



BSI Standards Publication

Cardiovascular implants — Cardiac valve prostheses

Part 1: General requirements

National foreword

This British Standard is the UK implementation of EN ISO 5840-1:2021+A1:2025. It is identical to ISO 5840-1:2021, incorporating amendment 1:2025. It supersedes BS EN ISO 5840-1:2021, which is withdrawn.

The start and finish of text introduced or altered by amendment is indicated in the text by tags. Tags indicating changes to ISO text carry the number of the ISO amendment. For example, text altered by ISO amendment 1 is indicated by A1 A1.

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

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English Version

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Implants cardiovasculaires - Prothèses valvulaires -
Partie 1: Exigences générales (ISO 5840-1:2021)

Herz- und Gefäßimplantate - Herzklappenprothesen -
Teil 1: Allgemeine Anforderungen (ISO 5840-1:2021)

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European foreword

This document (EN ISO 5840-1:2021) has been prepared by Technical Committee ISO/TC 150 "Implants for surgery" in collaboration with Technical Committee CEN/TC 285 "Non-active surgical implants" the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by August 2021, and conflicting national standards shall be withdrawn at the latest by August 2021.

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This document supersedes EN ISO 5840-1:2015.

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Endorsement notice

The text of ISO 5840-1:2021 has been approved by CEN as EN ISO 5840-1:2021 without any modification.

European foreword to Amendment 1

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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).

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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

A1 device-specific tool that is required to assist in the implantation and/or adjustment of the *heart valve substitute* (3.30), excluding the delivery system **A1**

3.2 adverse event AE

A1 untoward medical occurrence, disease or injury, or clinical signs (including abnormal laboratory findings) in patients, whether or not related to the investigational medical device and whether anticipated or unanticipated

Note 1 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators, whether anticipated or unanticipated.

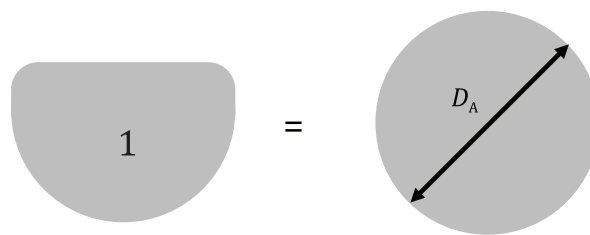
Note 2 to entry: This definition includes events related to the investigational medical device or the comparator, when applicable.

Note 3 to entry: This definition includes events related to the procedures involved. **A1**

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 (m²) 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;

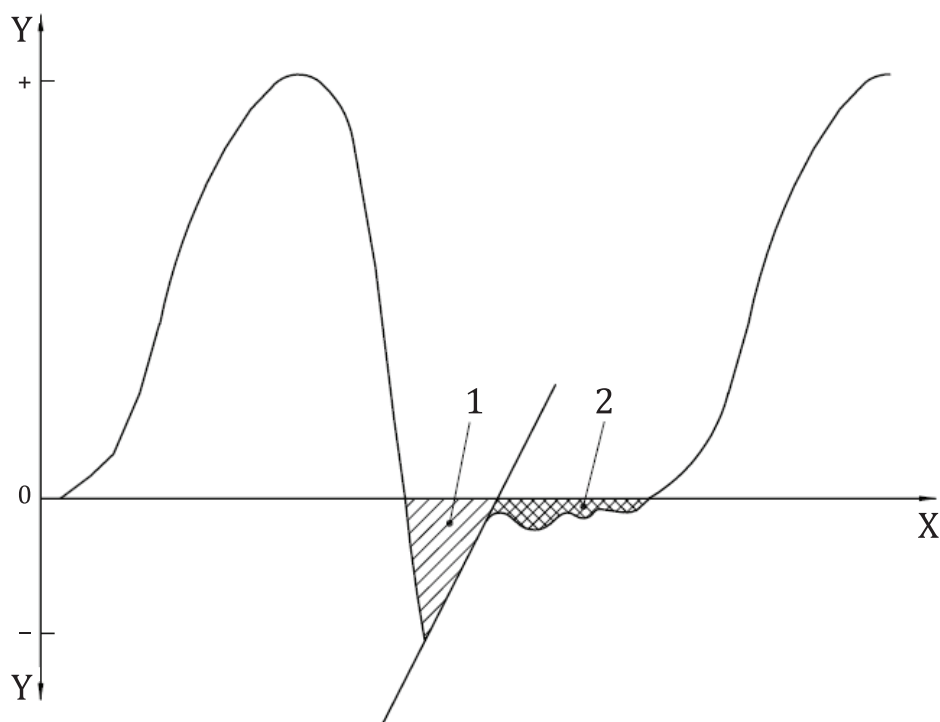
p_1 is the diastolic pressure, in mmHg;

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 (cm²);

$q_{v_{RMS}}$ 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/cm³).

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

A_1 volume of fluid that flows through and around 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 can only be possible to measure the leakage volume and does not always include the closing volume.

Note 2 to entry See Figure 2. A_1

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:

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

where

$q_{v_{\text{RMS}}}$ is the root mean square forward flow during the positive differential pressure period;

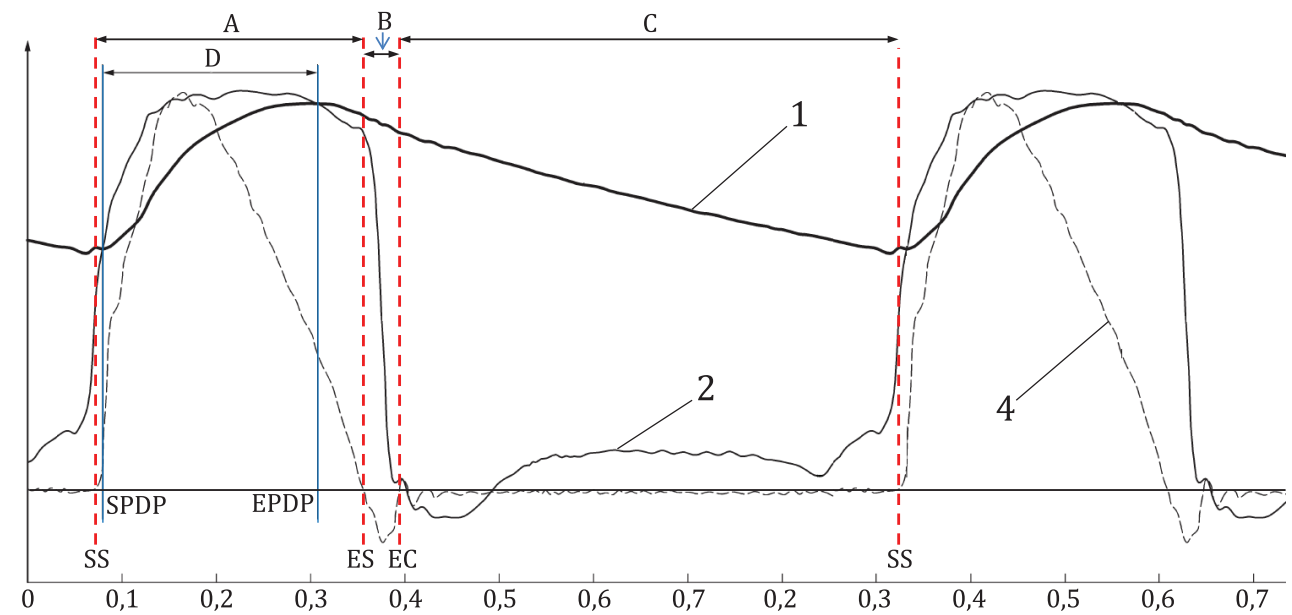
$q_v(t)$ is the instantaneous flow at time (t);

t_1 is the time at the start of the *positive differential pressure period* ([3.44](#));

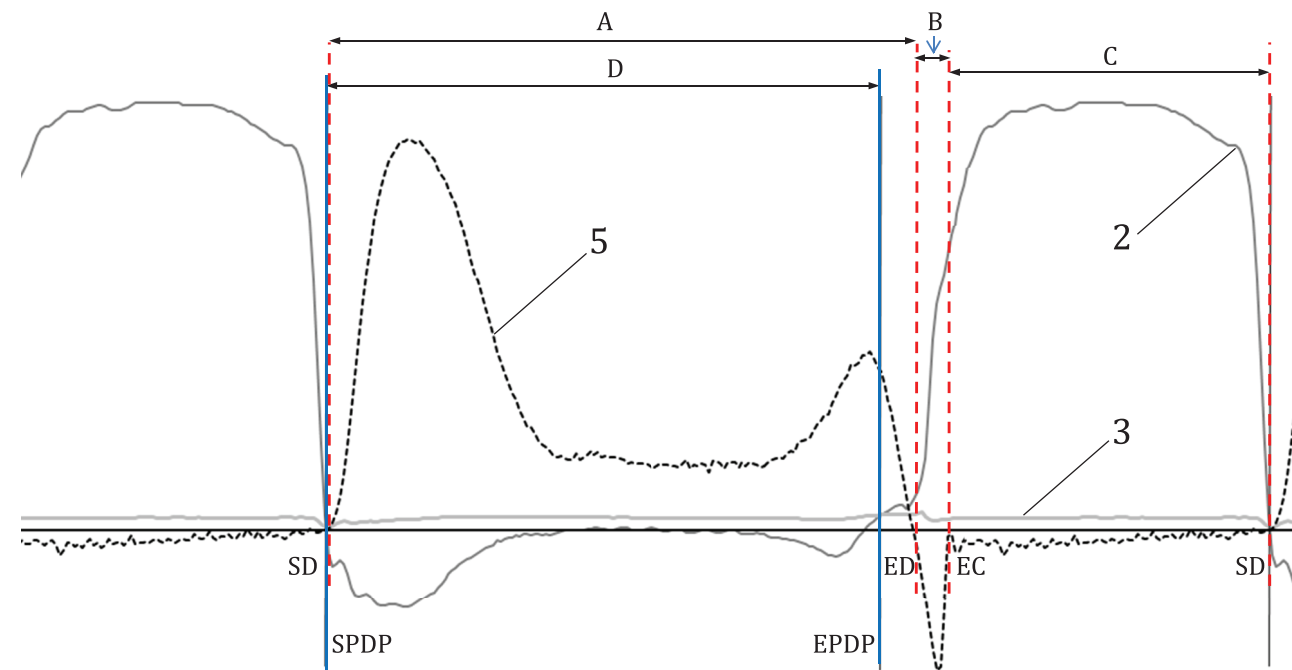
t_2 is the time at the end of the positive differential pressure period.

Note 3 to entry: The rationale for use of $q_{v_{\text{RMS}}}$ 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



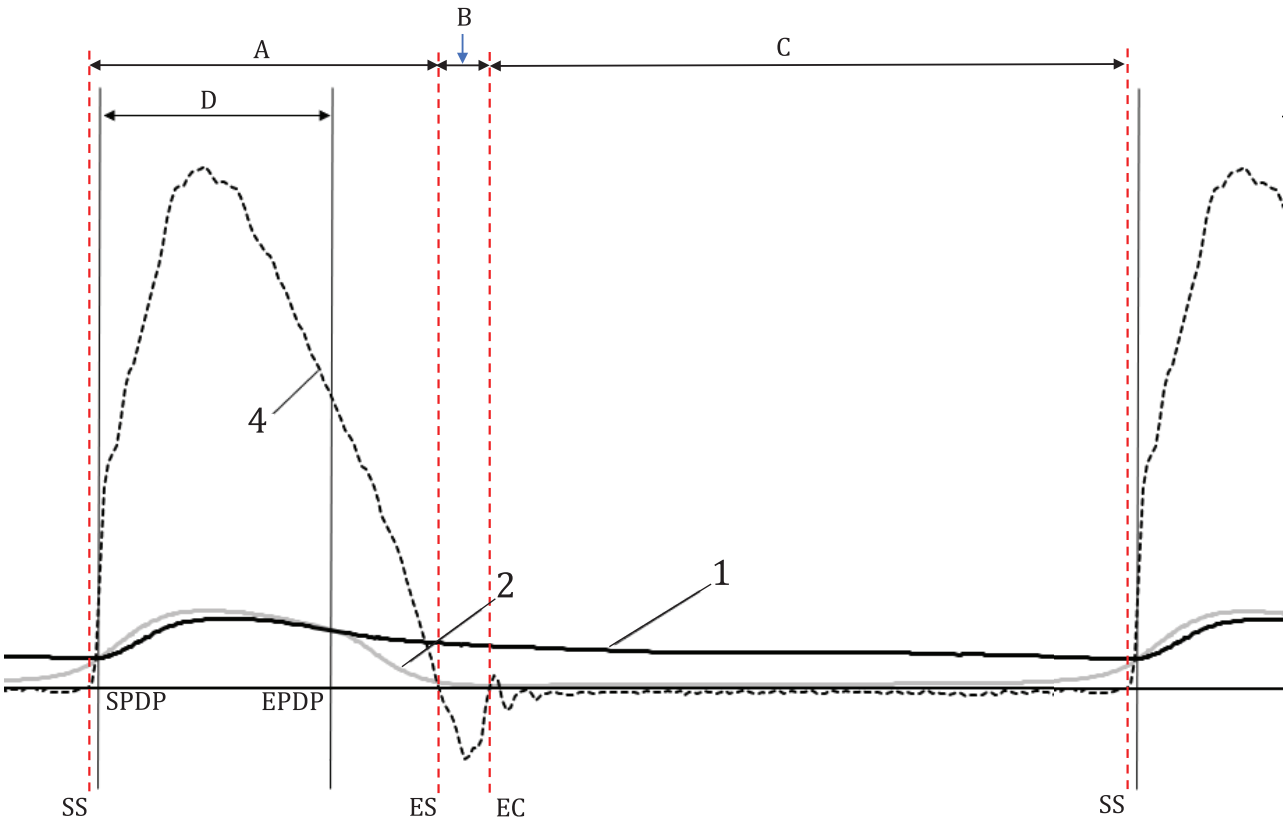
b) Mitral valve

Key

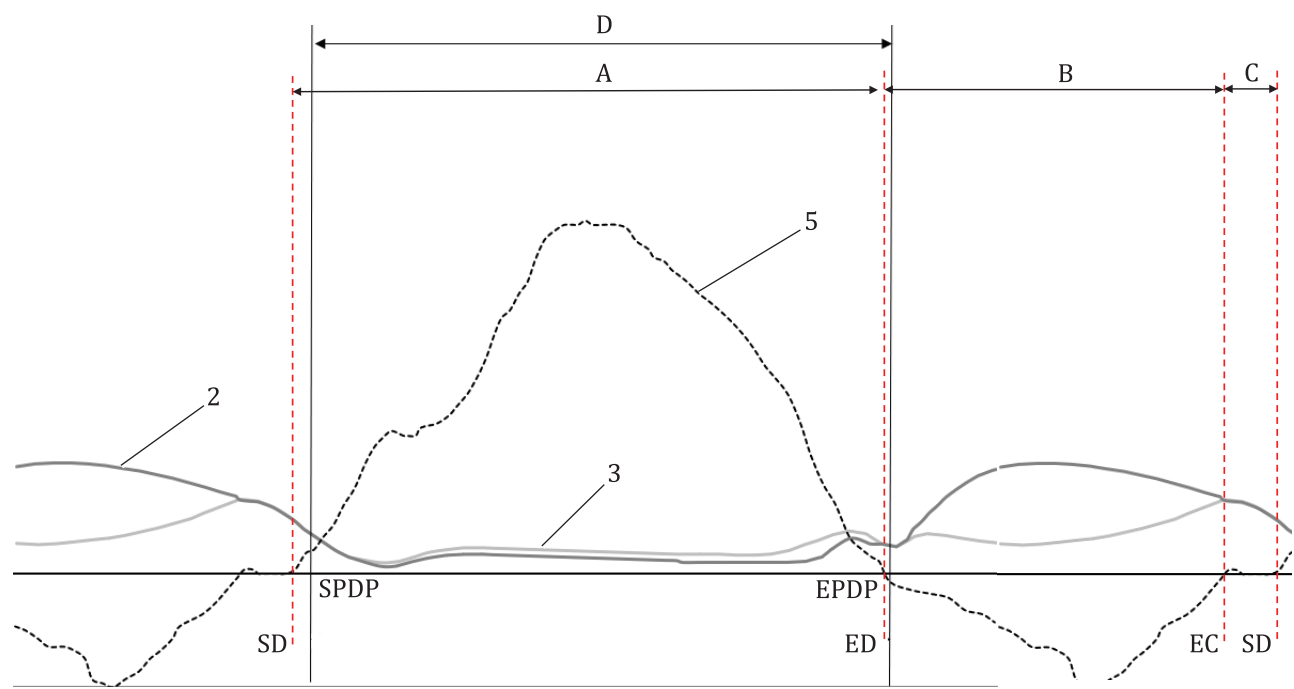
- | | |
|-----------------------------|---|
| 1 aortic pressure | A forward flow period |
| 2 left ventricular pressure | B closing flow period |
| 3 left atrial pressure | C leakage flow period |
| 4 aortic flow rate | D positive pressure differential period |
| 5 mitral flow rate | |

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 | A forward flow period |
| 2 right ventricular pressure | B closing flow period |
| 3 right atrial pressure | C leakage flow period |
| 4 pulmonary flow rate | D positive pressure differential period |
| 5 tricuspid flow rate | |

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 mmHg	Arterial end diastolic pressure mmHg	Peak differential pressure across closed valve ^a	
			Aortic ΔP_A mmHg	Mitral ΔP_M 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 $\approx$ 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

A1	Aortic peak systolic pressure	Aortic end diastolic pressure	Differential pressure across closed valve ^b	
	mmHg	mmHg	Aortic mmHg	Mitral mmHg
normotensive ^a	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

^a For *in vitro* hydrodynamic minimum performance device testing (i.e. Table 1 and Table 2 of ISO 5840-2:2021 and ISO 5840-3:2021), the aortic peak systolic pressure and aortic end diastolic pressure shall be the control pressures.

^b With durability testing, the “differential pressure across closed valve” shall define the differential pressure condition that shall be maintained for at least 5 % of the cycle. A1