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Cardiovascular implants — Cardiac valve prostheses —

Part 1:
General requirements

Implants cardiovasculaires — Prothèses valvulaires —

Partie 1: Exigences générales

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Foreword

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

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

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

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

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

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

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

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

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

ISO/TR 22442-4, *Medical devices utilizing animal tissues and their derivatives — Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes*

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/

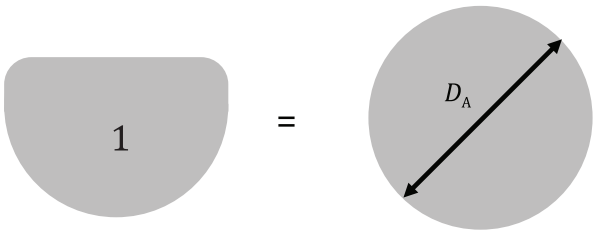
3.1
accessory
device-specific tool that is required to assist in the implantation of the *heart valve substitute* (3.30)

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

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

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



Key

1 area of valve

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

D_A = area-derived diameter

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

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

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

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

3.7
body surface area
BSA
total surface area (m^2) of the human body

Note 1 to entry: This can be calculated (Mosteller's formula) as the square root of the product of the weight in kg and the height in cm divided by 3 600 (see Mosteller, RD.).

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 (3.63) for aortic and pulmonary positions; between end of diastole (3.21) and start of leakage (3.63) 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;

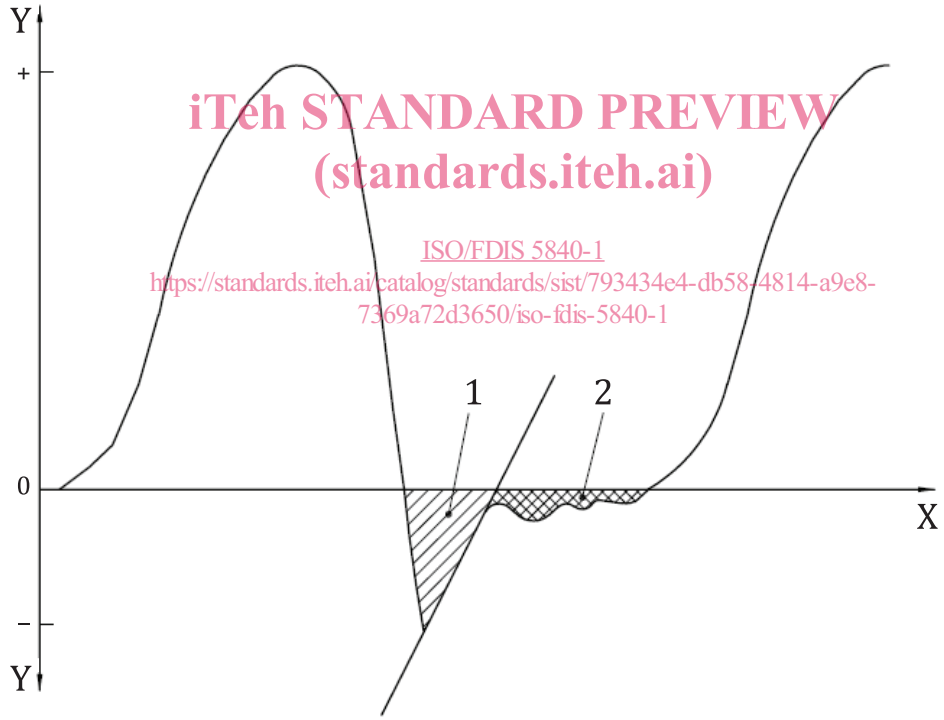
p_1 is the diastolic pressure, in mmHg;

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 reference ISO 25539-1.



Key

X	time	1	closing volume
Y	flowrate	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
one complete sequence in the action of a *heart valve substitute* (3.30) under pulsatile-flow conditions

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

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

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

3.17
device embolization
dislodgement from the intended and documented original position to an unintended and non-therapeutic location

3.18
device failure
inability of a device to perform its intended function

3.19
diastole
diastolic duration

portion of cardiac cycle time corresponding to ventricular filling

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

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

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

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

where

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

$q_{v_{RMS}}$ is the *root mean square forward flow* (3,58) (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/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 Figure 3 and Figure 4.

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 heart valve substitute
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 (3.27) and start of systole (3.61) for aortic and pulmonary positions; between end of closure (3.27) 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
see definition by Bleeding Academic Research Consortium

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). Akins C.W. et al.

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 Li J.S., Sexton D.J., Mick N. et al.

3.47
reference valve
heart valve substitute (3.30) with an established clinical experience used for comparative *in vitro* and pre-clinical 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 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 equation:

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

where

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

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

t_1 is time at start of positive differential pressure period (3.64);

t_2 is time at end of positive differential pressure period (3.25).

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