

American National Standard



ANSI/AAMI/ ISO 5840-3: 2022

Cardiovascular implants—
Cardiac valve prostheses—
Part 3: Heart valve substitutes
implanted by transcatheter
techniques



Cardiovascular implants—Cardiac valve prostheses— Part 3: Heart valve substitutes implanted by transcatheter techniques

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AAMI

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Abstract: 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 includes considerations for implantation of a transcatheter heart valve substitute inside pre-existing prosthetic device configurations.

Keywords: clinical, design, implant, input, mechanical, operation, output, performance, risk

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Committee representation

Association for the Advancement of Medical Instrumentation

Cardiac Valve Prostheses Committee

The adoption of ISO 5840-2:2021 as an American National Standard was initiated by the AAMI Cardiac Valve Prostheses Committee. AAMI/CV provides input to the *U.S. TAG to ISO/TC150/SC2; Cardiovascular implants and extracorporeal systems*, which is the responsible group for providing the U.S. input to the relevant group in US ISO/TC150/SC2. U.S. representatives from AAMI Cardiac Valve Prostheses Committee and the U.S. TAG played an active part in developing the ISO document.

At the time this document was published, the **AAMI Cardiac Valve Prostheses Committee** has the following members:

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Jeffrey Borer, SUNY Downstate Medical Center
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NOTE Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 5840-3:2021

As indicated in the foreword to the main body of this document (page ix), the Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Subcommittee 150/SC2, Cardiovascular implants and extracorporeal systems, to provide standardization in the field of cardiac valve prostheses.

U.S. participation in ISO/TC150/SC2 is organized through the U.S. Technical Advisory Group, TAG for TC/150/SC2, administered by the Association for the Advancement of Medical Instrumentation. Experts from the United States made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of general requirements for cardiac valve substitutes. Upon review of ISO 5840-3 Ed.2, the U.S. Technical Advisory Group, TAG for TC/150/SC2 and the AAMI Cardiac Valve Prostheses Committee decided to adopt it verbatim, as a second edition which is a revision of ANSI/AAMI/ ISO 5840-3:2013.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited.

“May” is used to indicate that a course of action is permissible within the limits of the standard. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

NOTE Users of this standard are advised that this document is an AAMI identical adoption of an ISO document and that the following international conventions have been carried over to the AAMI publication:

- British English spelling (e.g. colour instead of color)
- Use of SI units (e.g. metres instead of feet, Celsius instead of Fahrenheit, etc.)
- Decimal comma instead of a decimal point (e.g. 1 000,15 instead of 1,000.15)

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

NOTE Beginning with the ISO foreword on page ix, this American National Standard is identical to ISO 5840-3:2021.

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 5840-3:2013), 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.

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 used in conjunction with ISO 5840-1 and ISO 5840-2.

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.

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

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 5840-1:2021, *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 5840-1:2021 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>
- 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

detectable movement or displacement of the heart valve substitute from its original position within the implant position and without device embolization

3.6

loading

crimping

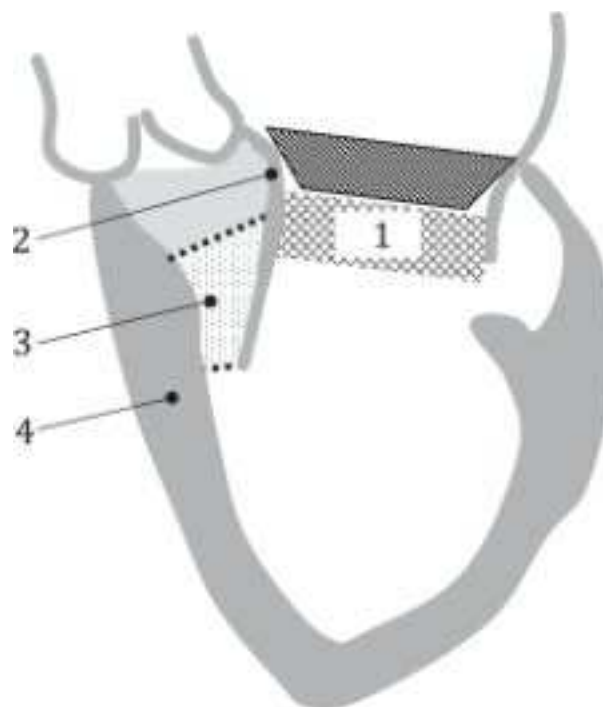
process to affix or attach a transcatheter heart valve substitute onto a delivery device and collapse the valve (i.e. reduce its diameter) for insertion via the delivery system (3.4) (e.g. catheter), performed either during manufacture or in the clinic

3.7

neo-LVOT

neo-left ventricular outflow tract

region between native anterior mitral leaflet/ transcatheter mitral valve implantation (TMVI) and septal wall, proximal to the aortic valve (see Figure 1)



Key

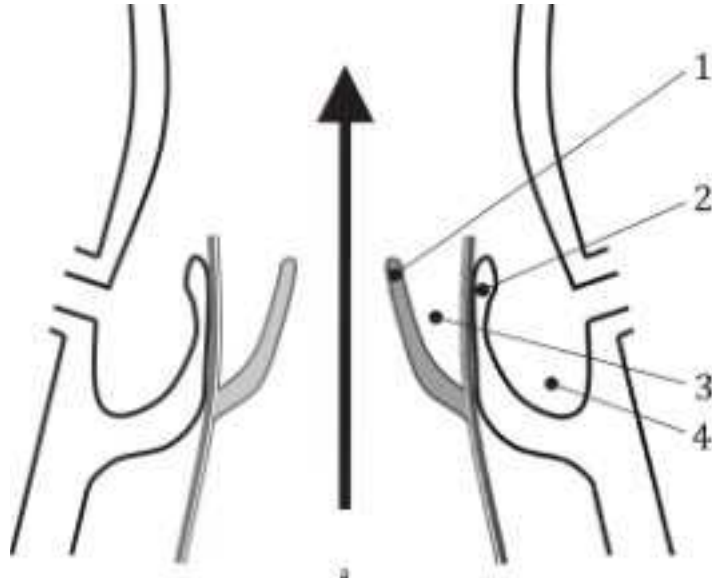
- 1 TMVI
- 2 native anterior mitral leaflet
- 3 neo-LVOT
- 4 septal wall

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)



Key

- 1 transcatheter aortic valve implantation (TAVI) leaflet
- 2 native leaflet
- 3 neo-sinus
- 4 native sinus
- a The arrow indicates the direction of the forward flow.

Figure 2—Neo-sinus formation behind an aortic leaflet

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.

AE	adverse event
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
PMCF	post-market clinical follow-up
PVL	paravalvular leakage
RMS	root mean square
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

5 Fundamental requirements

See ISO 5840-1:2021, Clause 5.

6 Device description

6.1 General

See ISO 5840-1:2021, 6.1.

6.2 Intended use

See ISO 5840-1:2021, 6.2.

6.3 Design inputs

6.3.1 Operational specifications

See ISO 5840-1:2021, 6.3.1.

6.3.2 Performance specifications

6.3.2.1 General

See ISO 5840-1:2021, 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.

6.3.2.3 Implantable device

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

- 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 the coronary ostia, the anterior mitral leaflet and the 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 an 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;
- 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 are not 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.

6.3.3 Implant procedure

See ISO 5840-1:2021, 6.3.3.

6.3.4 Packaging, labelling and sterilization

See ISO 5840-1:2021, 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 list of terms that may be used in describing transcatheter heart valve system components.

6.4 Design outputs

See ISO 5840-1:2021, 6.4. See Reference [18] for information relevant to TMVI.

6.5 Design transfer (manufacturing verification/validation)

See ISO 5840-1:2021, 6.5.

6.6 Risk management

See ISO 5840-1:2021, 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.

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 5840-1:2021, 7.1. 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

The requirements shall be as specified in ISO 5840-1:2021, 7.2.

7.2.2 Test conditions, sample selection and reporting requirements

The requirements shall be as specified in ISO 5840-1:2021, 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.

7.2.3 Material property assessment

7.2.3.1 General

The requirements shall be as specified in ISO 5840-1:2021, 7.2.3.

7.2.3.2 Biological safety

The requirements shall be as specified in ISO 5840-1:2021, 7.2.3.2.

7.2.3.3 Material and mechanical property testing

The requirements shall be as specified in ISO 5840-1:2021, 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 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 5840-1:2021, Annex I provides guidelines for conducting and reporting steady-flow 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 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 hydrodynamic performance of the device to the minimum performance requirements provided in Table 1. Guidelines for designing test fixtures and test parameters are provided in Annex C and 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 and 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 hydrodynamic performance of the device to the minimum performance requirements provided in Table 2. Guidelines for designing test fixtures and test parameters are provided in Annex C and 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 Table 1 and Table 2.

The minimum performance values contained in Table 1 and Table 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.

The minimum *in vitro* performance requirements in Table 1 and Table 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 5840-1:2021, 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 5840-1:2021, Annex E for paediatric parameters).

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 (cm2) 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 <i>in vitro</i> testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage volume.								

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 (cm2) 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 <i>in vitro</i> testing, regurgitant fraction includes closing volume, transvalvular leakage and paravalvular leakage volume.						

For transcatheter pulmonary and tricuspid valve substitutes and paediatric devices, minimum performance requirements are not provided in this document; however, the manufacturer shall justify the acceptability of hydrodynamic performance of the devices. The test chamber shall be representative of the critical aspects of the target implant site (e.g. compliance, geometry, native valve or pre-existing prosthetic device) for the target patient population.

For all transcatheter valve substitutes, additional hydrodynamic characterization testing shall be conducted over a range of test conditions as described in Annex C and C.2.6.

7.2.5 Structural performance assessment

7.2.5.1 General

The requirements shall be as specified in ISO 5840-1:2021, 7.2.5.

7.2.5.2 Implant durability assessment

The requirements shall be as specified in ISO 5840-1:2021, 7.2.5.2.

For ViV and ViR indications, testing shall be conducted in devices that are representative of the anticipated range of configurations.

7.2.5.3 Device structural component fatigue assessment

See ISO 5840-1:2021, 7.2.5.3.

7.2.5.4 Component corrosion assessment

See ISO 5840-1:2021, 7.2.5.4.

For ViV and ViR indications, the manufacturer shall consider all interactions with the pre-existing device in terms of corrosion potential (e.g. galvanic corrosion, fretting corrosion).

7.2.6 Design- or procedure-specific testing

7.2.6.1 General

The following design evaluation requirements shall apply as appropriate. Justification shall be provided for those requirements that are deemed not applicable to a particular design. Additional design evaluation requirements might be applicable as per ISO 25539-1. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific device design. See Annex E for examples of design specific evaluation requirements to be considered.

7.2.6.2 Device migration resistance

The ability of the implanted device to remain in the target implant site (e.g. native valve or pre-existing prosthesis) shall be assessed under simulated operating conditions. Consideration shall be given to variation in deployed shape, deployed size as prescribed in the product specification, implanted depth, implant site characteristics (e.g. native valve, degree and distribution of calcification) and mechanical properties (e.g. compliance) along with consideration for surrounding anatomical structures (e.g. native leaflets, LVOT). For ViV and ViR indications, the manufacturer shall consider simulated operating conditions of the existing device and all interactions with the existing device in terms of device migration potential. The pressure conditions specified in ISO 5840-1:2021, Tables 3 and 4, and other loading conditions, shall be considered as applicable. See ISO 5840-1:2021, Annex E for guidelines regarding suggested test conditions for the paediatric population.

7.2.6.3 Implant foreshortening (length to diameter)

The manufacturer shall determine the decrease in length of the implant between the catheter-loaded condition and the deployed diameters up to the maximum labelled diameter (see ASTM F2081 for guidance). The results shall be reported in terms of a percentage of the loaded length as shown below:

$$P_f = 100 \times (l_c / l_i)$$

where

P_f is the percentage of foreshortening;