces pressure and flow waveforms that approximate physiological conditions over the required physiological range.

F.4.2.2 The pulse duplicator should have had its properties and performance established by means of testing reference valves of different sizes.

F.4.2.3 The pulse duplicator should permit measurement of time-dependent pressures, volumetric flow rates, velocity fields, and turbulent shear stress fields.

F.4.2.4 The repeatability of the test system should be evaluated and documented.

F.4.2.5 Relevant dimensions of the cardiac chambers and vessels should be simulated.

F.4.2.6 In cases where the compliance may affect the pressure difference or regurgitation characteristics of the valve (e.g., the aortic compliance in an unstented aortic valve), the relevant chamber compliance should be simulated (see Annex B for guidelines on compliant chambers).

F.4.2.7 The chamber should allow the observer to view and photograph the surgical heart valve substitute at all stages of the cycle.

F.4.3 Test procedure

F.4.3.1 Tests should be carried out on each valve in the position in which it is intended to be used. Qualitative and quantitative assessments should be made.

F.4.3.2 Pressure difference should be measured at four simulated cardiac outputs between 2 l/min and 7 l/min (e.g., 2 l/min, 3.5 l/min, 5 l/min, 7 l/min), at a single simulated normal heart rate (e.g., 70 cycles/min).

F.4.3.3 Regurgitant volumes should be measured at three different pressure conditions representative of hypotensive, normotensive and severe hypertensive conditions (see Table 1 and Table 2 of ISO 5840-1).

Table F-1 – Regurgitant volume test conditions

Beat Rate (cycles/min)	Systolic Duration (%)	Cardiac Output (l/min)	Pressure Conditions
45	30	5	Hypotensive, Normotensive, Severe Hypertensive
70	35	5	Hypotensive, Normotensive, Severe Hypertensive
120	50	5	Hypotensive, Normotensive, Severe Hypertensive

F.4.3.4 At least ten measurements of each of the following variables should be obtained from either consecutive or randomly-selected cycles:

a) mean pressure difference across the surgical heart valve substitute;

b) mean and root mean square (RMS) flow rates through the surgical heart valve substitute;

c) forward flow volume;

d) beat rate;

e) mean arterial pressure over the whole cycle;

f) systolic duration;

g) regurgitant volume, including the closing volume, the leakage volume (see ISO 5840-1, Figure 1), and the corresponding mean pressure difference across the closed valve.

F.4.3.5 Assess the flow fields (velocity and shear) in the immediate vicinity of the surgical heart valve substitute, including within the valve "housing" mechanism (e.g., within the hinge region of a bileaflet rigid valve design). Techniques for such measurements include laser Doppler velocimetry (LDV), particle image velocimetry (PIV), and computational fluid dynamics (CFD). The CFD code should be verified to make sure that the right equations and physics are being modeled as applied to the valve design being evaluated. CFD results should be validated by comparison with experimental results.

F.4.3.6 Assess the hemolytic and thrombogenic potential of the valve design in each position of intended use, either in the studies described in F.4.3.5, or other relevant *in vitro*, computational, and/or *in vivo* studies. Measures such as shear rate magnitude versus duration and particle residence time should be considered.

F.4.4 Test report

The pulsatile flow test report should include the following information:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity, and specific gravity under the test conditions;

b) a description of the pulse duplicator, as specified in F.4.2, and its major components and associated apparatus, including a schematic diagram of the system giving the relevant chamber dimensions and valve orientation, chamber compliance (if a compliant chamber is used), details of the location of the pressure-measuring sites relative to the mid-plane of the surgical heart valve substitute sewing ring, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at approximately 70 cycles/min, simulated cardiac output of 5 l/min and mean arterial pressure of 13 kPa (100 mm Hg);

c) an assessment, including appropriate documentation, of the opening and closing action of a surgical heart valve substitute and, if appropriate, its adjacent flow field under stated conditions;

d) a permanent recording of at least ten consecutive or randomly selected cycles of the time-dependent simultaneous pressures, proximal and distal to the surgical heart valve substitute, and the volume flow through it. Details of mean, range, and standard deviation of the performance test variables (e) to (m) at each simulated cardiac output for each surgical heart valve substitute and reference valve should be presented in tabular and graphic form;

e) simulated cardiac output;

f) beat rate;

g) systolic duration;

h) forward flow volume;

i) mean and RMS flow rates;

j) mean pressure difference;

k) effective orifice area;

l) regurgitant volume, closing volume, and leakage volume, expressed in milliliters and as a percentage of forward flow volume; the corresponding mean pressure difference across the closed valve;

m) mean arterial pressure over the whole cycle;

n) appropriate qualitative photographic documentation and quantitative analyses of the opening and closing characteristics for the surgical heart valve substitute;

o) appropriate documentation and quantitative analyses of the velocity and shear stress fields in the immediate vicinity, including where appropriate within the valve housing;

p) appropriate assessment of the hemolytic and thrombogenic potential.

Annex G
(informative)

Durability testing

G.1 General

This annex provides guidance on test equipment, formulation of test protocols, and test methods for the durability assessment of surgical heart valves. The surgical heart valve substitutes should be tested under appropriate loads while simulating device function in an appropriate fluid environment to a specified number of cycles required to demonstrate *in vitro* device durability. Where test frequency may influence the results of durability tests (e.g., where components are manufactured from viscoelastic materials) real time testing should be considered.

G.2 Measuring equipment accuracy

The pressure measurement system used to measure the transvalvular pressure difference should have a natural or resonant frequency at least 50 times the test cycle rate and a minimum measurement accuracy of ± 0,65 kPa (± 5 mm Hg) unless otherwise justified. Data sampling rate should be appropriate.

G.3 Real time testing

In addition to accelerated wear testing, wear testing at physiologic conditions (e.g., beat rates <200 bpm) to cycle counts less than 200 million cycles may be considered. The results of this testing may be used to evaluate the validity of accelerated durability test results.

G.4 Dynamic Failure Mode

Potential modes of failure associated with structural valve deterioration (Annex A) should be identified. A possible evaluation method is subjecting samples of valves that have survived the minimum number of required cycles of durability testing to extended accelerated durability testing under the same or more severe conditions. Other testing strategies and evaluation methods may be employed depending on the device design, materials, construction, and statistical approaches employed (such as Bayesian/Weibull reliability techniques). The method(s) used should be justified.

G.5 Results evaluation

Some minor damage is expected on valves after completing durability testing. Failures, however, are characterized by excessive structural damage and/or functional impairment. A clear definition of “failure” should be established and be consistent with respect to the specific failure mode(s) identified by the risk analysis. Any observed damage not identified in the risk analysis must be evaluated for relevance and impact on the risk analysis or be justified as a test artifact. Examples of structural deterioration include holes, tears, gross delamination, fraying, incomplete coaptation, fracture, excessive deformation, failure of any individual component, other mechanical breakdown and/or wear. Examples of functional impairment include excessive regurgitation and/or excessive transvalvular forward flow pressure difference.

G.6 Report requirements

The durability assessment report should include:

a) a list of the valves, including reference valves, used to conduct the testing;

b) justification for the reference valve used;

c) justification for rates used;

d) a description of the fluid used for the assessment, including biological origin or chemical components, temperature, viscosity, and specific gravity under the test conditions;

e) descriptions, specifications, and validations of all test equipment and references to and/or descriptions of any procedures used in order to complete the assessment;

f) a list of pertinent test conditions (e.g., cycle rate, average peak closed pressure difference), sample pressure waveforms, and rationale for any deviations from those test conditions specified for durability testing;

g) verification of full occluder opening/closing and verification that targeted pressures across the closed valve were attained for 5 % or more of the cycle during at least 95 % of the test cycles;

h) a detailed description of the appearance of the surgical heart valve substitutes at the completion of the test, at the periodic intervals during the test, and upon the development of structural change and/or failure. Any damage should be characterized by using the appropriate means, e.g., histology or surface characterization. It should be indicated if the valves were intact for the duration of the evaluation;

i) the pass/fail criteria and, justification for the criteria and, a comparison of the durability results between the test and reference valves and whether the valves met the pass/fail criteria.

Annex H
(informative)

Examples of design specific testing

H.1 Sewing ring integrity

A measure of the resistance to sewing ring dehiscence. Dehiscence may result from suture failure, suture retention failure, fabric tensile strength failure, fabric weave failure, or fabric seam failure.

H.2 Stent creep

An assessment of the potential for structural creep (e.g., polymeric stents) of the surgical heart valve substitute and its structural components should be performed in order to evaluate the risk associated with potential hazards that may be, fully or in part, related to cyclic stent creep.

H.3 Leaflet impingement force (rigid valves)

Determination of the maximum radial compressive force (annular load) that can be applied to the valve housing before the housing distorts sufficiently to produce leaflet impingement. Evaluation should consider engineering tolerances of the component features and assembly tolerances. The timing of annular loads and position of the occluder should be considered in the evaluation.

H.4 Leaflet escape force (rigid valves)

Determination of the maximum radial compressive force that can be applied to the valve housing before the housing distorts sufficiently to allow leaflet escape. Evaluation should consider engineering tolerances of the component features and assembly tolerances. The timing of annular loads and position of the occluder should be considered in the evaluation.

H.5 Environmental degradation

The degradation resistance of all materials including potential particulate generation (under stress if appropriate) should be determined in a physiological environment. If cyclic loading is present, tests should be conducted under the same type of loading at a frequency that will not mask any possible forms of localized attack. Final forming methods, such as welding, should be considered.

H.6 Static pressure; “burst” test

A measurement of the hydrostatic load at which failure, e.g., leaflet or orifice fracture or leaflet escape, occurs. For a flexible valve, failure could result in cusp prolapse or tear.

H.7 Sewing ring push-off

A measurement of the strength of the sewing ring attachment to the surgical heart valve substitute.

Particular attention should be paid to the potential for the attachment mechanism to be damaged during implantation.

H.8 Sewing ring torque (rigid valves)

A measurement of the torque required to rotate the valve within the sewing ring.

H.9 Calcification (flexible valve)

A measurement of the rate and degree of calcification of the surgical heart valve substitute using *in vivo* or *in vitro* models.

H.10 Leaflet kinematics

An assessment of the opening and closing kinematics of the occluder of each surgical heart valve substitute under pulsatile-flow conditions (e.g., occluder opening times and characteristics).

H.11 Device Migration resistance

The ability of the implantable device to remain in the target implant site under simulated operating conditions See ISO 5840-3.

Annex I
(informative)

Fatigue assessment

I.1 General

A fatigue assessment consists of

a) a stress or strain analysis of the components/valve under simulated *in vivo* loading conditions. At a minimum, moderate hypertensive pressure conditions and other relevant loading modes must be considered;

b) a fatigue characterization of the structural material/component;

c) a fatigue lifetime assessment of the component/valve.

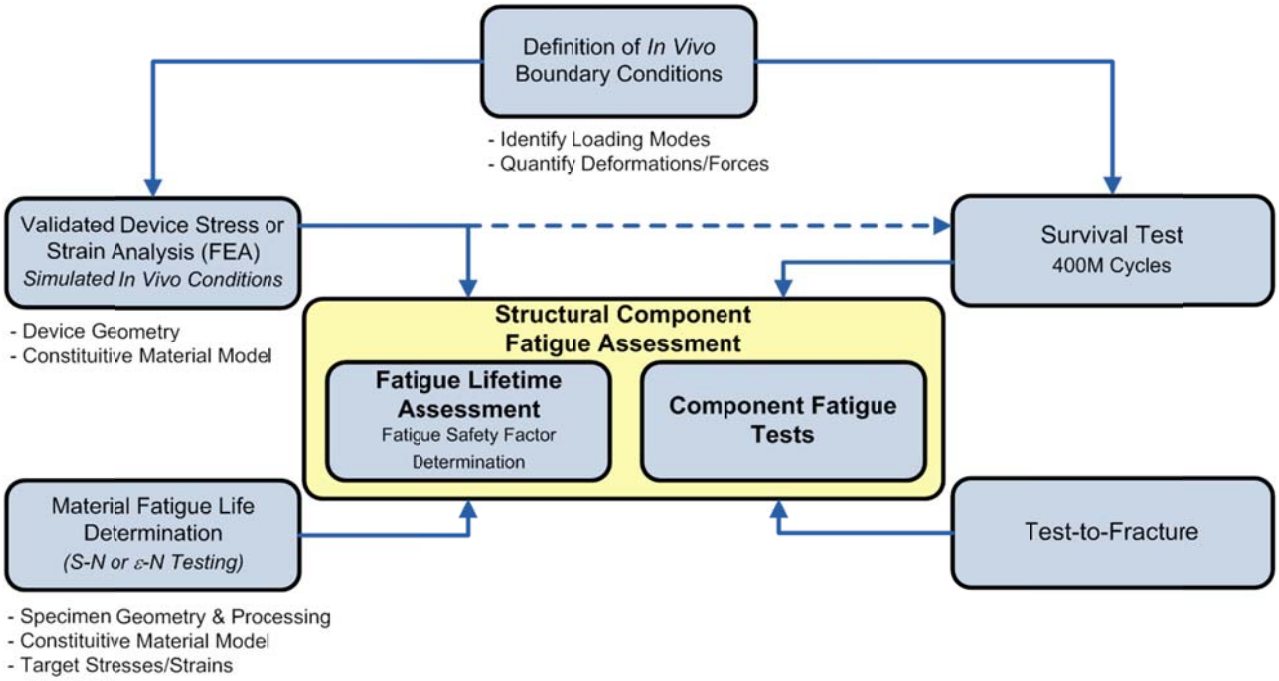


Figure I.1 – Example schematic of a structural component fatigue assessment using a stress- or strain-life approach

NOTE The selection of stress analysis or strain analysis should be employed depending on the material of the structural component.

I.2 Stress/strain analysis under simulated *in vivo* conditions

A validated stress/strain analysis of the structural components of the surgical heart valve substitute under simulated *in vivo* conditions should be performed. Valve components such as leaflets, sutures, or cloth should be considered for their reaction loads but would not necessarily require analysis.

Stress or strain analyses should be performed on structural components associated with the valve tissue annulus diameter (size) and anatomical implant position in which the highest stresses develop, termed the worst-case size.

However, due to differences in component dimensions and/or pressure loading differences between implant positions, the worst-case size may not be the largest size valve and may be specific to each structural component. Thus, while the stress/strain analysis of structural components is only necessary for the worst-case size, it will be necessary to establish this worst-case size for each structural component, which may involve additional analyses.

The analysis should account for static stresses resulting from differential pressures across the valve and transient stresses occurring during opening and closing (e.g., impact stresses, inertial loadings). The manufacturer should identify and justify the pressure loading conditions used in the stress/strain analysis. Pressures associated with normal, hypertensive, and hypotensive conditions are given in Table 1 and Table 2 in ISO 5840-1 (see 6.2.1). See Annex E in ISO 5840-1 for guidelines regarding suggested test conditions for the paediatric population. The stress/strain analysis should, at a minimum, use pressures associated with moderate hypertensive conditions.

Stress/strain analysis should account for all physiologic loading conditions to which the device will be subjected. It might not be feasible to simulate all combined loading modes in a single analysis; however, any de-coupling or superposition of loading modes should be justified. Physiologic loading will depend on the implant site and device design, and may include, but is not limited to:

- differential pressures across the closed valve (minimum pressures associated with moderate hypertensive conditions);
- transient stresses occurring during opening and closing;
- radial dilatation and compression;
- torsion;
- bending;
- axial tension;
- axial compression;
- linear/transverse compression (e.g. crushing).

These items should be considered in the context of anatomic variability and physiologic changes within the implantation site.

Residual stresses/strains resulting from manufacturing processes that were not included in test specimens (e.g., material coupons) and any stress concentrations associated with the manufacturing process should be included in the stress/strain analysis. For some novel designs (e.g. sutureless valves), residual stresses/strains might result from the crimping process, loading the device onto the delivery system, and deployment.

Valve motion and closure geometry is not always symmetric. It is important to ensure that the maximum stresses are not underestimated. For this reason, stress/strain analyses should be performed on entire valve/component geometries unless it is demonstrated that the use of a simplified model with symmetry conditions is representative of the full analysis.

An appropriate constitutive model for each material should be used in any stress/strain analysis, including time-dependent and/or nonlinear models as appropriate. Development of constitutive models or evaluation of appropriate constants for existing constitutive models should be based on testing of material that is representative of the actual structural component, including material processing and environmental exposure (e.g., sterilization).

Validation of any stress/strain analysis should be performed in order to demonstrate sufficient confidence in the predicted results. While it is left to the manufacturer to develop and justify such a validation, the validation should include comparisons of predicted FEA results against independent experimental measurements.

I.3 Fatigue characterization

I.3.1 General

Fatigue characterization generally falls into four main categories:

a) stress/life (S/N) for use with classical stress/life assessment;
b) strain/life (ε/N) for use with classical strain/life assessment;
c) fatigue crack growth for use in damage tolerance analysis (DTA);
d) component testing for use in demonstrating fatigue resistance.

The manufacturer should determine and justify the most appropriate characterization(s) and assessment approach(es) for the specific material and valve design. However, the particular characterization technique should be consistent with the subsequent lifetime assessment approach used. Fatigue characterization of each structural material/component should be performed so that all properties necessary for the fatigue analysis are appropriately determined.

Coupon test specimens used to determine material properties should be produced in such a way as to ensure the specimen is representative of the actual material in the surgical heart valve component (e.g., microstructure, crystallinity, density). Valve components used as test specimens should be representative of actual clinical components (e.g., fabrication methods, defect population). All test specimens should be exposed to all of the environments encountered in clinical valve fabrication. Stress or strain levels specified for the fatigue characterization should be justified by the manufacturer and should encompass the worst case anticipated stresses or strains experienced by the component *in vivo*. Cyclic test rates/frequencies should be justified by the manufacturer. Testing should be performed in an environment that is representative of the physiological environment with respect to its effect on fatigue behavior. The testing should fully represent the range of valve sizes and the loading conditions associated with the implant position. If all valve sizes are not tested, it will be necessary to conduct an analysis to identify the size(s) of the device with the greatest potential for fatigue failure.

Fatigue testing should be performed in such a manner as to preserve the anticipated *in vivo* failure mechanism; e.g., the failure mechanism can undergo transition from ductile to brittle with increased test frequency for some materials such as polymers. If an accelerated protocol is used (e.g., increased test frequency), the manufacturer should justify the appropriateness of the test frequency chosen.

I.3.2 Stress/life (S/N) characterization

Classical S/N characterization is performed by generating failure data at various cyclic stress levels and/or load ratios in order to determine the maximum permissible stress for a specified design lifetime.

Testing should be performed at stress levels, including both amplitude and mean values, at least as severe as those predicted by the FEA under moderate hypertensive pressures and other relevant *in vivo* loading conditions with a safety factor justified by the manufacturer. Test frequency and environment, including test temperature and physiologically representative fluid, should be specified and justified by the manufacturer.

An endurance limit, as classically defined, might not exist for all materials, particularly when exposed to corrosive environments.

I.3.3 Strain/life (ε/N) characterization

While stress has traditionally been the basis for controlling fatigue tests and as a means of monitoring fatigue performance and failure for conventional engineering materials, strain may provide a more practical and appropriate means of analyzing materials such as nitinol given its superelastic properties. Strain life (ε/N) characterization is performed by generating failure data at various cyclic strain amplitude levels and mean strain levels in order to determine the maximum allowable strain for a specified design lifetime. In such cases where stress-life characterization for nitinol is preferred, this alternative approach should be justified by the manufacturer.

Testing should span a sufficient range of both amplitude and mean strain conditions in order to establish and characterize the fatigue response of the material. Strain levels specified for the fatigue characterization will be justified by the manufacturer and should encompass the worst case anticipated stresses or strains experienced by the component *in vivo*. Test frequency and environment, including test temperature and physiologically representative fluid, should be specified and justified by the manufacturer.

An endurance limit, as classically defined, might not exist for all materials, especially when exposed to corrosive environments.

I.3.4 Fatigue crack growth (da/dN) characterization

Fatigue crack growth testing is used in association with damage tolerance analyses, which employ a fatigue crack growth relation governing crack propagation from inherent flaws in the material/component. Thus, the fracture toughness and fatigue crack growth behavior relating the rate of crack growth, da/dN, to an appropriate measure of the cycling crack driving force (commonly taken as the cyclic stress intensity factor, ΔK, although others exist and may be more appropriate depending on material) are determined for the component material.

Fatigue crack growth testing may be performed on test specimens or actual components. In either case, an appropriate measure of the crack driving force should be known, which is why it is often more convenient and common to use more standard fracture specimens whose crack driving force solutions are readily known and available. Because crack growth kinematics depend on the mode of loading (e.g., opening versus shear), testing should also be performed so as to preserve the anticipated *in vivo* mode of crack growth.

Unless plane strain conditions are assured for the test specimen, testing should be performed on specimens whose thickness is at least as thick as the actual component. While machined notches may be used to aid and control the formation of a crack, it may be necessary to pre-crack the specimen prior to generating acceptable crack growth and/or toughness data. However, care should be taken in pre-cracking so as not to overload the specimen. For some materials, like metals, overloads can cause large compressive stresses to develop near cracks, resulting in retarded growth and non-conservative crack growth relations. For the same reason, testing should generally be performed under increasing crack driving force in order to mitigate potential retardation effects.

Testing should span the range of crack driving force from threshold, or minimum anticipated driving force, to near toughness in order to adequately establish and characterize the fatigue crack growth behavior of the material. Not all materials exhibit threshold behavior, below which no crack growth occurs. If a threshold is to be used in subsequent damage tolerance analyses, the manufacturer should establish and verify its existence.

I.3.5 Component testing

Fatigue testing of components may be used to demonstrate fatigue lifetimes under conditions that exceed those experienced by the component *in vivo*. Testing should produce stresses or strains that are representative of the worst case anticipated stresses or strains experienced by the component *in vivo* with a fatigue safety factor justified by the manufacturer. Because component testing might only approximate *in vivo* loadings, a validated stress/strain analysis of the component testing might be required to demonstrate that testing is representative of the *in vivo* loadings.

A clear definition of “failure” should be established and be consistent with respect to the specific failure mode(s) identified by the risk analysis. Samples should be characterized and evaluated for failure prior to, during and after testing. Evaluation and documentation during testing should be performed, at intervals justified by the manufacturer, to distinguish fatigue-induced damage from testing artifacts. Testing artifacts should in no way influence the potential for the test to cause fatigue-induced damage.

I.4 Fatigue lifetime assessment

I.4.1 General

Based on fatigue characterization completed per I.3, a lifetime assessment of the structural components should be performed in order to evaluate risks associated with fatigue-related failure modes. While it is left to the discretion of the manufacturer to determine and justify the most appropriate lifetime assessment approach(es) for the specific material and valve design, the particular approach should be consistent with the appropriate supporting characterization technique. If a general material fatigue characterization (i.e., ε/N or fatigue crack growth) was developed, it could be used in fatigue lifetime assessments of several failure modes provided the material data is representative of the material and loadings of each particular failure mode. Deterministic or probabilistic approaches may be employed for fatigue life assessments. If fatigue safety factors are reported, the method by which safety factors were computed should be explained.

I.4.2 Stress-life (S/N) assessment

The S/N structural fatigue life is based on the S/N data in order to determine the predicted lifetime at the maximum stress as determined from the stress analysis. The stress-life assessment should reflect the inherent variability in the fatigue data as well as a measure of confidence in the stress analysis.

The stress-life assessment should identify and account for the effects of allowable variances such as dimensional tolerances and manufacturing-related defects, material variations (e.g., voids, impurities, material property variations), and assess whether the methodologies for assuring variances are maintained within the manufacturer’s justified acceptance criteria.

I.4.3 Strain-life (ε/N) assessment

The ε/N structural fatigue life is based on the ε/N data in order to determine the predicted lifetime at the maximum mean and alternating strains as determined from the strain analysis. The strain-life assessment should reflect the inherent variability in the fatigue data as well as a measure of confidence in the strain analysis.

The strain-life assessment should identify and account for the effects of allowable variances such as dimensional tolerances and manufacturing-related defects, material variations (e.g., voids, impurities, material property variations), and assess whether the methodologies for assuring variances are maintained within the manufacturer's justified acceptance criteria.

I.4.4 Damage tolerance analysis (DTA)

A damage tolerance analysis (DTA) approach is based on the premise that all materials contain defects that may eventually grow to a critical length (defined from the fracture toughness), resulting in failure. The lifetime of a structural component based on a damage tolerance approach is the predicted duration for a minimally detected flaw to grow to failure under *in vivo* conditions. This may require the postulation of initial flaws in critical locations of a component (typically at locations of high stress) and estimates of crack driving forces associated with those locations.

Since the lifetime is a direct function of the initial flaw size, the manufacturer should demonstrate sufficient probability of detecting the minimum flaw size, through inspection and/or proof testing, with appropriate confidence.

In order to perform damage tolerance analyses from fatigue crack growth data generated from fracture specimens, simulated *in vivo* stress analyses should be coupled with fracture mechanics analyses in which validated crack driving forces associated with actual components are obtained. In some cases, more simplified but well-known driving forces may be reasonably used to approximate *in vivo* driving forces (e.g., a crack in a leaflet might be reasonably approximated by a crack in a beam experiencing an equivalent bending load). In such cases, the manufacturer should justify the approximation and include any associated uncertainty in the DTA.

The damage tolerance assessment should identify and account for effects of permissible variances such as dimensional tolerances, material property variations (particularly with respect to fracture/fatigue crack properties and their determination), variations and confidence in identifying initial flaws, and the methodologies for assuring variances are maintained within acceptable levels.

I.4.5 Component demonstration assessment

Component demonstration assessments involve verification that component testing demonstrates sufficient survival with an appropriate confidence level.

Component testing is typically used to demonstrate probability of survival with associated confidence of components subjected to conditions that meet or exceed anticipated *in vivo* conditions. Unless testing is performed under several loading conditions, it might not be possible to extrapolate significantly beyond the duration of the component demonstration testing. As a result, component testing is often used to supplement other lifetime assessments. However, if component testing is performed over a sufficient range of conditions, it might be possible to predict the component lifetime at *in vivo* conditions.

Note that the confidence of the demonstration assessment should reflect the number of components tested and their representation of the actual component population, the ability to detect failures in the test, and a measure of confidence in the simulated *in vivo* and test stress analyses.

I.4.6 Test to Failure

To compare the predicted areas of high stress or strain from computational analyses to the observed failure areas of the specimen, a sample of new specimens or a selection of specimens that have survived fatigue testing should continue testing and/or should be subjected to exaggerated stress or strain levels (i.e., step-stress paradigm) to determine the manner in which they will fail. The manufacturer should justify the number of samples and test conditions used. The manufacturer should use these specimen failures, if applicable, to demonstrate consistency with stress/strain analysis predictions.

I.4.7 Post Fatigue Corrosion Evaluation

After completion of fatigue testing, specimens should be subjected to detailed microscopic surface inspection for any evidence of corrosion.

Annex J
(normative)

Methods of evaluating clinical data

J.1 General

Methods of evaluating clinical data shall include comparing all late complications to objective performance criteria (OPC). Frequentist or Bayesian statistical methods may be used. The manufacturer is responsible for proposing and justifying the specific methodology used.

J.2 Objective performance criteria methodology

Safety can be assessed over the defined timeframe by comparing the occurrence of late (> 30 days post-implant) complications to objective performance criteria (OPC). The OPCs are the average rates of valve-related complications as assessed by linearized occurrence rates. The values in Table J.1 may be used in the comparison, without further justification.

Table J.1—Objective performance criteria for surgical heart valve substitutes

Adverse Event (Endpoint)	**Bioprosthetic**		**Mechanical**	
	Aortic	Mitral	Aortic	Mitral
Thromboembolism	1,5	1,3	1,6	2,2
Valve thrombosis	0,04	0,03	0,1	0,2
Major hemorrhage	0,6	0,7	1,6	1,4
Major paravalvular leak	0,3	0,2	0,3	0,5
Endocarditis	0,5	0,4	0,3	0,3

NOTE—Values are in % per valve-year.

The data in Table J.1 were derived using the same methodology as the original OPCs, an analysis of safety and effectiveness data submitted by manufacturers in pursuit of premarket approval of bioprosthetic and mechanical valves (yielding 38,359 follow-up years) combined with an analysis of recent literature from 1999 to 2012 (yielding 208,585 follow-up years). There was no significant heterogeneity between the two sources of data, either in methods of data collection or in complication rates. See Wu, Y, X, et al. (2014).

The formal statistical method applied to OPCs specifies that the observed rates should be numerically less than twice the OPC.

For a single position valve, a sample size of 800 patient-years is required. If the investigational design is for use in both the aortic and mitral positions, the data must be presented stratified. A minimum of 400 patient-years are required for each valve position; however, it is recommended that more than 400 patient-years are collected in both positions, if possible, to enable more reliable comparisons to OPCs.

Assuming a one-sided type one error rate of 5 %, with 800 patient-years, only thromboembolism (all positions, both bioprosthetic and mechanical) and major hemorrhage (mechanical only) are likely to have at least 80 % power to satisfy the OPC described in the previous paragraph.

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