

American
National
Standard

ANSI/AAMI/
ISO 5840-1:
2022

Cardiovascular implants—
Cardiac valve prostheses—
Part 1: General requirements

Cardiovascular implants—Cardiac valve prostheses— Part 1: General requirements

Approved 13 December 2021 by
AAMI

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American National Standards Institute

Abstract: 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.

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

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Contents

Page

Committee representation.....	vi
Background of ANSI/AAMI adoption of ISO 5840-1:2021	vii
Foreword.....	viii
Introduction	ix
1 Scope.....	1
2 Normative references.....	1
3 Terms and definitions.....	2
4 Abbreviations	14
5 Fundamental requirements	15
6 Device description.....	15
6.1 General.....	15
6.2 Intended use.....	15
6.3 Design inputs.....	15
6.4 Design outputs	18
6.5 Design transfer (manufacturing verification/validation).....	18
6.6 Risk management	18
7 Design verification and validation.....	18
7.1 General requirements.....	18
7.2 In vitro assessment	19
7.3 Preclinical in vivo evaluation.....	24
7.4 Clinical investigations	24
Annex A (informative) Rationale for the provisions of ISO 5840-1	25
A.1 Rationale for a risk-based approach.....	25
A.2 Rationale for preclinical <i>in vivo</i> evaluation.....	25
A.3 Rationale for design verification and design validation testing	25
A.4 Rationale for echocardiographic assessment.....	26
A.5 Rationale for clinical evaluation reporting	26
A.6 Rationale for device sizing within labelling and instructions for use	26
A.7 Rationale for human factors engineering.....	27
Annex B (normative) Packaging.....	28
B.1 Requirements	28
B.2 Principle.....	28
B.3 Containers.....	28
Annex C (normative) Product labels, instructions for use, and training	29
C.1 General.....	29
C.2 Training for physicians and support staff.....	31
Annex D (normative) Sterilization.....	32
Annex E (normative) <i>In vitro</i> test guidelines for paediatric devices	33

E.1	General and paediatric definitions	33
E.2	Pulsatile flow test conditions — Left side.....	34
E.3	Pulsatile flow test conditions — Right side	34
E.4	Steady back pressure and forward flow conditions — Left side	35
E.5	Steady back pressure and forward flow conditions — Right side	35
E.6	Accelerated wear testing (AWT) test conditions — Left side	36
E.7	Accelerated wear testing (AWT) test conditions — Right side.....	36
E.8	FEA/life analysis conditions — Left side.....	37
E.9	FEA/life analysis conditions — Right side	37
Annex F (informative) Corrosion assessment		38
F.1	Rationale	38
F.2	General.....	38
F.3	Pitting corrosion.....	38
F.4	Crevice corrosion	39
F.5	Galvanic corrosion.....	39
F.6	Corrosion fatigue	39
F.7	Fretting (wear) and fretting corrosion	40
F.8	Post-fatigue corrosion evaluation	40
Annex G (informative) Echocardiographic protocol		41
G.1	General.....	41
G.2	Echocardiographic studies	42
G.3	Data collected.....	42
Annex H (informative) Assessment of implant thrombogenic and haemolytic potential		43
H.1	Rationale	43
H.2	General.....	43
H.3	Experimental flow field assessment	44
H.4	Computational flow field assessment	47
H.5	<i>Ex vivo</i> blood testing	50
Annex I (informative) Guidelines for hydrodynamic performance characterization by steady flow testing		54
I.1	General.....	54
I.2	Steady forward flow testing	54
I.3	Steady back flow leakage testing	57
Annex J (normative) Durability testing.....		61
J.1	Rationale	61
J.2	General.....	61
J.3	Accelerated wear testing	62
J.4	Dynamic failure mode testing	65
J.5	Real-time wear testing.....	67
Annex K (informative) Fatigue assessment.....		69
K.1	General.....	69
K.2	Determination of <i>in vivo</i> boundary conditions	70
K.3	Structural component stress/strain analysis	71

K.4	Material fatigue strength determination	72
K.5	Fatigue safety factor or probability of fatigue fracture determination	72
K.6	Component fatigue demonstration test.....	73
Annex L (normative) Clinical investigation endpoints for heart valve replacement devices.....		74
L.1	General.....	74
L.2	Single endpoints.....	74
L.3	Heart failure hospitalization definition	75
L.4	Composite endpoints.....	76
L.5	Timing of endpoints	76
Bibliography		77

Figures

Figure 1—Area-derived valve diameter for a non-circular device.....	3
Figure 2—Schematic representation of flow waveform, regurgitant volumes, and end of closure determination for one cycle.....	4
Figure 3—Schematic representation of aortic and mitral flow and pressure waveforms versus time from <i>in vitro</i> testing	10
Figure 4—Schematic representation of pulmonary and tricuspid flow and pressure waveforms versus time from <i>in vitro</i> testing	11
Figure H.1—Example of integrated thrombus and haemolytic potential assessment approach.....	44
Figure H.2—Example imaging planes (axial view) for symmetric trileaflet (left) and a symmetric D-shaped (right) valve	46
Figure H.3—Examples of flow domains for aortic/pulmonary valve (left) and mitral/tricuspid valve (right).....	49
Figure H.4—Example planes to be used for computational validation (intersections of planes define lines for comparison purposes).....	49
Figure I.1—Standard nozzle, forward flow	55
Figure I.2—Forward flow nozzle gradients.....	56
Figure I.3—Standard nozzle, back flow.....	58
Figure I.4—Back flow nozzle leakage rates	59
Figure J.1—Example of an integrated durability assessment	62
Figure K.1—Example schematic of a structural component fatigue assessment using a stress-life or strain-life approach	70

Tables

Table 1—Heart valve substitute operational environment for left side of heart — Adult population	16
Table 2—Heart valve substitute operational environment for right side of heart — Adult population.....	17
Table 3—Recommended pressure values for <i>in vitro</i> testing for left side of heart — Adult population	19
Table 4—Recommended pressure values for <i>in vitro</i> testing for right side of heart — Adult population	20
Table E.1—Paediatric definitions	33
Table E.2—Pulsatile flow test conditions — Left side	34
Table E.3—Pulsatile flow test conditions — Right side	34
Table E.4—Steady back pressure and forward flow conditions — Left side	35
Table E.5—Steady back pressure and forward flow conditions — Right side.....	35
Table E.6—AWT test conditions — Left side	36
Table E.7—AWT test conditions — Right side.....	36
Table E.8—FEA/life analysis conditions — Left side.....	37
Table E.9—FEA/life analysis conditions — Right side	37

Committee representation

Association for the Advancement of Medical Instrumentation

Cardiac Valve Prostheses Committee

The adoption of ISO 5840-1:2021 as an American National Standard was initiated by the AAMI Cardiac Valve Prostheses Committee. AAMI/CV provides input to the U.S. TAG to ISO/TC150/SC2 - *Cardiovascular implants and extracorporeal systems* which is the responsible group for providing the U.S. input to the relevant group in U.S. ISO/TC150/SC2. U.S. representatives from AAMI Cardiac Valve Prostheses Committee and the U.S. TAG played an active part in developing the ISO document.

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

Cochairs: Russ Joseph
Changfu Wu, Ph.D.

Members: Chad Abunassar, Abbott Laboratories
Pavan Atluri, Hospital of the University of Pennsylvania - CE Dept
Jeffrey Borer, SUNY Downstate Medical Center
Duke Edward Cameron, Massachusetts General Hospital
John Carney, University of Minnesota Medical Center - Fairview
James Conti, Dynatek Labs
Lakshmi Prasad Dasi, Individual
Russ Joseph, Edwards Lifesciences
Timothy Kelley, Medtronic Inc Campus
Shouyan Lee, Medical Implant Testing Lab, Inc
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Matthew Weston, Medtronic Inc Campus

NOTE Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 5840-1:2021

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

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

AAMI encourages its committees to harmonize their work with International Standards in the area of general requirements for cardiac valve substitutes. Upon review of ISO 5840-1:2021, the U.S. Technical Advisory Group, TAG for TC/150/SC2 and the AAMI Cardiac Valve Prostheses Committee decided to adopt it verbatim, as a second edition/ revision of ANSI/AAMI/ ISO 5840-1:2015.

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

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

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

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

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

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

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

NOTE Beginning with the ISO foreword on page viii, this American National Standard is identical to ISO 5840-1:2021.

Foreword

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

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

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

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

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

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

This second edition cancels and replaces the first edition (ISO 5840-1:2015), 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 (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

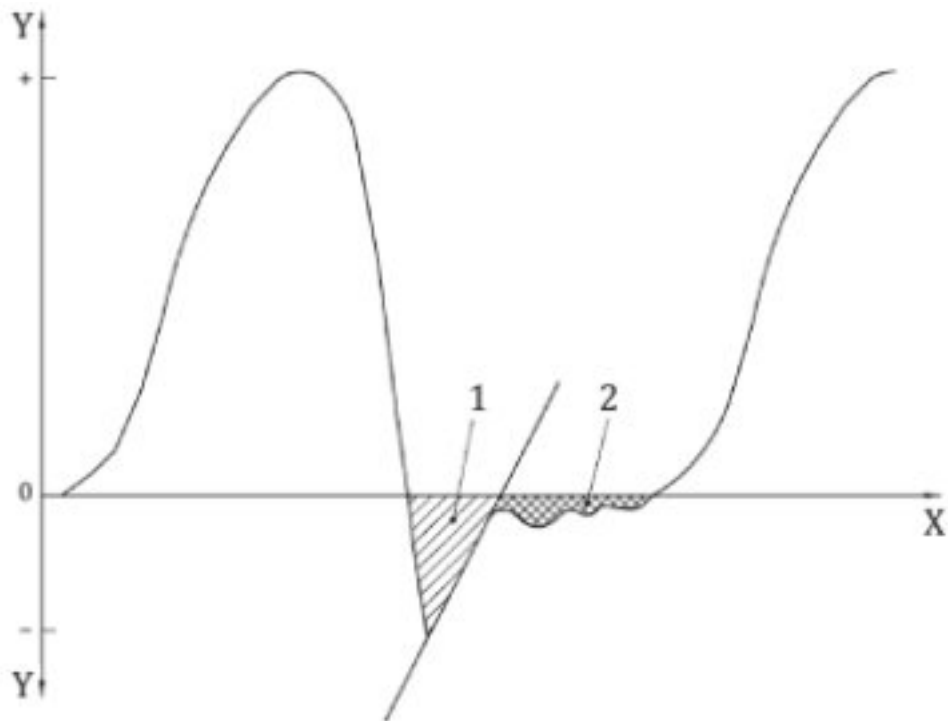
relationship between change in diameter and change in pressure of a deformable tubular structure (e.g. aorta, conduit) defined in ISO 5840 (all parts) as

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

where

- C is the compliance in units of % radial change/100 mmHg;
- p1 is the diastolic pressure, in mmHg;
- p2 is the systolic pressure, in mmHg;
- r1 is the inner radius at p1, in millimetres;
- r2 is the inner radius at p2, 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 Figure 3 a) and Figure 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

occlude

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:

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

where

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

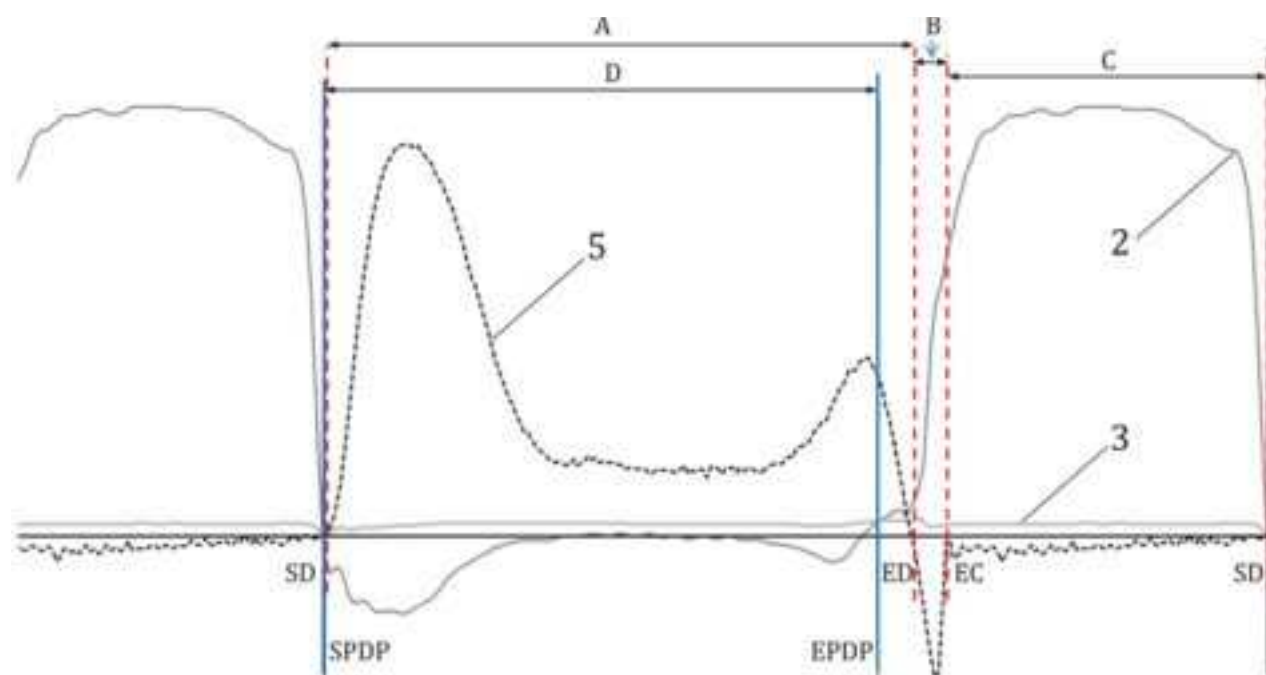
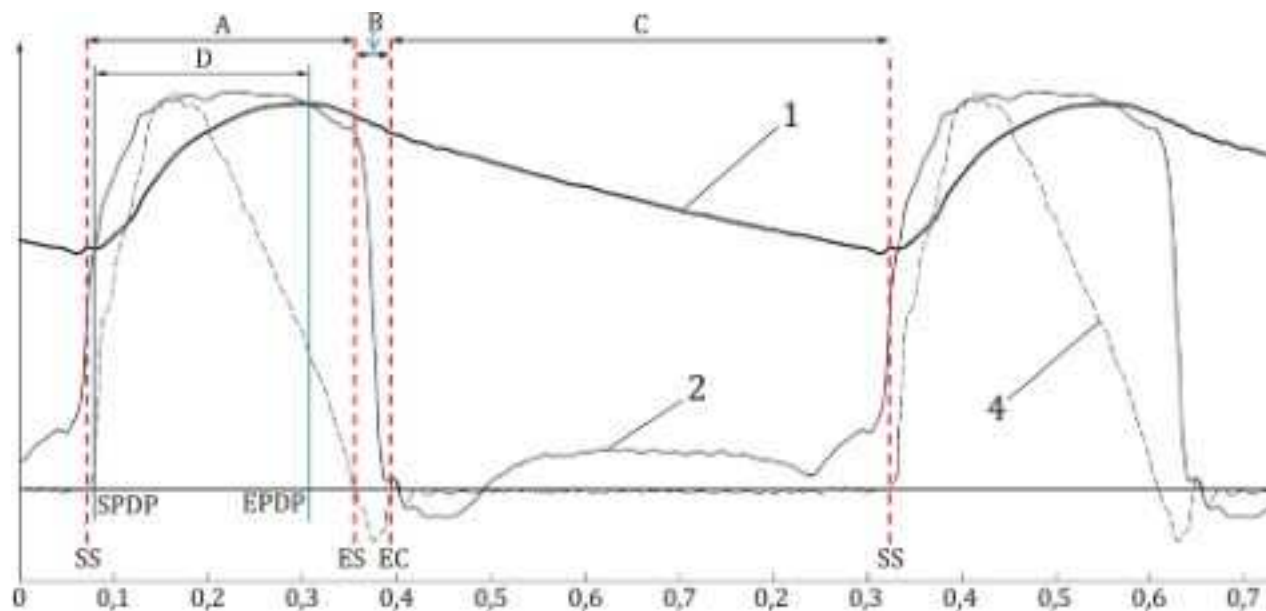
$q_v(t)$ is the instantaneous flow at time (t);

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.

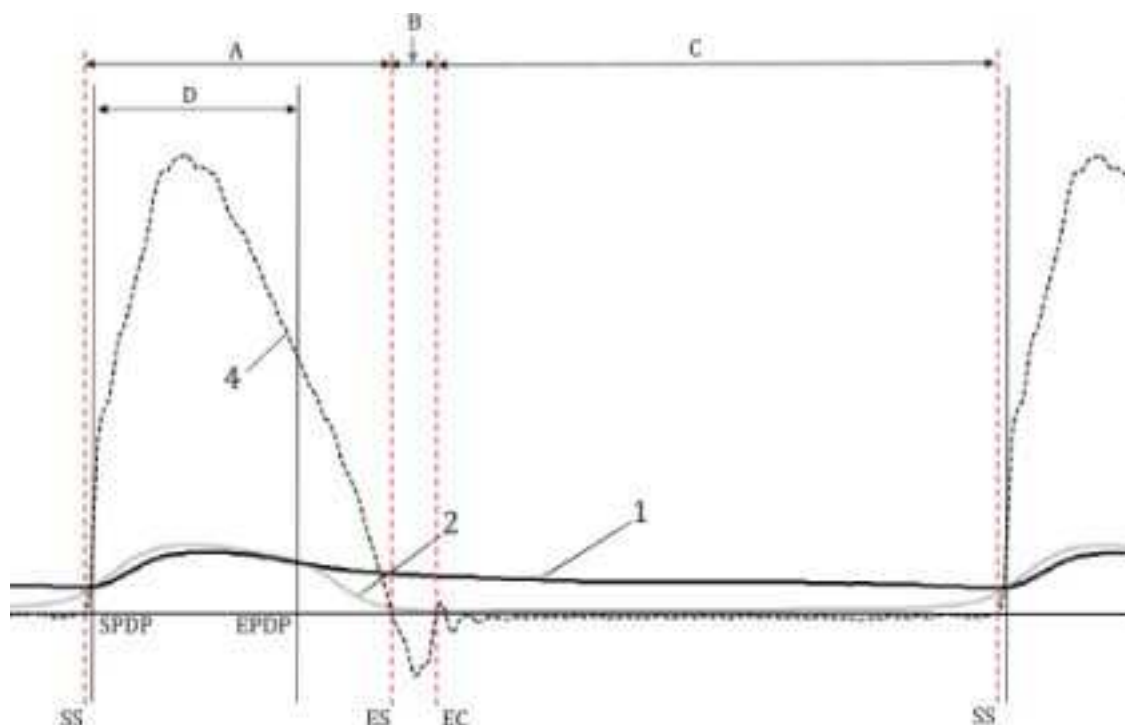


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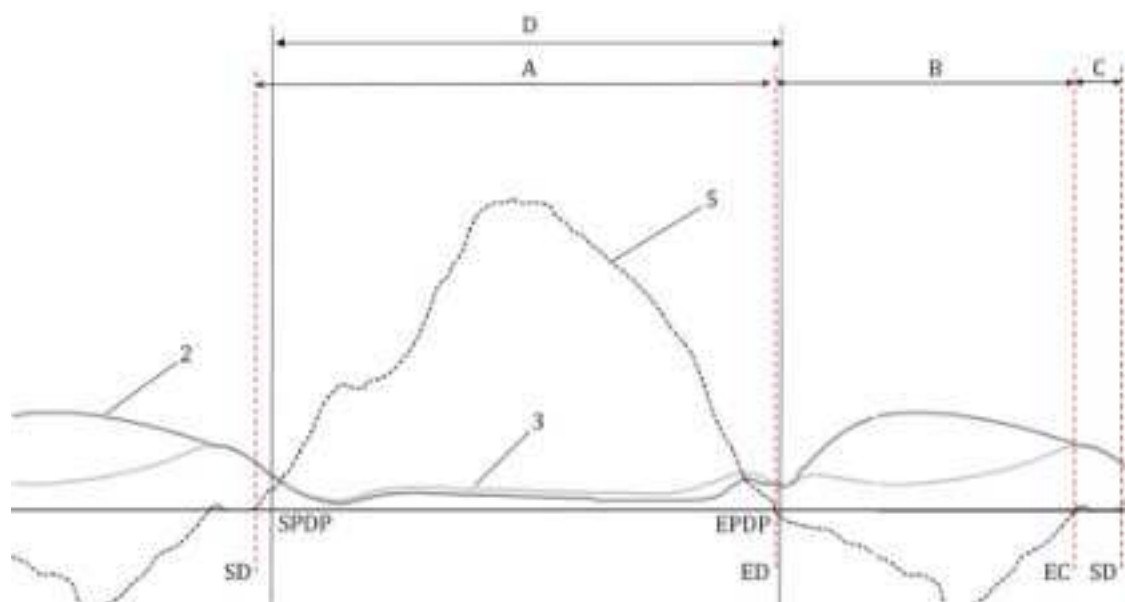
- | | | | |
|---|---------------------------|---|---------------------------------------|
| 1 | aortic pressure | A | forward flow period |
| 2 | left ventricular pressure | B | closing flow period |
| 3 | left atrial pressure | C | leakage flow period |
| 4 | aortic flow rate | D | positive pressure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

$$O_{sc} = V_{ff} \times r_b$$

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).