

BS EN ISO 5840-3:2013



BSI Standards Publication

Cardiovascular implants — Cardiac valve prostheses

Part 3: Heart valve substitutes
implanted by transcatheter techniques

bsi.

...making excellence a habit.
AVA Documents™
Document Sharing Hub

National foreword

This British Standard is the UK implementation of EN ISO 5840-3:2013.

The UK participation in its preparation was entrusted to Technical Committee CH/150/2, Cardiovascular implants.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

© The British Standards Institution 2013.
Published by BSI Standards Limited 2013.

ISBN 978 0 580 71177 0

ICS 11.040.40

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 30 April 2013.

Amendments issued since publication

Date	Text affected
------	---------------

English Version

Cardiovascular implants - Cardiac valve prostheses - Part 3:
Heart valve substitutes implanted by transcatheter techniques
(ISO 5840-3:2013)

Implants cardiovasculaires - Prothèses valvulaires - Partie
3: Valves cardiaques de substitution implantées par des
techniques transcathéter (ISO 5840-3:2013)

Herz- und Gefäßimplantate - Herzklappenprothesen - Teil
3: Durch minimal-invasive Methoden implantierter
Herzklappenersatz (ISO 5840-3:2013)

This European Standard was approved by CEN on 21 January 2013.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.



EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

Management Centre: Avenue Marnix 17, B-1000 Brussels

Foreword

This document (EN ISO 5840-3:2013) has been prepared by Technical Committee ISO/TC 150 "Implants for surgery" in collaboration with Technical Committee CEN/TC 285 "Non-active surgical implants" the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by September 2013, and conflicting national standards shall be withdrawn at the latest by September 2013.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this document.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 5840-3:2013 has been approved by CEN as EN ISO 5840-3:2013 without any modification.

Annex ZA (informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide one means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC, Medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table — ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC

Clause(s)/sub-clause(s) of this European Standard	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
Annex C	7.2	
7.2.2, 7.2.3 and 7.2.10	7.3	
7.2.2.2	8.2	
6.2.2.3 d), 6.4 and Annex C	8.3	
6.2.4 and Annex E	8.4	
6.4	8.5	
6.2.2.3 c) and 7.2.5.2	9.2, 3rd indent	
6.2.2.1 e) and 7.2.4	9.2, 4th indent	
D.1.3	13.1	For labelling requirements consider also ISO 14630:—, 11.2.
D.1.2 b)	13.3 a)	
D.1.1 d), D.1.2 e) and f)	13.3 b)	
D.1.1 e) and D.1.2 g)	13.3 c)	
D.1.1 c) and D.1.2 d)	13.3 d)	
D.1.1 f) and D.1.2 h)	13.3 e)	
D.1.1 g) and D.1.2 i)	13.3 f)	
D.1.2 j)	13.3 h)	
D.1.2 k)	13.3 i)	
D.1.2 l)	13.3 k)	
D.1.1 e) and D.1.2 g)	13.3 m)	
D.1.3 a), b), d), i), k), l) and m)	13.6 a)	

Table
(continued)

Clause(s)/sub-clause(s) of this European Standard	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
D.1.3 e) and u)	13.6 b)	
D.1.3 g)	13.6 c)	
D.1.3 p)	13.6 f)	
D.1.3 n)	13.6 g)	
D.1.3 r)	13.6 i)	
D.1.3 p)	13.6 n)	
D.1.3 c)	13.6 q)	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Contents

Page

Foreword.....	v
Introduction.....	vi
1 Scope.....	1
2 Normative references.....	1
3 Terms and definitions.....	2
4 Abbreviations.....	10
5 Fundamental requirements.....	10
6 Device description.....	10
6.1 Intended use.....	10
6.2 Design inputs.....	10
6.3 Design outputs.....	13
6.4 Design transfer (manufacturing verification/validation).....	13
6.5 Risk management.....	14
7 Design verification testing and analysis/design validation.....	14
7.1 General requirements.....	14
7.2 <i>In vitro</i> assessment.....	14
7.3 Preclinical <i>in vivo</i> evaluation.....	23
7.4 Clinical investigations.....	26
Annex A (informative) Rationale for the provisions of this part of ISO 5840.....	31
Annex B (informative) Examples of transcatheter heart valve substitutes, components and delivery systems.....	34
Annex C (normative) Packaging.....	40
Annex D (normative) Product labels, instructions for use and training.....	41
Annex E (normative) Sterilization.....	44
Annex F (informative) Valve description.....	45
Annex G (informative) Transcatheter heart valve substitute hazards, associated failure modes and evaluation methods.....	47
Annex H (informative) <i>In vitro</i> test guidelines for paediatric devices.....	51
Annex I (informative) Statistical procedures when using performance criteria.....	55
Annex J (informative) Examples and definitions of some physical and material properties of transcatheter heart valve substitutes and their components.....	56
Annex K (informative) Examples of standards applicable to testing of materials and components of transcatheter heart valve substitutes.....	69
Annex L (informative) Raw and post-conditioning mechanical properties for support structure materials.....	75
Annex M (informative) Corrosion assessment.....	77
Annex N (informative) Guidelines for verification of hydrodynamic performance.....	80
Annex O (informative) Durability testing.....	84
Annex P (informative) Fatigue assessment.....	86
Annex Q (informative) Preclinical <i>in vivo</i> evaluation.....	92
Annex R (normative) Adverse event classification during clinical investigation.....	95
Annex S (informative) Echocardiographic protocol.....	100

Bibliography	103
---------------------------	------------

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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 5840-3 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

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

— *Part 3: Heart valve substitutes implanted by minimally invasive techniques*

Introduction

No heart valve substitute is ideal. Therefore, a group of engineers, scientists and clinicians well aware of the problems associated with heart valve substitutes and their development has prepared this part of ISO 5840. In several areas, the provisions of this part of ISO 5840 have been deliberately left partially defined so as not to inhibit development and innovation. This part of ISO 5840 specifies types of tests, test methods and requirements for test apparatus. It requires documentation of test methods and results. This part of ISO 5840 deals with those areas that will ensure adequate mitigation of device-associated risks for patients and other users of the device, facilitate quality assurance, aid the cardiac surgeon and cardiologist in choosing a heart valve substitute, and ensure that the device will be presented in a convenient form. This part of ISO 5840 emphasizes the need to specify types of *in vitro* testing, preclinical *in vivo* and clinical evaluations as well as to report all *in vitro*, preclinical *in vivo* and clinical evaluations. It describes the labels and packaging of the device. Such a process involving *in vitro*, preclinical *in vivo* and clinical evaluations is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent problems.

With regard to *in vitro* testing and reporting, apart from basic material testing for mechanical, physical, chemical and biocompatibility characteristics, this part of ISO 5840 also covers important hydrodynamic and durability characteristics of transcatheter heart valve substitutes and their delivery systems. This part of ISO 5840 does not specify exact test methods for hydrodynamic and durability testing but it offers guidelines for the test apparatus.

This part of ISO 5840 should be revised, updated and amended as knowledge and techniques in heart valve substitute technology improve.

This part of ISO 5840 is to be used in conjunction with ISO 5840:2005, which will be replaced by ISO 5840-1 in future.

Cardiovascular implants — Cardiac valve prostheses —

Part 3: Heart valve substitutes implanted by transcatheter techniques

1 Scope

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

This part of ISO 5840 is applicable to all devices intended for implantation in human hearts as a transcatheter heart valve substitute.

This part of ISO 5840 is applicable to both newly developed and modified 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 part of ISO 5840 excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

This part of ISO 5840 excludes valve-in-valve configurations and homografts.

This part of ISO 5840 does not specifically address non-traditional surgically implanted heart valve substitutes (e.g. sutureless). For these devices, the requirements of both this part of ISO 5840 and ISO 5840:2005 might be relevant and can be considered.

NOTE A rationale for the provisions of this part of ISO 5840 is given in [Annex A](#).

2 Normative references

The following referenced documents are indispensable for the application 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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO/TS 11135-2, *Sterilization of health care products — Ethylene oxide — Part 2: Guidance on the application of ISO 11135-1*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

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

ISO 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

ISO 14630:2012, *Non-active surgical implants — General requirements*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

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

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

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

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

ASTM F2052, *Standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment*

ASTM F2503, *Standard practice for marking medical devices and other items for safety in the magnetic resonance environment*

ASTM F2213, *Standard test method for measurement of magnetically induced torque on medical devices in the magnetic resonance environment*

ASTM F2182, *Standard test method for measurement of radio frequency induced heating near passive implants during magnetic resonance imaging*

ASTM F2119, *Standard test method for evaluation of MR image artifacts from passive implants*

3 Terms and definitions

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

NOTE Additional definitions can be found in the informative annexes.

3.1

accessories

device-specific tools that are required to assist in the implantation of the transcatheter heart valve substitute

3.2

adverse event

AE

untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with study treatment

Note 1 to entry: An AE can be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporary or permanent, whether or not related to the prosthetic valve implantation or procedure.

3.3

arterial end diastolic pressure

minimum value of the arterial pressure during diastole

3.4

arterial peak systolic pressure

maximum value of the arterial pressure during systole

3.5

back pressure

differential pressure applied across the valve during the closed phase

3.6

body surface area

A_{bs}

total surface area (m^2) of the human body

Note 1 to entry: This can be calculated (Mosteller's formula) as the square root of product of the weight in kg times the height in cm divided by 3 600 (see Reference [\[12\]](#)).

3.7

cardiac index

cardiac output (CO, l/min) divided by the body surface area (A_{bs} , m^2), in units l/min/ m^2

3.8

closing volume

portion of the regurgitant volume that is associated with the dynamics of the valve closure during a single cycle

Note 1 to entry: See [Figure 1](#).

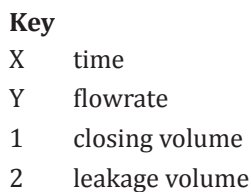


Figure 1 — Schematic representation of flow waveform and regurgitant volumes for one cycle

3.9 coating

thin-film material that is applied to an element of a heart valve substitute to modify its physical or chemical properties

3.10 compliance

relationship between change in diameter and change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit), defined in this part of ISO 5840 as

$$C = 100\% \times \frac{(r_2 - r_1) \times 100}{r_1 \times (p_2 - p_1)}$$

where

C is the compliance in units of % radial change/100 mmHg;

p_1 is the diastolic pressure, in mmHg;

p_2 is the systolic pressure, in mmHg;

r_1 is the inner radius at p_1 , in millimetres;

r_2 is the inner radius at p_2 , in millimetres.

Note 1 to entry: See ISO 25539-1.

3.11

component-joining material

material, such as a suture, adhesive or welding compound, used to assemble the components of a heart valve substitute, thereby becoming part of the implant device

Note 1 to entry: See examples in [Annex B](#).

3.12

cycle

one complete sequence in the action of a heart valve substitute under pulsatile flow conditions

3.13

cycle rate

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

3.14

delivery approach

anatomical access used to deliver the implant to the implant site (e.g. transfemoral, transapical, transeptal)

3.15

delivery system

catheter or other device-based system used to deliver the implant to the implant site

3.16

deployed valve diameter

outer diameter (mm) of the implantable device when deployed within the target implant site in an idealized circular configuration

3.17

device embolization

dislodgement from the intended and documented original position to an unintended and non-therapeutic location

3.18

device failure

inability of a device to perform its intended function sufficient to cause a hazard

3.19

device migration

detectable movement or displacement of the device from its original position within the implant site, without embolization

3.20

effective orifice area

EOA

orifice area that has been derived from flow and pressure or velocity data

3.21

failure mode

mechanism of device failure

Note 1 to entry: Catastrophic support structure fracture, calcification and prolapse are examples of failure modes.

3.22

follow-up

continued assessment of patients who have received the heart valve substitute

3.23

forward flow volume

volume of flow ejected through the test heart valve substitute in the forward direction during one cycle

3.24

fracture

disruption, under the action of applied stress or strain, of any part of the transcatheter heart valve substitute that was previously intact

3.25

heart valve substitute

device used to replace the function of a natural valve of the heart

Note 1 to entry: See examples in [Annex B](#).

3.26

imaging modality

imaging method used to facilitate delivery and/or retrieval of the implant within the target implant site, as well as to assess valve performance after implantation

3.27

implant site

intended site of transcatheter heart valve substitute deployment

3.28

intended use

use of a product, process or service in accordance with the specifications, instructions and information provided by the manufacturer

3.29

leakage volume

component of the regurgitant volume that is associated with leakage during closed phase of a valve in a single cycle and is the sum of the transvalvular leakage volume and paravalvular leakage volume

Note 1 to entry: The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in [Figure 1](#) is just an example).

Note 2 to entry: See [Figure 1](#).

3.30

mean arterial pressure

time-averaged arithmetic mean value of the arterial pressure during one cycle

3.31

mean pressure difference

time-averaged arithmetic mean value of the pressure difference across a heart valve substitute during the forward flow phase of the cycle

3.32

non-structural valve dysfunction

abnormality extrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis, regurgitation or both)

3.33

occluder/leaflet

component that inhibits back flow

Note 1 to entry: See examples in [Annex B](#).

3.34

paravalvular leakage volume

component of the leakage volume that is associated with leakage around the closed heart valve substitute during a single cycle

3.35

reference valve

heart valve substitute with a known clinical experience used for comparative preclinical and clinical evaluations

3.36

regurgitant fraction

regurgitant volume expressed as a percentage of the forward flow volume

3.37

regurgitant volume

volume of fluid that flows through a heart valve substitute in the reverse direction during one cycle and is the sum of the closing volume and the leakage volume

Note 1 to entry: See [Figure 1](#).

3.38

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

3.39

retrieval

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

3.40

risk

combination of the probability of occurrence of harm and the severity of that harm

Note 1 to entry: Adapted from ISO 14971.

3.41

risk analysis

systematic use of available information to identify hazards and to estimate the associated risks

Note 1 to entry: Adapted from ISO 14971.

3.42

risk assessment

overall process comprising a risk analysis and a risk evaluation

Note 1 to entry: Adapted from ISO 14971.

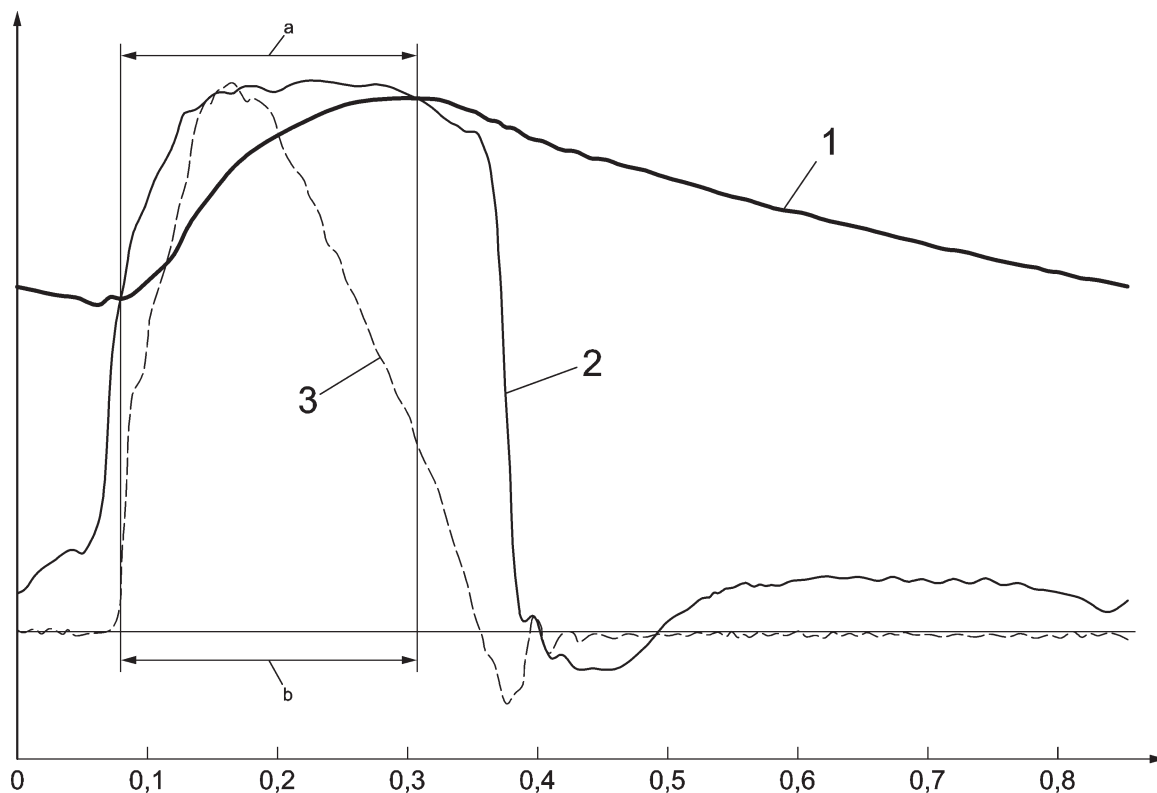
3.43

root mean square forward flow

RMS forward flow

square root of the integral of the volume flow rate waveform squared during the positive differential pressure interval of the forward flow phase used to calculate EOA

Note 1 to entry: See [Figure 2](#).



Key title

- 1 aortic pressure
- 2 left ventricular pressure
- 3 aortic flow rate
- a Positive pressure range.
- b Q_{rms} range.

Figure 2 — Schematic representation of the positive pressure period of an aortic forward flow interval

3.44

safety

freedom from unacceptable risk

Note 1 to entry: Adapted from ISO 14971.

3.45

severity

measure of the possible consequences of a hazard

Note 1 to entry: Adapted from ISO 14971.

3.46

special processes

processes for which the product cannot be fully verified by inspection or test

3.47
sterility assurance level
SAL

probability of a single viable microorganism occurring on an item after sterilization

Note 1 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3} . When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3} .

[ISO/TS 11139, definition 2.46]

3.48
sterilization

validated process used to render product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: See **sterility assurance level** (3.47).

Note 3 to entry: Adapted from ISO/TS 11139.

3.49
structural component failure

degradation of structural integrity of the support structure (e.g. strut fractures) that results in the functional performance of the implant no longer being acceptable and/or that results in adverse events

3.50
structural valve dysfunction

structural abnormality intrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis and/or transvalvular and/or paravalvular regurgitation)

3.51
support structure

portion of the transcatheter heart valve substitute that transfers loads between occluder and implant site and anchors the device within the implant site

3.52
surgically implanted heart valve substitute

heart valve substitute generally requiring direct visualization and cardiopulmonary bypass for implantation

3.53
transcatheter heart valve substitute

heart valve substitute implanted in a manner generally not involving direct visualization, and generally involving a beating heart

3.54
transcatheter heart valve system

implantable device, delivery system, accessories, packaging, labelling and instructions

3.55
transvalvular leakage volume

component of the leakage volume that is associated with leakage through the closed valve during a single cycle

3.56
usability

characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction

3.57

valve loading

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

4 Abbreviations

For the purposes of this part of ISO 5840, the following abbreviations apply.

AE	Adverse event
EOA	Effective orifice area
AWT	Accelerated wear testing
CFD	Computational fluid dynamics
ECG	Electrocardiogram
FEA	Finite element analysis
IFU	Instructions for use
LV	Left ventricle, left ventricular
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging

5 Fundamental requirements

The manufacturer shall determine, at all stages of the product life cycle, the acceptability of the product for clinical use.

6 Device description

6.1 Intended use

The manufacturer shall identify the physiological condition(s) to be treated, the intended patient population, potential adverse events and intended claims.

6.2 Design inputs

6.2.1 Operational specifications

The manufacturer shall define the operational specifications for the device, including the principles of operation, intended device delivery approach/process, expected device lifetime, shelf life, shipping/storage limits, and the physiological environment in which it is intended to function. The manufacturer shall carefully define all relevant dimensional parameters that will be required to accurately select the size of device to be implanted. [Table 1](#) and [Table 2](#) define the expected physiological parameters of the intended adult patient population for transcatheter heart valve substitutes for both normal and pathological patient conditions.

Table 1 — Heart valve substitute operational environment for left side of heart — Adult population

Parameter	General condition			
Surrounding medium	Human heart/human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 l/min to 15 l/min			
Blood pressures and resultant pressure loads by patient condition	Arterial peak systolic pressure mmHg	Arterial end diastolic pressure mmHg	Peak differential pressure across closed valve ^a	
			Aortic Δp_A mmHg	Mitral Δp_M mmHg
Normotensive	120	80	100	120
Hypotensive	60	40	50	60
Hypertensive				
Mild	140 to 159	90 to 99	115 to 129	140 to 159
Moderate	160 to 179	100 to 109	130 to 144	160 to 179
Severe	180 to 209	110 to 119	145 to 164	180 to 209
Very severe	≥ 210	≥ 120	≥ 165	≥ 210
^a Peak differential pressure across closed aortic valve is estimated using the following relationship: — Δp_{Aortic} approximately pressure associated with dicrotic notch assuming LV pressure is zero approximately arterial end diastolic pressure + 1/2(arterial peak systolic pressure – arterial end diastolic pressure). — Peak differential pressure across closed mitral valve estimated to be equivalent to arterial peak systolic pressure.				

Table 2 — Heart valve substitute operational environment for right side of heart — Adult population

Parameter	General condition			
Surrounding medium	Human heart/human blood			
Temperature	34 °C to 42 °C			
Heart rate	30 bpm to 200 bpm			
Cardiac output	3 l/min to 15 l/min			
Forward flow volume	25 ml to 100 ml			
Blood pressures and resultant pressure loads by patient condition	Right ventricle peak systolic pressure mmHg	Pulmonary artery end diastolic pressure mmHg	Peak differential pressure across closed valve ^a	
			Pulmonary Δp_P mmHg	Tricuspid Δp_T mmHg
Normotensive	18 to 35	8 to 15	13 to 25	18 to 35
Hypotensive	15	5	10	15
Hypertensive				
Mild	40 to 49	15 to 19	28 to 34	40 to 49
Moderate	50 to 59	20 to 24	35 to 42	50 to 59
^a Peak differential pressure across closed pulmonary valve is estimated using the following relationship: — $\Delta p_{pulmonic}$ approximate pressure associated with dicrotic notch assuming RV pressure is zero approximately pulmonary artery end diastolic pressure + 1/2(right ventricle peak systolic pressure – pulmonary artery end diastolic pressure). — Peak differential pressure across closed tricuspid valve estimated to be equivalent to right ventricle peak systolic pressure.				

Table 2 (continued)

Parameter	General condition			
Severe	60 to 84	25 to 34	43 to 59	60 to 84
Very severe	85 to 120	≥ 35	60 to 78	85 to 120
^a Peak differential pressure across closed pulmonary valve is estimated using the following relationship: — $\Delta P_{\text{pulmonic}}$ approximate pressure associated with dicrotic notch assuming RV pressure is zero approximately pulmonary artery end diastolic pressure + 1/2(right ventricle peak systolic pressure – pulmonary artery end diastolic pressure). — Peak differential pressure across closed tricuspid valve estimated to be equivalent to right ventricle peak systolic pressure.				

6.2.2 Performance specifications

The manufacturer shall establish (i.e. define, document and implement) the clinical performance requirements of the device and the corresponding device performance specifications for the intended use and device claims. The following list of desired clinical and device-based performance characteristics describe a safe and effective transcatheter heart valve substitute system.

6.2.2.1 Implantable device

The design attribute requirements of ISO 14630:2012, Clause 5, shall apply. The intended performance of the transcatheter heart valve substitute shall take into account at least the following:

- the ability to be consistently, accurately and safely loaded onto the delivery system;
- the ability to be consistently, accurately and safely deployed;
- the ability to be safely retrieved and/or repositioned (if applicable);
- the ability to ensure effective fixation within the target implant site;
- the ability to maintain structural and functional integrity during the expected lifetime of the device;
- the ability to conform with anatomical structures within the implant site (e.g. in the aortic position, there is potential for interaction with coronary ostia, anterior mitral leaflet, AV bundle branch);
- the ability to allow forward flow with acceptably small mean pressure difference;
- the ability to prevent retrograde flow with acceptably small regurgitation, including paravalvular leakage;
- the ability to resist migration and embolization during the expected lifetime of the device;
- the ability to minimize haemolysis;
- the ability to minimize thrombus formation;
- the ability to maintain its functionality for the intended application consistent with the target patient population.

6.2.2.2 Delivery system

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

- the ability to permit consistent, accurate and safe access, delivery, placement and deployment of the transcatheter heart valve substitute to the intended implant site;
- the ability to permit consistent and safe withdrawal of the delivery system prior to and after deployment of transcatheter heart valve substitute;

- c) the ability to minimize haemolysis;
- d) the ability to minimize thrombus formation;
- e) the ability to minimize blood loss (haemostasis);
- f) the ability to retrieve, reposition and/or remove the transcatheter heart valve substitute (if applicable).

6.2.2.3 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 compliance of the transcatheter heart valve system with the requirements of ISO 10993-1 and appropriate other parts of ISO 10993;
- b) the visibility of the transcatheter heart valve system under fluoroscopy or other imaging modalities;
- c) compatibility with magnetic resonance imaging (MRI);
- d) the ability of the transcatheter heart valve system to maintain its functionality and sterility for its specified shelf life prior to implantation.

6.2.3 Implant procedure

The entire system shall provide intended users with the ability to safely and effectively perform all required pre-operative, intra-operative and post-operative procedural tasks and achieve all desired objectives. This shall include all other tools and accessories that intended users will use to complete the procedure.

NOTE For guidance on how to determine and establish design attributes pertaining to the use of the system to conduct the implant procedure, see IEC 62366.

6.2.4 Packaging, labelling and sterilization

The transcatheter heart valve substitute system shall meet the requirements for packaging, labelling and sterilization contained within [Annex C](#), [Annex D](#) and [Annex E](#), respectively.

The manufacturer shall provide sufficient information and guidance in the labelling to allow for appropriate preparation of the implant site (e.g. balloon valvuloplasty), accurate selection of appropriate implant size and reliable implantation of the transcatheter heart valve substitute.

6.3 Design outputs

The manufacturer shall establish (i.e. define, document and implement) a complete specification of the transcatheter heart valve substitute system, including component and assembly-level specifications, delivery system, accessories, packaging and labelling. [Annex F](#) contains a listing of terms that may be used in describing various valve models. In addition to the physical components of the heart valve substitute system, the implant procedure itself should be considered an important element of safe and effective heart valve therapy.

6.4 Design transfer (manufacturing verification/validation)

The manufacturer shall generate a flowchart identifying the manufacturing process operations and inspection steps. The flowchart shall indicate the input of all components and important manufacturing materials.

As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification activities necessary to demonstrate the acceptability of the process ranges chosen.

The manufacturer shall establish the adequacy of full scale manufacturing by validation of the manufacturing process. The manufacturer shall validate all special processes and process software, and document the results of the validation.

NOTE See ISO 13485.

6.5 Risk management

The manufacturer shall define and implement a risk management program in accordance with ISO 14971.

[Annex G](#) contains a list of potential hazards specific to heart valve substitutes that can serve as the basis for a risk analysis.

7 Design verification testing and analysis/design validation

7.1 General requirements

The manufacturer shall perform verification testing to demonstrate that the device specifications result in a transcatheter heart valve substitute system that meets the design specifications (design output meets design input). The manufacturer shall establish tests relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, set-up, equipment (specifications, calibration, etc.), test conditions (with a justification of appropriateness to anticipated *in vivo* operating conditions for the device), acceptance criteria and sample quantities tested.

The manufacturer shall validate the design of the transcatheter heart valve substitute system.

7.2 *In vitro* assessment

7.2.1 Test conditions, sample selection and reporting requirements

7.2.1.1 Test specimens shall represent, as closely as possible, the finished product to be supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, process chemicals, aging effects, and any catheter loading and deployment steps (including repositioning and recapturing, if applicable) in accordance with all manufacturing procedures and IFU, where appropriate. Any deviations of the test specimens from the finished product shall be justified.

7.2.1.2 The specimens selected for testing shall fully represent the total implant size range. Depending on the particular test, testing might not necessarily have to be completed for each discrete valve size, but shall at least be completed for the largest and smallest sizes, each deployed to the largest and smallest deployed diameters as per the IFU. Sampling shall ensure adequate representation of the expected variability in the manufacture of devices. A rationale for device size selection shall be provided.

7.2.1.3 For all tests, the number of samples shall be justified based on the specific intent of the test. Additional recommendations regarding sampling and sample conditioning are included within each test method defined herein, as appropriate.

7.2.1.4 Where simulation of *in vivo* conditions is applicable to the test method, consideration shall be given to those operational environments given in [Table 1](#) and [Table 2](#) for the adult population. See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population. Where applicable, testing shall be performed using a test fluid of isotonic saline, blood, or a blood-equivalent fluid whose physical properties (e.g. specific gravity, viscosity at working temperatures) are appropriate to the test being performed. The test fluid used shall be justified. The testing shall be performed at the intended operating temperature as appropriate.

7.2.1.5 Test methods for verification testing shall be appropriately validated. Refer to applicable sections of ISO/IEC 17025.

7.2.1.6 Each test report shall include:

- a) rationale for the test;
- b) identification and description of the transcatheter heart valve substitute system elements tested (e.g. batch number);
- c) identification and description of the reference valve(s) where appropriate;
- d) number of specimens tested, and rationale for sample size;
- e) detailed description of the test method including preconditioning to simulate intended use;
- f) verification that appropriate quality assurance standards have been met (e.g. Good Laboratory Practice);
- g) test results and conclusions.

Statistical procedures, such as the ones described in [Annex I](#), may be used to assist data analysis.

7.2.2 Material property assessment

7.2.2.1 General

Properties of the transcatheter heart valve substitute system components (e.g. support structure, valve leaflets) shall be evaluated as applicable to the specific design of the system as determined by the risk assessment. The materials requirements of ISO 14630:2012, Clause 6, shall apply. Additional testing specific to certain materials shall be performed to determine the appropriateness of the material for use in the design. For example, materials dependent on shape memory properties shall be subjected to testing in order to assess transformation properties.

7.2.2.2 Biological safety

The biocompatibility of the materials and components used in the transcatheter heart valve substitute system shall be determined in accordance with ISO 10993-1. The test plan recorded in the risk management file shall comprise a biological safety evaluation programme with a justification for the appropriateness and adequacy of the information obtained. The documentation shall include a rationale for the commission of any biological safety tests carried out to supplement information obtained from other sources and for the omission of any tests identified by ISO 10993-1 but not performed. During the hazard identification stage of a biological safety evaluation, sufficient information shall be obtained to allow the identification of toxicological hazards and the potential for effects on relevant haematological characteristics. Where an identified hazard has the potential for significant clinical effects, the toxicological risk shall be characterized through evaluation of data on, for example, mode of action, dose-response, exposure level, biochemical interactions and toxicokinetics.

For transcatheter heart valve substitutes using animal tissue or their derivatives, the risk associated with the use of these materials shall be evaluated in accordance with ISO 22442-1, ISO 22442-2 and ISO 22442-3.

7.2.2.3 Material and mechanical property testing

The material properties of all constituent materials comprising the transcatheter heart valve substitute system and each element thereof shall be evaluated as applicable to its specific design. Scientific literature citations or previous characterization data from similar devices can be referenced; however, the applicability of the literature data to the transcatheter heart valve substitute shall be justified.

Mechanical properties shall be characterized at various stages of manufacture, as applicable: a) for the structural component raw materials, b) for the structural component in its final manufactured state, and c) for the finished device after applicable catheter loading and deployment states. Environmental conditions that might affect device or component performance or durability shall be evaluated and included in testing protocols (e.g. shelf life testing). [Annex I](#) provides potentially relevant physical, mechanical and chemical properties by material class and components. [Annex K](#) provides a list of

standards that might be applicable to the testing of materials and components. [Annex L](#) provides guidance on mechanical property characterization of raw and conditioned materials. [Annex M](#) provides guidance on corrosion assessment.

7.2.3 Device hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid mechanical performance of the transcatheter heart valve substitute and provide indicators of valve performance in terms of load to the heart and potential for blood stasis and damage. The implant shall be deployed into the test fixtures using the loading and deployment steps in accordance with the IFU. The test chamber shall be representative of the critical aspects of the target implant site (e.g. compliance, geometry) for the target patient population. The test chamber details shall be justified by the manufacturer. The measurement accuracy and repeatability of the test system shall be evaluated and documented.

A guideline for the performing and reporting of hydrodynamic tests is provided in [Annex N](#). The detailed protocols shall be defined based on the findings of the risk assessment.

The minimum performance requirements provided in [Table 3](#) and [Table 4](#), provided as a function of deployed valve diameter (in mm), shall be used as a frame of reference for assessing transcatheter heart valve substitute performance. The parameters in [Table 3](#) and [Table 4](#) assume a circular deployed valve diameter; however, anticipated variation in deployed shapes shall be evaluated (e.g. round, out-of-round). For deployed valve diameters outside the ranges listed in [Table 3](#) and [Table 4](#), justification of performance parameters shall be provided by the manufacturer. When assessing retrograde flow, the manufacturer shall evaluate both the transvalvular regurgitant volume and the combined transvalvular and paravalvular regurgitant volume independently for comparison against the corresponding values listed in [Table 3](#) and [Table 4](#). EOA and regurgitant fraction values that do not comply with those listed in [Table 3](#) and [Table 4](#) shall be justified by the manufacturer. At a minimum, the performance shall be characterized at the smallest and largest intended deployed diameters; the deployed valve diameter within the relevant region of the implant site may be smaller than the unconstrained valve diameter. The minimum performance requirements correspond to the following pulsatile flow conditions: beat rate = 70 cycles/min, simulated cardiac output = 5,0 l/min, mean aortic pressure = 100 mmHg, and systolic duration = 35 %. These pulsatile flow conditions are based on a healthy normal adult and might not be applicable for paediatric device evaluation (see [Annex H](#) for paediatric parameters). The minimum performance requirements are based on values in the published scientific literature^{[2][13][22]}.

Table 3 — Minimum device performance requirements, aortic

Parameter	Deployed valve diameter within implant site mm							
	17	19	21	23	25	27	29	31
A_{EO} (cm ²) greater than or equal to	0,70	0,85	1,05	1,25	1,45	1,70	1,95	2,25
Transvalvular regurgitant fraction (% of forward flow volume) less than or equal to	10	10	10	10	15	15	20	20
Total regurgitant fraction (% of forward flow volume) less than or equal to	15	15	20	20	20	20	25	25

Table 4 — Minimum device performance requirements, mitral

Parameter	Deployed valve diameter within implant site mm					
	23	25	27	29	31	33
A_{EO} (cm ²) greater than or equal to	1,05	1,25	1,45	1,65	1,90	2,15
Transvalvular regurgitant fraction (% of forward flow volume) less than or equal to	15	15	15	20	20	20
Total regurgitant fraction (% of forward flow volume) less than or equal to	20	20	20	25	25	25

The total regurgitant fraction shall include closing volume, transvalvular leakage volume and paravalvular leakage volume.

$$EOA = \frac{q_{v\text{RMS}}}{51,6 * \sqrt{\frac{\Delta p}{\rho}}}$$

where

EOA is the effective orifice area (cm²);

$q_{v\text{RMS}}$ is the root mean square forward flow (ml/s) during the positive differential pressure period;

Δp is the mean pressure difference (measured during the positive differential pressure period) (mmHg);

ρ is the density of the test fluid (g/cm³).

NOTE 1 This formula is derived from a simplified version of the Bernoulli Equation and as such has limitations. The constant (51,6) is not dimensionless, thus this equation is only valid with the units shown.

NOTE 2 Defining the time interval for flow and pressure measurement as the positive pressure period of the forward flow interval for EOA computation provides repeatable and consistent results for comparison to the [Table 3](#) and [Table 4](#) reference values. It is recognized that this approach may not equate to the EOA computation approaches employed clinically.

NOTE 3 RMS forward flow is calculated using the equation

$$q_{v\text{RMS}} = \sqrt{\frac{\int_{t_1}^{t_2} q_V(t)^2 dt}{t_2 - t_1}}$$

where

$q_{v\text{RMS}}$ is root mean square forward flow;

$q_V(t)$ is instantaneous flow at time t ;

t_1 is time at start of positive pressure;

t_2 is time at end of positive pressure.

NOTE 4 The rationale for use of $q_{v\text{RMS}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate, and it is the mean pressure difference that is required.

7.2.4 Structural performance assessment

An assessment of the ability of the implant 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.

7.2.4.1 Device durability assessment

An assessment of the durability of the valve shall be performed in order to assess continued function over a reasonable lifetime. Unless the labelling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to demonstrate reasonable assurance that transcatheter heart valve substitutes will remain functional for at least 200 million *in vitro* test cycles. For materials without established clinical history as a valve leaflet/occluder, testing durations of greater than 200 million cycles shall be considered, and scientifically justified if not performed. If the labelling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to support the labelling claim.

The requirements of [7.2.1.1](#) shall apply. One equivalent size reference valve shall be tested under identical hydrodynamic loading conditions for each valve size tested. Tests shall be performed at a defined differential pressure consistent with normotensive conditions specified in [Table 1](#) or [Table 2](#). See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population. During the durability testing, the defined target peak differential pressure across the closed valve shall be maintained for 95 % or more of all the test cycles. Each test valve shall experience a differential pressure equal to or greater than the defined differential pressure for 5 % or more of the duration of each cycle. Cycle rates used for durability testing shall be justified based on the valve design, anticipated failure modes, and the behaviour of time-dependent materials. Test valves shall experience the full range of leaflet/occluder motion associated with normotensive conditions (see [Table 1](#), [Table 2](#) and [Annex H](#)) during testing.

If transcatheter heart valve substitutes identical in design are intended for implant in multiple valve positions, testing shall include the differential pressure conditions defined for the worst case valve position. Consideration shall be given to variation in deployed valve shape (e.g. round, out-of-round) and intended operating temperature. In addition, test fixturing shall be designed to be representative of critical aspects of the target implant site (e.g. compliance, geometry).

The implant shall be deployed into the test fixturing using the loading and deployment steps in accordance with the IFU. Valves undergoing cycling in durability testers shall be observed at regular and frequent intervals (e.g. daily or weekly). Valves shall also be functionally evaluated at intervals of 50 million cycles or less for the duration of the test. A detailed description of the appearance of the heart valve and hydrodynamic performance shall be documented prior to testing, throughout the test at the established inspection intervals, and at the completion of test. The durability assessment shall be performed by characterization of the test valve in terms of the observed damage and the extent of damage and by imposing pass/fail criteria for identified damage. The durability test setup parameters shall be verified by use of an appropriate reference valve. The failure modes to be considered and the pass/fail criteria for the test shall be determined based upon the risk assessment.

Dynamic failure mode testing shall be conducted. Guidelines for durability testing, including dynamic failure mode evaluation, are provided in [Annex O](#).

7.2.4.2 Device structural component fatigue assessment

An assessment of the fatigue performance of the transcatheter heart valve substitute support structure shall be conducted; all components comprising the support structure, including anchoring features, shall be appropriately considered. Unless the labelling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to demonstrate reasonable assurance that the support structure will remain functional for a minimum of 400 million cycles for critical loading modes. If the labelling for a particular device includes an explicit statement about anticipated *in vivo* device lifetime, testing shall be performed to support the labelling claim. Failure criteria for fatigue testing shall be justified by the manufacturer based on the results of the risk assessment.

The manufacturer shall identify and justify the appropriate *in vivo* loading and environmental conditions used. Fatigue test and analysis shall, at a minimum, use conditions consistent with pressures associated with moderate hypertensive conditions listed in [Table 1](#) and [Table 2](#) and other relevant *in vivo* loading conditions. See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population. In addition, dynamic effects imparted by leaflet/occluder motion on resulting stress/strain magnitudes during valve closure shall be addressed.

Test specimens shall represent, as closely as possible, the finished product as supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, process chemicals, aging effects, and any catheter crimping, loading and deployment steps in accordance with manufacturing procedure and IFU. Consideration shall be given to anticipated variations in the deployed device shape. Devices shall be tested at the intended operating temperatures and environmental conditions. In addition, test fixtures shall be designed to be representative of critical aspects of the target implant site (e.g. compliance, geometry). The implant shall be deployed into the test fixtures using the loading and deployment steps in accordance with the IFU.

A validated stress/strain analysis of the structural components of the implant under simulated *in vivo* conditions shall be performed on all structural components. Loading from all valve components shall be considered. For example, where analysis is only required for the support structure, it might be necessary to include reaction loads associated with dynamic effects of leaflet/occluder closure in the analysis in order to simulate *in vivo* loading realistically. An appropriate validated constitutive model for each material shall be used in any stress analysis, including time-dependent, temperature-dependent and/or non-linear models.

Fatigue characterization and lifetime assessment of the structural components under simulated *in vivo* conditions shall be performed in order to evaluate risks associated with fatigue-related failure modes. The manufacturer shall determine and justify the fatigue assessment approach and associated characterization technique adopted in order to best determine the structural lifetime for the specific material and valve/component design. Suggested guidelines are provided in [Annex P](#) and [Annex L](#).

7.2.4.3 Component corrosion assessment

An assessment of the corrosion resistance of all constituent materials comprising the transcatheter heart valve substitute system shall be conducted. It is well established that metal corrosion potential can be sensitive to variations in manufacturing processes (e.g. heat treatment, chemical etching, electropolishing). Therefore, the corrosion resistance shall be characterized using the finished component. [Annex M](#) provides guidance on corrosion resistance characterization.

The manufacturer shall provide rationale for the selected test methods and justify that all corrosion mechanisms and conditions have been considered through testing or theoretical assessments.

7.2.5 Additional implant design evaluation requirements

The following implant design evaluation requirements shall apply as appropriate. Justification shall be provided for those requirements that are deemed not applicable to a particular design. Additional implant design evaluation requirements could 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.

7.2.5.1 Device migration resistance

The ability of the implantable device to remain in the target implant site under simulated operating conditions shall be assessed. Consideration shall be given to variation in deployed shape, deployed size, implant site characteristics (e.g. degree and distribution of calcification) and mechanical properties (e.g. compliance). The pressure conditions specified in [Table 1](#) and [Table 2](#), and other loading conditions, shall be considered as applicable. See [Annex H](#) for guidelines regarding suggested test conditions for the paediatric population. One suitable method to assess device migration resistance is to utilize a pulsatile test conducted by ramping up the pressure in a step-wise manner.

7.2.5.2 Device MRI safety

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI as per ASTM standards F2052, F2213, F2182, F2119, and F2503.

7.2.5.3 Implant foreshortening (length to diameter)

The manufacturer shall determine the relationship between implant length and expanded implant diameter. Depending on the design, the length of a device might change with deployed diameter. The specific implant length could affect implant function.

7.2.5.4 Crush resistance

The manufacturer shall determine the ability of the support structure to resist deformation due to crushing loads over a diameter range that spans the recommended range of deployed diameters per the IFU. This is accomplished by the following evaluations:

- the crush resistance test with a radially applied load measures the ability of the non-self-expanding support structure to resist permanent deformation when subjected to a circumferentially uniform radial load;
- the crush resistance test using parallel plates measures the ability of the support structure to resist permanent deformation along the entire length of the device when subjected to a load uniformly applied over the length of the device.

7.2.5.5 Recoil (balloon expandable stents)

Determine the amount of device diameter elastic recoil (percent of device diameter reduction) after the deployment of the implant. Correlate this recoil to recommended sizing.

7.2.5.6 Dimensional verification

Determine the appropriate dimensions for conformance with design specifications.

7.2.5.7 Radial resistive force

For self-expanding support structures, the manufacturer shall characterize the force exerted by the support structure as it resists radial compression from its maximum diameter to its minimum crimp diameter per the IFU. See nitinol-specific definitions in [Annex J](#).

7.2.5.8 Chronic outward force (COF)

For self-expanding support structures, the manufacturer shall characterize the force exerted by the support structure as it attempts to expand to its maximum unconstrained diameter after being radially compressed to its minimum crimp diameter as per the IFU. Depending on the support structure design, the COF might be different in different regions of the support structure and should be evaluated accordingly. See nitinol-specific definitions in [Annex J](#).

7.2.6 Delivery system design evaluation requirements

ISO 25539-1 and ISO 10555-1 were used as a basis for defining delivery system design evaluation requirements specified herein. Justification shall be provided for those requirements that are not applicable. The manufacturer shall define all applicable requirements based on the results of the risk assessment for the specific delivery system design and delivery approach (e.g. transfemoral, transapical).

7.2.6.1 Implant interactions with delivery system

The manufacturer shall evaluate interactions between the implant and delivery system during use in accordance with the IFU to ensure no damage is induced to the implant or delivery system. The following aspects shall be evaluated as applicable:

- crimping/loading and attachment of the device to the delivery system;
- loading device into the delivery sheath;
- positioning/deployment of the device within the target implant site;
- repositioning/recapturing of the device (if applicable) including damage to the valve if intended for immediate re-use;
- withdrawal of the delivery system from the patient;
- component dimensional compatibility with ancillary devices.

7.2.6.2 Loading of the device into the delivery system

The manufacturer shall define all specific performance parameters to be evaluated to verify safe and reliable loading of the device into the delivery system. The manufacturer shall demonstrate that the implantable device can be reliably attached to the delivery system in accordance with the IFU and satisfy attachment performance requirements, such as:

- attachment strength between the device and the delivery system;
- no damage to the device or the delivery system;
- crimped diameter;
- crimped shape (uniform or non-uniform);
- proper orientation of the device into the delivery system;
- dislodgement force;
- device sterility;
- device rinsing;
- delivery system flushing (de-airing);
- component dimensional compatibility with ancillary devices.

7.2.6.3 Ability to access and deploy

The manufacturer shall demonstrate that the attachment between the device and the delivery system shall be sufficient to permit safe, repeatable and reliable delivery of the device to the intended implant site, release of the device from the delivery system and safe removal of the delivery system from the patient in accordance with the IFU. The manufacturer shall define all specific performance parameters to be evaluated to verify safe and reliable deployment of the device within the intended implant site, such as:

- force to deploy;
- all relevant forces required to reposition the device (if applicable);
- flex/kink resistance;
- bond strength (tensile and torque);
- torquability;

- pushability;
- trackability;
- access angle between apex and annular plane for trans-apical delivery approach;
- haemostasis;
- time to deploy, including time of flow restriction or blockage, and time to restore flow;
- component dimensional compatibility with ancillary devices;
- balloon characteristics (if applicable);
- inflation/deflation time;
- relationship between the implant diameter and balloon inflation pressure, including assessment of effects associated with over-inflation and under-inflation;
- mean burst pressure;
- rated burst pressure;
- rated fatigue.

7.2.7 Design-specific testing

In order to assess failure modes identified by the risk assessment that may not be related to durability or component fatigue, design-specific testing may be necessary. In some cases, design-specific testing may have direct implications for the overall structural lifetime of a component or valve and additional tests may be required e.g. support structure creep, static pressure test, particulate generation, burst/circumferential strength, leaflet kinematics, retrievability of device, repositionability of device, effects of device post-dilatation.

7.2.8 Visibility

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

7.2.9 Simulated use

The ability to permit safe, consistent and accurate deployment of the transcatheter heart valve substitute within the intended implant site shall be evaluated using a model that simulates the intended use conditions. This assessment will include all elements of the transcatheter heart valve substitute system required to facilitate delivery and implantation of the implantable device. The model shall consider anatomical variation in intended patient population with respect to vasculature and intended implant site, temperature effects, pulsatile flow, etc. Justification for critical parameters of the simulated use model shall be provided. Potential hazards associated with inaccurate valve position and deployment and resulting effects on valve performance and unintended anatomical interactions (i.e. coronary occlusion, anterior mitral impingement) shall be documented within the risk assessment.

7.2.10 Human factors/usability assessment

In addition to conducting simulated use to evaluate the functionality of the transcatheter heart valve substitute, simulated use shall also be conducted as part of the required usability assessment (or "usability testing") as per IEC 62366. The main objective of the usability assessment is to validate that intended users of the device or system can use it safely and effectively to deliver and deploy the device in the patient. Usability assessment performance measurements shall be based on use error analysis results. The assessment shall primarily focus on whether or not the design attributes of the device or

system used to conduct the implant procedure appropriately mitigate identified potential use errors that can occur. It is recommended that usability assessment be conducted throughout the design cycle.

7.3 Preclinical *in vivo* evaluation

7.3.1 Overall requirements

A preclinical *in vivo* test programme shall be conducted in order to address transcatheter heart valve substitute system delivery, deployment and imaging characteristics and transcatheter heart valve substitute safety and performance. The preclinical programme design should 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. The use of alternative implantation sites (e.g. chronic pulmonary valve replacement rather than aortic valve replacement), alternative implantation techniques (e.g. transapical delivery, surgical) and acute as well as chronic studies might be justified to accommodate specific transcatheter heart valve substitute design features and species-specific anatomic differences. Due to anatomic species differences and use of non-diseased animal models, in some cases more reliance on *in vitro* testing might be necessary to assess the potential for migration, embolization and the effect of heart valve substitute post-implantation changes in shape on haemodynamic performance.

The preclinical *in vivo* evaluation shall:

- a) evaluate the extent to which the haemodynamic performance of the transcatheter heart valve substitute reflects the intended clinical use;
- b) assess delivery deployment, implantation procedure and imaging characteristics of the transcatheter heart valve system. Consideration should be given, but not limited, to the following items:
 - 1) ease of use;
 - 2) delivery system handling characteristics (e.g. pushability, trackability);
 - 3) proper valve alignment relative to flow (e.g. note the presence of device angulation, bends, kinks);
 - 4) post-implantation changes in shape and structural components of the transcatheter heart valve;
 - 5) imaging characteristics;
 - 6) migration or embolization of the heart valve substitute;
 - 7) ability to recapture and re-deploy the heart valve substitute, if applicable;
- c) assess the *in vivo* response to the heart valve substitute. Consideration should be given, but not limited, to the following items:
 - 1) healing characteristics (e.g. pannus formation, tissue overgrowth);
 - 2) effect of post-implantation changes in shape and structural components on haemodynamic performance;
 - 3) haemolysis;
 - 4) thrombus formation;
 - 5) embolization of material from the implant site, delivery device or heart valve substitute;
 - 6) migration or embolization of the heart valve substitute;
 - 7) proper alignment relative to flow (note the presence of angulations, bends, kinks);
 - 8) biological response (e.g. inflammation, rejection);

- 9) calcification;
- 10) structural and non-structural dysfunction;
- d) use the final clinical design and condition of the transcatheter heart valve substitute system. The system shall be prepared, deployed and imaged using the same procedures (e.g. preparation of the device for delivery and deployment) as intended for clinical use. Consideration shall also be given to effects of maximum allowable conditioning steps (e.g. maximum sterilization cycles, maximum crimp time, maximum crimp cycles);
 - 1) if needed, ancillary short-term studies could be conducted to evaluate unique design and delivery aspects of the device;
 - 2) the manufacturer shall justify any modifications to the device or system that may be required for implantation in the animal model;
- e) investigate transcatheter heart valve substitute system in positions for which it is intended (e.g. aortic, mitral, pulmonic); if species-specific anatomic features or the use of a non-diseased animal model confound the ability to evaluate the transcatheter heart valve substitute in positions for which it is intended, provide a justification for implantation in an alternative site or the use of alternative implantation procedures;
- f) subject comparably sized reference heart valve substitutes to identical anatomic and physiological conditions as the test device;
- g) be performed by appropriately experienced and knowledgeable test laboratories;
- h) address animal welfare in accordance with the principles provided 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 is provided in [Annex Q](#). The intent of these studies is to mimic as closely as possible the clinical use and haemodynamic performance of the transcatheter heart valve system (delivery, deployment, imaging and test 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, serious adverse events arising during or after valve implantation shall be carefully analysed and interpreted in order to identify the cause of the adverse event.

The investigator should seek to control as many variables as possible within each study arm (e.g. species, gender and age). Animals suffering from periprocedural complications (e.g. endocarditis) may be excluded from the group of study animals, but they shall be reported.

The number of animals used for implantation of test and reference heart valve substitutes shall be justified for each test based on risk assessment.

For long-term studies, the specified duration of the observation period of the animals shall be justified according to the parameter(s) under investigation. The observation period shall be appropriately justified in each study protocol, but will not be less than 90 days.

A macroscopic, radiographic and histological post-mortem examination shall be performed, focusing on device integrity and delivery system/device related pathology. The report shall include this information from all animals that have been entered into the study.

The assessment shall provide at least the following:

- a) any detectable pathological consequences, including but not limited to: migration or embolization; valve alignment relative to flow noting the presence of angulations, bends or kinks; post-implantation changes in shape of structural components; thrombo-embolic phenomena; pannus formation; and inflammatory responses involving the transcatheter heart valve substitute and/or in the major organs;

- b) any macro- or microscopic or radiographic detectable structural alterations in the transcatheter heart valve substitute and macroscopic examination of the delivery system, (e.g. damage, 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 haematology and clinical chemistry parameters;
- d) delivery and deployment characteristics, including but not limited to ease of use, handling characteristics, imaging, sizing technique, retrieval and redeployment;
- e) haemodynamic performance over a range of cardiac outputs (e.g. 2,5 to 6 l/min) in the same animal;
- f) serious adverse events (e.g. myocardial infarction, significant cardiac arrhythmias, embolization); refer to ISO 14155 for serious adverse events definitions;
- g) any other system or procedure-related complication or events.

7.3.3 Test report

The laboratory performing the preclinical *in vivo* study shall produce the test report, which shall include a description of the risk evaluation, the complete original study protocol, all data generated from the preclinical *in vivo* evaluation, and a summary of the data generated during the course of the investigation, addressing the results, including serious adverse events, deviations from the protocol and their significance, generated by evaluations described in [Annex Q](#).

The test report shall include:

- a) identification of each of the system components (delivery system, transcatheter heart valve substitute and other auxiliary devices) used in the procedure (product description, serial number and other appropriate identification);
- b) detailed description of the animal model used, the rationale and justification for its use. The pre-procedural assessment of each animal shall include documentation of health status as well as gender, weight and age of the animal;
- c) description of the imaging technique(s), the implantation procedure, including delivery, deployment and sizing technique, valve position and any procedural difficulties;
- d) description of the pre-procedural and post-procedural clinical course of each animal including clinical observations, medication(s) and interventions used to treat serious adverse events. Describe anticoagulation or antiplatelet drug and regimen used as well as therapeutic level monitoring methods;
- e) any deviations from the protocol or amendments to the protocol and their significance;
- f) names of the investigators and their institutions along with information about the implanting personnel and the laboratory's experience with heart valve substitute implantation and animal care;
- g) interpretation of data and a recommendation relative to the clinical safety and performance of the transcatheter heart valve substitute system under investigation;
- h) the study pathologist's report that includes gross and radiographic examination and histopathology findings for each explanted heart valve substitute;
- i) detailed full necropsy reports for each animal enrolled in the study that includes an assessment of the entire body or such findings as thromboembolism or any other adverse effects putatively from the heart valve substitute;

Further details of the test report depend on the defined test protocol.

7.4 Clinical investigations

7.4.1 General

Clinical investigations shall be performed for new or modified transcatheter heart valve systems to investigate those risks and aspects of clinical performance that cannot be fully evaluated from pre-clinical or other available data. Clinical investigations shall be carried out in accordance with this part of ISO 5840 and ISO 14155. If a determination is made that clinical investigations are not required, justification shall be documented in the risk management file.

Clinical studies shall be designed to fully evaluate the transcatheter heart valve system in its intended uses. The studies shall include an assessment of adverse events related to risks arising from the use of the transcatheter heart valve system and from the procedure. The clinical investigation shall include pre-procedure, peri-procedure, and follow-up data from a specified number of patients, each with a follow-up appropriate for the device and its intended use. The clinical data shall provide substantial evidence of acceptable performance and safety (i.e. freedom from unacceptable risk).

The study protocols should specify primary and secondary end points as well as specific study related adverse events with consideration of [Annex R](#) and published definitions. The definitions of the outcome measures should be consistent with those employed in previous studies of heart valves, when appropriate. The study protocol shall include a data analysis plan and success criteria.

The manufacturer is responsible for ensuring collection of appropriate information. The design shall be consistent with the aims of the protocol. For a given study, data collection forms should be the same for each institution and investigator. The protocol shall ensure consistency between the study aims and the inclusion/exclusion criteria.

Studies should employ measures to minimize bias. The use of an independent clinical events adjudication committee to classify events against pre-established criteria, and core laboratories are recommended for outcome variables that might be prone to inter-observer variability.

To ensure patient safety, a safety monitoring plan shall be established. Study oversight may be provided by a data safety monitoring committee.

Study designs may vary depending on the purposes of the assessment (randomized/contemporaneously controlled superiority or non-inferiority, observational/registry, etc.), and the intended duration of implantation (e.g. bridge to next planned valve reoperation versus permanent implant). To the extent feasible, study populations shall be representative of the intended post-market patient population. If registries are a part of the study design, the registries shall be constructed to include consecutive series of patients. Further, studies shall be designed to ensure ascertainment of protocol specified follow-up information for a relevant duration in all patients entered into the study unless patients specifically withdraw consent for follow-up. In this case, follow-up in these patients will end at the time of the withdrawal, except that, depending on local legal requirement relevant to patient privacy, survival may still be followed.

7.4.2 Statistical considerations

The size, scope and design of the clinical trial shall be based on (i) the intended use of the device, (ii) the results of the risk analysis, (iii) measures that will be evaluated, and (iv) the expected clinical outcomes. The basis for the sample size shall be documented. The manufacturer is responsible for proposing and justifying the specific statistical methodology used. The methods may come from either a frequentist or Bayesian framework. If a Bayesian design is used, the prior information incorporated in the model should be prespecified. Designs may use fixed sample size or pre-specified adaptive methodology.

Prior to embarking on a large clinical trial, a feasibility study may be considered when the risks or clinical performance of the new device are not well understood.

A randomized controlled study, assessing superiority or non-inferiority as appropriate, should be considered to minimize bias when existing objective performance and safety metrics are inadequate.