

Redline version
compares Second edition to
First edition



Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

Implants cardiovasculaires — Prothèses valvulaires —

Partie 1: Exigences générales
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- Text example 1 — Text has been added (in green)
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DISCLAIMER

This marked-up version highlights the main changes in this edition of the document compared with the previous edition. It does not focus on details (e.g. changes in punctuation).

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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 WTO World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL, see [Foreword – Supplementary Information www.iso.org/iso/foreword.html](http://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 of ISO 5840-1, together with ISO 5840-2 and 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 consists of the following parts, under the general title can be found on the *Cardiovascular implants – Cardiac valve prostheses* ISO website.

- ~~Part 1. General requirements~~
- ~~Part 2. Surgically implanted heart valve substitutes~~
- ~~Part 3. Heart valve substitutes implanted by transcatheter techniques~~

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/or requirements for test apparatus and test apparatuses and requires documentation of test methods and results. The areas with which the ISO 5840 series are concerned are those which will 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 will be presented at the operating table in a convenient form. Emphasis has been placed on specifying types of *in vitro* testing, on preclinical *in vivo* and clinical evaluations, on reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations, and on 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 incomplete in several areas. It 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.

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Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

1 Scope

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

This ~~part of ISO 5840~~ document is applicable to ~~both~~ newly developed and modified heart valve substitutes and to the ~~accessories~~ accessory devices, packaging, and labelling required for their implantation and for determining the appropriate size of the heart valve substitute to be implanted.

This ~~part of~~ ISO 5840-1 outlines an approach for ~~qualifying~~ 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.

This ~~part of~~ ISO 5840-1 defines operational conditions for heart valve substitutes.

This ~~part of~~ ISO 5840-1 ~~excludes~~ ~~homografts~~ further 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 this ~~part of~~ ISO 5840-1 is given in Annex A.

2 Normative references

The following documents, ~~in whole or in part, are normatively referenced in this document and are indispensable for its application~~ 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 14630-2012, *Non-active surgical implants — General requirements*

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

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

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

ISO 17665-22442 (all parts), *Sterilization of health care products — Moist heat* *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

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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

~~accessories~~ **accessory**

device-specific ~~tools that are~~ **tool that is** required to assist in the implantation of the *heart valve substitute* (3.283.30)

3.2

adverse event

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

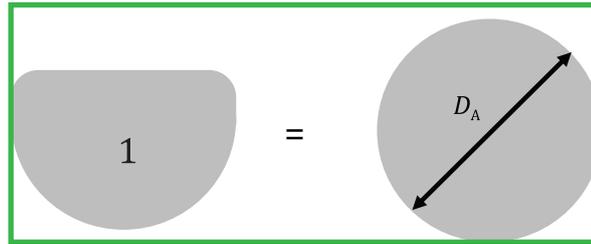
Note 1 to entry: An AE can be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporary or permanent, whether or not related to the ~~prosthetic valve~~ *heart valve substitute* (3.30) or implantation or procedure.

3.3

~~actuarial methods~~ **area-derived valve diameter**

D_A
~~statistical technique for calculating event rates over time~~ **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: ~~Standard actuarial methods calculate the probability of freedom from events within pre-specified intervals of time. When the intervals approach zero width, the methods are called Kaplan-Meier methods.~~ 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* (3.63.68)**3.6****back pressure**

differential pressure applied 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 times and the height in cm divided by 3 600 (see Reference [3.126]).

~~**3.8**~~~~**cardiac index**~~~~cardiac output (3.9) (CO, L/min) divided by the body surface area (3.7) (BSA, m²) with units L/min/m²~~~~**3.9**~~**3.8****cardiac output****CO**

stroke volume (3.59.3.64) times heart rate

~~**3.10**~~**3.9****closing volume**portion of the *regurgitant volume* (3.48.3.49) that is associated with the dynamics of valve closure during a single cycle (3.15.3.13)

Note 1 to entry: See Figure 12.

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.

~~**3.11**~~**3.10****coating**thin-film material that is applied to an element of a *heart valve system* (3.29.3.31) to modify its surface physical or chemical properties

~~3.12~~ 3.11

compliance

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

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

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

where

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

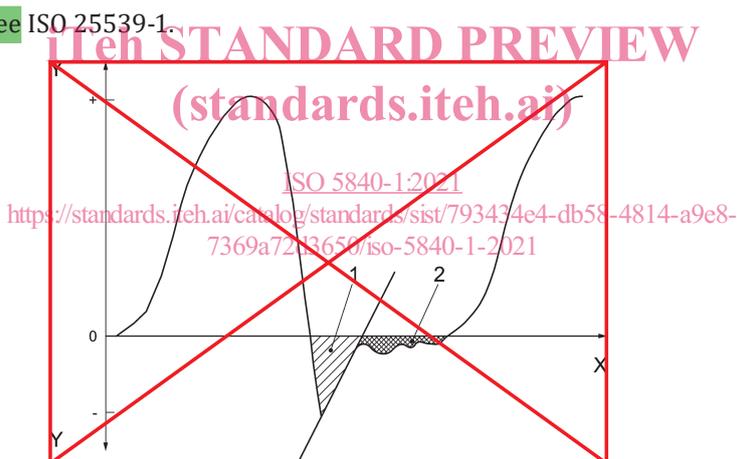
p_1 is the diastolic pressure, in mmHg;

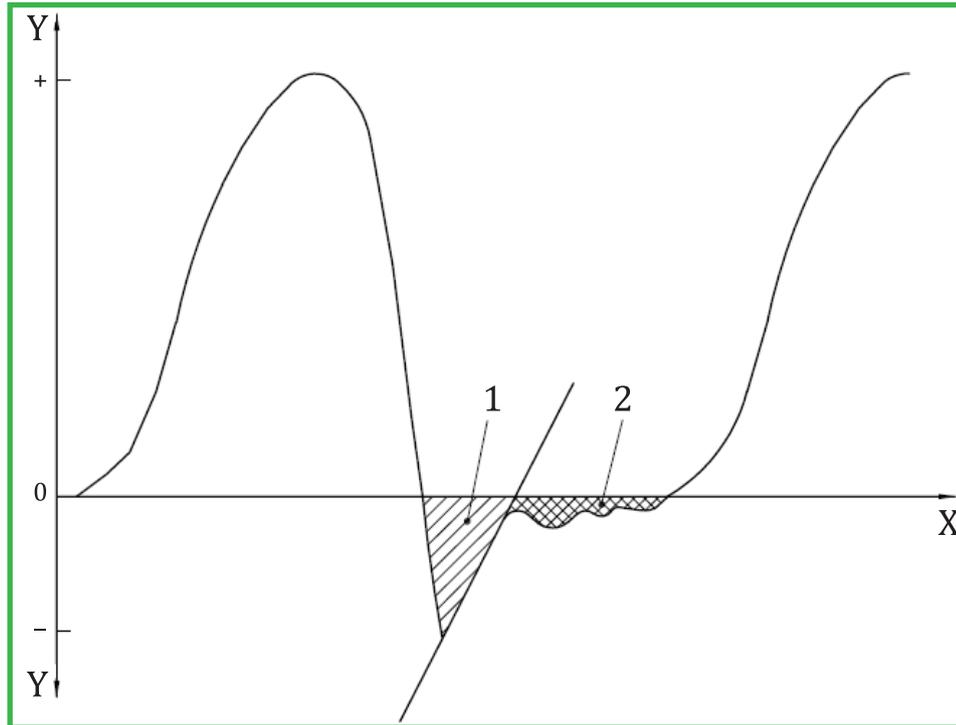
p_2 is the systolic pressure, in mmHg;

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: Reference See ISO 25539-1.



**Key**

X time

Y flowrate

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1 closing volume

2 leakage volume

NOTE

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

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Figure 12 — Schematic representation of flow waveform and regurgitant volumes, regurgitant volumes, and end of closure determination for one cycle

3.13**component joining material**

material such as a suture, adhesive, or welding compound used to assemble the components of a heart valve system (3.29)

3.14 3.12**cumulative incidence control valve**

statistical technique where events other than death can be described by the occurrence of the event over time without including death of the subjects heart valve substitute for preclinical and clinical evaluations of similar design and constructed of similar material as the investigational device

Note 1 to entry: Cumulative incidence is also known as “actual” analysis. The control valve should have a known clinical history.

3.15 3.13**cycle**

one complete sequence in the action of a heart valve substitute (3.29 3.30) under pulsatile-flow conditions

3.16 3.14**cycle rate****beat rate**

number of complete cycles (3.15 3.13) per unit of time usually expressed as cycles per minute (cycles/min or beats/min [bpm])

~~3.17~~ 3.15

design verification

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

~~3.18~~ 3.16

design validation

establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (~~3.31~~ 3.33)

~~3.19~~ 3.17

device embolization

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

~~3.20~~ 3.18

device failure

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

~~3.21~~ 3.19

~~device migration~~ **diastole**

diastolic duration

~~detectable movement or displacement of the portion of heart valve substitute (3.20) from its original position within the implant position (3.30) and without device embolization (3.19)~~ cardiac cycle time corresponding to ventricular filling

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

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~~3.22~~ 3.20

effective orifice area

EOA

orifice area that has been derived from flow and pressure or velocity data ~~For *in vitro* testing, EOA is defined as:~~

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

~~where~~

~~EOA is the Effective Orifice Area (cm²);~~

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

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

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

Note 1 to entry: See 3.53. 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/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

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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.

~~3.23~~ 3.25 failure mode

mechanism of *device failure* (~~3.20~~3.18)

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

~~3.24~~ 3.26 flexible ~~surgical heart valve substitute~~

~~surgical heart valve substitute~~ (~~3.62~~3.30) wherein the *occluder* (~~3.40~~3.42) is flexible under physiological conditions (e.g. bioprostheses)

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

~~3.25~~ 3.27 follow-up

continued assessment of patients who have received the *heart valve substitute* (~~3.20~~3.30)

~~3.26~~3.28

forward flow volume

volume of flow ejected through the *heart valve substitute* (~~3.28~~3.30) ~~in the forward direction during one cycle (3.15)~~ 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

~~3.27~~3.29

fracture

complete separation of any structural component of the *heart valve substitute* (~~3.28~~3.30) that was previously intact

~~3.28~~3.30

heart valve substitute

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

~~3.29~~3.31

heart valve system

~~implantable device~~, set of elements provided to replace the native heart valve, consisting of the heart valve substitute, accessories (3.1), packaging, labelling, and instructions

~~3.30~~3.32

~~implant site/implant position~~

implant position

intended location of *heart valve substitute* (~~3.28~~3.30) implantation or deployment

~~3.31~~3.33

intended use

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

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~~3.32~~3.34

~~Kaplan-Meier methods~~ **method**

statistical ~~approaches~~ approach for calculating event rates over time when the actual dates of events for each person in the population are known

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~~3.33~~3.35

leakage volume

portion of the *regurgitant volume* (~~3.48~~3.49) which is associated with leakage during the closed phase of a valve in a single cycle (~~3.15~~3.13) and is the sum of the *transvalvular leakage volume* (~~3.66~~3.71) and *paravalvular leakage volume* (~~3.43~~3.45)

Note 1 to entry: ~~The point of separation between the closing and leakage volumes is obtained according to a defined and stated criterion (the linear extrapolation shown in Figure 1 is just an example)~~ Leakage volume is the volume of flow occurring between *end of closure* (3.24) and ~~leakage volumes is obtained according to a defined~~ *start of systole* (3.61) and ~~and stated criterion (the linear extrapolation shown in Figure 1 is just an example)~~ *start of diastole* (3.58) for mitral and tricuspid positions.

~~3.34~~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.

~~3.35~~3.37

major bleeding

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

~~3.36~~ 3.38**major paravalvular leak**

paravalvular leakage leading to **or causing any of the following:** death or reintervention, ~~or causing,~~ heart failure requiring additional medication, ~~or causing,~~ moderate or severe regurgitation ~~or prosthesis “rocking” on investigation even in the apparent absence of symptoms, or causing hemolytic anemia;~~ or haemolytic anaemia

~~3.37~~ 3.39**mean arterial pressure**

time-averaged arithmetic mean value of the arterial pressure during one *cycle* (~~3.15~~3.13)

~~3.38~~ 3.40**mean pressure difference/mean pressure gradient****mean pressure gradient**

time-averaged arithmetic mean value of the pressure difference across a *heart valve substitute* (~~3.28~~3.30) during the positive differential pressure period of the *cycle* (~~3.15~~3.13)

~~3.39~~ 3.41**nonstructural non-structural valve dysfunction**

abnormality extrinsic to the *heart valve substitute* (~~3.28~~3.30) that results in stenosis, regurgitation, and/or haemolytic anemia ~~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].

~~3.40~~ 3.42**occluder/leaflet****leaflet**

component that inhibits backflow

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~~3.41~~**outflow tract profile height**

~~maximum distance that the *heart valve substitute* (3.28) extends axially into the outflow tract in the open or closed position, whichever is greater, measured from the valve structure intended to mate with the top (atrial or aortic/pulmonic side) of the patient's annulus~~

~~3.42~~ 3.43**pannus**

ingrowth of tissue onto **or around** the *heart valve substitute* (~~3.28~~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

~~3.43~~ 3.45**paravalvular leakage volume**

portion of the *leakage volume* (~~3.33~~3.35) that is associated with leakage around the closed heart valve substitute during a single *cycle* (~~3.15~~3.13)

~~3.44~~ 3.46**profile height prosthetic endocarditis**

~~maximal axial dimension of infection involving~~ a *heart valve substitute* (~~3.28~~3.30) in the open or closed position, whichever is greater

Note 1 to entry: See Reference [23].