INTERNATIONAL STANDARD

ISO 5840-2

Redline version compares Second edition to First edition

Cardiovascular implants — Cardiac valve prostheses —

Part 2: Surgically implanted heart valve substitutes

Implants cardiovasculaires — Prothèses valvulaires —
Partie 2: Prothèse valvulaires implantées chirurgicalement

Reference number
ISO 5840-2:redline:2021(E)

IMPORTANT

This marked-up version uses the following colour-coding:

Text example 1 — Text has been added (in green)

~~Text example 2~~ — Text has been deleted (in red)

 — Graphic figure has been added

 — Graphic figure has been deleted

1.x ... — If there are changes in a clause/subclause, the corresponding clause/subclause number is highlighted in yellow in the Table of contents

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

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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~~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~~www.iso.org/patents).

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For an explanation ~~on the~~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.

~~The committee responsible for this document is~~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 ~~first~~second edition ~~of ISO 5840-2, together with ISO 5840-1 and~~ cancels and replaces the first edition (ISO 5840-~~3~~2:2015~~, cancels and replaces ISO 5840:2005~~), 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 ~~consists of the following parts, under the general title *Cardiovascular implants — Cardiac valve prostheses:*~~have been updated to current specifications and integrated and harmonized across all of its parts.

~~— *Part 1: General requirements*~~

~~— *Part 2: Surgically implanted heart valve substitutes*~~

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

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

This ~~part of ISO 5840~~document has been prepared for surgical heart valve substitutes with emphasis on ~~specifying types of~~providing guidance for *in vitro* testing, preclinical *in vivo* and clinical evaluations, reporting of all *in vitro*, preclinical *in vivo*, and clinical evaluations and labelling and packaging of the device. This process is intended to clarify the required procedures prior to market release and to enable prompt identification and management of any subsequent issues.

This ~~part of ISO 5840~~document is ~~to be~~ used in conjunction with ISO 5840-1 and ISO 5840-3.

Cardiovascular implants — Cardiac valve prostheses —

Part 2:
Surgically implanted heart valve substitutes

1 Scope

This ~~part of ISO 5840~~document is applicable to heart valve substitutes intended for implantation in human hearts, generally requiring cardiopulmonary bypass and generally with direct visualization. See Annex E for examples of surgical heart valve substitutes and their components.

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

This ~~part of ISO 5840 outlines~~document establishes an approach for ~~qualifying~~verifying/validating the design and manufacture of a surgical 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 surgical heart valve substitutes and of their materials and components. The tests can also include those for pre-clinical *in vivo* evaluation and clinical evaluation of the finished surgical heart valve substitute.

This ~~part of ISO 5840 defines~~document defines operational conditions and performance requirements for surgical heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

For ~~novel surgical~~some heart valve substitutes (e.g. sutureless), the requirements of both this ~~International Standard~~document and ISO 5840-3:2021 ~~might~~can be relevant and ~~shall be~~are considered as applicable to the specific device design and ~~shall be~~are based on the results of the risk analysis.

~~This part of ISO 5840 excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.~~

~~This part of ISO 5840 excludes homografts.~~

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 5840-1:~~2015~~2021, *Cardiovascular implants ~~and extracorporeal systems~~ — Cardiac valve prostheses — Part 1: General requirements*

ISO ~~10993-1~~5840-3, ~~*Biological evaluation of medical devices*~~*Cardiovascular implants — Cardiac valve prostheses — Part ~~1. Evaluation and testing within a risk management process~~3: Heart valve substitutes implanted by transcatheter techniques*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14630, *Non-active surgical implants — General requirements*

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

ISO 16061, *Instrumentation for use in association with non-active surgical implants — General requirements*

~~ISO/IEC 17025:2005, *General requirements for the competence of testing and calibration laboratories*~~

~~ISO 22442 (all parts), *Medical devices utilizing animal tissues and their derivatives*~~

~~ASTM F2052, *Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment*~~

~~ASTM F2119, *Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants*~~

~~ASTM F2182, *Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging*~~

~~ASTM F2213, *Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment*~~

~~ASTM F2503, *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*~~

3 Terms and definitions

For the purposes of this document, the ~~following~~ terms and definitions given in ISO 5840-1:2021 and the following 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
~~cycle rate~~acute assessment
~~number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)~~intra-procedural and immediate post-procedural results used to assess *in vivo* safety and performance

Note 1 to entry: All animals entered into acute short-term assessment shall remain under general anaesthesia for the duration of the study.

3.2
chronic assessment
long-term results following the procedure used to assess chronic *in vivo* safety and performance after the animal has recovered from anaesthesia

Note 1 to entry: The endpoints and durations of these studies should be determined by risk analysis.

3.3
component-joining material
material such as a suture, adhesive, or welding compound used to assemble the components of a heart valve system

[SOURCE: ISO 5840-1:2021, 3.31]

3.4
external sewing ring diameter
ESRD
outside diameter in millimetres of the sewing ring at the largest point

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.5, 3.7 and 3.8.

~~3.2~~3.5
prosthesis minimum internal ~~orifice~~ diameter
<flexible surgical heart valve> numerical indication of the minimum diameter within a fully assembled flexible surgical heart valve substitute ~~through which blood flows~~and which is measured with a standard validated procedure, taking the entire flow channel into consideration

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.2 and 3.4.

3.6
prosthesis minimum internal diameter
<rigid surgical heart valve> measurement of the prosthesis minimum internal housing diameter

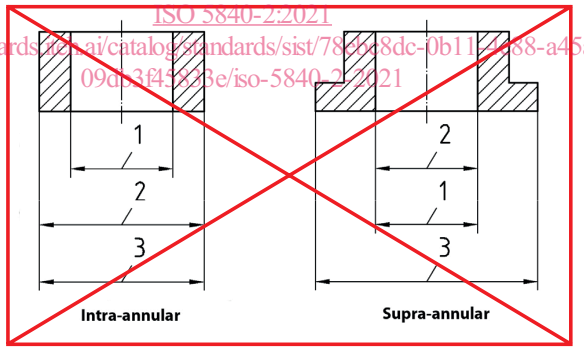
Note 1 to entry: See Figure 1.

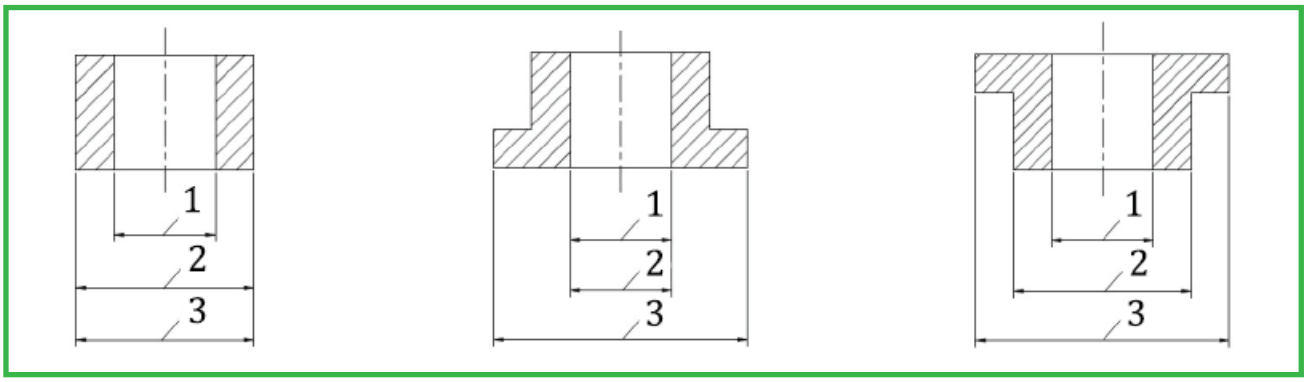
Note 2 to entry: See also 3.2 and 3.4.

~~3.3~~3.7
intra-annular ~~sewing ring~~
~~sewing ring designed to secure the surgical heart valve wholly or mostly~~wholly or partially within the patient's ~~tissue~~ annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also ~~3.2~~3.4, ~~3.10~~3.5 and ~~3.12~~3.8.





a) Aortic/pulmonic intra-annular	b) Aortic/pulmonic supra-annular	c) Mitral/tricuspid intra-annular

Key

1 prosthesis minimum internal ~~orifice~~ diameter

2 ~~tissue~~patient annulus diameter

3 external sewing ring diameter

Figure 1 — Designation of dimensions of surgical heart valve substitute sewing ring configurations

~~**3.4**~~
~~**major bleeding**~~
~~any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion~~

~~**3.5**~~
~~**major paravalvular leak**~~
~~paravalvular leakage leading to death or re-intervention, 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~~

~~**3.6**~~
~~**nonstructural valve dysfunction**~~
~~abnormality extrinsic to the heart valve substitute that results in stenosis, regurgitation, and/or haemolytic anemia~~

~~**3.7**~~
~~**prosthetic valve endocarditis**~~
~~any infection involving a valve in which an operation has been performed, based on reoperation, autopsy or the Duke Criteria for Endocarditis~~

~~Note 1 to entry: See Reference [16].~~

~~**3.8**~~
~~**structural valve deterioration**~~
~~change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation~~

~~Note 1 to entry: This definition excludes infection or thrombosis of the heart valve substitute. It 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, and stent creep.~~

~~**3.9**~~
~~**support structure**~~
~~component of a heart valve substitute that houses the occluder(s)~~

~~EXAMPLE Stent, frame, housing.~~

3.103.8
supra-annular sewing ringannulus
sewing ring designed to secure the valveregion wholly above the patient's tissue annulus

Note 1 to entry: See Figure 1.

Note 2 to entry: See also 3.4, 3.5, and 3.7.

3.11
thromboembolism
any embolic event that occurs in the absence of infection after the immediate perioperative period and may be manifested by a neurological event or a nonCerebral embolic event

3.123.9
tissuepatient **annulus diameter**
TADPAD
diameter in millimetres of the smallest flow area within the patient's valve annulus

Note 1 to entry: See Figure 1.

3.133.10
valve size
designated valve size
manufacturer's designation of a surgical heart valve substitute which indicates the tissue annulus diameter (TAD in millimetres) of the patient into whom the surgical heart valve substitute is intended to be implanted (i.e. TAD = designated valve size)intended patient annulus diameter

Note 1 to entry: The valve size is equivalent to the *PAD* (3.9).

Note **1**2 to entry: This takes into consideration the manufacturer's recommended implant position relative to the annulus and the suture technique.

3.14
valve thrombosis
any thrombus not caused by infection attached to or near an operated valve that occluded part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment

Note 1 to entry: See Reference [14].

4 Abbreviations

For the purposes of this document, the following abbreviations apply.

EOA Effective Orifice Area

CFD Computational Fluid Dynamics

FEA Finite Element Analysis

IFU Instructions For Use

OPC Objective Performance Criteria

AE adverse event

CIP clinical investigation plan

CRF case report form

CT computed tomography

EOA	effective orifice area
FEA	finite element analysis
IFU	instructions for use
LVOT	left ventricular outflow tract
MRI	magnetic resonance imaging
OPC	objective performance criteria
PMCF	post-market clinical follow-up
PVL	paravalvular leak
RMS	root mean square
SAE	serious adverse event
TEE	transoesophageal echo
TTE	transthoracic echo

5 Fundamental requirements

~~The manufacturer shall determine, at all stages of the product life cycle, the acceptability of the product for clinical use~~Refer to ISO 5840-1:2021, clause 5.

6 Device description

6.1 ~~Intended use~~General

~~The manufacturer shall identify the physiological condition(s) to be treated, the intended patient population, potential adverse events, and intended claims~~Refer to ISO 5840-1:2021, 6.1.

6.2 Intended use

Refer to ISO 5840-1:2021, 6.2.

~~6.2~~6.3 Design inputs

~~6.2.1~~6.3.1 Operational specifications

~~The manufacturer shall define the operational specifications for the device, including the principles of operation, 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 will be required to accurately select the size of device to be implanted.~~ Refer to ISO 5840-1:~~2015~~2021, ~~Table 1 and Table 2~~ 6.3.1~~define the expected physiological parameters of the intended adult patient population for surgical heart valve substitutes for both normal and pathological patient conditions~~.

~~NOTE See the paediatric annex of ISO 5840-1:2015, Annex E.~~

~~6.2.2~~6.3.2 Performance specifications

~~6.2.2.1~~6.3.2.1 General

~~The manufacturer shall establish (i.e. define, document, and implement) the clinical performance requirements of the device and the corresponding device performance specifications~~Refer to ISO 5840-1:2021, 6.1 for ~~the intended use and device claims. The following list of desired clinical and device-based performance characteristics describes a safe and effective surgical heart valve substitute.~~ general requirements.

~~NOTE For novel devices, portions of ISO 5840-3 can be applicable~~

~~6.2.2.2~~6.3.2.2 Surgical heart valve substitute minimum performance requirements

~~Specifications shall be defined with respect to at least the following performance characteristics~~Surgical heart valves shall meet the following minimum performance specifications:

— ~~ability to~~ allow forward flow with acceptably small mean pressure difference;

— ~~ability to~~ prevent retrograde flow with acceptably small regurgitation;

— ~~ability to~~ resist embolization;

— ~~ability to resist~~avoid haemolysis;

— ~~ability to~~ resist thrombus formation;

— be biocompatible;

— be compatible with *in vivo* diagnostic techniques;

— be deliverable and implantable in the target population;

— ~~ability~~be able to ensure effective fixation within the target implant site;

— ~~has~~have an acceptable noise level;

— ~~has~~have reproducible function;

— ~~maintains~~maintain structural and functional integrity during the expected lifetime of the device;

— ~~maintains~~maintain its functionality and sterility for a reasonable shelf life prior to implantation.

6.3.2.3 Accessories

The requirements of ISO 16061 for instruments used with surgical implants shall apply. Surgical heart valve accessories shall mitigate the risk of the valve being inadvertently implanted upside down.

Examples of surgical valve accessories, including sizing tools and valve handles, are shown in Annex E.

6.3.2.4 Implant procedure

Refer to ISO 5840-1:2021, 6.3.3.

~~6.2.3~~6.3.3 Packaging, labelling, and sterilization

Refer to ISO 5840-1:2021, 6.3.4.

~~The surgical heart valve substitute and accessories shall meet the requirements for packaging, labelling, and sterilization contained within~~In addition to the items specified in ISO 5840-1:~~2015~~2021,

C.1.3, ~~Annexes B, C, and D, respectively.~~outer container labelling for the valve implant shall include in diagrammatic and/or tabular form the following items:

— intended valve to be replaced;

— intended position in relation to the annulus;

— inflow internal orifice diameter;

— prosthesis minimum internal diameter;

— external sewing ring diameter (ESRD).

Annex D contains a list of terms that may be used in describing various valve models.

~~6.3~~6.4 Design outputs

~~6.3.1 General~~

~~The manufacturer shall establish (i.e. define, document, and implement) a complete specification of the surgical heart valve substitute system, which includes component and assembly-level specifications, accessories, packaging, and labelling.~~

~~Annex E contains a listing of components and terms that may be used in describing various valve types.~~

Refer to ISO 5840-1:2021, 6.4.

~~6.4~~6.5 Design transfer (manufacturing ~~qualification~~verification/validation)

~~6.4.1 The manufacturer shall generate a manufacturing flowchart identifying the manufacturing process operations and inspection steps. The input of all components and important manufacturing materials shall be indicated on the flowchart.~~

~~6.4.2 As part of the risk management process, the manufacturer shall establish the control measures and process conditions necessary to ensure that the device is safe and suitable for its intended use. The risk management file shall identify and justify the verification activities necessary to demonstrate the acceptability of the process ranges chosen.~~

~~6.4.3 The manufacturer shall establish the adequacy of full-scale manufacturing by validation of the manufacturing process. The manufacturer shall document the results of the validation of all special processes and the validation of all process software.~~

~~NOTE See ISO 13485.~~

Refer to ISO 5840-1:2021, 6.5.

~~6.5~~6.6 Risk management

~~The manufacturer shall define and implement a risk management program in accordance with~~Refer to ISO ~~14971~~ 5840-1:2021, 6.6.

Annex A contains a list of potential hazards specific to surgical heart valve substitutes that can serve as the basis for a risk analysis.

7 Design verification ~~testing and analysis/design~~and validation

7.1 General requirements

In vitro~~The manufacturer shall perform verification testing in order to demonstrate that the device specifications result in a surgical heart valve substitute system that meets the design specifications (design output meets design input). The manufacturer shall establish those tests relating to hazards identified from~~ assessment shall be used to mitigate the risks identified in the risk analysis. ~~The protocols shall identify the test purpose, set-up, equipment (specifications, calibration, etc.), test conditions (with a justification of appropriateness to anticipated in vivo~~General requirements that are applicable to all heart valve systems are provided in ~~operating conditions~~ISO 5840-1:2021, 7.1 ~~for the device), acceptance criteria, and sample quantities tested~~. Specific considerations for surgical heart valve substitutes are provided in this document.

~~NOTE See ISO 16061.~~

~~For novel surgical heart valve substitutes (e.g. sutureless), the requirements of both this part of ISO 5840 and ISO 5840-3 might be relevant and shall be considered, if applicable to the specific device design and based on the results of the risk analysis.~~

~~The manufacturer shall validate the design of the surgical heart valve substitute, its packaging/labelling, and accessories.~~

7.2 *In vitro* assessment

7.2.1 General

Refer to ISO 5840-1:2021, 7.2.1.

~~7.2.1~~7.2.2 Test conditions, sample selection, and reporting requirements

~~7.2.1.1 Test conditions and sample selection~~

~~Test specimens shall represent, as closely as possible, the finished product to be supplied for clinical use, including exposure to the maximum number of recommended sterilization cycles, process chemicals, and aging effects in accordance with all manufacturing procedures and Instructions for Use, where appropriate. Any deviations of the test specimens from the finished product shall be justified.~~

~~The specimens selected for testing shall fully represent the total implant size range. Depending on the particular test, testing might not necessarily have to be completed for each discrete valve size, but shall at least be completed for the smallest, intermediate, and largest sizes. A rationale for device size selection shall be provided.~~

~~For all tests, the number of samples shall be justified based on the specific intent of the test (see ISO 5840-1:2015, Annex F). Sampling shall ensure adequate representation of the expected variability in the manufacture of devices. Additional recommendations regarding sampling and sample conditioning are included within each test method defined herein, as appropriate.~~

~~Where simulation of *in vivo* conditions is applicable to the test method, consideration shall be given to those operational environments given in ISO 5840-1:2015, Table 1 and Table 2 for the adult population. See ISO 5840-1:2015, Annex E for guidelines regarding suggested test conditions for the paediatric population. Where applicable, testing shall be performed using a test fluid of isotonic saline, blood, or a blood-equivalent fluid whose physical properties (e.g. specific gravity, viscosity at operating temperatures) are appropriate to the test being performed. The test fluid used shall be justified. Testing shall be performed at the intended operating temperature as appropriate.~~

~~Test methods for design verification testing shall be appropriately validated. Refer to applicable sections of ISO/IEC 17025:2005.~~