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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

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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.

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 of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 285, *Non-active surgical implants*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 5840-2:2015), which has been technically revised.

The main changes compared to the previous edition are as follows: the engineering and clinical requirements in the ISO 5840 series have been updated to current specifications and integrated and harmonized across all of its parts.

A list of all parts in the ISO 5840 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document has been prepared for surgical heart valve substitutes with emphasis on providing guidance for *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 document is used in conjunction with ISO 5840-1:2020 and ISO 5840-3:2020.

Cardiovascular implants — Cardiac valve prostheses —

Part 2: Surgically implanted heart valve substitutes

1 Scope

This document is applicable to heart valve substitutes intended for implantation in human hearts, generally requiring cardiopulmonary bypass and generally with direct visualization. See Annex E for examples of surgical heart valve substitutes and their components.

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

This document establishes an approach for verifying/validating 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 can include those to assess the physical, chemical, biological, and mechanical properties of surgical heart valve substitutes and of their materials and components. The tests can also include those for pre-clinical *in vivo* evaluation and clinical evaluation of the finished surgical heart valve substitute.

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

For some heart valve substitutes (e.g. sutureless), the requirements of both this document and ISO 5840-3:2020 can be relevant and are considered as applicable to the specific device design and are based on the results of the risk analysis.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5840-1:2020, *Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements*

ISO 5840-3:2020, *Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques*

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

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
acute assessment
intra-procedural and immediate post-procedural results used to assess *in vivo* safety and performance

Note 1 to entry: All animals entered into acute short-term assessment shall remain under general anaesthesia for the duration of the study.

3.2
chronic assessment
long-term results following the procedure used to assess chronic *in vivo* safety and performance after the animal has recovered from anaesthesia

Note 1 to entry: The endpoints and durations of these studies should be determined by risk analysis.

3.3
component-joining material
material such as a suture, adhesive, or welding compound used to assemble the components of a *heart valve system*

[SOURCE: ISO 5840-1:2020, 3.31]

3.4
external sewing ring diameter
ESRD
the outside diameter in millimetres of the sewing ring at the largest point

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.3, 3.4, and 3.5.

3.5
prosthesis minimum internal diameter
for a flexible surgical heart valve, the prosthesis minimum internal diameter is the numerical indication of the minimum diameter within a fully assembled flexible surgical heart valve substitute and is measured with a standard validated procedure, taking the entire flow channel into consideration. For a rigid surgical heart valve, the prosthesis minimum ID is defined by measuring the prosthesis minimum internal housing diameter

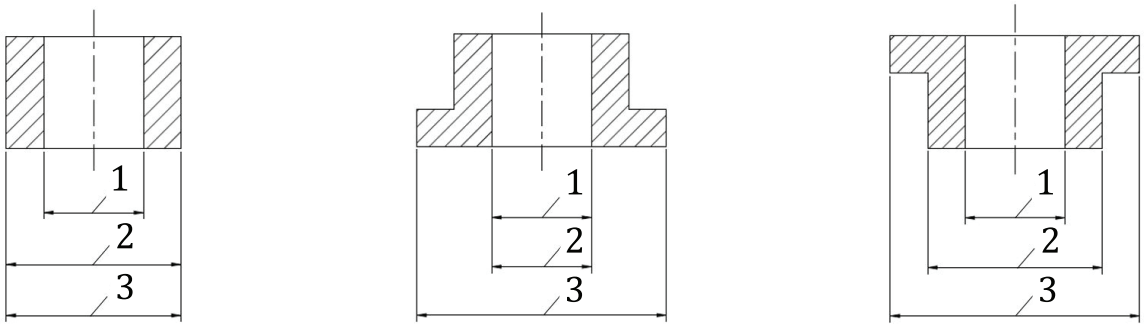
Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2, 3.4, and 3.5.

3.6
intra-annular
wholly or partially within the patient's annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2, 3.3, and 3.5.



A B C

Key

1 prosthesis minimum internal diameter
2 patient annulus diameter
3 external sewing ring diameter
A aortic/pulmonic intra-annular
B aortic/pulmonic supra-annular
C mitral/tricuspid intra-annular

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

3.7
supra-annular
wholly above the patient's annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2, 3.3, and 3.4.

3.8
patient annulus diameter
PAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

Note 1 to entry: See Figure 1.

3.9
valve size
designated valve size
manufacturer's designation of a surgical heart valve substitute which indicates the intended patient annulus diameter (valve size = PAD)

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

4 Abbreviations

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

CIP Clinical investigation plan

CRF Case report form

CT Computed tomography

EOA	Effective orifice area
FEA	Finite element analysis
LVOT	Left ventricular outflow tract
MRI	Magnetic resonance imaging
OPC	Objective performance criteria
PMCF	Post market clinical follow-up
RMS	Root mean square
TEE	Transoesophageal echo
TTE	Transthoracic echo

5 Fundamental requirements

Refer to ISO 5840-1:2020, Clause 5.

6 Device description

6.1 General

Refer to ISO 5840-1:2020, 6.1.

6.2 Intended use

Refer to ISO 5840-1:2020, 6.2.

6.3 Design inputs

6.3.1 Operational specifications

Refer to ISO 5840-1:2020, 6.3.1.

6.3.2 Performance specifications

6.3.2.1 General

Refer to ISO 5840-1:2020, 6.1 for general requirements.

6.3.2.2 Surgical heart valve substitute minimum performance requirements

Surgical heart valves shall meet the following minimum performance specifications:

— allows forward flow with acceptably small mean pressure difference;

— prevents retrograde flow with acceptably small regurgitation;

— resists embolization;

— avoids haemolysis;

— resists thrombus formation;

— biocompatible;

— compatible with *in vivo* diagnostic techniques;

— deliverable and implantable in the target population;

— able 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.

6.3.2.3 Accessories

The requirements ISO 16061 of requirements for instruments used with surgical implants shall apply. Surgical heart valve accessories shall mitigate the risk of the valve being inadvertently implanted upside down.

Examples of surgical valve accessories include sizing tools and valve handles are shown in Annex E.

6.3.2.4 Implant procedure

Refer to ISO 5840-1:2020, 6.3.3.

6.3.3 Packaging, labelling, and sterilization

Refer to ISO 5840-1:2020, 6.3.4.

In addition to the items specified in ISO 5840-1:2020, C.1.2, outer container labelling for the valve implant shall include in diagrammatic and/or tabular form the following items:

— Intended valve to be replaced

— Intended position in relation to the annulus

— Inflow internal orifice diameter

— Prosthesis minimum internal diameter

— External sewing ring diameter (ESRD)

Annex D of this document contains a listing of terms that may be used in describing various valve models.

6.4 Design outputs

Refer to ISO 5840-1:2020, 6.4.

6.5 Design transfer (manufacturing verification/validation)

Refer to ISO 5840-1:2020, 6.5.

6.6 Risk management

Refer to ISO 5840-1:2020, 6.6.

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 and validation

7.1 General requirements

In vitro assessment shall be used to mitigate the risks identified in the risk analysis. General requirements that are applicable to all heart valve systems are provided in ISO 5840-1:2020. Specific considerations for surgical heart valve substitutes are provided in this document.

7.2 *In vitro* assessment

7.2.1 General

Refer to ISO 5840-1:2020, 7.2.1.

7.2.2 Test conditions, sample selection, and reporting requirements

Refer to ISO 5840-1:2020, 7.2.2.

7.2.3 Material property assessment

Refer to ISO 5840-1:2020, 7.2.3.

7.2.4 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid dynamic performance of the surgical heart valve substitute. ISO 5840-1:2020, Annex I provides guidelines for conducting and reporting steady hydrodynamic tests. Guidelines for conducting and reporting of pulsatile hydrodynamic tests are provided in Annex F. For pulsatile flow testing, the performance of the pulse duplicator shall be characterized. Refer to F.2.2.2 for guidelines related to pulse duplicator characterization. The measurement accuracy and repeatability of the test system(s) shall be evaluated and documented. The hydrodynamic waveforms produced by the pulse duplicator shall reasonably simulate physiological conditions. Representative waveforms used to generate hydrodynamic test results shall be documented in the test report. Wu C. et al. provides characteristics of reasonable aortic and mitral waveforms.

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, largest, and an intermediate size. 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 1 and Table 2, which are given as a function of valve size. The minimum performance requirements correspond to the following nominal pulsatile-flow conditions: beat rate = 70 cycles/min, simulated cardiac output = 5,0 l/min, and systolic duration = 35 %, at normotensive pressure conditions, as specified in ISO 5840-1:2020, Table 3 or Table 4. These pulsatile flow conditions are based on a healthy normal adult and might not be applicable for paediatric device evaluation (see ISO 5840-1:2020, Annex E for paediatric parameters). The minimum performance requirements are based on values in the published scientific literature. The values in Table 1 and Table 2 are applicable to new or modified heart valve substitutes which have not been clinically proven or evaluated under previous versions of ISO 5840 series.

For pulmonary and tricuspid heart valve substitutes and paediatric devices, minimum performance requirements are not provided; however, the manufacturer shall justify the acceptability of hydrodynamic performance of the devices.

Additional hydrodynamic characterization testing shall be conducted over a range of test conditions as described in Annex F, F.2.3.2 and F.2.3.3. This testing is for characterization purposes only without corresponding minimum performance requirements.

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 and leakage volume (see ISO 5840-1:2020, Figure 2). For traditional surgical valve designs with a sewing ring, the ring fabric may be sealed to prevent paravalvular leakage during testing. For novel surgical valve designs without a sewing ring (e.g. sutureless), sealing shall be justified and paravalvular leakage shall be included in the leakage volume.

7.2.5 Structural performance assessment

7.2.5.1 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.

7.2.5.2 Implant durability assessment

The requirements of ISO 5840-1:2020 shall apply.

7.2.5.3 Device structural component fatigue assessment

The requirements of Annex H and of ISO 5840-1:2020 shall apply.

7.2.5.4 Component corrosion assessment

The requirements of ISO 5840-1:2020 shall apply.

7.2.5.5 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 assessment). 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.

7.2.6 Design- or procedure-specific testing

7.2.6.1 General

See Annex G for examples of design specific or procedure specific testing to be considered. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific device design.

7.2.6.2 Visibility

The ability to visualize the implanted device using the manufacturer's recommended imaging modalities (e.g. fluoroscopy, MRI, CT, echocardiography) shall be evaluated.

7.2.7 Device MRI compatibility

Refer to ISO 5840-1:2020, 7.2.7.

7.2.8 Simulated use

The requirements of ISO 5840-1:2020, 7.2.8 shall apply.

The model shall consider anatomical variation in intended patient population with respect to intended implant site as well as physiologic factors (e.g. temperature effects, pulsatile flow). In the case where device anchoring relies on specific interactions with the native anatomy (e.g. annulus, aortic root), testing of the interactions shall be included in the simulated use evaluation. Justification for critical parameters of the simulated use model shall be provided.

7.2.9 Human factors/usability assessment

The requirements of ISO 5840-1:2020, 7.2.9 shall apply.

7.2.10 Implant thrombogenic and haemolytic potential assessment

The requirements of ISO 5840-1:2020, 7.2.10 shall apply.

7.3 Preclinical *in vivo* evaluation

7.3.1 General

The general requirements of ISO 14630 shall be considered.

7.3.2 Overall requirements

A preclinical *in vivo* test programme shall be conducted for new or modified devices in order to address the safety and performance of the surgical heart valve substitute. For design modifications to surgical heart valve substitutes with established clinical history, omission or abbreviation of preclinical *in vivo* evaluation shall be appropriately justified.

The preclinical programme design shall be based on risk assessment and appropriate ISO guidance documents. This programme may involve the use of different species and implant durations to address the key issues identified in the risk assessment.

The preclinical *in vivo* evaluation shall:

a) evaluate the haemodynamic performance of the surgical heart valve substitute;

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 shall be given but not limited to the following items:

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

   2) haemolysis;

   3) thrombus formation;

   4) embolization of material from the heart valve substitute;

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

   6) calcification (flexible valves);

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

   8) structural valve deterioration and/or non-structural valve 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 process chemicals and the maximum number of allowed sterilization cycles;

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

f) subject comparably sized control 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 control 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.

7.3.3 Methods

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 adverse events arising after valve implantation can be attributed to the implanted valve, the procedure, and/or the environment into which it is implanted, including interactions among these. Therefore, adverse clinical events arising during or after valve implantation shall be carefully analysed 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 substitute shall be assessed in anatomical positions for which it is intended to be used clinically. Animals suffering from perioperative complications not related to the heart valve substitute may be excluded from the group of study animals with appropriate justification, but information about them shall be reported.

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

For all studies, the specified duration of the observation period of the animals shall be justified according to the parameter(s) under investigation. New devices (e.g. new design or novel blood-contacting materials) require an extended duration of the observation period (not less than 140 days). A minimum duration less than 140 days may be suitable for evaluating minor modifications of an existing surgical heart valve system, such as investigations of healing. Any pre-clinical investigation with a designated