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Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

Implants cardiovasculaires et circuits extra-corporels — Dispositifs de réparation de valves cardiaques

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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 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 the following URL: www.iso.org/iso/foreword.html.

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

Introduction

No heart valve repair device is ideal. Therefore, a group of engineers, scientists, and clinicians, experts well aware of the problems associated with heart valve repair devices and their development, has prepared this document. This document specifies types of tests, test methods, and requirements for test apparatus. It requires documentation of test methods and results. This document deals with those areas that will ensure adequate mitigation of device-associated risks for patients and other users of the device, facilitate quality assurance, aid the heart team in choosing a heart valve repair device, and ensure that the device will be provided in a convenient and usable form. This document emphasizes the need to specify and report types of *in vitro* testing, preclinical *in vivo* and clinical evaluations. It describes the labels and packaging of the device. Such a process involving *in vitro*, preclinical *in vivo* and clinical evaluations is intended to clarify the requirements 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, this document also covers important functional and durability characteristics of heart valve repair devices and their accessories. This document does not specify exact test methods for functional and durability testing but it offers guidelines for the test apparatus.

This document should be revised, updated, and amended as knowledge and techniques in heart valve repair device technology improve.

Cardiovascular implants and extracorporeal systems — Cardiac valve repair devices

1 Scope

1.1 This document applies to all heart valve repair systems that have an intended use to repair and/or improve the function of native human heart valves by acting either on the valve apparatus or on the adjacent anatomy (e.g. ventricle, coronary sinus).

1.2 This document outlines an approach for verifying/validating the design and manufacture of a heart valve repair system through risk management. The selection of appropriate verification/validation tests and methods are derived from the risk assessment. The tests include assessments of the physical, chemical, biological, and mechanical properties of components and materials of heart valve repair systems. The tests also include preclinical *in vivo* evaluation and clinical investigation of the finished heart valve repair system to assess the safety and effectiveness of the heart valve repair system.

NOTE For the purposes of this document, effectiveness endpoint includes clinical performance and benefits.

1.3 This document defines operational conditions and performance requirements for heart valve repair systems where adequate scientific and/or clinical evidence exists for their justification.

1.4 This document excludes Cardiac Resynchronization Therapy (CRT) devices, paravalvular leakage closure devices, systems that do not leave an implant in place (e.g. ablation, radio frequency annuloplasty), apical conduits and devices with components containing viable cells. This Standard also excludes materials not intended for repairing and/or improving the function of human heart valves according to its intended use (e.g. patch material and sutures used in general surgical practice).

NOTE A rationale for the provisions of this document 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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

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

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 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

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

ISO 15223-2, *Medical devices — Symbols to be used with medical device labels, labelling, and information to be supplied — Part 2: Symbol development, selection and validation*

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

ISO 17664, *Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO/TS 17665-2, *Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1*

ISO/TS 17665-3, *Sterilization of health care products — Moist heat — Part 3: Guidance on the designation of a medical device to a product family and processing category for steam sterilization*

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 62366-1, *Medical devices — Part 1: 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:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

NOTE Additional definitions can be found in the informative annexes.

3.1
abnormal use
act or omission of an act by the operator or user of a medical device as a result of conduct which is beyond any means of risk control by the manufacturer

3.2
accessory
device-specific tool that is required to assist in the implantation and/or adjustment of the heart valve repair device, excluding the delivery system

3.3
active comparator
active control
intervention generally accepted or demonstrated to be safe and effective for the condition of interest that can be used as a basis of comparison of the safety and effectiveness of the heart valve repair device

Note 1 to entry: The active comparator is generally the standard of care for the condition.

3.4
actuarial analysis
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.

3.5
adverse event
AE
untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the heart valve repair device implantation, adjustment or procedure

3.6
auxiliary device
device used during the procedure, not including accessories (e.g. sheath, guidewire) and delivery system

3.7
back pressure
differential pressure applied across the valve during the closed phase

3.8
body surface area
BSA
total surface area (m^2) of the human body

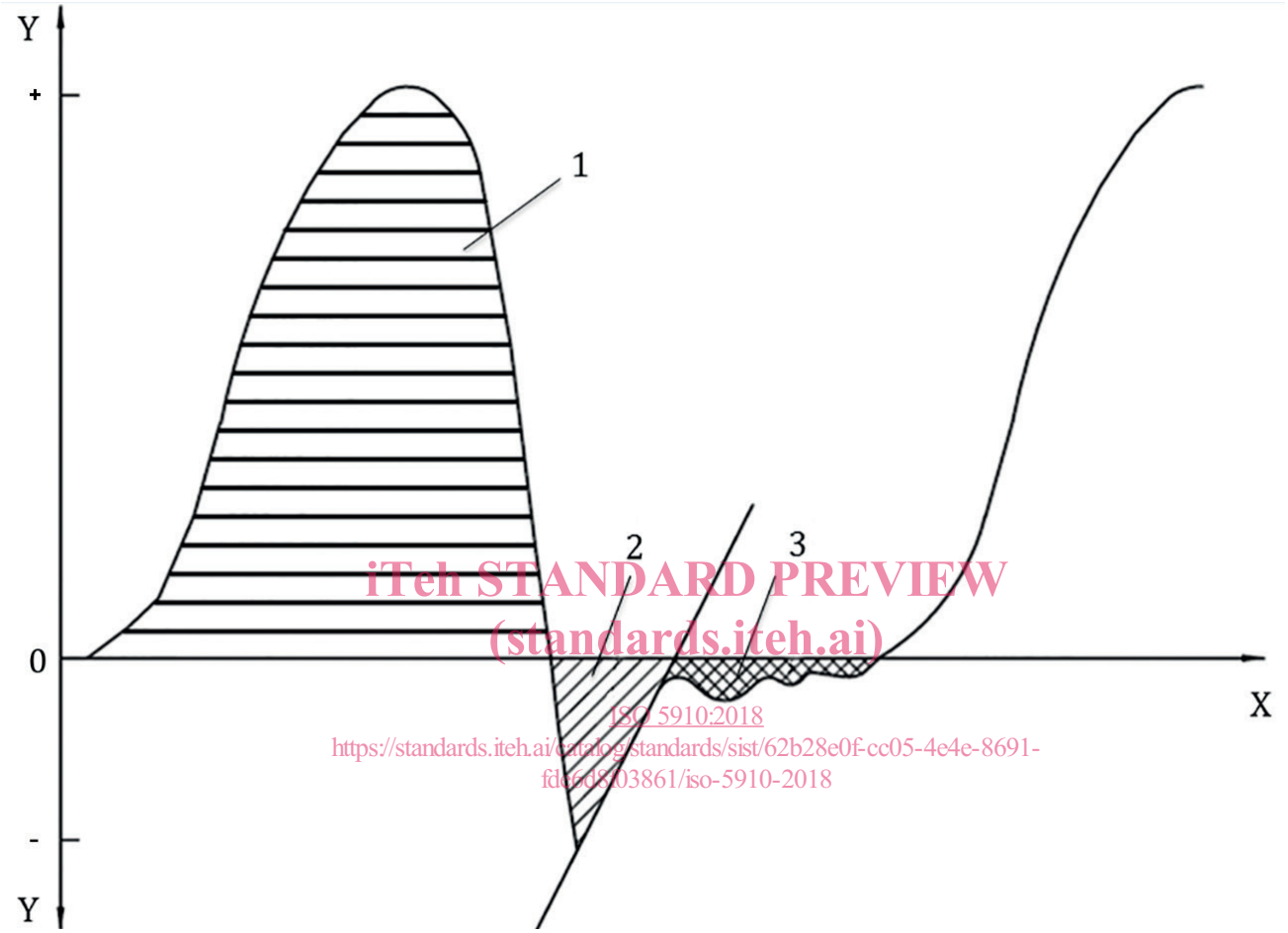
Note 1 to entry: This can be calculated as the square root of product of the weight in kg times the height in cm divided by 3 600. See Reference [30].

3.9
cardiac index
cardiac output (3.10) (CO, l/min) divided by the *body surface area* (3.8) (BSA, m^2), with units l/min/m^2

3.10
cardiac output
CO
stroke volume multiplied by heart rate

3.11
closing volume
portion of the regurgitant volume that is associated with the dynamics of the valve closure during a single cycle

Note 1 to entry: See Figure 1.



Key
X time
Y flowrate
1 forward flow volume
2 closing volume
3 leakage volume

Figure 1 — Schematic representation of flow waveform and regurgitant volumes for one cycle

3.12
coating
thin-film material that is applied to an element of a heart valve repair device to modify its properties

3.13
compliance

relationship between change in radius and change in pressure of a deformable tubular structure (e.g. valve annulus, aorta, conduit), defined in this document 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: See Reference [7].

3.14
component-joining material
material, such as a suture, adhesive or welding compound, used to assemble the components of a heart valve repair device, thereby becoming part of the implanted device

3.15
cycle
one complete sequence in the action of a heart valve under pulsatile flow conditions

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

3.17
delivery system
system used to deliver, deploy, attach or adjust the device in the implant site

3.18
design validation
establishment by objective evidence that device specifications conform with user needs and *intended use(s)* (3.34)

3.19
design verification
establishment by objective evidence that the design output meets the design input requirements

3.20
device embolisation
dislodgement from the intended and documented original position to an unintended and nontherapeutic location

3.21
device failure
inability of a device to perform its intended function sufficient to cause a hazard

3.22
device migration
unintended movement or displacement of the device from its original position within the implant site, without embolisation

3.23
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:

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

where

EOA is the effective orifice area (cm^2);

$q_{v_{RMS}}$ 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/cm^3).

3.24
failure mode
mechanism of *device failure* (3.21)

3.25
follow-up
continued assessment of subjects who have received the heart valve repair device

3.26
forward flow volume
volume of flow ejected through the heart valve in the forward direction during one cycle, not including any regurgitant flow through the valve

Note 1 to entry: See Figure 1.

3.27
fracture
complete separation of any part of the *heart valve repair device* (3.28) that was previously intact

3.28
heart valve repair device
implant (3.31) intended to improve the function of native human heart valves by acting either on the valve apparatus or on the adjacent anatomy (e.g. ventricle, coronary sinus)

Note 1 to entry: See examples in Annex B.

3.29
heart valve repair system
heart valve repair device, delivery system, other accessories as applicable, packaging, labelling, and instructions

3.30
imaging modality
method used to visualize and assess native anatomy and/or device position, geometry and/or function

3.31
implant
device placed surgically or non-surgically into the human body and intended to remain in place after the procedure

3.32
implant site
location of heart valve repair device implantation or deployment

3.33
indication for use
clinical condition of the patient population that the heart valve repair device is intended to treat or improve

3.34
intended use
purpose of a heart valve repair device, in accordance with the specifications, instructions, and information provided by the manufacturer

3.35
Kaplan-Meier methods
statistical approaches to calculating event rates over time when the actual dates of events for each person in the population are taken into account

3.36
leakage volume
component of the regurgitant volume that is associated with leakage during closed phase of a valve in a single cycle

Note 1 to entry: See Figure 1. 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).

3.37
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.

3.38
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one cycle

3.39
mean pressure difference
time-averaged arithmetic mean value of the pressure difference across a heart valve during the positive differential pressure period of the cycle

Note 1 to entry: See Figure 2 for representative aortic and mitral flow and pressure waveforms. See Figure 3 for representative pulmonary and tricuspid flow and pressure waveforms.

3.40
non-structural dysfunction
abnormality extrinsic to the heart valve repair device that results in abnormal function of the device or causes clinical symptoms

3.41
pannus
ingrowth of tissue onto the heart valve repair device which may interfere with normal functioning

3.42
pull-out
situation in which the suture or anchoring device remains structurally intact but tears through the tissue in which it is implanted

3.43
reference device
heart valve substitute or heart valve repair device with known clinical history used for comparative preclinical and clinical evaluations

3.44
regurgitant fraction
regurgitant volume expressed as a percentage of the total ventricular stroke volume

3.45
regurgitant volume
volume of fluid that flows through a heart valve in the reverse direction during one cycle and is the sum of the closing volume and *leakage volume* (3.36)

Note 1 to entry: See Figure 1.

3.46
repositioning
intentional change of implant position of a partially or fully deployed heart valve repair device

3.47
retrieval
removal of a partially or fully deployed heart valve repair device

3.48
risk
combination of the probability of occurrence of harm and the *severity* (3.53) of that harm

Note 1 to entry: See ISO 14971.

3.49
risk analysis
systematic use of available information to identify hazards and to estimate the associated *risks* (3.48)

Note 1 to entry: See ISO 14971.

3.50
risk assessment
overall process comprising a *risk analysis* (3.49) and a risk evaluation

Note 1 to entry: See ISO 14971.

3.51
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:

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

where

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

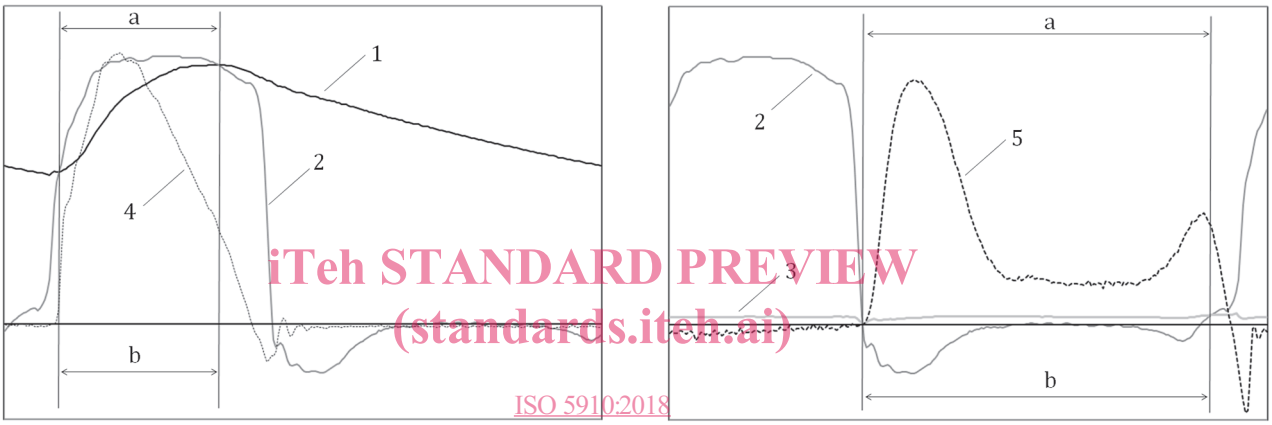
$q_v(t)$ is the instantaneous flow at time t;

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 $q_{v_{RMS}}$ is that the instantaneous pressure difference is proportional to the square of instantaneous flow rate, and it is the mean pressure difference that is required.

Note 4 to entry: See Figure 2 for representative aortic and mitral flow and pressure waveforms from *in vitro* testing. See Figure 3 for representative pulmonary and tricuspid flow and pressure waveforms from *in vitro* testing.



Key

1 aortic pressure
2 left ventricular pressure
3 left atrial pressure
4 aortic flow rate
5 mitral flow rate
a Positive pressure range.
b $q_{v_{RMS}}$ range.

Figure 2 — Schematic representation of aortic and mitral flow and pressure waveforms versus time from *in vitro* testing