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Cardiovascular implants — Cardiac valve prostheses —

Part 2: Surgically implanted heart valve substitutes

Implants cardiovasculaires — Prothèses valvulaires —
Partie 2: Prothèse valvulaires implantées chirurgicalement

Reference number
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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems.*

This first edition of ISO 5840-2, together with ISO 5840-1 and ISO 5840-3, cancels and replaces ISO 5840:2005, which has been technically revised.

ISO 5840 consists of the following parts, under the general title *Cardiovascular implants — Cardiac valve prostheses:*

— *Part 1: General requirements*

— *Part 2: Surgically implanted heart valve substitutes*

— *Part 3: Heart valve substitutes implanted by transcatheter techniques*

Introduction

This part of ISO 5840 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 — Cardiac valve prostheses —

Part 2: Surgically implanted heart valve substitutes

1 Scope

This part of ISO 5840 is applicable to heart valve substitutes intended for implantation in human hearts, generally requiring cardiopulmonary bypass and generally with direct visualization.

This part of ISO 5840 is applicable to both newly developed and modified surgical heart valve substitutes and to the accessories, packaging, and labelling required for their implantation and for determining the appropriate size of the surgical heart valve substitute to be implanted.

This part of ISO 5840 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.

This part of ISO 5840 defines performance requirements for surgical heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

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.

This part of ISO 5840 excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

This part of ISO 5840 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 5840-1:2015, *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 within a risk management process*

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

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

ISO 14630, *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/IEC 17025:2005, *General requirements for the competence of testing and calibration laboratories*

ISO 22442 (all parts), *Medical devices utilizing animal tissues and their derivatives*

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 given in ISO 5840-1 and the following apply.

3.1
cycle rate
number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

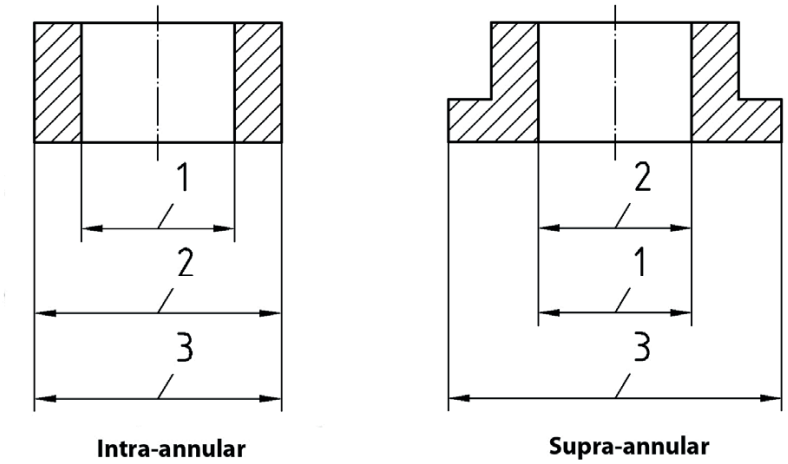
3.2
internal orifice diameter
numerical indication of the minimum diameter within a surgical heart valve substitute through which blood flows

Note 1 to entry: See Figure 1.

3.3
intra-annular sewing ring
sewing ring designed to secure the surgical heart valve wholly or mostly within the patient's tissue annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2, 3.10, and 3.12.



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

3.4
major bleeding
any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion

3.5
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

3.6
nonstructural valve dysfunction
abnormality extrinsic to the heart valve substitute that results in stenosis, regurgitation, and/or haemolytic anemia

3.7
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 1 to entry: See Reference [16].

3.8
structural valve deterioration
change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation

Note 1 to entry: 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.

3.9
support structure
component of a heart valve substitute that houses the occluder(s)

EXAMPLE Stent, frame, housing.

3.10
supra-annular sewing ring
sewing ring designed to secure the valve wholly above the patient's tissue annulus

Note 1 to entry: See Figure 1.

3.11
thromboembolism
any embolic event that occurs in the absence of infection after the immediate perioperative period and may be manifested by a neurological event or a noncerebral embolic event

3.12
tissue annulus diameter
TAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

3.13
valve size
manufacturer's designation of a surgical heart valve substitute which indicates the tissue annulus diameter (TAD in millimetres) of the patient into whom the surgical heart valve substitute is intended to be implanted (i.e. TAD = designated valve size)

Note 1 to entry: This takes into consideration the manufacturer's recommended implant position relative to the annulus and the suture technique.

3.14
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 1 to entry: See Reference [14].

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. ISO 5840-1:2015, Table 1 and Table 2 define the expected physiological parameters of the intended adult patient population for surgical heart valve substitutes for both normal and pathological patient conditions.

NOTE See the paediatric annex of ISO 5840-1:2015, Annex E.

6.2.2 Performance specifications

6.2.2.1 The manufacturer shall establish (i.e. 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 describes a safe and effective surgical heart valve substitute.

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

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

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

— ability to prevent retrograde flow with acceptably small regurgitation;

— ability to resist embolization;

— ability to resist haemolysis;

— ability to resist thrombus formation;

— biocompatible;

— compatible with *in vivo* diagnostic techniques;

— deliverable and implantable in the target population;

— 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, labelling, and sterilization

The surgical heart valve substitute and accessories shall meet the requirements for packaging, labelling, and sterilization contained within ISO 5840-1:2015, 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 labelling.

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.

6.4.2 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.

6.4.3 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 part of ISO 5840 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/labelling, 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 5840-1:2015, 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 5840-1:2015, Table 1 and Table 2 for the adult population. See ISO 5840-1:2015, Annex E for guidelines regarding suggested test conditions for the paediatric 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/IEC 17025:2005.

7.2.1.2 Reporting requirements

Each test report shall include the following, at a minimum:

a) 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 5840-1:2015, 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 5840-1:2015, Annex G provides potentially relevant physical, mechanical, and chemical properties by material class and components. ISO 5840-1:2015, Annex H provides a list of standards that might be applicable to the testing of materials and components. ISO 5840-1:2015, Annex I provides guidance on mechanical property characterization of raw and conditioned materials. ISO 5840-1:2015, Annex 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 part of ISO 5840 are applicable to new or modified heart valve substitutes

which have not been clinically proven or evaluated under the previous version of ISO 5840:2005. The haemodynamic waveforms produced by the pulse duplicator shall reasonably simulate physiological conditions as shown in ISO 5840-1:2015, 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 ISO 5840-1:2015, 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 References [20], [17], and [21].