INTERNATIONAL STANDARD

ISO 5840-1

Second edition
2021-01

Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

Implants cardiovasculaires — Prothèses valvulaires —

Partie 1: Exigences générales

Reference number
ISO 5840-1:2021(E)

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Published in Switzerland

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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

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

This second edition cancels and replaces the first edition (ISO 5840-1:2015), which has been technically revised.

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

There is, as yet, no heart valve substitute which can be regarded as ideal.

The ISO 5840 series has been prepared by a group well aware of the issues associated with heart valve substitutes and their development. In several areas, the provisions of the ISO 5840 series deliberately have not been specified to encourage development and innovation. It does specify the types of tests, provides guidance for test methods and test apparatuses and requires documentation of test methods and results. The areas with which the ISO 5840 series are concerned are those which ensure that associated risks to the patient and other users of the device have been adequately mitigated, facilitate quality assurance, aid the clinician in choosing a heart valve substitute, and ensure that the device is presented in a convenient form. Emphasis has been placed on specifying types of *in vitro* testing, preclinical *in vivo* and clinical evaluations, reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations, and the labelling 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, the ISO 5840 series also covers important hydrodynamic and durability characteristics of heart valve substitutes and systems required for their implantation. The ISO 5840 series does not specify exact test methods for hydrodynamic and durability testing, but it offers guidelines for the test apparatus.

The ISO 5840 series is intended to be revised, updated, and/or amended as knowledge and techniques in heart valve substitute technology improve.

This document is used in conjunction with ISO 5840-2 and ISO 5840-3.

Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

1 Scope

This document is applicable to heart valve substitutes intended for implantation and provides general requirements. Subsequent parts of the ISO 5840 series provide specific requirements.

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

ISO 5840-1 outlines an approach for verifying/validating the design and manufacture of a 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 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.

ISO 5840-1 defines operational conditions for heart valve substitutes.

ISO 5840-1 furthermore defines terms that are also applicable to ISO 5840-2 and ISO 5840-3.

ISO 5840-1 does not provide requirements specific to homografts, tissue engineered heart valves (e.g. valves intended to regenerate *in vivo*), and heart valve substitutes designed for implantation in circulatory support devices. Some of the provisions of ISO 5840-1 can be applied to valves made from human tissue that is rendered non-viable.

NOTE A rationale for the provisions of ISO 5840-1 is given in Annex A.

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 5840-2, *Cardiovascular implants — Cardiac valve prostheses —Part 2: Surgically implanted heart valve substitutes*

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

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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

ISO 11137 (all parts), *Sterilization of health care products — Radiation*

ISO 11607 (all parts), *Packaging for terminally sterilized medical devices*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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, *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 15223-1, *Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

ISO 22442 (all parts), *Medical devices utilizing animal tissues and their derivatives*

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

3 Terms and definitions

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

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

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

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

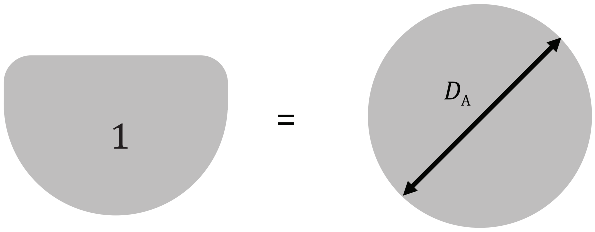
3.1
accessory
device-specific tool that is required to assist in the implantation of the *heart valve substitute* (3.30)

3.2
adverse event
AE
untoward medical occurrence in a study subject which does not necessarily 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 *heart valve substitute* (3.30) or implantation procedure.

3.3
area-derived valve diameter
D_A
calculated valve diameter based on area (A) of the device [i.e. a “D-Shaped” transcatheter mitral valve implantation (TMVI) device; refer to Figure 1]: $D_A = \sqrt{4A/\pi}$

Note 1 to entry: This approach is typically used for labelling the sizes of TMVI devices where valves are designed for a noncircular geometry.



Key

1 area of valve

$D_A = \sqrt{4A/\pi}$

D_A = area-derived diameter

Figure 1 — Area-derived valve diameter for a non-circular device

3.4
arterial end diastolic pressure
minimum value of the arterial pressure during diastole

3.5
arterial peak systolic pressure
maximum value of the arterial pressure during *systole* (3.68)

3.6
back pressure
differential pressure across the valve during the closed phase

3.7
body surface area
BSA
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 the product of the weight in kg and the height in cm divided by 3 600 (see Reference [26]).

3.8
cardiac output
CO
stroke volume (3.64) times heart rate

3.9
closing volume
portion of the *regurgitant volume* (3.49) that is associated with the dynamics of valve closure during a single *cycle* (3.13)

Note 1 to entry: See Figure 2.

Note 2 to entry: The volume of flow occurring between *end of systole* (3.23) and *start of leakage* (3.59) for aortic and pulmonary positions; between *end of diastole* (3.21) and start of leakage for mitral and tricuspid positions.

3.10
coating
thin-film material that is applied to an element of a *heart valve system* (3.31) to modify its surface physical or chemical properties

3.11
compliance
relationship between change in diameter and change in pressure of a deformable tubular structure (e.g. aorta, conduit) defined in ISO 5840 (all parts) as

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

where

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

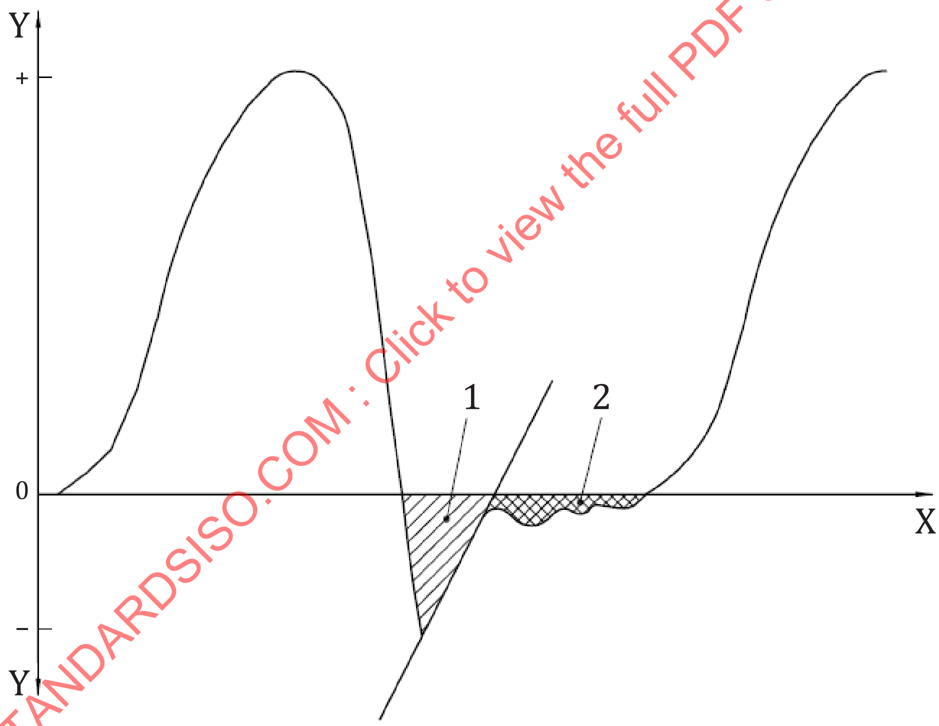
p_1 is the diastolic pressure, in mmHg;

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.



Key

X time

Y flowrate

1 closing volume

2 leakage volume

NOTE The total regurgitant volume is the sum of the closing volume and the leakage volume.

Figure 2 — Schematic representation of flow waveform, regurgitant volumes, and end of closure determination for one cycle

3.12
control valve
heart valve substitute for preclinical and clinical evaluations of similar design and constructed of similar material as the investigational device

Note 1 to entry: The control valve should have a known clinical history.

3.13
cycle
complete sequence in the action of a *heart valve substitute* (3.30) under pulsatile-flow conditions

3.14
cycle rate
beat rate
number of complete *cycles* (3.13) per unit of time usually expressed as cycles per minute (cycles/min or beats/min [bpm])

3.15
design verification
establishment by objective evidence that the design output meets the design input requirements

3.16
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.33)

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

3.19
diastole
diastolic duration
portion of cardiac cycle time corresponding to ventricular filling

Note 1 to entry: Refer to Figure 3 and Figure 4.

3.20
effective orifice area
EOA
orifice area that has been derived from flow and pressure or velocity data

Note 1 to entry: For *in vitro* testing, EOA is defined as:

$$A_{eo} = \frac{q_{V_{RMS}}}{51{,}6 \times \sqrt{\frac{\Delta p}{\rho}}}$$

where

A_{eo} is the effective orifice area (cm^2);

$q_{V_{RMS}}$ is the *root mean square forward flow* (3.54) (ml/s) during the *positive differential pressure period* (3.44);

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

ρ is the density of the test fluid (g/cm^3).

3.21
end of diastole
ED
end of forward flow (zero crossing of flow to negative) for mitral and tricuspid positions

Note 1 to entry: ED corresponds to the start of valve closure (SC) for the mitral and tricuspid positions. Refer to Figure 3 and Figure 4.

3.22
end of positive differential pressure
EPDP
second crossing of aortic and left ventricular pressure waveforms for aortic position; second crossing of pulmonary and right ventricular pressure waveforms for pulmonary position; second crossing of atrial and ventricular pressure waveforms for mitral and tricuspid position

Note 1 to entry: Refer to Figure 3 and Figure 4.

3.23
end of systole
ES
end of forward flow (zero crossing of flow to negative) for aortic and pulmonary positions

Note 1 to entry: ES corresponds to the start of valve closure (SC) for the aortic and pulmonary positions. Refer to Figures 3 a) and 4 a).

3.24
end of closure
EC
point in the cardiac cycle at which the valve is fully closed

Note 1 to entry: EC corresponds to the first zero crossing of the flow waveform from negative to positive flow.

Note 2 to entry: If there is no zero crossing from negative to positive flow, EC can be defined from a linear extrapolation of the maximum slope of the flow to the zero line (refer to Figure 2).

Note 3 to entry: Refer to Figure 3 and Figure 4.

3.25
failure mode
mechanism of *device failure* (3.18)

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

3.26
flexible valve
heart valve substitute (3.30) wherein the *occluder* (3.42) is flexible under physiological conditions (e.g. bioprostheses)

Note 1 to entry: The orifice ring might or might not be flexible.

3.27
follow-up
continued assessment of patients who have received the *heart valve substitute* (3.30)

3.28
forward flow volume
volume of flow ejected through the *heart valve substitute* (3.30) between start of systole (3.61) and end of systole (3.23) for aortic and pulmonary positions; between start of diastole (3.58) and end of diastole (3.21) for mitral and tricuspid positions

3.29
fracture
complete separation of any structural component of the *heart valve substitute* (3.30) that was previously intact

3.30
heart valve substitute
device used to replace the function of a native valve of the heart

3.31
heart valve system
set of elements provided to replace the native heart valve, consisting of the heart valve substitute, *accessories* (3.1), packaging, labelling, and instructions

3.32
implant site
implant position
intended location of *heart valve substitute* (3.30) implantation or deployment

3.33
intended use
use of a product or process in accordance with the specifications, instructions, and information provided by the manufacturer

3.34
Kaplan-Meier method
statistical approach for calculating event rates over time when the actual dates of events for each person in the population are known

3.35
leakage volume
portion of the *regurgitant volume* (3.49) which is associated with leakage during the closed phase of a valve in a single *cycle* (3.13) and is the sum of the *transvalvular leakage volume* (3.71) and *paravalvular leakage volume* (3.45)

Note 1 to entry: Leakage volume is the volume of flow occurring between *end of closure* (3.24) and *start of systole* (3.61) for aortic and pulmonary positions; between end of closure and *start of diastole* (3.58) for mitral and tricuspid positions.

3.36
linearized rate
total number of events divided by the total time under evaluation

Note 1 to entry: Generally, the rate is expressed in terms of percent per patient year.

3.37
major bleeding
episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion

3.38
major paravalvular leak
paravalvular leakage leading to or causing any of the following: death or reintervention; heart failure requiring additional medication; moderate or severe regurgitation; or haemolytic anaemia

3.39
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one *cycle* (3.13)

3.40
mean pressure difference
mean pressure gradient
time-averaged arithmetic mean value of the pressure difference across a *heart valve substitute* (3.30) during the positive differential pressure period of the *cycle* (3.13)

3.41
non-structural valve dysfunction
abnormality extrinsic to the *heart valve substitute* (3.30) that results in stenosis, regurgitation, and/or haemolytic anaemia

Note 1 to entry: Examples include entrapment by pannus, tissue or suture; paravalvular leak; inappropriate sizing or positioning, residual leak or obstruction after implantation and clinically important haemolytic anaemia. This definition excludes infection or thrombosis of the heart valve substitute and intrinsic factors, which cause structural valve deterioration (3.65). See Reference [14].

3.42
occluder
leaflet
component that inhibits backflow

3.43
pannus
ingrowth of tissue onto or around the *heart valve substitute* (3.30) which can interfere with normal functioning

3.44
positive differential pressure period
time period between start of positive differential pressure and end of positive differential pressure

3.45
paravalvular leakage volume
portion of the *leakage volume* (3.35) that is associated with leakage around the closed heart valve substitute during a single *cycle* (3.13)

3.46
prosthetic endocarditis
infection involving a *heart valve substitute* (3.30)

Note 1 to entry: See Reference [23].

3.47
reference valve
heart valve substitute (3.30) with an established clinical experience used for comparative *in vitro* evaluations

Note 1 to entry: The reference valve should approximate the test heart valve substitute in type (if available), configuration, and size; it may be an earlier model of the same valve, if it fulfils the necessary conditions. The characteristics of the reference valve should be well documented with clinical data.

3.48
regurgitant fraction
regurgitant volume (3.49) expressed as a percentage of the *forward flow volume* (3.28)

3.49
regurgitant volume
volume of fluid that flows through a *heart valve substitute* (3.30) in the reverse direction during one *cycle* (3.13) and is the sum of the *closing volume* (3.9) and the *leakage volume* (3.35)

Note 1 to entry: Clinically, it might only be possible to measure the leakage volume and might not include the closing volume.

Note 2 to entry: See Figure 2.

3.50
rigid valve
rigid heart valve substitute
heart valve substitute (3.30) wherein the *occluder(s)* (3.42) and orifice ring are non-flexible under physiological conditions (e.g. mechanical heart valves)

3.51
risk
combination of the probability of occurrence of harm and the *severity* (3.56) of that harm

[SOURCE: ISO 14971:2019, 3.18]

3.52
risk analysis
systematic use of available information to identify hazards and to estimate the associated *risks* (3.51)

[SOURCE: ISO 14971:2019, 3.19, modified — the word "associated" was added.]

3.53
risk assessment
overall process comprising a *risk analysis* (3.52) and a risk evaluation

[SOURCE: ISO 14971:2019, 3.20]

3.54
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 the EOA

Note 1 to entry: 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 minimum device performance requirements.

Note 2 to entry: This is calculated using the following formula:

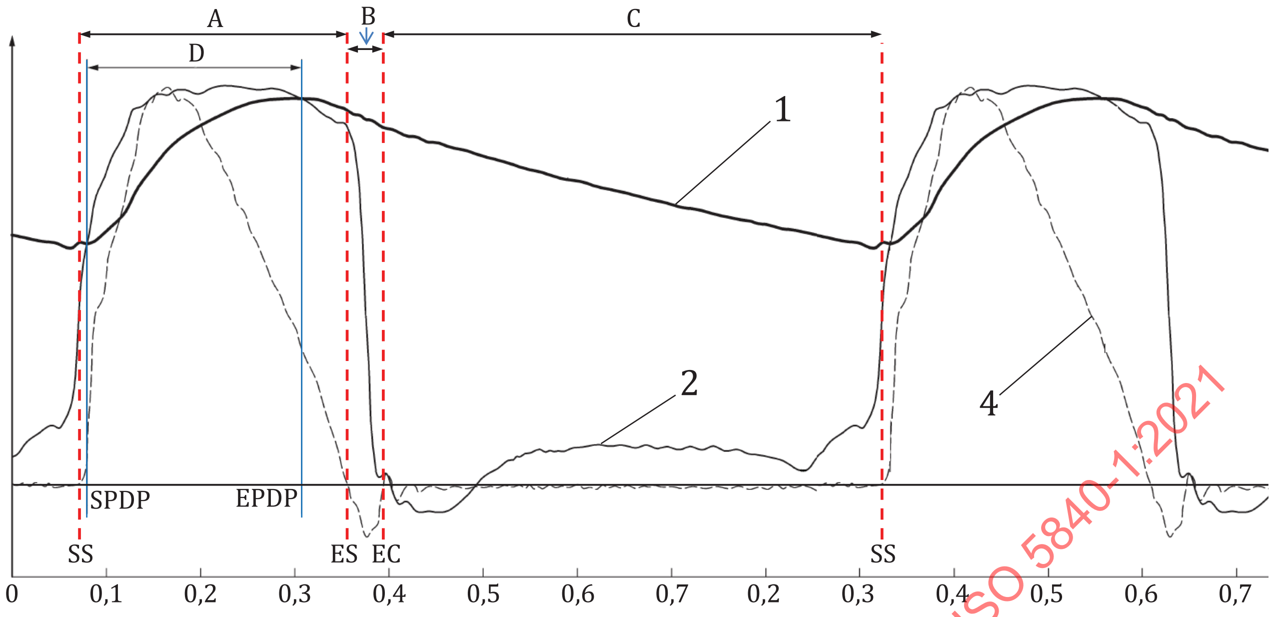
$$q_{v_{\mathrm{RMS}}} = \sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 \, \mathrm{d}t}{t_2 - t_1}}$$

where

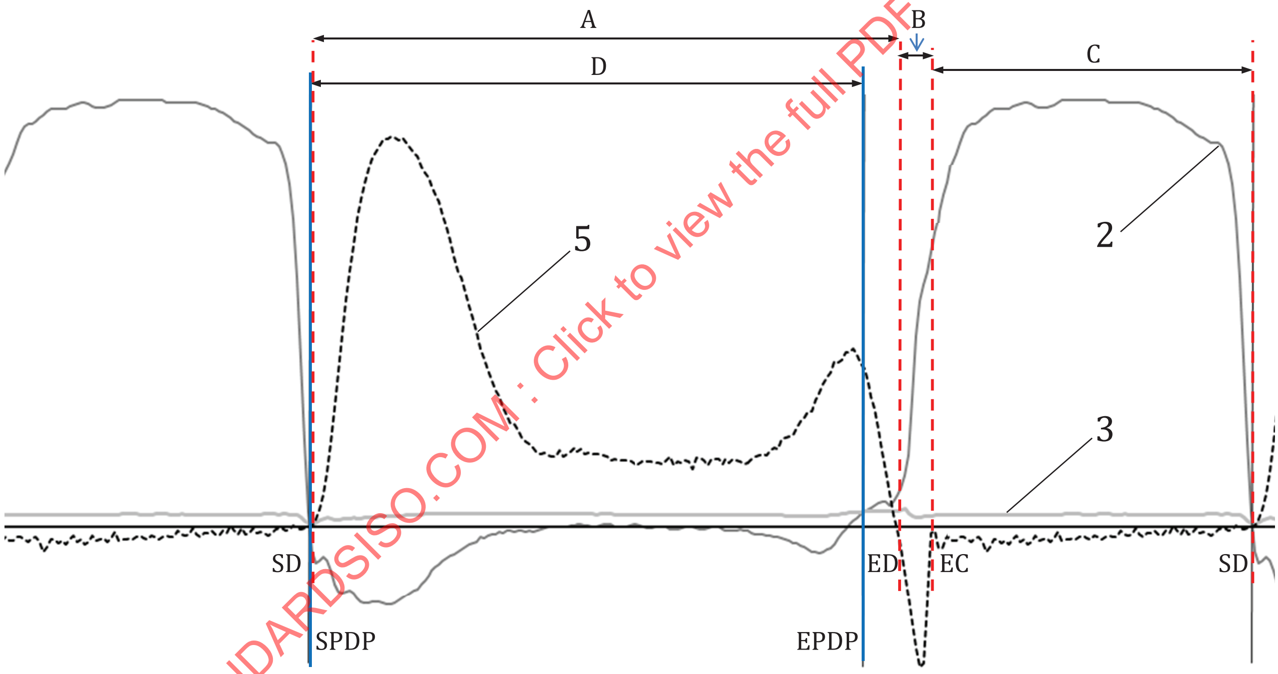
$q_{v_{\mathrm{RMS}}}$	is the root mean square forward flow during the positive differential pressure period;
$q_V(t)$	is the instantaneous flow at time (t);
t_1	is the time at the start of the *positive differential pressure period* (3.44);
t_2	is the time at the end of the positive differential pressure period.

Note 3 to entry: The rationale for use of $q_{v_{\mathrm{RMS}}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate and it is the *mean pressure difference* (3.43) that is required.

Note 4 to entry: See Figure 3 for representative aortic and mitral flow and pressure waveforms from *in vitro* testing. See Figure 4 for representative pulmonary and tricuspid flow and pressure waveforms from *in vitro* testing.



a) Aortic valve



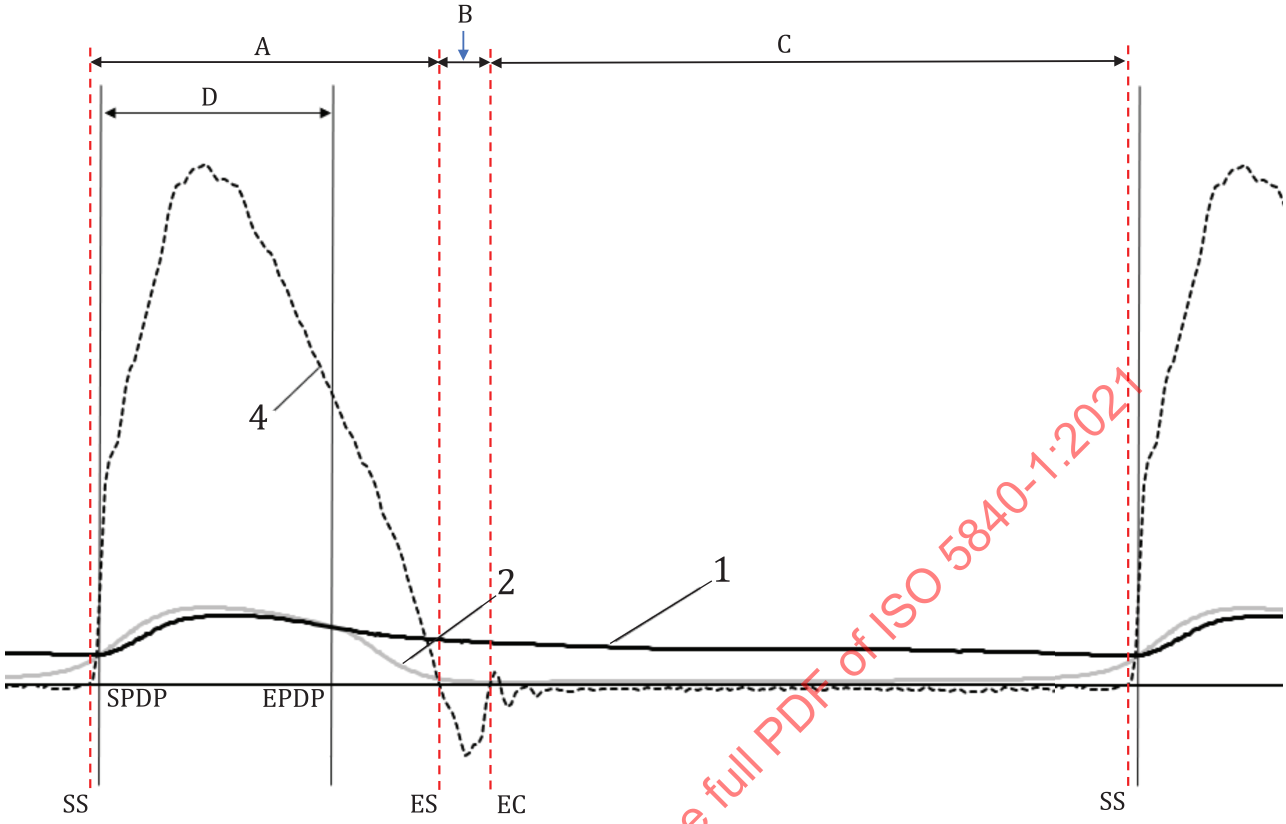
b) Mitral valve

Key

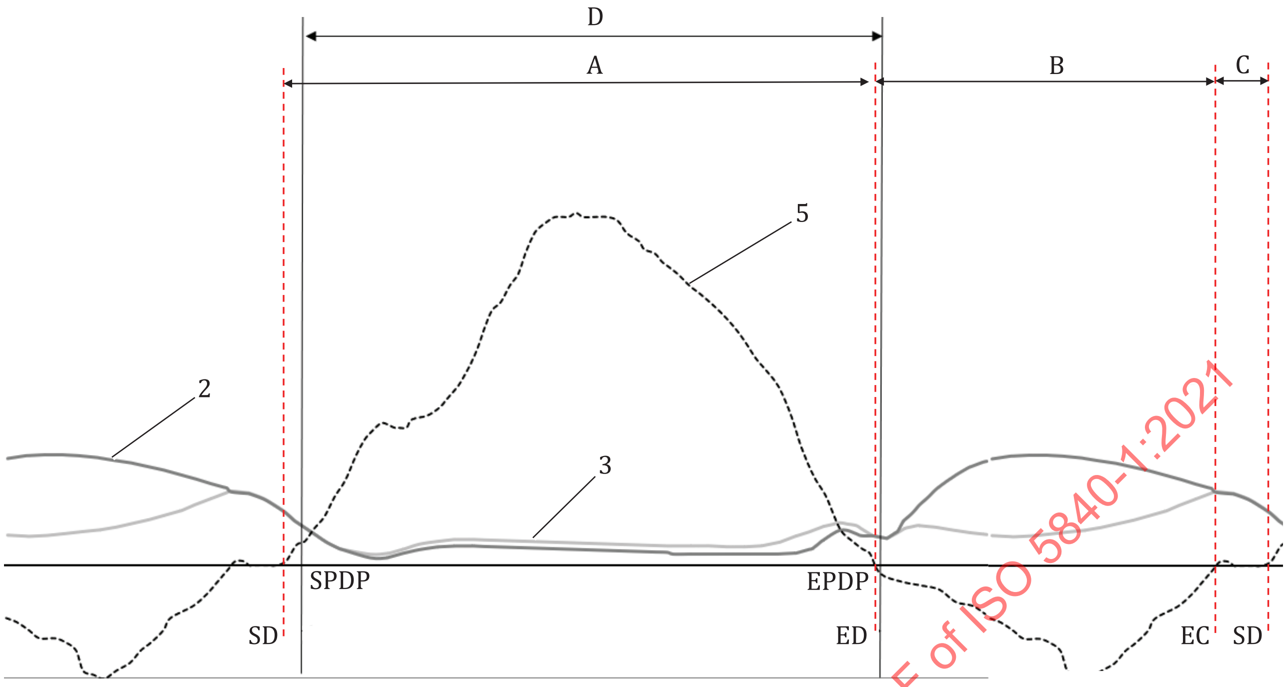
1	aortic pressure	A	forward flow period
2	left ventricular pressure	B	closing flow period
3	left atrial pressure	C	leakage flow period
4	aortic flow rate	D	positive pressure differential period
5	mitral flow rate		

NOTE Dashed vertical lines relate to the flow trace. Solid vertical lines relate to the pressure traces.

Figure 3 — Schematic representation of aortic and mitral flow and pressure waveforms versus time from *in vitro* testing



a) Pulmonary valve



b) Tricuspid valve

Key

1 pulmonary pressure
2 right ventricular pressure
3 right atrial pressure
4 pulmonary flow rate
5 tricuspid flow rate

A forward flow period
B closing flow period
C leakage flow period
D positive pressure differential period

NOTE Dashed vertical lines relate to the flow trace. Solid vertical lines relate to the pressure traces.

Figure 4 — Schematic representation of pulmonary and tricuspid flow and pressure waveforms versus time from *in vitro* testing

3.55
safety
freedom from an unacceptable risk

[SOURCE: ISO 14971:2019, 3.26]

3.56
severity
measure of the possible consequences of a hazard

[SOURCE: ISO 14971:2019, 3.27]

3.57
simulated cardiac output
forward flow volume (3.28) times the heart rate

Note 1 to entry: For *in vitro* testing, simulated *cardiac output* (3.8) rather than cardiac output is used:

$$o_{sc} = v_{ff} \times r_b$$

Note 2 to entry: where

o_{sc} is the simulated cardiac output;

v_{ff} is the forward flow volume;

r_b is the beat rate.

3.58
start of diastole
SD
beginning of the forward flow (zero crossing of flow to positive) for mitral and tricuspid positions

Note 1 to entry: Refer to Figure 3 and Figure 4.

3.59
start of leakage
SL
end of closure

Note 1 to entry: Refer to Figure 3 and Figure 4.

3.60
start of positive differential pressure
SPDP
first point in the cardiac cycle at which the pressure on the inflow side of the valve exceeds the pressure on the outflow side

Note 1 to entry: SPDP can be determined as the first crossing of the aortic and left ventricular pressure waveforms for the aortic valve position; the first crossing of the pulmonary and right ventricular pressure waveforms for the pulmonary valve position; or the first crossing of the atrial and ventricular pressure waveforms for the mitral and tricuspid positions. Refer to Figure 3 and Figure 4.

3.61
start of systole
SS
beginning of the forward flow (zero crossing of flow to positive) for aortic and pulmonary positions

Note 1 to entry: Refer to Figure 3 and Figure 4.

3.62
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after *sterilization* (3.63)

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275]

3.63
sterilization
validated process used to render a product free from viable microorganisms

Note 1 to entry: In a sterilization process, the rate of microbial inactivation is exponential and thus, the survival of a microorganism on an individual item can be expressed in terms of probability (3.63). While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: See 3.62.

[SOURCE: ISO 11139:2018, 3.277, modified — the word "nature" was changed to "rate" and Note 2 to entry was added.]

3.64
stroke volume
SV
volume of blood pumped by a ventricle in one systolic contraction

3.65
structural valve deterioration
SVD
change in the function of a *heart valve substitute* (3.30) resulting from an intrinsic abnormality that causes stenosis or regurgitation

Note 1 to entry: This definition includes intrinsic changes such as wear, fatigue failure, stress fracture, occluder escape, suture line disruption of components of the prosthesis, calcification, cavitation erosion, leaflet tear, leaflet abrasion, stent creep, and fabric tear. It excludes extrinsic changes, which cause non-structural valve dysfunction (3.41).

3.66
support structure
structural components (e.g. stent, frame, housing) of a *heart valve substitute* (3.30) that houses the occluder(s) (3.42) and supports valve loading

Note 1 to entry: For a transcatheter valve or a sutureless surgical valve, the support structure may also anchor the valve within the implant site.

3.67
surgical heart valve substitute
heart valve substitute (3.30) generally requiring direct visualization and cardiopulmonary bypass for implantation

3.68
systolic duration
systole
portion of a cardiac cycle time corresponding to ventricular contraction

Note 1 to entry: See Figure 3 and Figure 4 for *in vitro* definition.

3.69
thromboembolism
embolic event involving a clot(s) that occurs in the absence of infection

Note 1 to entry: Thromboembolism might be manifested by a neurological event or an embolic event to another organ or limb (e.g. ocular, coronary, mesenteric, femoral).

3.70
transcatheter heart valve substitute
heart valve substitute (3.30) delivered through a catheter and implanted in a manner generally not involving direct visualization and generally involving a beating heart

3.71
transvalvular leakage volume
component of the *leakage volume* (3.35) that is associated with leakage through the closed valve during a single *cycle* (3.13)

3.72
usability
characteristic of the user interface that facilitates use and thereby establishes effectiveness, efficiency, and user satisfaction in the intended use environment

[SOURCE: IEC 62366-1:2015, 3.16, modified — Note 1 to entry has been deleted.]

3.73
valve thrombosis
thrombus, not caused by infection, attached to or adjacent to the heart valve substitute

4 Abbreviations

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

AP	anterio-posterior
AWT	accelerated wear testing
BSA	body surface area
CT	computed tomography
DPIV	digital particle image velocimetry
ECG	electrocardiogram
EOA	effective orifice area
FEA	finite element analysis
IEC	international electrotechnical commission
IFU	instructions for use
LDV	laser Doppler velocimetry
LV	left ventricle, left ventricular
LVOT	left ventricular outflow tract
MAP	mean arterial pressure
MRI	magnetic resonance imaging
RV	right ventricle, right ventricular
SC	start of valve closure
TAVI	transcatheter aortic valve implantation [also known as transcatheter aortic valve replacement (TAVR)]
TEE	transoesophageal echocardiography (also known as TOE)
TMVI	transcatheter mitral valve implantation [also known as transcatheter mitral valve replacement (TMVR)]
TTE	transthoracic echocardiography
ViV	valve-in-valve
ViR	valve-in-ring

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 General

The requirements of ISO 14630 shall apply.

6.2 Intended use

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

6.3 Design inputs

6.3.1 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 are 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 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			
Forward flow volume	25 ml to 100 ml			
Blood pressures and resultant pressure loads by patient condition	Arterial peak systolic pressure	Arterial end diastolic pressure	Peak differential pressure across closed valve[a]	
			Aortic ΔP_A	Mitral ΔP_M
	mmHg	mmHg	mmHg	mmHg
Normotensive	90 to 140	60 to 90	80 to 115	90 to 140
Hypotensive	<90	<60	<80	<90
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 estimated clinically using the following relationship:

— $\Delta P_A \approx$ pressure associated with dicrotic notch assuming LV pressure is zero ≈ 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 28	18 to 35
Hypotensive	<18	<8	<13	<18
Hypertensive				
Mild	35 to 49	15 to 19	28 to 34	35 to 49
Moderate	50 to 59	20 to 24	35 to 42	50 to 59
Severe	60 to 84	25 to 34	43 to 59	60 to 84
Very severe	≥85	≥35	≥60	≥85

[a] Peak differential pressure across closed pulmonic valve estimated clinically using the following relationship:

— ΔP_P approximately 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.

6.3.2 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 specific performance specifications are provided in ISO 5840-2 and ISO 5840-3.

6.3.3 Implant procedure

The heart valve system shall provide intended users 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 device specific tools and accessories that intended users 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 (all parts).

6.3.4 Packaging, labelling, and sterilization

The heart valve system shall meet the requirements for packaging, labelling, and sterilization contained within Annex B, Annex C, and Annex D, respectively.

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

6.4 Design outputs

The manufacturer shall establish (i.e. define, document, and implement) a complete specification of the heart valve system including component and assembly-level specifications, delivery system (if applicable), accessories, packaging, and labelling. In addition to the physical components of the heart valve system, the implant procedure itself should be considered an important element of safe and effective heart valve therapy.

6.5 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 validate any processes for production where the resulting output cannot be, or is not, verified by subsequent monitoring or measurement. Process software shall also be validated. Results of validations shall be documented.

6.6 Risk management

The manufacturer shall implement a risk management process in accordance with ISO 14971 and define and justify a risk management programme, which should be specified in the risk management plan.

7 Design verification and validation

7.1 General requirements

The manufacturer shall perform design verification to demonstrate that the design output of a heart valve system meets the design input. The manufacturer shall establish tests relating to hazards identified from the risk analysis. The protocols shall identify the test purpose, setup, equipment (e.g. specifications, calibration), test conditions (with a justification of appropriateness to anticipated *in vivo* operating conditions for the device), acceptance criteria, and sample quantities tested. Test methods for verification testing shall be appropriately validated. Refer to the applicable clauses of ISO/IEC 17025.

The manufacturer shall also validate the design of the heart valve system in accordance with ISO 13485 to ensure that the device meets user needs and is suitable for the intended use.

Additional requirements for design verification testing are provided in ISO 5840-2 for surgical heart valve substitutes and ISO 5840-3 for transcatheter heart valve substitutes. For novel heart valve substitutes (e.g. sutureless surgical valves), the requirements of both ISO 5840-2 and ISO 5840-3 can be relevant and shall be considered, if applicable to the specific device design and based on the results of the risk analysis.

7.2 *In vitro* assessment

7.2.1 General

In vitro assessment shall be used to mitigate the risks identified in the risk analysis.

7.2.2 Test conditions, sample selection and reporting requirements

7.2.2.1 Test articles and sample selection

Test articles shall represent, as closely as possible, the finished heart valve system to be supplied for clinical use. Test articles shall be appropriately preconditioned prior to testing, including exposure to the maximum number of allowed sterilization cycles, process chemicals, aging effects, shipping/handling, and any loading and deployment steps (including repositioning and recapturing, if applicable) in accordance with all manufacturing procedures and instructions for use, where appropriate. Any deviations of the test articles from the finished product shall be justified.

The articles selected for testing shall fully represent all device configurations (e.g. sizes, deployment shapes, use ranges, and implant sites). Depending on the particular test, testing might not necessarily have to be completed for each device configuration. A rationale for device configuration selection shall be provided.

For all tests, the sample size shall be justified based on the specific intent of the test and risk assessment. Sampling shall ensure adequate representation of the manufacturing variability. Additional information regarding sampling and conditioning of the test article shall be included within each test method defined herein, as appropriate.

7.2.2.2 Test conditions

Where simulation of *in vivo* haemodynamic conditions is applicable to the test method, consideration shall be given to the operational environments given in Table 1 and Table 2 for the adult population and in Annex E for the paediatric population. In particular, recommended pressure values provided in Table 3 and Table 4 shall be utilized for the *in vitro* testing. 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. When animal or human blood is utilized, the recommendations of ISO 10993-4 and ASTM F1830 should be considered. The testing shall be performed at the intended operating temperature as appropriate. The measurement parameters shall be defined by the manufacturer based on the design inputs.

Table 3 — Recommended pressure values for *in vitro* testing for left side of heart — Adult population

	Aortic peak systolic pressure mmHg	Aortic end diastolic pressure mmHg	Peak differential pressure across closed valve	
			Aortic ΔP_A mmHg	Mitral ΔP_M mmHg
Normotensive	120	80	100	120
Hypotensive	60	40	50	60
Mild hypertensive	150	95	125	150
Moderate hypertensive	170	105	140	170
Severe hypertensive	195	115	155	195
Very severe hypertensive	210	120	165	210

Table 4 — Recommended pressure values for *in vitro* testing for right side of heart — Adult population

	Pulmonary artery peak systolic pressure mmHg	Pulmonary artery end diastolic pressure mmHg	Peak differential pressure across closed valve	
			Pulmonary ΔP_P mmHg	Tricuspid ΔP_T mmHg
Normotensive	25	10	20	25
Hypotensive	15	5	10	15
Mild hypertensive	45	17	30	45
Moderate hypertensive	55	22	40	55
Severe hypertensive	75	30	50	75
Very severe hypertensive	85	35	60	85

7.2.2.3 Reporting requirements

Each test report shall include:

a) purpose, scope and rationale for the test;

b) identification and description of the heart valve system elements tested (e.g. batch number, size, configuration);

c) identification, description and rationale for selection of the reference device(s) where appropriate;

d) number of samples tested and rationale for sample size;

e) detailed description of the test method including preconditioning to simulate clinical use;

f) pre-specified acceptance criteria, if applicable;

g) verification that appropriate quality assurance standards have been met (e.g. good laboratory practice, ISO/IEC 17025);

h) deviations, if any, and discussions of the effect of the deviations on the scientific validity of the test results;

i) test results and conclusions (i.e. interpretation of the results).

The statistical procedures used in data analysis and the rationale for their use shall be described. Test results and the conclusions shall be used as an input to the risk management documentation to assess the risk associated with a hazard/failure mode under evaluation.

7.2.3 Material property assessment

7.2.3.1 General

Properties of the heart valve 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 material requirements of ISO 14630 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.

7.2.3.2 Biological safety

The biocompatibility of the materials and components used in the heart valve 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 a rationale for the adequacy of the available data in addressing the risk associated with each biological endpoint identified as relevant by ISO 10993-1. During the hazard identification stage of a biological safety evaluation, 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 established methods (e.g. mode of action, dose-response, exposure level, biochemical interactions, toxicokinetics).

For heart valve substitutes using animal tissue or their derivatives, the risk associated with the use of these materials shall be evaluated in accordance with the ISO 22442 series.

7.2.3.3 Material and mechanical property testing

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

c) for the finished device after deployment.

Environmental conditions that might affect device or component performance or durability shall be evaluated and included in testing protocols (e.g. shelf life testing).

7.2.4 Hydrodynamic performance assessment

Hydrodynamic testing shall be performed to provide information on the fluid dynamic performance of the heart valve substitute. Annex I provides guidelines for conducting and reporting steady flow hydrodynamic tests. Guidelines for conducting and reporting of pulsatile hydrodynamic tests are provided in ISO 5840-2 for surgical heart valve substitutes and ISO 5840-3 for transcatheter heart valve substitutes.

7.2.5 Structural performance assessment

7.2.5.1 General

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.

7.2.5.2 Implant durability assessment

The primary goals of the durability assessment are to demonstrate a minimum *in vitro* durability lifetime, determine the anticipated durability-related failure modes of a heart valve substitute, and provide insight regarding the potential failure consequences (e.g. immediate total loss of valve function or gradual degradation of valve function). However, it is recognized that results from a single durability test method may provide limited predictive capabilities regarding these goals and the expected *in vitro* durability performance. As such, an integrated approach utilizing a combination of complementary assessment methods provides a more comprehensive process to enable conclusions to be drawn regarding expected *in vitro* durability performance.

A combination of test methods including accelerated wear testing (AWT), dynamic failure mode testing (DFM), and real-time wear testing (RWT) may be used to provide a comprehensive assessment of *in vitro* durability of a heart valve substitute. Computational methods, such as FEA, may be used in conjunction with these durability test methods. Other results, such as those from chronic pre-clinical *in vivo* evaluations, may provide data to augment the *in vitro* durability assessment conclusions.

A transcatheter valve or surgical valve may be utilized as a reference valve for the durability testing. It is acknowledged that limitations exist in drawing conclusions about clinical performance from *in vitro* durability tests. However, it is possible to conduct a comparison between the study valve and a reference heart valve in terms of durability performance under the *in vitro* test conditions.

The manufacturer shall determine and justify the integrated approach and associated test methods utilized. At a minimum, AWT and DFM testing shall be performed within the durability assessment. An overall conclusion for the durability assessment based on the integrated approach shall be reported using pre-specified acceptance criteria and a comparison to the reference valve (if applicable).

The requirements and suggested guidelines for AWT, DFM and RWT test methods described in Annex J shall be followed.

7.2.5.3 Device structural component fatigue assessment

An assessment of the fatigue performance of the heart valve substitute structural components shall be conducted; all components comprising the support structure, including anchoring features, shall be appropriately considered. Testing shall be performed to demonstrate that the support structure will remain functional for a minimum of 400 million cycles. 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 Tables 3 and 4 and other relevant *in vivo* loading conditions. Annex K makes recommendations for loading modes that should be considered and Annex E gives for guidelines regarding suggested test conditions for the paediatric population.

A validated stress/strain analysis of the implant under simulated *in vivo* conditions shall be performed on all structural components. Validation of the stress/strain analysis shall be performed in order to demonstrate confidence in the predicted results (ASME V&V 40). While it is left to the manufacturer to develop and justify the validation approach, the validation shall include comparisons of predicted FEA results against independent experimental measurements. Consideration shall be given to critical aspects of the target implant site (e.g. compliance, geometry, native valve or pre-existing prosthetic device) when determining loading and boundary conditions. Loading from all valve components shall be considered. Valve motion and closure geometry is not always symmetric; as such, stress/strain analyses shall be performed on entire valve/component geometries unless it is demonstrated that the use of a simplified model with symmetry conditions is representative of the full analysis. An appropriate validated constitutive model for each material shall be used in any stress/strain analysis.

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 fatigue resistance for the specific material and valve/component design. The use of material fatigue characterization data from the literature without sufficient justification is not acceptable. Residual stresses/strains resulting from manufacturing processes that were not included in fatigue test specimens (e.g. material coupons) shall be included in the stress/strain analysis. The fatigue assessment shall account for all stress/strain contributions, including residual stresses/strains resulting from the component manufacturing processes and residual stresses/strains resulting from loading the device into/onto the delivery system and device deployment, as applicable to the device design.

7.2.5.4 Component corrosion assessment

An assessment of the corrosion resistance of all constituent metallic materials comprising the heart valve 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) and device loading and deployment with the delivery system. Therefore, the corrosion resistance shall be characterized using the finished conditioned component.

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. For example, the potential for fretting (wear) and fretting corrosion post durability testing should be evaluated in designs that allow micromotion between components (e.g. ViV, ViR, woven wires) that might disrupt an associated coating or passive film. Suggested guidelines are provided in Annex F.

7.2.6 Design- or procedure-specific testing

In order to assess failure modes identified by the risk assessment that might not be related to durability or component fatigue, design-specific testing might be necessary. In some cases, design-specific testing might have direct implications for the overall structural lifetime of a component or valve and additional tests might be required. See ISO 5840-2:2021, Annex G and ISO 5840-3:2021, Annex F for examples of design specific testing.

7.2.7 Device MRI compatibility

The manufacturer shall evaluate the safety and compatibility of the implant with the use of MRI. Reference ASTM F2052, ASTM F2213, ASTM F2182, ASTM F2119, and ASTM F2503 for guidance. For transcatheter valves, the presence of any pre-existing prosthesis into which the implant is deployed shall be considered.

7.2.8 Simulated use

The ability to permit safe, consistent, and accurate implantation of the heart valve system within the intended implant position shall be evaluated using a model that simulates the intended use conditions. This assessment shall include all elements of the heart valve substitute. Guidelines for conducting simulated use evaluations are provided in ISO 5840-2 for surgical heart valve substitutes and ISO 5840-3 for transcatheter heart valve substitutes.

7.2.9 Human factors/usability assessment

In addition to conducting simulated use to evaluate the functionality of the heart valve system, simulated use shall also be conducted as part of the required usability assessment (or “usability testing”) as per IEC 62366 (all parts). 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 system used to conduct the implant procedure appropriately mitigate identified potential use errors that can occur.

7.2.10 Implant thrombogenic and haemolytic potential assessment

An assessment of the thrombogenic and haemolytic potential of the heart valve substitute shall be conducted. Methods such as digital particle image velocimetry (DPIV), computational fluid dynamics (CFD), and *ex-vivo* methods (e.g. blood loops) might provide a determination of the potential for thrombus formation; however, other methods (e.g. preclinical *in vivo* evaluation as described in 7.3) may also be used as part of this assessment. To perform such an assessment, it is recognized that results from a single method might not be definitive; an integrated approach utilizing a combination of complementary methods might provide the most comprehensive conclusion. The manufacturer shall determine and justify the integrated approach and associated characterization techniques utilized for assessment of the thrombogenic and haemolytic potential based upon the results of the risk analysis. See Annex H for guidelines regarding suggested methods for assessing the thrombogenic and haemolytic potential of the device.

The manufacturer shall identify and justify the appropriate *in vivo* loading and environmental conditions used, including deployment of the device into pre-existing prostheses, if applicable. The assessment shall include the immediate vicinity (inflow and outflow) of the heart valve substitute, including within the valve (e.g. leaflet commissures and cusps). Analysis shall, at a minimum, use conditions consistent with a low and elevated cardiac output (stroke volume times heart rate) (e.g. 3 l/min with hypotensive pressure conditions and 7 l/min with elevated pressure conditions) at 70 beats per min as listed in Tables 3 and 4. See Annex E for guidelines regarding suggested test conditions for the paediatric population.

The results of the integrated approach shall be interpreted based on comparison to metrics from literature and/or testing of a reference device (e.g. nominal deployed transcatheter valve or surgical device with clinical history). A conclusion regarding the thrombogenic and haemolytic potential shall be made based on the risk assessment.

Suggested guidelines are provided in Annex H.

7.3 Preclinical *in vivo* evaluation

A preclinical *in vivo* test program shall be conducted in order to address the heart valve system, placement, imaging characteristics, and safety and performance. The preclinical program design should be based on risk management assessment. The specific preclinical requirements are provided in ISO 5840-2 for surgical heart valve substitutes and ISO 5840-3 for transcatheter heart valve substitutes. Requirements for preclinical evaluation from ISO 14630 also apply.

7.4 Clinical investigations

The requirements of ISO 14630 and ISO 14155 shall apply. Clinical investigations shall be performed for new heart valve systems and expanded indications for use. For modifications of an existing heart valve system, if a determination is made based on the risk analysis that clinical investigations are not required, scientific justification addressing safety and effectiveness shall be provided. For design changes of a marketed device that might affect safety and effectiveness (e.g. novel blood-contacting materials, changes that alter the flow characteristics or haemodynamics, and changes that affect the mechanical loading on the valve), the need for a clinical investigation shall be determined and justified on the basis of a risk analysis.

Reference the following text for clinical assessments:

— Annex G for echocardiographic protocol;

— Annex L shall be followed for clinical investigation endpoints for heart valve replacement devices;

— ISO 5840-2 for specific clinical investigation requirements for surgical heart valve substitutes;

— ISO 5840-3 for specific clinical investigation requirements for transcatheter heart valve substitutes.

Annex A
(informative)

Rationale for the provisions of ISO 5840-1

A.1 Rationale for a risk-based approach

The rationale for basing ISO 5840-1 on risk management is that the traditional requirements-based model cannot keep up with the speed of technological innovation. With the requirements-based model, manufacturers have to spend their time looking for ways to comply with the requirements of the standard rather than on developing new technologies that could lead to inherently safer products. The risk-based model challenges the manufacturer to continually evaluate known and theoretical risks of the device to develop the most appropriate methods for reducing the risks of the device and to implement the appropriate test and analysis methods to demonstrate that the risks have been sufficiently reduced.

ISO 5840-1 combines a requirement for implementing the risk-based model with best practice methods for verification testing appropriate to heart valve system evaluation. The intent of the risk assessment is to identify the hazards along with the corresponding failure modes and causes in order to identify the requisite testing and analysis necessary to evaluate the risk associated with each specific hazard. The risk management process provides the opportunity for the manufacturer to evaluate the best practice methods included within ISO 5840-1. The manufacturer may choose to follow the best practice method as defined within ISO 5840-1 or may deviate from the method and provide a scientific justification for doing so. The risk management file required by ISO 14971 should document these decisions with rationale.

The risk-based model requires a collaborative environment between the device developer (the manufacturer) and the body responsible for verifying compliance with the applicable regulation regarding safety and performance of the device. The manufacturer should strive for continuous improvement in device design, as well as test methodologies that can ensure safety and performance of a device with less reliance on years of patient experience for evidence of effectiveness.

A.2 Rationale for preclinical *in vivo* evaluation

The overall objective of preclinical *in vivo* evaluation is to test the safety and function of the heart valve system in a biological environment with the closest practically feasible similarity to human conditions.

The preclinical *in vivo* evaluation is the final investigational step prior to human implantation. Therefore, it should provide the regulatory body with an appropriate level of assurance that the heart valve system will perform safely.

No single uniformly acceptable animal model has been established. Therefore, the animal model(s) selected should be properly justified in order to ensure the highest degree of human compatible conditions for the heart valve system pertinent to the issues being investigated. Since chronic studies are conducted to elucidate heart valve substitute haemodynamic performance, biological responses, structural integrity, and delivery system and valve-related pathology in a specific anatomical position, it is preferable to undertake this longer-term testing of the valves in anatomical positions for which it is intended.

The concurrent implantation of reference heart valve substitutes enhances the comparative assessment by providing a bridge to known clinical performance.

A.3 Rationale for design verification and design validation testing

Verification and validation testing includes materials testing, preclinical bench testing, preclinical *in vivo* evaluation, and clinical investigations. Although clinical investigations are usually considered to be part of design validation, some of the requirements established under design input might be verifiable only under clinical conditions. The tests specified herein do not purport to comprise a complete test program. A comprehensive test program for the heart valve system should be defined as part of the risk assessment activities. Where the manufacturer's risk assessment concludes that the safety and performance is better demonstrated by other tests or by modifying the test methods included in this standard, the manufacturer should include in the risk assessment a justification of the equivalence or superiority of the alternative test or test method.

The manufacturer should validate the design of the heart valve system, its packaging, labelling, and accessories. For a new heart valve system, design validation typically occurs in two phases. In the first phase, the manufacturer reviews the results of all verification testing and the manufacturing process validation prior to the first human implant. The review might also include analysis of the scientific literature, opinions of clinicians and other experts who will use the device, and comparisons to historical evidence from similar designs. The output of the review should be that the device is safe and suitable for human clinical investigations. The second phase of design validation occurs in conjunction with the outcomes of the pre-marketing approval of the clinical investigation. The data from the approval phase clinical investigation should be reviewed to ensure that the device, its packaging, labelling, and accessories are safe and suitable for their intended use and ready for market approval. These validation activities should be documented.

For a modification to an existing heart valve system design or manufacturing method, the concepts of verification and validation continue to be applicable but might be limited in scope. The risk analysis should define the scope of the verification and validation.

The use of clinical grade materials and components as opposed to generic test samples is important since fillers, additives, and processing aids can have profound implications on material properties. Testing should be designed to evaluate areas where materials are joined (e.g. welded, sutured, or glued) since these are potential areas for failure.

A.4 Rationale for echocardiographic assessment

Echocardiography is presently accepted as a practical and available method for evaluating human cardiac function and the function of heart valve substitutes. The accuracy of these diagnostic procedures depends upon the skill of the operator. All investigating institutions involved in the clinical evaluation of a specific heart valve substitute should employ the same echocardiographic protocol and the results should be checked by a core laboratory (see G.1.4).

A.5 Rationale for clinical evaluation reporting

A heart valve system undergoing clinical evaluation should function as intended with valve complication rates within broadly acceptable performance criteria limits. To enable appropriate risk assessment, pre-operative, peri-operative, and follow-up data should be collated, analysed, and reported.

The clinical evaluation of a heart valve system requires documentation of specified complications. A new or modified heart valve system should have an acceptable level of risk-benefit for the patient when compared to the current standard of care. Where appropriate, randomized clinical trials should be conducted comparing the new heart valve system against existing heart valve systems and/or medical therapy. The clinical evaluation also requires formal statistical evaluation of the clinical data. Unanticipated valve-related complications will be reported and evaluated prior to the completion of the formal methods of overall performance evaluation. Statistical evaluation methods and assessment criteria of clinical data could be different between paediatric and adult study populations. Given the perceived risks associated with heart valve systems, post-market surveillance protocols should be established.

A.6 Rationale for device sizing within labelling and instructions for use

In the past, problems have been reported with the labelling and instructions for use associated with size designations and sizing procedures for replacement heart valves. This has led to confusion among users about which size valve to implant in a particular patient. This has also led to confusion about how to compare results (published or otherwise) from one valve model to another. A solution to the problem can be achieved by providing more complete and accurate sizing information (e.g. prosthesis true internal diameter) which will ultimately benefit the clinician and the patient.

A.7 Rationale for human factors engineering

Manufacturers should incorporate human factors engineering in accordance with IEC 62366 (all parts) into their overall product development process in order to ensure the design and development of safe, effective, and easy-to-use heart valve systems.

Annex B
(normative)

Packaging

B.1 Requirements

The requirements of ISO 14630:2012, Clause 10 and the requirements of ISO 11607 (all parts) shall apply.

B.2 Principle

Packaging shall be designed to ensure that the user is provided with a heart valve system whose characteristics and performance are unaltered by normal transit or storage. The packaging shall maintain the characteristics and performance of the package contents under normal conditions of handling, transit, and storage and shall permit the contents to be presented for use in an aseptic manner. If necessary, based on risk assessment, there shall be a means to show if the packaging was exposed to abnormal conditions (e.g. freezing, excessive heat, container damage) during transit or storage that damaged the heart valve system.

B.3 Containers

B.3.1 Unit container(s)

The heart valve system shall be packaged in unit container(s) designed so that any damage to the unit container(s) seal is readily apparent. The unit container(s) shall meet the requirements of ISO 11607 (all parts).

B.3.2 Outer container

The unit container(s) shall be packaged in an outer container(s) (sales/storage package) to protect the unit container(s).

Annex C
(normative)

Product labels, instructions for use, and training

C.1 General

C.1.1 General requirements

The requirements of ISO 14630:2012, Clause 11 shall apply.

Labels, instructions for use, and training programs shall be designed to ensure that the user is provided with information on handling and implanting the heart valve substitute and shall be approved and reviewed as part of the risk and quality management systems. Labels, IFUs, implant card (where applicable), and instructions for use shall meet country-specific language requirements. All symbols used shall comply with the requirements of ISO 15223-1. Labelling of heart valve substitutes that have been on the market before the publication of this document shall be re-evaluated based on risk assessment and be modified if necessary, to conform to current standards (additional user training may be necessary).

C.1.2 Unit-container label

Each unit container shall be marked with at least word(s), phrase(s), and/or symbol(s) (see ISO 15223-1:2016) for the following:

— name or trade name;

— model number;

— serial/lot number;

— size and device type, if applicable (e.g. 21 mm, aortic);

— word “Sterile” if applicable and the method of sterilization;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— reference to see instructions for use for user information.

C.1.3 Outer-container label

In addition to applicable storage instructions, each outer container shall be marked with at least word(s), phrase(s), and/or symbol(s) (see ISO 15223-1:2016) for the following:

— name or trade name of device;

— name, address, and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It might also be necessary to have the name and address of the importer established within the importing country or an authorized representative of the manufacturer established within the importing country;

— model number;

— serial/lot number;

— size and device type;

— net contents;

— the word “Sterile” and method of sterilization if applicable;

— for sterile devices, the use by date or the expiration date;

— statement regarding single use only (if applicable);

— devices intended for clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions as indicated in the device specification;

— warning against use of the device if the unit container has been opened or damaged;

— reference to see instructions for use for user information.

C.1.4 Instructions for use

Each heart valve system shall have a physical or electronic copy of instructions for use that shall include at least the following:

— name or trade name of device;

— name, address, and phone number of manufacturer and/or distributor and other methods of contacting the manufacturer (e.g. facsimile number, email address). It might also be necessary to have the name and address of the importer established within the importing country or an authorized representative of the manufacturer established within the importing country;

— revision level of IFU and implementation date;

— net contents;

— indications for use and any known contraindications (the approved indications for use shall be fully consistent with evidence gained from the patients studied);

— device description including available models and user required dimensions;

— description of any accessories required and reference to their instructions for their use;

— how the device is packaged/supplied;

— the word “Sterile” and method of sterilization if applicable;

— statement that the device can or cannot be resterilized;

— statement regarding single use only (if applicable);

— devices intended for clinical investigations shall bear identification that the device is intended for investigational use only;

— any special storage or handling conditions;

— warning against use of the device if the unit container has been opened or damaged;

— any warnings regarding handling or implanting the device;

— any other warnings or precautions specific for the device including, but not limited to concomitant procedures of use with other devices;

- instructions for resterilization (if applicable) including the maximum number of resterilization cycles, parameters which have been proven to be capable of achieving sterility of the device, and appropriate information relevant to other methods, apparatus, containers, and packaging;
- specific instructions for device preparation (i.e. rinsing requirements for tissue valves);
- specific instructions for implanting or using the device;
- specific instructions for sizing target implant site and selecting appropriate device size;
- list of potential complications;
- summary of clinical experience where applicable;
- appropriate magnetic resonance (MR) safety designation (MR conditional, MR safe, or MR unsafe) and a statement regarding MRI compatibility;
- any information or instructions which are intended to be communicated from the physician to the patient.

C.1.5 Labels for medical records

The manufacturer shall provide peel-off, self-adhering labels, or equivalent with each heart valve system that enables transfer of device information to the appropriate records. Each label shall contain the name or model designation, size, and serial number of the heart valve substitute and manufacturer identification.

The size of the labels shall be sufficient to display the required information in a legible format. The number of required labels may vary based on individual country policies.

C.2 Training for physicians and support staff

If it is required by the risk assessment, the manufacturer shall establish a structured training program for the physician and staff who are involved in the peri-procedural care of the patient. The training program shall be designed to provide the physician and staff with the information and experience necessary to control user-associated risks when the device is used in accordance with the instructions for use. Training records shall be maintained as evidence that physicians have received appropriate training.

The training programme shall include the following elements where appropriate:

a) description of all system components, as well as a summary of the basic principle of operation;

b) complete review of the instructions for use including the indications for use, patient selection, contraindications, precautions, warnings, potential adverse events, pre-procedure setup, sizing the valve, implant procedure, and post-procedure patient care;

c) review of imaging modalities that can be used for implanting the device;

d) hands-on bench top demonstration of the heart valve system in a simulated model;

e) use of the device in an animal model or other appropriate models such as a robotic simulation system;

f) clinical training program including proctored cases;

g) user verification/validation determined by predefined criteria.

Annex D
(normative)

Sterilization

The requirements of ISO 14630:2012, Clause 9 shall apply together with the following.

For devices or accessories supplied sterile, sterilization shall occur by an appropriate method and SAL, and shall be validated in accordance with internationally recognized criteria as specified in ISO 17665, ISO 11135, ISO 11137 (all parts), ISO 14160, and ISO 14937. If the manufacturer states that the heart valve system can be resterilized prior to implantation, adequate instructions shall be provided by the manufacturer including parameters that have been proven to be capable of achieving sterility of the device.

For any reusable devices or accessories, the instructions for use shall contain information on the appropriate processes to allow reuse including cleaning, disinfection, packaging, and, where appropriate, the method of sterilization and any restriction on the number of reuses.

Annex E
(normative)

In vitro test guidelines for paediatric devices

E.1 General and paediatric definitions

Traditionally, heart valve systems have been designed, tested, and labelled for the adult population. Many real and perceived scientific, marketing, and regulatory barriers have limited the development of paediatric heart valve substitutes. These include the need for small device sizes, patient growth requiring multiple reoperations, problems with enhanced calcification of bioprosthetic tissue, a perceived small market size, and a lack of sufficient patients to fill a typical clinical trial. These questions were addressed at a paediatric heart valve workshop held in Washington, DC on January 12, 2010 which was attended by clinicians, device industry representatives, academicians, and the US Food and Drug Administration. The following guidelines for *in vitro* testing of devices intended for the paediatric population are from a publication based on the workshop. See Tables E.1 to E.9.

NOTE See Reference [35].

Some definitions of paediatrics include only four groups (new-born, infant, child, and adolescent), but input from paediatric clinicians led to the addition of the "toddler" subpopulation.

Table E.1 — Paediatric definitions

Paediatric subpopulation	Definition
newborn	$0 < A < 30$ d
infant	30 d $\leq A <$ 1 year
toddler	1 year $\leq A <$ 5 years
child	5 years $\leq A <$ 13 years
adolescent	13 years $\leq A <$ 22 years
Key *A* : age	

E.2 Pulsatile flow test conditions — Left side

Table E.2 — Pulsatile flow test conditions — Left side

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate[a] bpm	Cardiac output[a] l/min
newborn	50	45	60, 150, 200	0,3; 0,5; 1; 1,5
infant	50	55	60, 120, 200	0,5; 1; 2; 3
toddler	45	65	60, 100, 160	1,5; 3; 4,5
child	40	80	60, 80, 140	2; 3,5; 5
adolescent	35	100	45, 70, 120	2, 5, 7

[a] See Reference [35].

E.3 Pulsatile flow test conditions — Right side

Table E.3 — Pulsatile flow test conditions — Right side

Paediatric subpopulation	Systolic duration %	MAP mmHg	Beat rate[a] bpm	Cardiac output[a] l/min
newborn	50	20	60, 150, 200	0,3; 0,5; 1; 1,5
infant	50	20	60, 120, 200	0,5; 1; 2; 3
toddler	45	20	60, 100, 160	1,5; 3; 4,5
child	40	20	60, 80, 140	2; 3,5; 5
adolescent	35	20	45, 70, 120	2, 5, 7

a See Reference [35].

E.4 Steady back pressure and forward flow conditions — Left side

Table E.4 — Steady back pressure and forward flow conditions — Left side

Paediatric subpopulation	Steady back pressure[a] mmHg	Steady forward flow rates[a] l/min
newborn	40, 80	1,5; 3; 5; 10
infant	40, 80, 120	3; 5; 10; 15
toddler	40, 80, 120	5, 10, 15, 20
child	40, 80, 120, 160	5, 10, 15, 20, 25
adolescent	40, 80, 120, 160, 200	5, 10, 15, 20, 25, 30

a See Reference [35].

E.5 Steady back pressure and forward flow conditions — Right side

Table E.5 — Steady back pressure and forward flow conditions — Right side

Paediatric subpopulation	Steady back pressure[a] mmHg	Steady forward flow rates[a] l/min
newborn	5, 10, 20	1,5; 3; 5; 10
infant	5, 10, 20	3; 5; 10; 15
toddler	5, 10, 20	5, 10, 15, 20
child	5, 10, 20, 30	5, 10, 15, 20, 25
adolescent	5, 10, 20, 30, 40	5, 10, 15, 20, 25, 30

a See Reference [35].

E.6 Accelerated wear testing (AWT) test conditions — Left side

Table E.6 — AWT test conditions — Left side

Paediatric subpopulation	Minimum mitral peak differential pressure[a] mmHg	Minimum aortic peak differential pressure[a] mmHg
Newborn	75	50

a See Reference [35].

Table E.6 *(continued)*

Paediatric subpopulation	Minimum mitral peak differential pressure[a] mmHg	Minimum aortic peak differential pressure[a] mmHg
Infant	90	60
Toddler	97	67
Child	105	75
Adolescent	120	90

[a] See Reference [35].

E.7 Accelerated wear testing (AWT) test conditions — Right side

Table E.7 — AWT test conditions — Right side

Paediatric subpopulation	Minimum tricuspid peak differential pressure[a] mmHg	Minimum pulmonary peak differential pressure[a] mmHg
newborn	30	10
infant	30	10
toddler	30	10
child	30	10
adolescent	30	10

[a] See Reference [35].

E.8 FEA/life analysis conditions — Left side

Table E.8 — FEA/life analysis conditions — Left side

Paediatric subpopulation	FEA peak differential pressure/CO[a] mmHg/ l/min	Rigid valves equivalent years	Flexible valves equivalent years
newborn	90/1,5	5	2
infant	100/3	7	5
toddler	110/4,5	10	5
child	135/5	10[b]	5
adolescent	160/7	10[b]	5

[a] See Reference [35].

[b] Reference [35] states 15 equivalent years, which comes from US FDA.

E.9 FEA/life analysis conditions — Right side

Table E.9 — FEA/life analysis conditions — Right side

Paediatric subpopulation	FEA peak differential pressure/CO[a] mmHg/ l/min	Rigid valves equivalent years	Flexible valves equivalent years
Newborn	40/1,5	5	2
Infant	40/3	7	5
Toddler	40/4,5	10	5
Child	40/5	10[b]	5
Adolescent	40/7	10[b]	5

a See Reference [35].

b Reference [35] states 15 equivalent years, which comes from US FDA.

Annex F
(informative)

Corrosion assessment

F.1 Rationale

Corrosion of the heart valve substitute components can cause or contribute to structural component failure. In addition, corrosion by-products (e.g. metallic ion release) can cause biological and tissue responses.

Many types of corrosion mechanisms can act, often simultaneously, on the device over time. While some corrosion mechanisms are predominantly related to material properties, surface finish, and manufacturing of the component (e.g. uniform corrosion, pitting corrosion, and intergranular corrosion), others relate more to the device design (e.g. crevice corrosion and galvanic corrosion) or the operational conditions (e.g. fretting corrosion, corrosion fatigue, and stress corrosion cracking). The planning, selection, design, and execution of corrosion tests should ensure that all relevant corrosion mechanisms and their interactions are identified and assessed to obtain the information needed to evaluate the device performance during its service life.

Corrosion assessment may include a variety of electrochemical, microscopic, and gravimetric methods. Often, combinations of qualitative observations, quantitative measurements, and statistical analyses are needed to provide an overall assessment of corrosion. Standard corrosion tests developed by ASTM, NACE, and ISO address the technical requirements specified in the test method, but may need to be modified to appropriately address conditions applicable to device applications. If a standard is followed where no acceptance criteria are prescribed, the manufacturer shall justify the final acceptance criteria adopted.

NOTE See Reference [29].

F.2 General

Commonly used standard methods for medical device components include, but are not limited to, ASTM F2129 and ASTM F746. Non-destructive methods such as electrochemical impedance spectroscopy (ASTM G106) and electrochemical noise measurements (ASTM G199) can be advantageous for monitoring corrosion properties and events during accelerated or real-time testing.

The corrosion mechanisms described below are often applicable to materials and conditions representative of implantable heart valve substitutes, although other mechanisms are possible. The manufacturer should provide rationale for the selected test methods and justify that all applicable corrosion mechanisms and conditions have been addressed through testing or theoretical assessments.

F.3 Pitting corrosion

Pitting corrosion is a localized form of corrosion. It occurs when discrete areas of a material lose their passive state and undergo corrosion attack while the majority of the surface remains unaffected. The localized corrosion attack creates small holes (pits) which can rapidly penetrate the material and contribute to failure. Pitting of a material depends strongly on the presence of aggressive ionic species (e.g. chloride ions) in the environment having a sufficient oxidizing potential.

The assessment of the pitting corrosion susceptibility of the device is of relevance both for storage solution and in simulated *in vivo* conditions. Literature citations or previous experience with similar devices could be referenced. However, the materials, design, and fabrication processes specific to the device under analysis can reduce or eliminate the applicability of generic literature. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and electropolishing. Therefore, the pitting corrosion susceptibility of the finished nitinol support structure should be characterized. To capitalize on previous experience with similar devices, it is necessary to show that their surface chemistries are equivalent.

Pitting corrosion can be assessed by electrochemical methods such as potentiodynamic and potentiostatic measurements described in ASTM F2129 and ASTM F746. Crevice corrosion occurs at lower potentials than pitting and therefore, interference from crevices on the test sample can lead to an underestimation of the pitting resistance. It is recommended to perform microscopic examination (e.g. as described in ASTM G161) of the samples after testing to evaluate the presence of pits and/or crevice corrosion because it is difficult to mount a test sample without introducing a crevice at the sample/mount interface.

Depending on the results of pitting corrosion testing, it might be necessary to perform additional testing such as surface characterization, nickel leaching analysis or open circuit potential.

NOTE See Reference [22].

F.4 Crevice corrosion

Crevice corrosion is a form of localized corrosion which occurs in areas where parts of the material are in contact with small volumes of stagnant liquid. In short, the limited mass transfer within the stagnant liquid in the crevice creates a deoxygenized zone with increased salt and acid concentration compared to the rest of the liquid. This difference shifts the electrochemical potential within the crevice to a more negative value which causes passivity to breakdown and the onset of active dissolution (corrosion).

Crevice corrosion can result from the design of the component or from formation of deposits that introduce a critical crevice. This corrosion mechanism occurs mainly, but not exclusively, on materials which are protected by a passive oxide.

Literature citations or previous experience with similar devices can be referenced. However, as the presence of critical crevices is strongly related to device design and the material passivity is affected by the specific fabrication processes, generic literature might not be applicable. To capitalize on previous experience with similar devices, it is necessary to show that their surface chemistries and crevices are equivalent. Crevice corrosion can be assessed by immersion test methods, as well as electrochemical methods under open circuit conditions or applied potential/current such as those described in ASTM F2129, ASTM F746, and ISO 16429.

F.5 Galvanic corrosion

Galvanic (or bimetallic) corrosion is a form of corrosion in which one metal corrodes preferentially when it is in electrical contact with a different metal. Enhanced corrosion of the more negative (less noble) metal is experienced together with partial or complete cathodic protection of the more positive (more noble) metal.

If the device contains more than one type of metal such as a support structure with marker bands, the manufacturer should demonstrate the design's resistance to galvanic corrosion. It is recommended that the risk of galvanic corrosion is addressed by theoretical methods such as Evans Diagram and ASTM G82. If overlapping of devices is expected during clinical procedures, then the potential for galvanic corrosion of contacting dissimilar materials should be addressed. Test methods described in ASTM G71 or equivalent methods can be used or modified by incorporating the experimental setup described in ASTM F2129.

F.6 Corrosion fatigue

Corrosion fatigue can be defined as materials failure mechanism which depends on the combined action of repeated cyclic stresses and a chemically reactive environment. One example is that localized corrosion-deformation interactions on smooth surfaces act as crack initiation sites at thresholds lower than those estimated from linear elastic fracture mechanics. The total damage due to corrosion fatigue is usually greater than the sum of the mechanical and chemical components acting separately.

NOTE 1 See Reference [13].

Crack growth is often rate limited by one of the slow steps in the mass-transport and crack surface reaction sequence and as a consequence, slow loading rates enhance corrosion fatigue damage. Hence, testing at low frequency can be necessary to adequately address the corrosion fatigue mechanisms acting on the device. ASTM F1801 outlines corrosion fatigue testing of standard material specimens for medical implant applications. Corrosion fatigue experiments follow directly from procedures for mechanical tests and can be assessed as part of the fatigue assessment of the device or in separately designed corrosion fatigue tests for the support structure component as justified by the manufacturer.

NOTE 2 See Reference [15].

F.7 Fretting (wear) and fretting corrosion

Fretting is defined as the wear process occurring between contacting surfaces having relative oscillatory motion. Fretting corrosion is caused by corrosion reactions which occur at the interface of two closely fitting surfaces when they are subjected to slight relative oscillatory motion with or without the abrasive effects of corrosion product debris between them.

The potential for fretting (wear) and fretting corrosion should be addressed in designs that allow micromotion between components (e.g. woven wires) that can disrupt an associated coating or passive film.

F.8 Post-fatigue corrosion evaluation

After completion of fatigue testing and/or device durability testing, specimens should be examined for any evidence of corrosion.

Annex G
(informative)

Echocardiographic protocol

G.1 General

G.1.1 Echocardiography is the standard modality for the routine clinical assessment of replacement heart valves.

G.1.2 Imaging facilities should be equipped with systems that have been validated for the intended applications in the assessment. They should also utilize personnel that have been specifically trained to conduct the required assessments.

G.1.3 Studies should be performed according to defined protocols. Additionally, study-specific training should be conducted prior to the study to ensure that all involved personnel clearly understand protocol objectives.

G.1.4 A third party core lab should evaluate studies to:

a) ensure quality image acquisition and provide a mechanism for feedback;

b) standardise measurement methods;

c) exclude studies of inadequate quality.

The core lab should have established expertise in echocardiography, particularly as it relates to the disease process targeted for therapy, as well as experience in the assessment of surgical and transcatheter replacement heart valves.

G.1.5 Imaging studies should be recorded and archived for review in DICOM format. Data should be reviewed soon after recording a study so that deviations from the protocol can be detected early and, if necessary, a further study can be performed. A high level of interpretability is essential for unbiased data. A statement on imaging quality should include percentage of subjects imaged (if not 100 %, how they were selected), and the percentage of images which were poor, inadequate or uninterpretable.

G.1.6 Centres should minimize the number of operators performing the protocol-required exams and also the number of machines used. Likewise, core laboratories should limit the number of observers evaluating studies.

G.1.7 Echocardiography should be performed before discharge after implantation to detect major abnormalities and should usually be repeated at approximately 4 months to 6 months and at 12 months and thereafter at least annually.

G.1.8 Consistent imaging methodologies should be used for all time points. For example, TEE and TTE should not be mixed during follow-up. Likewise, protocol-specified images collected should remain consistent throughout the course of the study.

G.1.9 Most studies are performed using TTE. TEE should be considered in the presence of mitral and tricuspid valves for the detection of thrombus and regurgitation. Refer to Reference [37].

G.2 Echocardiographic studies

G.2.1 Echocardiographic studies should be conducted to capture protocol prescribed information to address study end points. Typically, this involves standard imaging views in both 2D and colour Doppler modalities. Imaging planes usually include parasternal long-axis, parasternal short-axis at aortic, mitral, and papillary muscle levels, apical 4-chamber, apical 2-chamber, and apical long-axis and any additional views per applicable guidelines. For adequate assessment of replacement heart valves, it is often necessary to use off-axis views to minimize the effect of shielding. Spectral Doppler is essential.

G.2.2 Image sets of sufficient duration (three-cycle clips) should be collected to ensure a thorough evaluation. Typically, in addition to still images, video loops demonstrating the previous and following beats should be collected. In the case of patients with arrhythmias such as atrial fibrillation, longer image sets should be collected to allow for an assessment of the impact of the dysrhythmia on the indices being evaluated.

G.2.3 Electrocardiogram (ECG) and blood pressure should be recorded as part of the imaging study. Height and weight should be recorded since some parameters require indexing to body surface area.

G.3 Data collected

G.3.1 A comprehensive study should be carried out describing all chambers and valves in addition to the replacement valve. Examples of information that can be collected include:

— LV: end-systolic and end-diastolic dimensions, wall motion, wall thickness at the interventricular septum and posterior wall, ejection fraction, diastolic function;

— RV: dimensions, function, estimated pulmonary artery systolic pressure;

— left atrium (LA), right atrium (RA): dimensions, volume;

— estimated pulmonary artery pressures (peak and mean pressures);

— presence of concomitant valvular disease;

— presence/severity of intracardiac shunt (when applicable);

— size and haemodynamic effect of pericardial effusion.

G.3.2 Indices for the characterization of a replacement valve include:

— peak transvalvular velocity;

— mean gradient;

— effective orifice area using the continuity formulae;

— position of the device;

— appearance and motion of cusps;

— presence and degree of regurgitation through and around the valve.

G.3.3 Reporting of structural valve deterioration: echocardiographic definitions of SVD shall include evidence of deterioration of leaflet morphology and haemodynamic changes, either an increase in gradient from baseline or new or worsening transvalvular regurgitation. The use of a single threshold gradient alone is not appropriate. All degrees of SVD should be reported irrespective of whether an intervention is required.

Annex H
(informative)

Assessment of implant thrombogenic and haemolytic potential

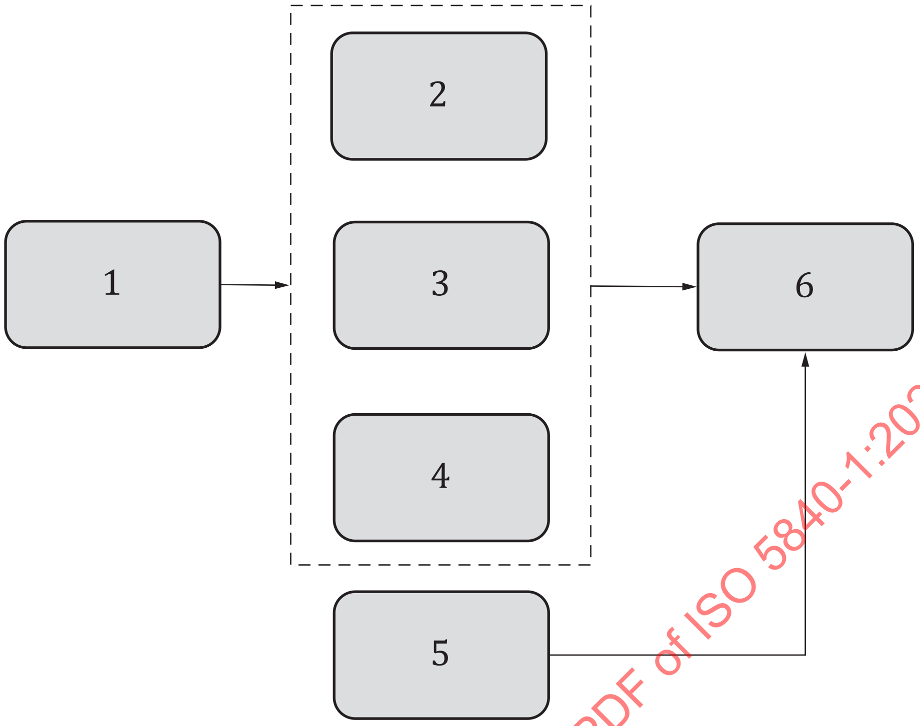
H.1 Rationale

A quantitative assessment of the thrombogenic and haemolytic potential of heart valve replacements is an integral part of the design verification for these devices. These devices are typically designed using a variety of materials (e.g. metallic stents, biological leaflets), which might adversely interact with blood components post implantation. In addition, variations in deployed geometry of these devices might affect their thrombogenic and haemolytic potential (see Reference [36]). A detailed understanding of these interactions might help predict the thrombogenic potential post device implantation. The risk associated with any loading processes should be assessed by using suitable test methods.

Blood damage modelling remains a challenging issue due to the presence of multi-scale linked haemodynamic and biochemical processes, such as platelet activation/rupture due to high shear stresses, platelet deposition, and clot formation at blood/material interfaces. In relation to heart valves, the presence of disturbed flow, such as flow stagnation and high shear stresses, have been implicated in the processes leading up to blood damage. In this context, a variety of approaches have been adopted towards understanding the key factors that might cause blood damage, including experimental and computational approaches. Due to this complexity, a combination of these approaches may be appropriate, as described in this annex.

H.2 General

This annex provides general guidelines for assessing the thrombogenic and haemolytic potential of heart valve replacements using a combination of approaches. An example of an integrated approach is provided in Figure H.1.



Key

1 definition of *in vivo* boundary conditions
2 experimental flow field assessment (e.g. PIV)
3 computational flow field assessment (e.g. CFD, FSI)
4 *ex vivo* flow testing (e.g. blood loops)
5 pre-clinical *in vivo* assessment
6 integrated thrombus and haemolytic assessment

Figure H.1 — Example of integrated thrombus and haemolytic potential assessment approach

In this approach, the appropriate boundary conditions are first defined using available *in vivo* data – this includes the range of deployment variations and relevant haemodynamic conditions. These boundary conditions are utilized for experimental flow field assessment in representative test fixtures and compared to reference devices with known clinical performance. Simultaneously, these boundary conditions are utilized to develop computational models of flow through the device. The computational tools developed are validated using experimental data by comparing relevant metrics and observations under the conditions studied. Subsequently, the computational tool is utilized to investigate thrombogenic and haemolytic potential for deployment and anatomical variations that the device might encounter. *Ex vivo* flow studies (e.g. blood loop testing) and preclinical *in vivo* assessment can also provide insights into the thrombogenic and haemolytic potential of these devices by identifying locations and features with increased risk for thrombus formation. An integrated assessment utilizing complementary approaches can identify the thrombogenic and haemolytic potential of heart valve replacements.

H.3 Experimental flow field assessment

H.3.1 General

The experimental assessment of heart valve flow fields should be conducted using qualitative and quantitative flow visualization in pulse duplicator systems, similar to those described in ISO 5840-2:2021, F.2.2 or in ISO 5840-3:2021, C.2.3. This subclause provides guidance on test equipment, test equipment validation, formulation of test protocols and reporting requirements for flow visualization using digital particle image velocimetry (DPIV); however, other methods such as laser Doppler velocimetry (LDV) may also be utilized. The results of this experimental assessment may be utilized for validation of computational flow assessment.

H.3.2 Test apparatus requirements

H.3.2.1 A DPIV system with appropriate spatial, temporal and optical resolution to resolve the flow fields under investigation should be utilized. Alternatively, phase locked measurements may be used when calculating quantities based on averaged values.

H.3.2.2 A high power pulsed laser with sufficient power to illuminate seeding particles should be utilized. Appropriate optics should be used to create laser sheets to illuminate the plane/volume of interest. Neutrally buoyant particles of appropriate size should be chosen to track accurately the fluid flow in the chosen test medium. Fluorescent particles and appropriate camera filters can be used to filter scattered illumination from heart valve components. Particle area density should be controlled to ensure quality cross-correlation results.

NOTE See References [27], [28] and [29] for recommended DPIV system specifications.

H.3.2.3 The DPIV system should have its performance established by testing with standard nozzles or reference heart valves (e.g. mechanical heart valves) with known flow fields. An uncertainty analysis of the system should also be conducted to estimate the accuracy of the DPIV system.

H.3.2.4 The flow and pressure measurement system used for DPIV should have similar characteristics to those referenced in ISO 5840-2:2021, F.2.2 or in ISO 5840-3:2021, C.2.3.

H.3.2.5 Relevant dimensions of the intended implant site should be simulated, including deployment variations as anticipated during implantation (e.g. out-of-round). Anatomical aspects of the implant site that might influence the flow fields in the vicinity of the device should also be simulated using the test apparatus.

H.3.3 Test procedure

H.3.3.1 Test devices should be conditioned per the requirements of 7.2.2.1 prior to DPIV testing.

H.3.3.2 For surgical valves, testing should be conducted on one valve from each of the smallest and largest valve sizes along with the appropriate reference valves for comparison.

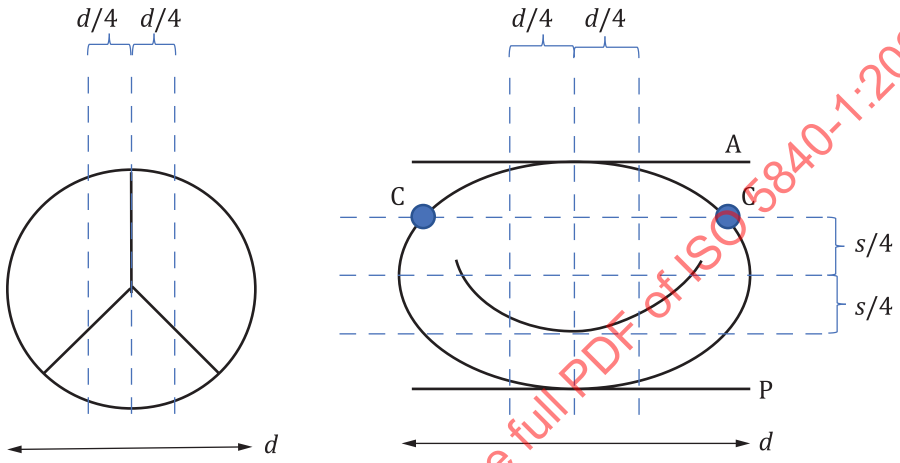
H.3.3.3 For TAVI devices, testing should be conducted on one of each of the smallest and largest deployed valve sizes along with the appropriate reference valves for comparison. Testing should also be conducted across the range of deployment variations (e.g. out-of-round) as determined in the risk assessment.

H.3.3.4 For TMVI devices, testing should be conducted on at least two deployed states that bracket the intended use range as determined by the manufacturer along with the appropriate reference valves for comparison. With regard to defining the deployed states, consideration shall be given to deployed valve size (small and large) and deployed valve aspect ratio (commissure to commissure to AP). Consideration shall also be given to the distance between the inner valve and outer sealing system and its effect at different deployed conditions. Areas of the ventricle and/or LVOT that might experience flow disturbances should also be studied for TMVI devices.

H.3.3.5 Tests should be carried out in the intended position of the device at simulated low and high cardiac outputs (e.g. 2 l/min and 7 l/min) at 70 beats/min with a 35 % systolic duration or as appropriate to the intended use of the valve. Table 3 and Table 4 can be used as references for appropriate choice of operating condition. The haemodynamic waveforms produced by the pulse duplicator shall reasonably simulate physiological conditions. See Annex E for guidelines regarding suggested test conditions for the paediatric population.

H.3.3.6 The test solution used should mimic the kinematic viscosity of blood (e.g. $\nu = 3{,}5\ mm^2/s$).

H.3.3.7 For each test case, the imaging planes should be chosen based on the device design and anatomical positioning to appropriately study the regions of interest (e.g. regions of high shear stress and/or stagnation). For example, imaging planes for a symmetric tri-leaflet design and a symmetric D-shaped valve are shown in Figure H.2. In each case, the light sheet planes target the areas of high shear stress and stagnation.



Key

A anterior

C commissure

P posterior

d diameter of major axis

s A-P distance

Figure H.2 — Example imaging planes (axial view) for symmetric trileaflet (left) and a symmetric D-shaped (right) valve

H.3.3.8 Image acquisition should be triggered using the pulse duplicator system or using an external trigger system to allow accurate identification of time points in the cardiac cycle. Pulse separation time for DPIV should be adjusted to ensure quality cross-correlation results.

H.3.3.9 Images should be collected for quantitative and qualitative assessment of flow through the heart valve. This can include a combination of sequential high-speed images and/or phase locked double pulse images at target operating conditions. The assessment should include measurements at multiple time points during the cardiac cycle including both systolic and diastolic phases (e.g. early systole, peak systole, late systole, early diastole, peak diastole, late diastole).

H.3.3.10 Image post-processing should be conducted to obtain velocity vector fields using cross-correlation algorithms, preferably using adaptive and recursive processing techniques. Vector field filtering should be utilized to remove outliers.

H.3.3.11 Analyse the acquired data to assess the flow fields (velocity and fluid shear) in the immediate vicinity of the test valve, including within the valve where possible. Consideration should be given to any unique valve features that might create any flow disturbances resulting in elevated shear stresses, turbulence and flow stagnation. The flow field should be investigated both proximal and distal to the valve, where such flow disturbances are expected to occur.

H.3.3.12 Additionally, an objective assessment of stagnation potential should be considered. For example, average velocity or shear stresses within the sinus region over the cardiac cycle and an estimation of recirculation can be assessed. Similarly, for mitral devices, velocities in left atrium and shear stresses in the left ventricle can be assessed. These estimates should be clearly defined and interpreted in the report.

H.3.4 Test report

The experimental flow field assessment report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity and specific gravity under the test conditions;

b) a description of the pulse duplicator, as specified in H.3.1, and its major components and associated apparatus, including a schematic diagram of the system giving the relevant chamber dimensions, chamber compliance (if a compliant chamber is used), details of the location of the pressure-measuring sites relative to the base of the leaflets of the heart valve substitute, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at nominal conditions;

c) a description of the DPIV system, as specified in H.3.2, including validation method and stated accuracy and resolution of calculated quantities (e.g. velocity, shear stress);

d) a description of the test conditions utilized for testing, including the device deployment configurations and hydrodynamic conditions during testing;

e) appropriate qualitative photographic documentation and quantitative analyses of the opening and closing characteristics for the heart valve substitute;

f) tabular or graphical illustration of the velocity, viscous shear stress, and if applicable, Reynolds stress fields distinguished by spatial and time components including magnitudes at peak systole and diastole;

g) an assessment using both qualitative (including photographs where possible) and quantitative measures of any occurrences of flow separation, flow stasis near the valve, turbulence during forward and regurgitant flow including any extreme turbulence that might lead to haemolysis or thrombus, vortex formation, induced jets, or any other observed fluid dynamic related phenomenon including any occurrences of valvular incompetence. The assessment should include a conclusion to its acceptability where possible.

H.4 Computational flow field assessment

H.4.1 General

This annex provides guidance on the computational setup, verification and validation, data evaluation and reporting requirements for the computational assessment of the thrombogenic and haemolytic potential of the device. Validation against and correlation to *in vitro* or *in vivo* experiments is an important aspect for the application of computational models. The computational assessment can help identify locations and features of the heart valve substitute with increased risk for haemolysis and thrombus formation.

See Reference [34] for best practices for computational flow field assessment.

H.4.2 Computational Model

H.4.2.1 A numerical solver that has appropriate governing formulae, adequate physical representation, and sufficient accuracy to perform flow and blood damage simulations should be applied. Code verification, estimation of the discretizational error, and validation against experiments should be performed to prove the applicability of the software and the computational model (see H.4.3).

H.4.2.2 All relevant aspects of the implantation scenario (e.g. device, vessel, anatomical surroundings) should represent the simulated *in vivo* or *in vitro* setup as closely as possible. Relevant dimensions of the intended implant site should be simulated. For validation purposes, the dimensions should correspond to the respective dimensions of the test apparatus for experimental flow field assessment as closely as possible. Simplifying assumptions should be justified appropriately (e.g. use of symmetric computational domains, neglecting chordae tendineae) and the fluid domain should be stated.

H.4.2.3 Appropriate operating and boundary conditions should be utilized. The boundary conditions (e.g. inlet, outlet, and wall) should represent the *in vivo* or *in vitro* conditions of the intended study. For physiological or pathological boundary conditions, methods such as lumped parameter modelling can be used. For validation purposes, data taken from the experiment assessment should be applied as the boundary conditions.

H.4.2.4 Appropriate fluid and material properties should be used in the simulations, including biological properties, temperature, viscosity, and specific gravity matching the *in vivo* or *in vitro* condition as closely as possible.

H.4.2.5 Adequate convergence criteria for momentum, continuity, fluid-structure coupling and turbulent quantities, if applicable, should be selected. All resolution and numerical convergence criteria values should be explicitly stated and physical convergence (e.g. monitoring of physically relevant fluid flow quantity at a monitoring point or surface location) should be shown.

H.4.3 Error analysis and estimation

H.4.3.1 A description of the software quality assurance (SQA) and numerical code verification (NCV) should be provided for the software used for the intended study. This may include a comparison to simplified systems which have an analytical solution. Available documentation and verification results from the software developer may be referenced.

H.4.3.2 Sufficient temporal and spatial resolutions should be used. Sensitivity analyses of the discretization scheme and solver parameters (e.g. time step, grid size) should be carried out for the actual system and the flow quantities used in this analysis should be explicitly stated. Finally, the total simulation time should ensure periodically stable simulation results.

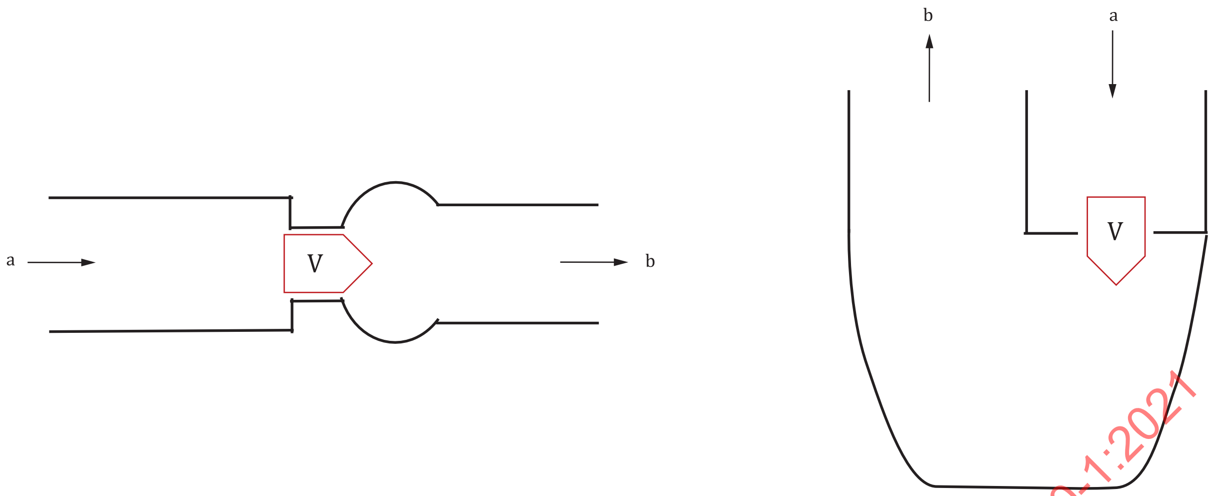
H.4.3.3 Computational codes should be verified to make sure that the correct formulae and physics are being modelled as applied to the valve design being evaluated. Simulation results should be validated by comparison with experimental results. Validation should be carried out in the intended position of the device at simulated low and high cardiac outputs (e.g. 2 l/min and 7 l/min) at 70 beats/min with a 35 % systolic duration or as appropriate to the intended use of the valve. The same fluid properties as in the experiment should be applied. The system geometry and properties should represent the recreated experimental setup as closely as possible (Figure H.3). Data (e.g. pressure or flow) taken from the experiment should be used as the boundary conditions.

The degree of agreement between the computational and experimental results should be discussed. Any discrepancy should be justified. Experimental uncertainty estimates should be described. For validation the following metrics should be considered:

— Quantitative comparison of fluid dynamic parameters (e.g. pressure/flow rates, cardiac output, maximum flow rate, maximum velocity, total ejection time)

— Quantitative comparison of leaflet kinematics (e.g. leaflet open area (profile, maximum, mean), valve opening/closing times)

— Quantitative comparison of flow pattern (e.g. velocity profile along certain lines as shown in Figure H.4)



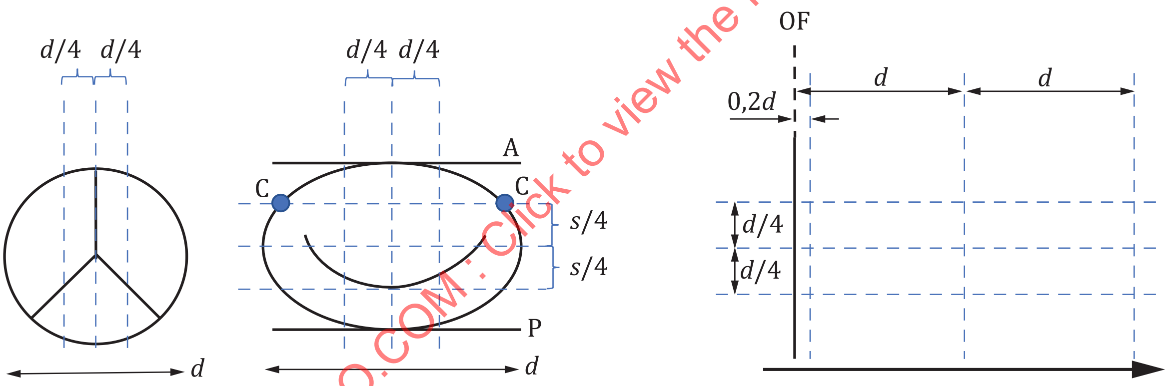
Key

V valve location

a Inflow direction.

b Outflow direction.

Figure H.3 — Examples of flow domains for aortic/pulmonary valve (left) and mitral/tricuspid valve (right)



Key

A anterior

C commissure

P posterior

OF device outflow plane

d diameter of major axis

s A-P distance

NOTE Views shown are axial (left two images) and top (rightmost image).

Figure H.4 — Example planes to be used for computational validation (intersections of planes define lines for comparison purposes)

H.4.4 Computational simulations

H.4.4.1 Simulations should be carried out in the intended position of the device at simulated low and high cardiac outputs (e.g. 2 l/min and 7 l/min) at 70 beats/min with a 35 % systolic duration or as appropriate to the intended use of the valve. Tables 3 and 4 can be used as references for appropriate choice of test condition for the adult population. See Annex E for guidelines regarding suggested test conditions for the paediatric population.

The geometry of the flow domain should represent the anatomical shape and deployment variations (e.g. based on CT scans). The fluid properties should mimic the properties of blood.

H.4.4.2 The evaluation of the results may include, but is not limited to, information about blood damage estimation, shear rates, platelet activation, wall shear stresses, and estimation of the washout time/recirculation/separation. The results of the computational assessment should be interpreted in conjunction with results from tests such as *ex vivo* blood testing.

H.4.5 Study report

The computational assessment report should include:

a) information regarding the used software tools (e.g. commercial solvers or open-source CFD packages, software used to generate the geometry (CAD) and anatomical models);

b) information regarding the system configuration (e.g. the geometry of the device, the computational domain, dimensions);

c) information regarding the governing formulae and/or constitutive laws used to perform the computational analysis;

d) information regarding the biological, chemical, and physical properties of the system (e.g. fluid properties, material properties) including the testing conditions to get the data;

e) information regarding the conditions that were imposed on the system, such as the boundary and loading conditions, initial conditions, and other constraints that control the system;

f) information regarding the numerical implementation used to solve the governing formulae;

g) information regarding code verification performed on the software used for the study;

h) information regarding the discretization and refinement techniques utilized during the numerical solution including the estimation of discretization errors;

i) information regarding validation of the computational model;

j) results of the computational assessment and discussion of the results;

k) limitations of the study (e.g. assumptions/simplifications) and conclusions.

H.5 *Ex vivo* blood testing

H.5.1 General

This subclause provides guidance on test equipment, test procedures, data evaluation and test reports for the experimental *ex vivo* assessment of the thrombogenic and haemolytic potential of the heart valve substitute using blood as a test medium. The tests can provide additional insights by identifying locations and features of the transcatheter heart valve substitute with increased risk for thrombus formation and can compare its overall thrombogenic and haemolytic potential with that of a reference valve.

NOTE See Reference [24].

H.5.2 Test apparatus requirements

H.5.2.1 The *ex vivo* blood testing should be conducted in pulse duplicator systems, similar to those described in ISO 5840-2:2021, F.2.2 or ISO 5840-3:2021, C.2.3. These systems should produce pressure and flow waveforms that approximate physiological conditions over a physiological flow range between 2 l/min and 7 l/min.

H.5.2.2 The test apparatus should have had its properties, performance and repeatability validated and documented by means of testing reference valves of different sizes in the intended position. Validation testing may 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 validation testing being performed. The test fluid used for validation testing should be justified. The validation testing shall be performed at the intended operating temperature as appropriate.

H.5.2.3 The test apparatus should permit measurement of time-dependent pressures and volumetric flow rates.

H.5.2.4 Relevant dimensions of the intended implant site should be simulated. The dimensions should correspond to the respective dimensions of the test apparatus for computational and/or experimental flow field assessment as closely as possible.

H.5.2.5 The chamber should allow for the usage of blood as test fluid. Particular consideration should be given to the haemocompatibility of all surfaces and system influences in blood contact (e.g. material, roughness) and physiological flow patterns (e.g. avoidance of stagnation, dead zones).

H.5.3 Test procedure

H.5.3.1 Test devices should be conditioned per the requirements of 7.2.2.1 prior to *ex vivo* blood testing.

H.5.3.2 For surgical valves, testing should be conducted on one of each of the smallest and largest valve sizes along with the appropriate reference valves for comparison.

H.5.3.3 For TAVI devices, testing should be conducted on one of each of the smallest and largest deployed valve sizes along with the appropriate reference valves for comparison. Testing should also be conducted across the range of deployment variations (e.g. out-of-round) as determined in the risk assessment.

H.5.3.4 For TMVI devices, testing should be conducted on at least one each of the smallest and largest valve sizes. Testing should also be conducted across the range of deployment variations as determined in the risk assessment. Testing should be also conducted on an appropriate reference valve for comparison. With regard to defining the deployed states, consideration shall be given to deployed valve size (small and large) and deployed valve aspect ratio (commissure to commissure distance to AP distance). Consideration shall also be given to the distance between the inner valve and outer sealing system and its effect at different deployed conditions.

H.5.3.5 Testing should be carried out in the intended position of the device at simulated low and high cardiac outputs (e.g. 2 l/min and 7 l/min) at 70 beats/min with a 35 % systolic duration or as appropriate to the intended use of the valve. Tables 3 and 4 can be used as references for appropriate choice of operating condition. The haemodynamic waveforms produced by the pulse duplicator shall reasonably simulate physiological conditions as shown in Figures 3 and 4. See Annex E for guidelines regarding suggested test conditions for the paediatric population. The blood temperature should be maintained at a temperature of (37 ± 1) °C during testing.

H.5.3.6 The test medium should be human blood, if available. Porcine or ovine blood may also be considered due to a similar coagulation system. Appropriate anticoagulation (e.g. low molecular weight heparin) should be used in order to reduce the probability of embolic thrombi.

H.5.3.7 The flow as well as the differential pressure across the valve should be monitored in order to guarantee the correct hydrodynamic parameters during the test procedure.

H.5.3.8 Before starting the test procedure, the prostheses should be weighed, and the following examples of blood characteristics should be characterized:

a) number of platelets (PLT);

b) haematocrit (HCT) (e.g. red blood cells or plasma);

c) activated clotting time (ACT);

d) clotting time (CT), e.g. using extrinsic thromboelastometry (ExTEM) or (TEG);

e) maximum clotting firmness (MCF), e.g. using ExTEM;

f) base excess (BE);

g) plasma-free haemoglobin (PfHb).

H.5.3.9 Blood samples should be obtained at regular intervals, e.g. at the beginning of the test, at least every 30 min and at the end of the test (see parameters listed in H.5.3.8).

H.5.3.10 The test should be terminated after a predefined duration (e.g. 4 h to 6 h), or whenever a predefined criterion is met (e.g. increase in differential pressure across the valve).

H.5.3.11 After the assessment, the blood samples should be analysed and compared to each other. A statistical evaluation of the parameters listed in H.5.3.8 over time should be conducted. The prostheses should be fixated, weighed and microscopically inspected for the presence of thrombus.

H.5.3.12 Additional consideration should be given to emboli that are present within the remaining blood after testing.

H.5.4 Test report

The *ex vivo* blood test report should include:

a) a list of the valves, including reference valves, used to conduct the testing;

b) a description and the dimensions of deployed valve configuration;

c) a justification for the reference valve used;

d) a description, specifications and validations of all test apparatus and references, to and/or descriptions of, any procedures used in order to complete the based assessment. The description of the test apparatus should include a schematic diagram of the system giving the relevant chamber dimensions, chamber compliance (if compliant chamber is used), details of the measurement and blood sampling locations, as well as details of the measurement instrumentation (e.g. type, frequency response, resolution, accuracy, calibration procedures).

e) a list of pertinent test conditions (e.g. cycle rate, cardiac output, pressures) including sample pressure and flow waveforms, and rationale for any deviations from those test conditions specified for *ex vivo* blood testing;

f) a description of the blood used for the assessment (e.g. species, origin, handling, transport time, concentrations of any additives used), as well as a statistical evaluation of the blood parameters over time regarding:

   1) PLT;

2) HCT;

3) ACT;

4) CT, e.g. using ExTEM;

5) MCF, e.g. using ExTEM;

6) BE;

7) PfHb.

g) an appropriate quantitative and qualitative documentation of any thrombogenic structure on any surface of the heart valve substitute regarding location, size and type of thrombus, as well as the weight of the heart valve substitute before and after the assessment;

h) a conclusion based on comparison to literature and/or reference valve.

Annex I
(informative)

Guidelines for hydrodynamic performance characterization by steady flow testing

I.1 General

Steady flow testing might provide a more consistent method for comparing hydrodynamic performance across valves. This annex provides guidance on test equipment, test equipment validation, formulation of test protocols and test methods for the hydrodynamic performance characterization of heart valves during steady flow testing. Equipment and test procedures should be appropriate for the valve's intended use, e.g. adult/paediatric, left/right-side, native valve/pre-existing prosthesis.

I.2 Steady forward flow testing

I.2.1 Measuring equipment accuracy

I.2.1.1 Differential pressure measurement should have a measurement accuracy of at least ±0,26 kPa (±2 mmHg).

I.2.1.2 All other measurement equipment should have a measurement accuracy of at least ±5 % of the maximum intended test measurement (e.g. flow meter accuracy ±1,5 l/min).

I.2.2 Test apparatus requirements

I.2.2.1 Steady flow testing for heart valve substitutes should be conducted in a straight tube having an internal diameter of 35 mm. For valves larger than 35 mm, larger diameters of tubes should be considered.

I.2.2.2 For transcatheter valve testing, refer to ISO 5840-3:2021, C.2.4 for definition of the aortic valve test fixture and ISO 5840-3:2021, C.2.5 for the mitral valve test fixture.

I.2.2.3 The test system should be capable of generating flow rates of at least 30 l/min.

I.2.2.4 Flow entering the test chamber should be fully developed; this can be achieved by use of a flow straightener upstream of the heart valve substitute.

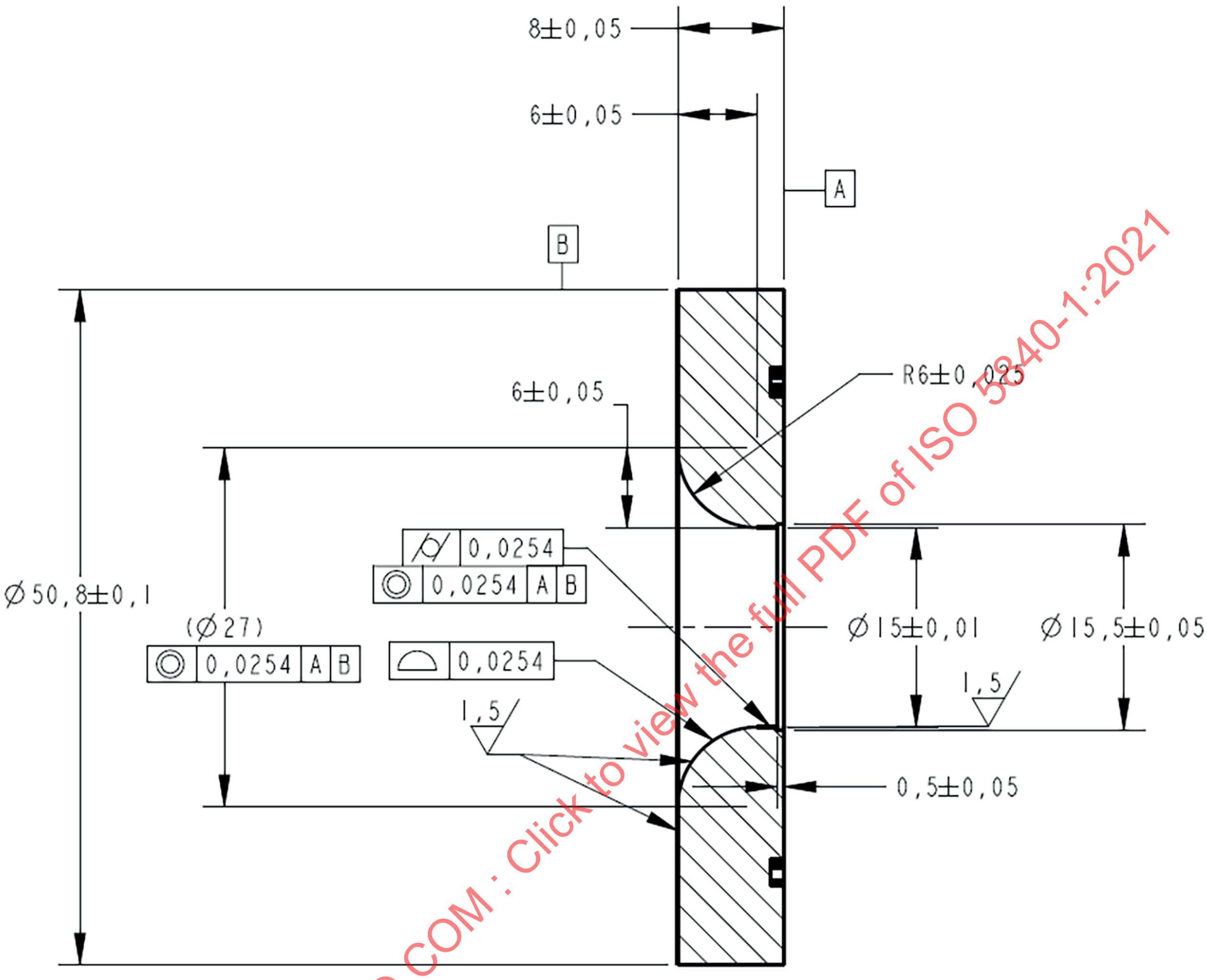
I.2.2.5 Pressure taps should be located one tube diameter upstream and three tube diameters downstream from the annular plane of the heart valve substitute. If sufficient data can be provided to demonstrate comparable results, other pressure tap configurations may be used.

I.2.2.6 Pressure taps should be flush with the inner wall of the tube.

I.2.2.7 A standard nozzle in accordance with Figure I.1 should be used to characterize the forward flow pressure and flow measuring equipment. A plot of expected values for the forward flow standard nozzle gradients can be found in Figure I.2. When accounting for acceptable accuracy tolerances, measured values should agree with these data. See Reference [25].

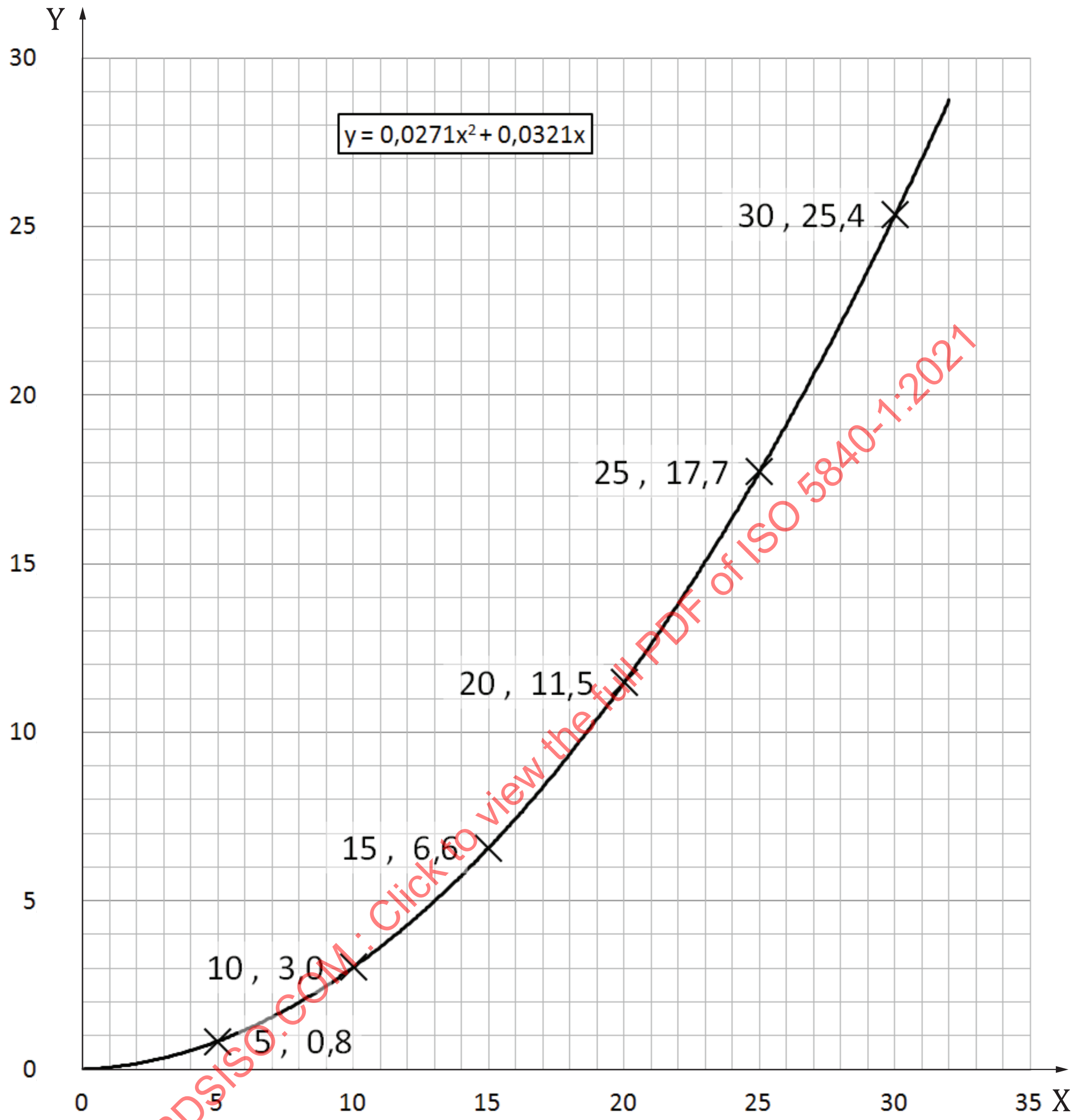
NOTE Based on physiological saline with specific gravity of 1,005 g/ml and viscosity of 1,0 cP.

Dimensions in millimetres



NOTE The nozzle outer diameter (*B*) is shown as 50,8 mm; this exact dimension varies based on the equipment used for conducting the study.

Figure I.1 — Standard nozzle, forward flow



Key

Y pressure drop (mmHg)

X flow rate (l/min)

NOTE This performance curve is defined for a straight tube with an inner diameter of 35 mm.

Figure I.2 — Forward flow nozzle gradients

I.2.3 Test procedure

Measure the difference across the test valve and the standard nozzle over a flow rate range of 5 l/min to 30 l/min in 5 l/min increments.

I.2.4 Test report

The test report should include the following:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity, and specific gravity;

b) a description of the steady flow apparatus;

c) details of the mean, range, and standard deviation of the following performance test variables at each simulated condition for each surgical heart valve substitute and standard nozzle should be presented in tabular and graphic form:

   1) steady flow rate;

   2) forward flow pressure differences;

   3) effective orifice area.

I.3 Steady back flow leakage testing

I.3.1 Measuring equipment accuracy

I.3.1.1 Steady flow leakage flowrate should have a minimum measurement accuracy of ±1 ml/s.

I.3.1.2 All other items of measuring equipment should have a minimum measurement accuracy of ±5 % of the maximum intended test measurement.

I.3.2 Test apparatus requirements

I.3.2.1 The steady back flow leakage testing should be conducted in an apparatus that is capable of generating constant back pressures appropriate for the intended device application in accordance with Tables 3 and 4. See Annex E for guidelines regarding suggested test conditions for the paediatric populations.

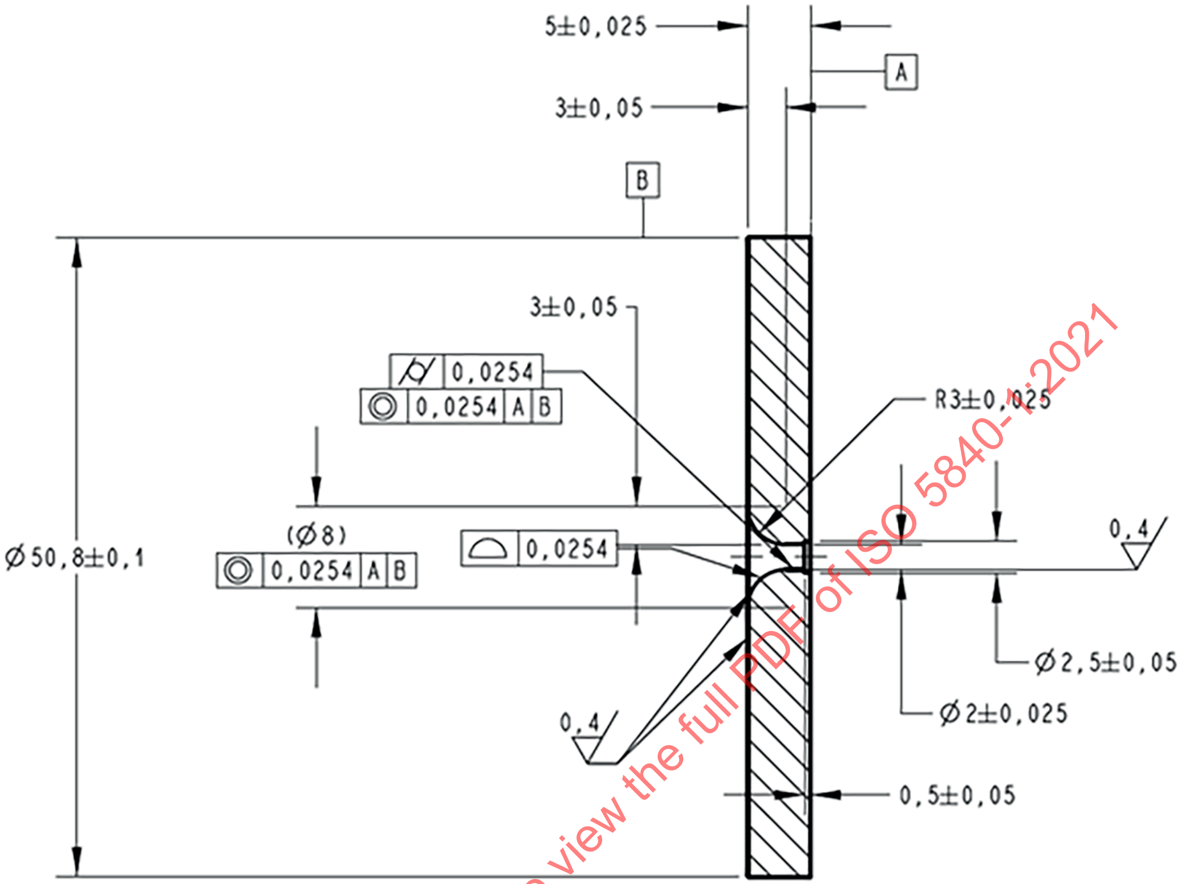
I.3.2.2 For surgical valves, the surgical heart valve substitute should be mounted in such a manner as to minimize leakage around and through the sewing ring.

I.3.2.3 For transcatheter valves, the heart valve substitute should be deployed within fixturing/simulated conduits representative of the intended implant site and deployed device diameters. For ViV and ViR indications, the heart valve substitute should be deployed into simulated operating configurations representative of the intended pre-existing prosthetic device.

I.3.2.4 A standardized nozzle in accordance with Figure I.3 can be used to characterize the back pressure, leakage volume flow rate and pressure measuring equipment. A plot of expected values for the backflow standard nozzle leakage rates can be found in Figure I.4. When accounting for acceptable accuracy tolerances, measured values should agree with these data.

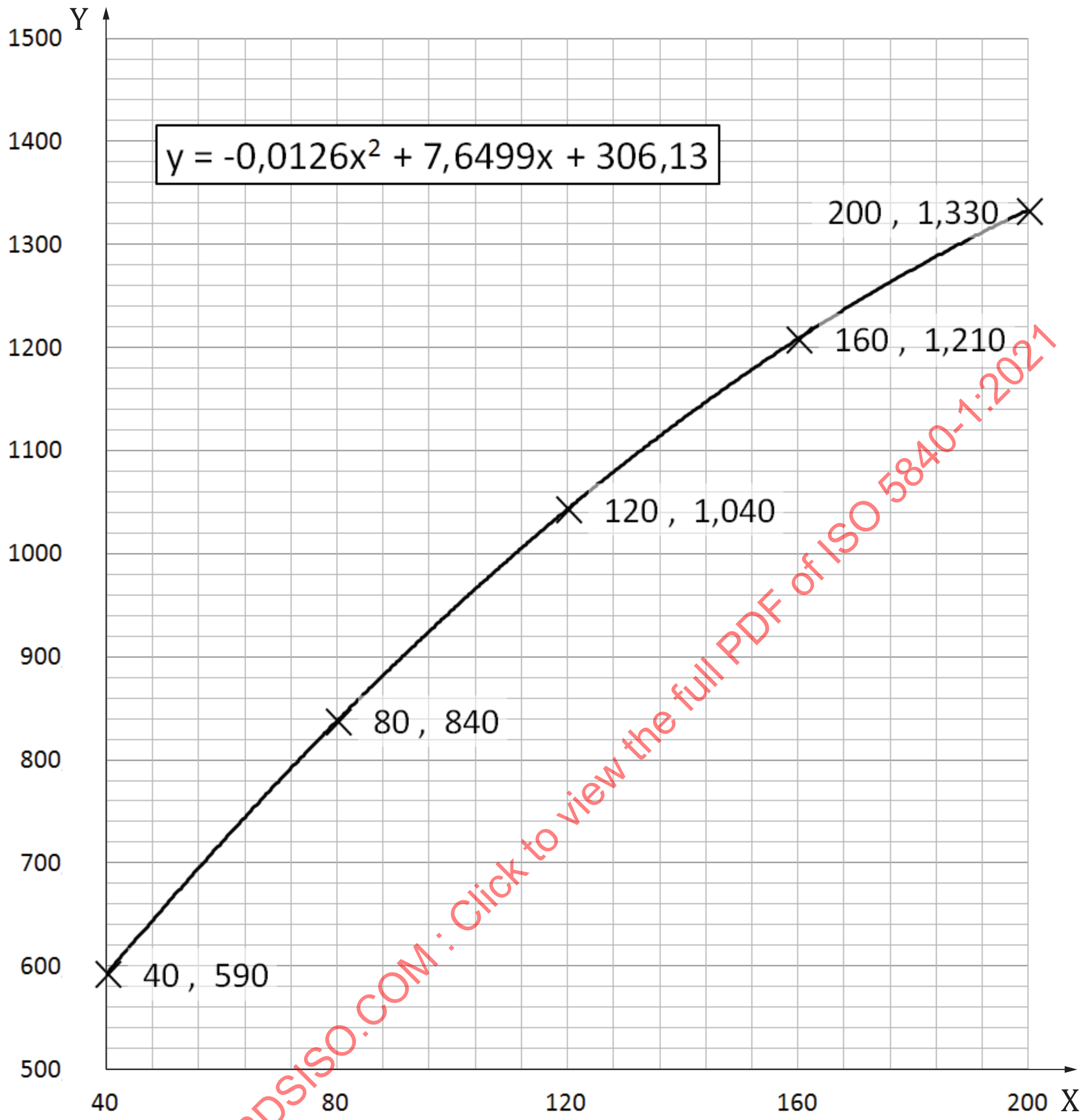
NOTE Results when using physiological saline with specific gravity of 1,005 g/ml and viscosity of 1,0 cP.

Dimensions in millimetres



NOTE The nozzle outer diameter (*B*) is shown as 50,8 mm; this exact dimension varies based on the equipment used for conducting the study.

Figure I.3 — Standard nozzle, back flow



Key

Y leakage (ml/min)

X pressure (mmHg)

Figure I.4 — Back flow nozzle leakage rates

I.3.3 Test procedure

Measure the leakage across the test valve and the standard nozzle at five equidistant back pressures appropriate for the intended device application in accordance with Tables 3 and 4. Collect at least five measurements at each level of back pressure. See Annex E for guidelines regarding suggested test conditions for the paediatric population.

I.3.4 Test report

The steady back flow test report should include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity and specific gravity under the test conditions;

b) a description of the steady flow apparatus;

c) details of the mean, range and standard deviation of the performance test variables, at each simulated condition for each test heart valve substitute and standard nozzle, presented in tabular and graphic form; i.e. leakage volume flow rate, expressed in l/min, as a function of back pressure.

Annex J
(normative)

Durability testing

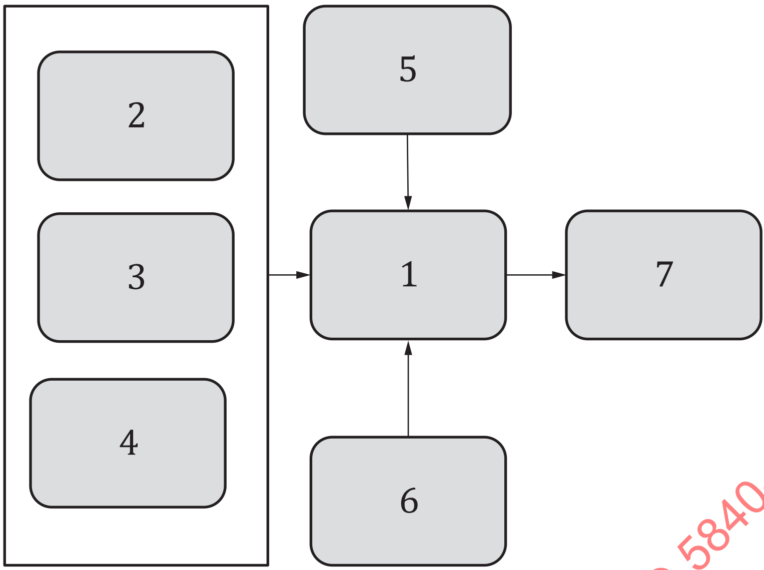
J.1 Rationale

A heart valve substitute is expected to last hundreds of millions of cycles, thus an accelerated approach is required to demonstrate device durability within a reasonable timeframe. However, assessing durability *in vitro* in an accelerated manner remains a challenge due to the absence of biological factors, and difficulties in replicating leaflet/occluder kinematics/load durations under accelerated conditions as each of these factors may impact the durability conclusion. Accelerating the cyclic operation of a heart valve in a manner that replicates valve loading conditions which approximate *in vivo* conditions (e.g. load durations, strain matching, inertial effects) has limitations due to the typical test frequencies used. To address these concerns, a variety of approaches are proposed to understand better the key factors that may affect device durability. Due to the complexity and test duration requirements, a combination of these test approaches (AWT, DFM and RWT) may be appropriate, as described in this annex.

A durability assessment of a heart valve substitute is an integral part of the device risk assessment. A heart valve substitute is typically engineered from a variety of materials (e.g. pyrolitic carbon, metallic frames, biological tissue or polymer materials) and can include variations in design and deployment methods (e.g. crimping, ballooning) which may affect device durability.

J.2 General

This annex provides general guidelines for assessing the durability of heart valve substitutes using a combination of methods. An example of an integrated durability assessment approach is provided in Figure J.1.



Key

1 integrated durability assessment
2 real-time wear testing
3 dynamic failure mode testing
4 accelerated wear testing
5 computational analysis results
6 pre-clinical *in vivo* evaluation results
7 inform risk assessment

Figure J.1 — Example of an integrated durability assessment

In this approach, the appropriate boundary conditions are first defined using available *in vivo* data; this may include the range of deployment variations and relevant haemodynamic conditions. These boundary conditions are utilized to define experimental test parameters. The AWT results are used to demonstrate a minimum *in vitro* durability lifetime. The DFM results are used to determine the anticipated durability-related failure modes of the heart valve substitute and provide insight regarding the potential failure consequences. RWT may be useful to verify the results from AWT. Computational methods, such as FEA, may be used in conjunction with durability test methods to translate test conditions imposed on the heart valve substitute into stress or strain metrics for interpretation of observed failure modes. Chronic pre-clinical *in vivo* study results may provide data to augment the *in vitro* durability assessment conclusion. It is expected that an integrated assessment utilizing multiple methods will provide a more comprehensive assessment of device durability. The conclusions from the durability assessment provide confirmatory data for input into the device risk assessment.

J.3 Accelerated wear testing

J.3.1 General

This annex provides requirements for test equipment, formulation of test protocols and test methods for the accelerated wear testing of heart valve substitutes. The heart valve substitutes shall be tested under appropriate loads while simulating device function in an appropriate fluid environment to a specified number of cycles required to demonstrate *in vitro* device durability.

Testing shall be performed to a minimum of 400 million cycles for heart valve substitutes that have the potential for failure modes resulting in immediate total loss of valve function. Testing shall be performed to a minimum of 200 million cycles for heart valve substitutes with failure modes that have been demonstrated to result in gradual degradation of valve function. For valve leaflet/occluder material types and/or processing methods without established clinical history, testing durations of greater than the minimum required cycle counts shall be considered, and scientifically justified if not performed.

J.3.2 Sample requirements

Test specimens shall comply with the requirements of 7.2.2.1.

For surgical heart valve substitutes, a minimum of 5 devices per labelled valve size shall be tested unless appropriate scientific justification for not testing all sizes is provided. However, at a minimum, the smallest, largest, and an intermediate size shall be tested. If surgical heart valve substitutes identical in design are intended for implant in multiple valve positions, testing shall be conducted at the worst-case valve conditions.

For transcatheter heart valve substitutes, the range of deployed configurations (e.g. ellipticity, minimum deployed size, maximum deployed size) shall be represented in the samples to be tested. When multiple deployed configurations exist for a given size, a minimum of three samples shall be tested per each deployed configuration. If the specific configuration(s) for a given size to be tested can be justified as being worst-case from a durability perspective, it may not be necessary to evaluate all possible configurations. When only a single deployed configuration is tested, a minimum of five samples shall be tested. All labelled valve sizes shall be tested unless appropriate scientific justification is provided. However, at a minimum, the smallest, largest, and an intermediate valve size shall be tested.

J.3.3 Test apparatus requirements

The equipment and test procedures shall be appropriate for the valve's intended indication (e.g. adult/paediatric, anatomical position). The test fixture shall be representative of the critical aspects of the target implant site, deployed size, and shape for the intended patient population. The test fixture design shall be justified by the manufacturer.

The pressure measurement system (e.g. transducers, sampling rate, filtering frequency) used to measure the transvalvular pressure difference shall be appropriate for the cycle rate being tested and pressure waveform being measured. Minimum accuracy for the differential pressure measurement shall be ±0,65 kPa (±5 mmHg) unless otherwise justified. The locations of the pressure transducers within the system shall be appropriately justified to ensure that the differential pressure targets across the closed test valves are achieved. The test system shall be capable of heating the test fluid and maintaining thermal stability with ability for temperature measurement.

J.3.4 Test procedure

Normotensive differential pressure conditions across the closed valve (see Tables 3 and 4) shall be applied for 5 % or more of a single cycle. The manufacturer shall statistically demonstrate that the differential pressure target is maintained for the required minimum number of cycles. Additional test cycles may be required to ensure the minimum number of test cycles at the target differential pressure have been attained. Tests shall be conducted at 37 ± 2 °C unless otherwise scientifically justified.

Test valves shall experience full range of leaflet/occluder motion associated with normotensive conditions. The hydrodynamic performance and valve leaflet/occluder opening and closing kinematics under normotensive conditions shall be characterized. The valve kinematics under AWT conditions shall be compared to those under pulse duplicator test conditions, and an assessment regarding the implications of any differences in observed leaflet/occluder kinematics shall be made. Quantitative comparison of performance parameters (e.g. geometric orifice area) can be useful in characterizing the extent of leaflet/occluder opening.

The test cycle rate shall be appropriately justified and should be established based on the heart valve substitute design and materials of construction, as these might influence the results of durability tests. Specifying test frequency without consideration to material response may result in unsatisfactory loading of the valve.

