SLOVENSKI STANDARD
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Vsadki (implantati) za srce in ožilje - Proteze za srčno zaklopko - 2. del: Kirurško vsajeni (implantirani) nadomestki srčne zaklopke (ISO/DIS 5840-2:2019)

Cardiovascular implants - Cardiac valve prostheses - Part 2: Surgically implanted heart valve substitutes (ISO/DIS 5840-2:2019)

Implants cardiovasculaires - Prothèses valvulaires - Partie 2: Prothèse valvulaires implantées chirurgicalement (ISO/DIS 5840-2:2019)

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11.040.40	Implantanti za kirurgijo, protetiko in ortetiko	Implants for surgery, prosthetics and orthotics

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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

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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).

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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 second edition of ISO 5840-2 cancels and replaces the first edition (ISO 5840-2:2015), 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 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 part of ISO 5840 is to be used in conjunction with ISO 5840-1 and ISO 5840-3.

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. See Annex E for examples of surgical heart valve substitutes and their components.

This part of ISO 5840 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 part of ISO 5840 outlines 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 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 can 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 operational conditions and 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.

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, *Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements*

ISO 5840-3, *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 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 5840-1 and the following apply.

3.1
external sewing ring diameter
ESRD
the outside diameter in millimetres of the sewing ring at the largest point

3.2
internal orifice diameter

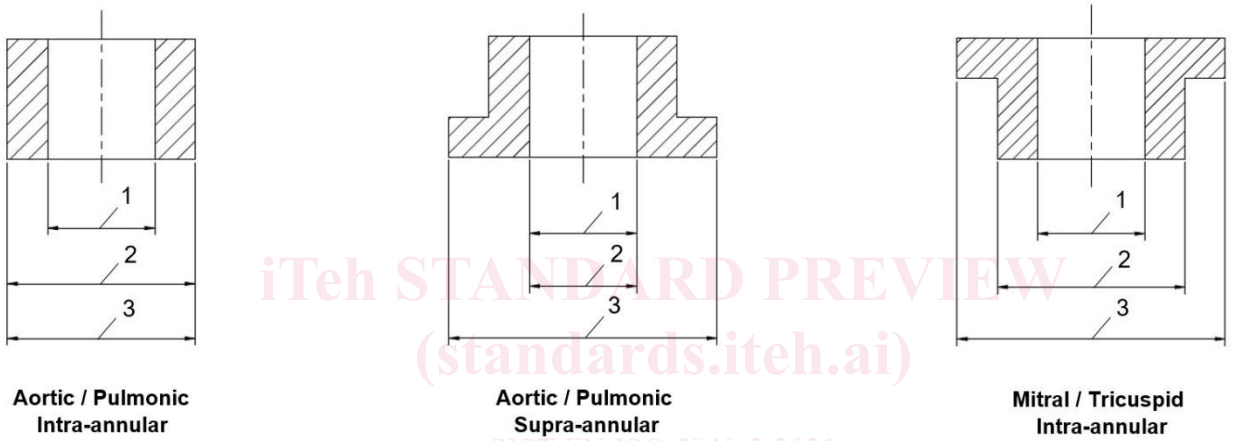
IOD
numerical indication of the minimum diameter in millimetres within a surgical heart valve substitute through which blood flows, excluding the hinge area for rigid bileaflet heart valve substitutes

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 3.1, 3.3, and 3.4.



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
prosthetic height (or valve projection)
- for an aortic valve, the largest height measured from the base of the valve to the tallest point of the open valve
- for a mitral valve, the ventricular projection as measured from the ventricular side of the sewing ring to the tallest point of the open valve

3.5
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.

3.6
tissue annulus diameter
TAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

3.7
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.

4 Abbreviations

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

CT	Computed Tomography
EOA	Effective Orifice Area
FEA	Finite Element Analysis
LVOT	Left Ventricular Outflow Tract
MRI	Magnetic Resonance Imaging
OPC	Objective Performance Criteria
RMS	Root Mean Square
TAD	Tissue Annulus Diameter
TEE	Transoesophageal Echo
TTE	Transthoracic Echo

5 Fundamental requirements

Refer to ISO 5840-1.

6 Device description

6.1 General

Refer to ISO 5840-1.

6.2 Intended use

Refer to ISO 5840-1.

6.3 Design inputs

6.3.1 Operational specifications

Refer to ISO 5840-1.

6.3.2 Performance specifications

6.3.2.1 General

Refer to ISO 5840-1 for general requirements. Specific requirements are listed in 6.3.2.2.

6.3.2.2 Surgical heart valve substitute

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 avoid 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.

6.3.3 Implant procedure

Refer to ISO 5840-1.

6.3.4 Packaging, labelling, and sterilization

Refer to ISO 5840-1.

In addition to the items specified in ISO 5840-1, Annex C, Section C.1.2, outer container labelling for the valve implant shall include a diagram containing the following items:

- Tissue annular diameter (TAD)
- Internal orifice diameter (IOD)
- External suture ring diameter (ESRD)
- Prosthetic height

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.

6.5 Design transfer (manufacturing verification/validation)

Refer to ISO 5840-1.

6.6 Risk management

Refer to ISO 5840-1.

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. Specific considerations for surgical heart valve substitutes are provided in this part of ISO 5840.

7.2 *In vitro* assessment

7.2.1 General

Refer to ISO 5840-1.

7.2.2 Test conditions, sample selection, and reporting requirements

Refer to ISO 5840-1.

7.2.3 Material property assessment

Refer to ISO 5840-1.

7.2.4 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid mechanical performance of the surgical heart valve substitute. Annex I of ISO 5840-1 provides guidelines for conducting and reporting steady hydrodynamic tests. Guidelines for conducting and reporting of pulsatile hydrodynamic tests is provided in Annex F. For pulsatile flow testing, the performance of the pulse duplicator shall be characterized by means of testing a commercially available reference valve(s) in the valve position(s) to be evaluated (e.g. aortic and/or mitral). 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. Reference [11] 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, 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 1 and 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 pressure conditions. These pulsatile flow conditions are based on a healthy normal adult and might not be applicable for paediatric device evaluation (see Annex E in ISO 5840-1 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.

For pulmonary and tricuspid heart valve substitutes, 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, Sections 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, transvalvular leakage volume, and paravalvular 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.

7.2.5.1.1 Implant durability assessment

See ISO 5840-1.

7.2.5.2 Device structural component fatigue assessment

See ISO 5840-1 and Annex H.

7.2.5.3 Component corrosion assessment

See ISO 5840-1.

7.2.5.4 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.

7.2.6 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. For example, novel surgically implanted heart valve substitutes (e.g. sutureless) may require additional testing as compared to traditional surgically implanted valves, and the requirements of both this International Standard and ISO 5840-3 might be relevant and shall be considered. See Annex E for examples of novel surgically implanted heart valve substitutes that may require additional evaluation.

7.2.6.2 Visibility

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

7.2.7 Device MRI compatibility

Refer to ISO 5840-1.

7.2.8 Simulated use

See ISO 5840-1.

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 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 shall be included in the simulated use evaluation. Justification for critical parameters of the simulated use model shall be provided. Potential hazards associated with inaccurate valve implantation and resulting effects on valve performance and unintended anatomical interactions (e.g. coronary occlusion, anterior mitral impingement, LVOT obstruction, systolic anterior motion) shall be documented within the risk assessment.

7.2.9 Human factors/usability assessment

See ISO 5840-1.

7.2.10 Implant thrombogenic and haemolytic potential assessment

See ISO 5840-1.

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 assessment.

For minor design modifications to clinically well-documented surgical heart valve substitutes, the manufacturer shall justify omission of animal experimental evaluation. Preclinical studies are recommended for design changes of a marketed device that may affect the safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, and changes that affect the mechanical loading on the valve).

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

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 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 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 not related to the heart valve substitute 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 and study endpoints shall be justified fully 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. Any pre-clinical investigation with a designated endpoint of less than 140 days requires a thorough justification with rationale as to why a longer survival period was not attempted. A minimum duration of 90 days is suitable for minor modifications to existing devices, such as investigations of healing. 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 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 haemolysis, 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 6,0 L/min/m^2);

f) any paravalvular leakage (PVL);

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

h) 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 the following:

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

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