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Cardiovascular implants — Cardiac valve prostheses —

Part 3:
Heart valve substitutes implanted by transcatheter techniques

Implants cardiovasculaires — Prothèses valvulaires —

Partie 3: Valves cardiaques de substitution implantées par des techniques transcathéter

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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 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.

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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).

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This second edition cancels and replaces the first edition (ISO 5840-3:2013), 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 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.

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Introduction

This document has been prepared for transcatheter 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 to be used in conjunction with ISO 5840-1 and ISO 5840-2.

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Cardiovascular implants — Cardiac valve prostheses —

Part 3: Heart valve substitutes implanted by transcatheter techniques

1 Scope

This document is applicable to all devices intended for implantation as a transcatheter heart valve substitute.

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

This document establishes an approach for verifying/validating the design and manufacture of a transcatheter heart valve substitute through risk management. The selection of appropriate verification/validation tests and methods are to be derived from the risk assessment. The tests can include those to assess the physical, chemical, biological and mechanical properties of heart valve substitutes and of their materials and components. The tests can also include those for preclinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

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

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This document includes considerations for implantation of a transcatheter heart valve substitute inside a pre-existing prosthetic device (e.g. valve-in-valve and valve-in-ring configurations).

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 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*

IEC 62366 (all parts), *Medical devices — Application of usability engineering to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 5840-1:2020 and the following 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

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— 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 will 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
delivery approach
anatomical access used to deliver the implant to the implant site (e.g. transfemoral, transapical, transseptal)

3.4
delivery system
catheter or other system used to deliver the implant to the implant site

3.5
device migration
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detectable movement or displacement of the heart valve substitute from its original position within the implant position and without device embolization
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3.6
loading
crimping
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process to affix or attach a transcatheter heart valve substitute onto a delivery device and collapse the valve (i.e. reduce its diameter) for insertion via the *delivery system* (3.4) (e.g. catheter), performed either during manufacture or in the clinic

3.7
neo-LVOT
region between native anterior mitral leaflet/TMVI and septal wall, proximal to the aortic valve (see Figure 1)

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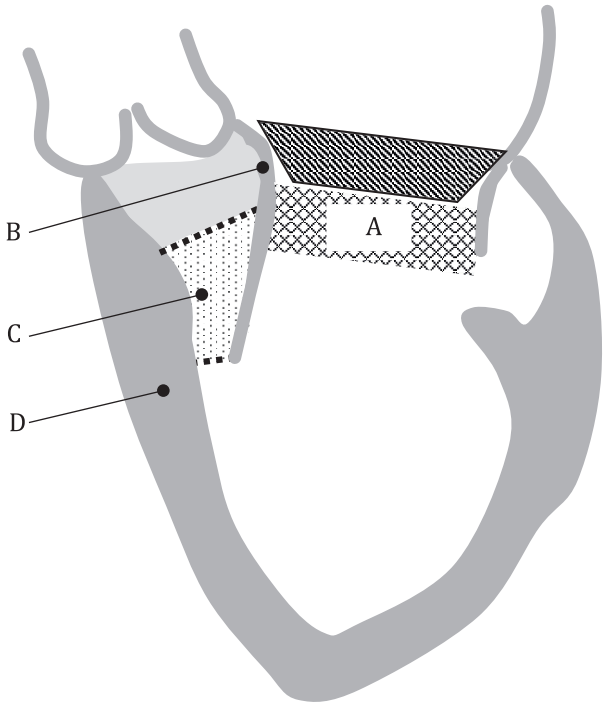

Key

A TMVI
B native anterior mitral leaflet
C neo-LVOT
D septal wall

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Figure 1 — Neo-LVOT formation behind a mitral leaflet

3.8
neo-sinus
region between implanted transcatheter aortic valve leaflet and native aortic leaflet/leaflet of existing bioprosthetic valve (see Figure 2)

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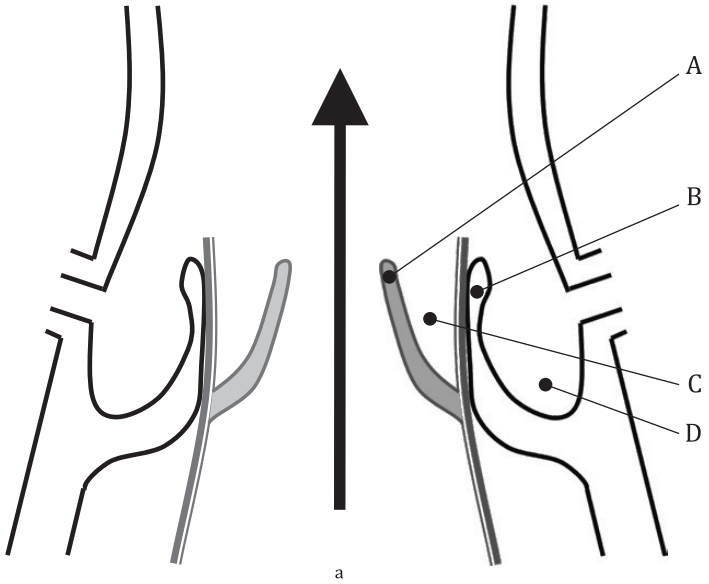

Key

A TAVI leaflet
B native leaflet
C neo-sinus
D native sinus
a Arrow points to the direction of the forward flow.

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Figure 2 — Neo-sinus formation behind an aortic leaflet

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3.9
repositioning
change in implant position of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique, possibly requiring full or partial recapturing of the device

3.10
retrieval
removal of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique

3.11
transcatheter heart valve system
implantable transcatheter device, *delivery system* (3.4), accessories, packaging, labels and instructions for use

3.12
valve-in-ring
implantation of a transcatheter heart valve substitute into a pre-existing annuloplasty ring

3.13
valve-in-valve
implantation of a transcatheter heart valve substitute into a pre-existing heart valve substitute

4 Abbreviations

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

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AE	Adverse event
AML	Anterior mitral leaflet
AWT	Accelerated wear testing
CIP	Clinical investigation plan
COF	Chronic outward force
CT	Computed tomography
ECG	Electrocardiogram
EOA	Effective orifice area
IFU	Instructions for use
LA	Left atrium
LAA	Left atrial appendage
LV	Left ventricle, left ventricular
LVOT	Left ventricular outflow tract
MRI	Magnetic resonance imaging
MR	Mitral regurgitation
PVL	Paravalvular leakage
SAE	Serious adverse event
TAVI	Transcatheter aortic valve implantation [also known as transcatheter aortic valve replacement (TAVR)]
TEE	Transoesophageal echo
TMVI	Transcatheter mitral valve implantation [also known as transcatheter mitral valve replacement (TMVR)]
TTE	Transthoracic echo
ViV	Valve-in-valve
ViR	Valve-in-ring

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5 Fundamental requirements

See ISO 5840-1:2020, Clause 5.

6 Device description

6.1 General

See ISO 5840-1:2020, 6.1.

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6.2 Intended use

See ISO 5840-1:2020, 6.2.

6.3 Design inputs

6.3.1 Operational specifications

See ISO 5840-1:2020, 6.3.1.

6.3.2 Performance specifications

6.3.2.1 General

See ISO 5840-1:2020, 6.3.2 for general requirements. Specific transcatheter system requirements are listed in 6.3.2.2 to 6.3.2.4. See Reference [18] for information relevant to TMVI.

6.3.2.2 Transcatheter heart valve system

The design attributes to meet the intended performance of the transcatheter heart valve system shall take into account at least the following:

a) the visibility of the transcatheter heart valve system under fluoroscopy or other imaging modalities;

b) the deliverability and implantability in the target population.

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6.3.2.3 Implantable device

The intended performance of the transcatheter heart valve substitute shall include, but not be limited to the following:

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a) the ability to be consistently, accurately and safely loaded onto the delivery system;

b) the ability to be consistently, accurately and safely deployed;

c) the ability to be safely retrieved and/or repositioned (if applicable);

d) the ability to ensure effective fixation or anchoring within the implant site;

e) the ability to maintain structural and functional integrity throughout the anticipated lifetime of the device;

f) the ability to conform or interact with anatomical structures within the implant site (e.g. in the aortic position, there is potential for interaction with coronary ostia, anterior mitral leaflet, conduction system; in the mitral position, there is potential for interaction with the aortic root, LA, LAA, LVOT and the subvalvular apparatus);

g) the ability to conform or interact with previously implanted device (e.g. surgical valve, annuloplasty ring, transcatheter valve, valve docking device), if applicable;

h) the ability to allow forward flow with acceptably small mean pressure difference in all anticipated configurations;

i) the ability to prevent retrograde flow with acceptably small regurgitation, including paravalvular leakage;

j) the ability to resist migration and embolization;

k) the ability to avoid haemolysis;

l) the ability to resist thrombus formation;

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m) biocompatibility;

n) the ability to maintain its functionality and sterility for a reasonable shelf life prior to implantation;

o) reproducibility of function.

6.3.2.4 Delivery system

In addition to the requirements in Annex D, the design attributes to meet the intended performance of the delivery system shall include, but not be limited to the following:

a) the ability to permit consistent, accurate and safe access, delivery, placement and deployment of the transcatheter heart valve substitute to the intended implant site;

b) the ability to permit consistent and safe withdrawal;

c) the ability to resist haemolysis;

d) the ability to resist thrombus formation;

e) the ability to resist blood loss (haemostasis);

f) the ability to recapture, retrieve, reposition and/or remove the transcatheter heart valve substitute (if applicable);

g) the ability to resist particulate generation.

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6.3.3 Implant procedure

See ISO 5840-1:2020, 6.3.3.

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6.3.4 Packaging, labelling and sterilization

See ISO 5840-1:2020, 6.3.4.

The manufacturer shall provide information and guidance (e.g. imaging modalities and sizing procedure) in the labelling to allow for appropriate preparation of the implant site (e.g. balloon valvuloplasty), selection of appropriate implant size and implantation of the transcatheter heart valve substitute. The manufacturer shall also provide MRI compatibility information in the labelling.

Annex A contains a listing of terms that may be used in describing transcatheter heart valve system components.

6.4 Design outputs

See ISO 5840-1:2020, 6.4. See Reference [18] for information relevant to TMVI.

6.5 Design transfer (manufacturing verification/validation)

See ISO 5840-1:2020, 6.5.

6.6 Risk management

See ISO 5840-1:2020, 6.6.

Annex B contains a hazard analysis example specific to transcatheter heart valve substitutes that can serve as the basis for a risk analysis.

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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 transcatheter heart valve substitutes are provided in this document. See Reference [18] for information relevant to TMVI.

7.2 *In vitro* assessment

7.2.1 General

See ISO 5840-1:2020, 7.2.

7.2.2 Test conditions, sample selection and reporting requirements

See ISO 5840-1:2020, 7.2.2.

For transcatheter valves, the steps of crimping or loading the implant into/onto a delivery catheter and tracking through simulated delivery pathways shall be followed in accordance with the IFU. The implant shall be maintained in the crimped configuration for a duration that mimics the worst-case expected clinical procedure time. If retrieval and repositioning is indicated for the implant in the IFU, the maximum allowable number of re-sheathing/recapturing and deployment cycles specified shall be simulated. Any deviations of the test articles from the finished device shall be justified. The test articles selected shall fully represent the total size range of the implant, the delivery system and accessories.

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7.2.3 Material property assessment

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7.2.3.1 General

See ISO 5840-1:2020, 7.2.3.

7.2.3.2 Biological safety

See ISO 5840-1:2020, 7.2.3.2.

7.2.3.3 Material and mechanical property testing

See ISO 5840-1:2020, 7.2.3.3.

For ViV and ViR indications, consideration shall be given to the material properties of the existing prosthesis, including bioprosthetic valve leaflet calcification, and their interactions with the materials of the transcatheter heart valve system.

7.2.4 Device hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid dynamic performance of the transcatheter heart valve substitute. The implant shall be deployed using the loading and deployment steps in accordance with the product specification and appropriately placed into the test chamber to simulate the device placement at the intended implant site. The device shall be inspected after loading, recapturing and/or deployment prior to fixturing and testing. 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 C. For pulsatile flow testing, the performance of the pulse duplicator shall be characterized. See C.2.3.2 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

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duplicator shall reasonably simulate physiological conditions. Representative waveforms used to generate hydrodynamic test results shall be documented in the test report. Reference [27] provides characteristics of reasonable aortic and mitral waveforms.

For transcatheter aortic valve substitutes, testing shall be performed to compare the device hydrodynamic performance to the minimum performance requirements provided in Table 1. Guidelines for designing test fixtures and test parameters are provided in Annex C, C.2.4. Testing shall be carried out on at least three transcatheter heart valve substitutes of each size in each configuration using requirements defined in Table C.2. The minimum performance requirements in Table 1 are provided as a function of deployed valve diameter within implant site (in mm). In addition, testing at challenge conditions shall also be considered to evaluate the device performance over a range of anticipated implant configurations (see Annex C, C.2.4.4 for examples of challenge conditions for transcatheter aortic valve substitutes).

For transcatheter mitral valve substitutes, testing shall be performed to compare the device hydrodynamic performance to the minimum performance requirements provided in Table 2. Guidelines for designing test fixtures and test parameters are provided in Annex C, C.2.5. Testing shall be carried out on at least three transcatheter heart valve substitutes of each size in each configuration using requirements defined in Table C.3. The minimum performance requirements in Table 2 are provided as a function of area-derived valve diameter (in mm).

For ViV and ViR indications, hydrodynamic testing shall be conducted in representative configurations of the pre-existing prosthetic devices to compare the device hydrodynamic performance to the minimum performance requirements provided in Tables 1 and 2.

The minimum performance values contained in Tables 1 and 2 reflect requirements against which heart valves substitutes under test shall be evaluated. If a device does not meet these minimum performance requirements, acceptability of the *in vitro* test results shall be justified by the manufacturer.

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The minimum *in vitro* performance requirements in Tables 1 and 2 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 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).

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Table 1 — Minimum *in vitro* hydrodynamic device performance requirements, aortic

Parameter	Deployed valve diameter within implant site 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
Regurgitant fraction (% of forward flow volume) less than or equal to[a]	20							
[a] For *in vitro* testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage.								

Table 2 — Minimum *in vitro* hydrodynamic device performance requirements, mitral

Parameter	Deployed area-derived valve diameter within implant site mm					
	23	25	27	29	31	≥33
EOA (cm^2) greater than or equal to[a]	1,05	1,25	1,45	1,65	1,90	2,15
Regurgitant fraction (% of forward flow volume) less than or equal to[b]	20					
[a] For measured mean pressure gradients ≤2 mmHg, computing of EOA is not required.						
[b] For *in vitro* testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage.						

For transcatheter pulmonary and tricuspid valve substitutes and paediatric devices, minimum performance requirements are not provided in this document; however, the manufacturer shall justify

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