INTERNATIONAL STANDARD

ISO 5840-1

First edition
2015-09-15

Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

Implants cardiovasculaires — Prothèses valvulaires —

Partie 1: Exigences générales

Reference number
ISO 5840-1:2015(E)

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Foreword

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

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary Information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems.*

This first edition of ISO 5840-1, together with ISO 5840-2 and ISO 5840-3, cancels and replaces ISO 5840:2005, which has been technically revised.

ISO 5840 consists of the following parts, under the general title *Cardiovascular implants — Cardiac valve prostheses:*

— *Part 1: General requirements*

— *Part 2: Surgically implanted heart valve substitutes*

— *Part 3: Heart valve substitutes implanted by transcatheter techniques*

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, test methods, and/or requirements for test apparatus 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 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. 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.

Cardiovascular implants — Cardiac valve prostheses —

Part 1: General requirements

1 Scope

This part of ISO 5840 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 is applicable to both newly developed and modified heart valve substitutes and to the accessories, 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 outlines an approach for qualifying 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 may include those to assess the physical, chemical, biological, and mechanical properties of heart valve substitutes and of their materials and components. The tests may also include those for preclinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

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

This part of ISO 5840 excludes homografts.

NOTE A rationale for the provisions of this part of ISO 5840 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. 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 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 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 17665 (all parts), *Sterilization of health care products — Moist heat*

3 Terms and definitions

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

3.1
accessories
device-specific tools that are required to assist in the implantation of the *heart valve substitute* (3.28)

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 implantation or procedure.

3.3
actuarial methods
statistical technique for calculating event rates over time

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.

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)

3.6
back pressure
differential pressure applied 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 times the height in cm divided by 3 600 (see Reference [31]).

3.8
cardiac index
cardiac output (3.9) (CO, L/min) divided by the *body surface area* (3.7) (BSA, m^2) with units L/min/m^2

3.9
cardiac output
CO
stroke volume (3.59) times heart rate

3.10
closing volume
portion of the *regurgitant volume* (3.48) that is associated with the dynamics of valve closure during a single *cycle* (3.15)

Note 1 to entry: See Figure 1.

3.11
coating
thin-film material that is applied to an element of a *heart valve system* (3.29) to modify its physical or chemical properties

3.12
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 as

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

where

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

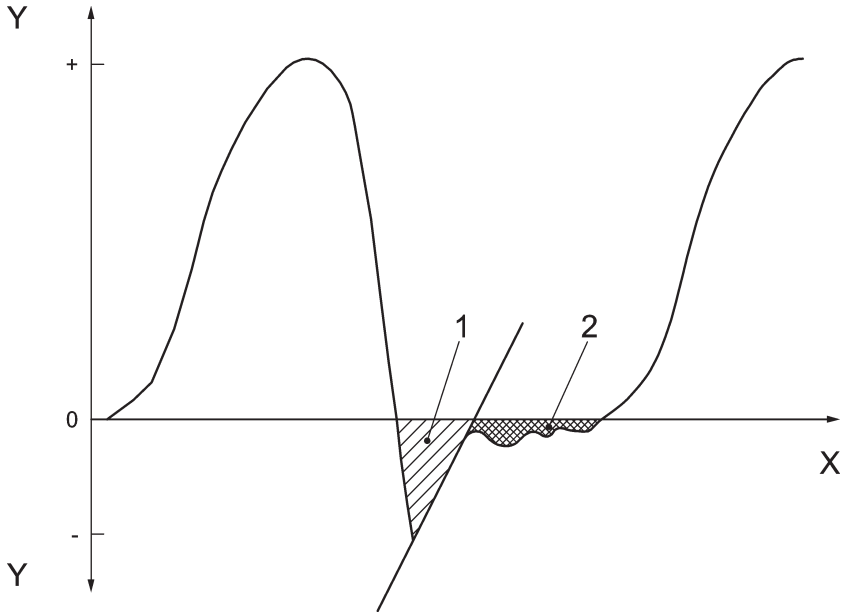
p_1 is the diastolic pressure, in mmHg;

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 ISO 25539-1.



Key

X time
Y flowrate
1 closing volume
2 leakage volume

Figure 1 — Schematic representation of flow waveform and regurgitant volumes 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
cumulative incidence
statistical technique where events other than death can be described by the occurrence of the event over time without including death of the subjects

Note 1 to entry: Cumulative incidence is also known as “actual” analysis.

3.15
cycle
one complete sequence in the action of a *heart valve substitute* (3.28) under pulsatile-flow conditions

3.16
cycle rate
number of complete *cycles* (3.15) per unit of time usually expressed as cycles per minute (cycles/min)

3.17
design verification
establishment by objective evidence that the design output meets the design input requirements

3.18
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.31)

3.19
device embolization
dislodgement from the intended and documented original position to an unintended and non-therapeutic location

3.20
device failure
inability of a device to perform its intended function sufficient to cause a hazard

3.21
device migration
detectable movement or displacement of the *heart valve substitute* (3.28) from its original position within the *implant position* (3.30) and without *device embolization* (3.19)

3.22
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: $\mathrm{EOA} = \dfrac{q_{V\,\mathrm{RMS}}}{51{,}6 \times \sqrt{\dfrac{\Delta p}{\rho}}}$

where

EOA is the Effective Orifice Area (cm^2);

$q_{V_{\mathrm{RMS}}}$ 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/cm^3).

Note 1 to entry: See 3.53.

3.23
failure mode
mechanism of *device failure* (3.20)

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

3.24
flexible surgical heart valve substitute
surgical heart valve substitute (3.62) wherein the *occluder* (3.40) is flexible under physiological conditions

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

3.25
follow-up
continued assessment of patients who have received the *heart valve substitute* (3.28)

3.26
forward flow volume
volume of flow ejected through the *heart valve substitute* (3.28) in the forward direction during one *cycle* (3.15)

3.27
fracture
complete separation of any structural component of the *heart valve substitute* (3.28) that was previously intact

3.28
heart valve substitute
device used to replace the function of a natural valve of the heart

3.29
heart valve system
implantable device, *accessories* (3.1), packaging, labelling, and instructions

3.30
implant site/implant position
intended location of *heart valve substitute* (3.28) implantation or deployment

3.31
intended use
use of a product or process in accordance with the specifications, instructions, and information provided by the manufacturer

3.32
Kaplan-Meier methods
statistical approaches for calculating event rates over time when the actual dates of events for each person in the population are known

3.33
leakage volume
portion of the *regurgitant volume* (3.48) which is associated with leakage during the closed phase of a valve in a single *cycle* (3.15) and is the sum of the *transvalvular leakage volume* (3.66) and *paravalvular leakage volume* (3.43)

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).

3.34
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
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
major paravalvular leak
paravalvular leakage leading to 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

3.37
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one *cycle* (3.15)

3.38
mean pressure difference/mean pressure gradient
time-averaged arithmetic mean value of the pressure difference across a *heart valve substitute* (3.28) during the positive differential pressure period of the *cycle* (3.15)

3.39
nonstructural valve dysfunction
abnormality extrinsic to the *heart valve substitute* (3.28) that results in stenosis, regurgitation, and/or haemolytic anemia

3.40
occluder/leaflet
component that inhibits backflow

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
pannus
ingrowth of tissue onto the *heart valve substitute* (3.28) which can interfere with normal functioning

3.43
paravalvular leakage volume
portion of the *leakage volume* (3.33) that is associated with leakage around the closed heart valve substitute during a single *cycle* (3.15)

3.44
profile height
maximal axial dimension of a *heart valve substitute* (3.28) in the open or closed position, whichever is greater

3.45
prosthetic valve endocarditis
any infection involving a prosthetic valve based on reoperation, autopsy, or the Duke Criteria for endocarditis

3.46
reference valve
heart valve substitute (3.28) with a known clinical experience used for comparative preclinical and clinical evaluations

3.47
regurgitant fraction
regurgitant volume (3.48) expressed as a percentage of the *forward flow volume* (3.26)

3.48
regurgitant volume
volume of fluid that flows through a *heart valve substitute* (3.28) in the reverse direction during one *cycle* (3.15) and is the sum of the *closing volume* (3.10) and the *leakage volume* (3.33)

Note 1 to entry: See Figure 1.

3.49
rigid surgical heart valve substitute
surgical heart valve substitute (3.62) wherein the *occluder(s)* (3.40) and orifice ring are non-flexible under physiological conditions

3.50
risk
combination of the probability of occurrence of harm and the *severity* (3.55) of that harm

[SOURCE: ISO 14971, 2.16]

3.51
risk analysis
systematic use of available information to identify hazards and to estimate the associated *risks* (3.50)

[SOURCE: ISO 14971, 2.17]

3.52
risk assessment
overall process comprising a *risk analysis* (3.51) and a risk evaluation

[SOURCE: ISO 14971, 2.18]

3.53
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 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;

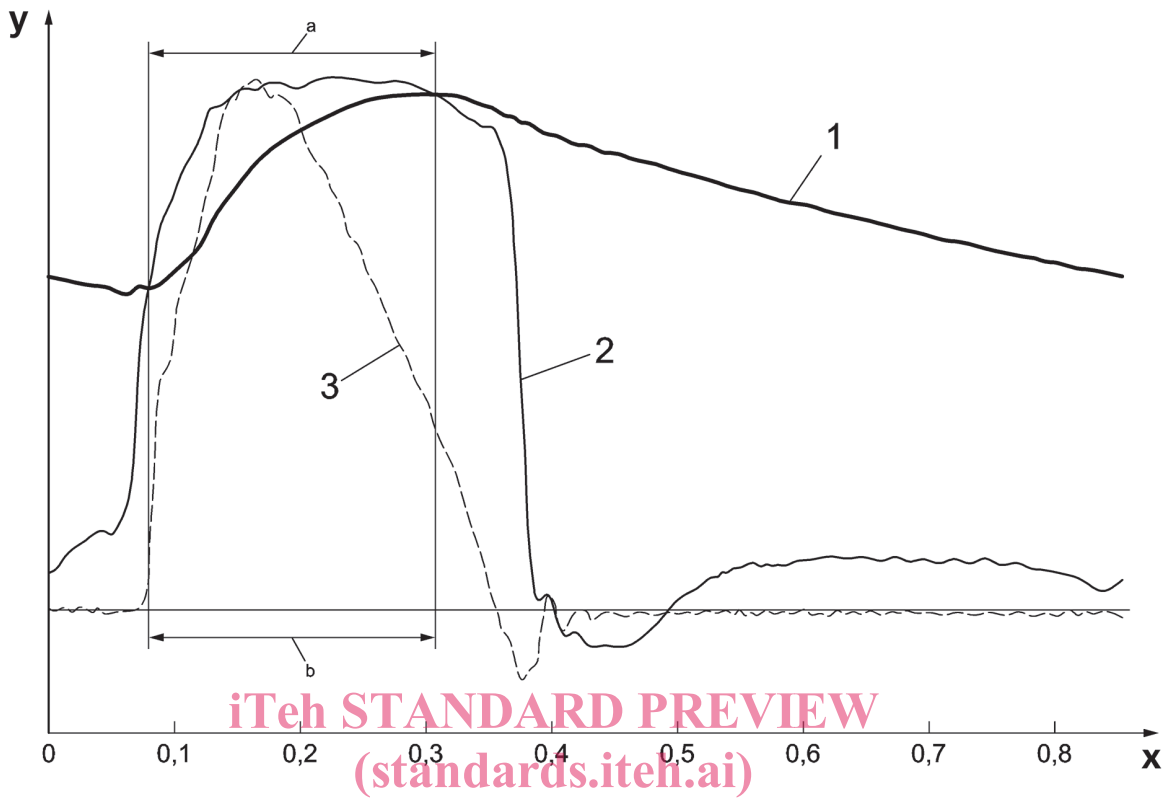
$q_V(t)$ is instantaneous flow at time (t);

t_1 is time at start of positive differential pressure period;

t_2 is time at end of positive differential pressure period.

Note 3 to entry: The rationale for use of $q_{V_{\mathrm{RMS}}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate and it is the *mean pressure difference* (3.38) that is required.

Note 4 to entry: See Figure 2.



Key

1 aortic pressure
2 left ventricle pressure
3 aortic flow rate
X time (sec)
Y pressure (mmHg) and flow (L/min)
a Positive pressure range.
b $q_{V_{\mathrm{RMS}}}$ range.

Figure 2 — Schematic representation of the positive pressure period of an aortic forward flow interval

3.54
safety
freedom from unacceptable risk

[SOURCE: ISO 14971, 2.24]

3.55
severity
measure of the possible consequences of a hazard

[SOURCE: ISO 14971, 2.25]