INTERNATIONAL STANDARD

ISO 5840

Fourth edition
2005-03-01

Cardiovascular implants — Cardiac valve prostheses

Implants cardiovasculaires — Prothèses valvulaires

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 5840 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This fourth edition cancels and replaces the third edition (ISO 5840:1996), which has been technically revised to include risk management.

Introduction

There is, as yet, no heart valve substitute that can be regarded as ideal.

This International Standard has been prepared by a group well aware of the problems associated with heart valve substitutes and their development. In several areas, the provisions of this International Standard have been deliberately left open as there has been no wish to inhibit development and innovation. It does specify types of tests, test methods and/or requirements for test apparatus, and requires documentation of test methods and results. The areas with which this International Standard is 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 surgeon 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, this International Standard also covers important hydrodynamic and durability characteristics of heart valve substitutes. The exact test methods for hydrodynamic and durability testing have not been specified, but guidelines for the test apparatus are given.

This International Standard 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.

Annexes A to S provide supplementary information, the content of Annexes P to S being necessary for the application of this International Standard.

Cardiovascular implants — Cardiac valve prostheses

1 Scope

1.1 This International Standard is applicable to all devices intended for implantation in human hearts, as a heart valve substitute.

1.2 This International Standard is applicable to both 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 heart valve substitute to be implanted.

1.3 This International Standard 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 pre-clinical *in vivo* evaluation and clinical evaluation of the finished heart valve substitute.

1.4 This International Standard imposes design specifications and minimum performance specifications for heart valve substitutes where adequate scientific and/or clinical evidence exists for their justification.

1.5 This International Standard excludes heart valve substitutes designed for implantation in artificial hearts or heart assist devices.

NOTE A rationale for the provisions of this International Standard is given in Annex A.

2 Normative references

The following referenced documents are indispensable for the application 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 8601:2000, *Data elements and interchange formats — Information interchange — Representation of dates and times*

ISO 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

ISO 10993-2:1992, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 11134:1994, *Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization*

ISO 11135:1994, *Medical devices — Validation and routine control of ethylene oxide sterilization*

ISO 11137:1995, *Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization*

ISO 11607:2003, *Packaging for terminally sterilized medical devices*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14155-1:2003, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin — Validation and routine control of sterilization by liquid chemical sterilants*

ISO 14630:—[1)], *Non-active surgical implants — General requirements*

ISO 14937:2000, *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 14971:2000, *Medical devices — Application of risk management to medical devices*

EN 12442-1, *Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 1: Analysis and management of risk*

EN 12442-2, *Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 2: Controls on sourcing, collection and handling*

EN 12442-3, *Animal tissues and their derivatives utilized in the manufacture of medical devices — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents*

Guidelines for reporting morbidity and mortality after cardiac valvular operations, American Association for Thoracic Surgery, European Association for Cardiothoracic Surgery, Society of Thoracic Surgeons, *Annals of Thoracic Surgery*, **62**, pp. 932-935, 1996

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

3.2
actuarial
statistical technique for estimating survival curves prior to the death of the last member of a cohort

NOTE Some examples are the “Kaplan-Meier” technique and the “life-table” technique.

3.3
anticoagulant-related haemorrhage
internal or external bleeding that causes death or stroke, or that requires transfusion, operation or hospitalization

NOTE This definition is restricted to patients who are receiving anticoagulants and/or antiplatelet drugs, and excludes minor bleeding events.

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

3.5
arterial peak systolic pressure
maximum value of the arterial pressure during systole

1) To be published. (Revision of ISO 14630:1997)

3.6
back pressure
differential pressure applied across the closed valve

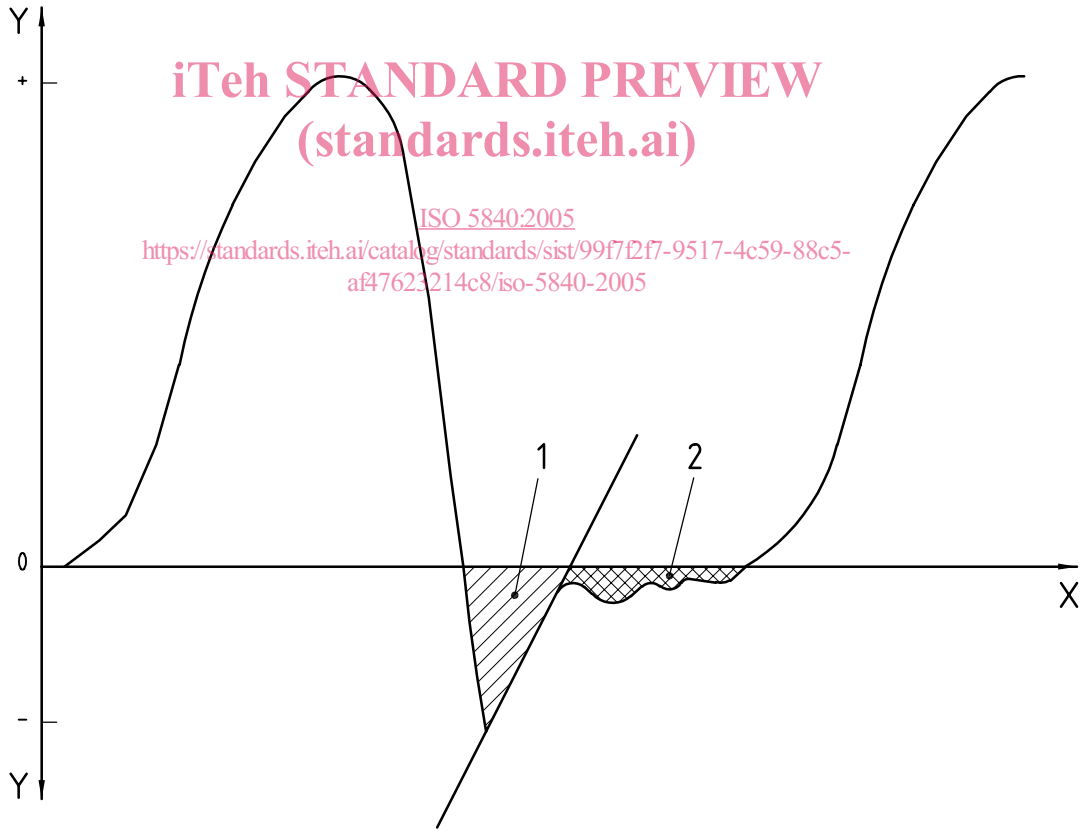
3.7
blood-equivalent fluid
fluid whose physical properties, e.g. specific gravity, viscosity, approximate those of blood

3.8
closing volume
component of the regurgitant volume that is associated with the dynamics of valve closure during a single cycle

See Figure 1.

3.9
control valve
heart valve substitute for preclinical and clinical evaluations of similar design and constructed of similar material as the investigational device

NOTE The control valve should have a known clinical history.



Key
X time
Y flowrate
1 closing volume
2 leakage volume

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

3.10
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 Cumulative incidence is also known as 'actual' analysis.

3.11
cycle
one complete sequence in the action of a heart valve substitute under pulsatile-flow conditions

3.12
cycle rate
number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min)

3.13
design verification
establishment by objective evidence that the design output meets the design input requirements

3.14
design validation
establishment by objective evidence that device specifications conform with user needs and intended use(s)

3.15
effective orifice area
A_{EO}
orifice area that has been derived from flow and pressure or velocity data

3.16
failure
inability of a device to perform its intended function at any point during its intended lifetime

NOTE The inability to perform the intended function may manifest itself as a reduced operating effectiveness and/or as hazards.

3.17
failure mode
mechanism of failure which can result in a hazard

NOTE Stent fracture, calcification and prolapse are examples of failure modes.

3.18
flexible heart valve substitute
heart valve substitute wherein the occluder is flexible under physiological conditions

NOTE The orifice ring may or may not be flexible. This category was previously known as biological heart valve substitute because of the biological source of the flexible occluder(s) but, at a minimum, should also include flexible polymer occluder(s).

3.19
forward-flow phase
portion of the cycle time during which forward flow occurs through a heart valve substitute

3.20
hazard
known or potential source of harm which results from a given failure mode

3.21
harm
physical injury or damage to the health of the patient or end-user of the device

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definition 3.3.

3.22
heart valve substitute
device used to replace or supplement a natural valve of the heart

See also 3.18 and 3.48, and examples in Figures J.1, J.2, J.3, J.4 and J.5.

3.23
intended use
use of a product, process or service in accordance with the specifications, instructions and information provided by the manufacturer

3.24
internal orifice area
IOA
numerical indication of the area within a prosthetic heart valve through which blood flows

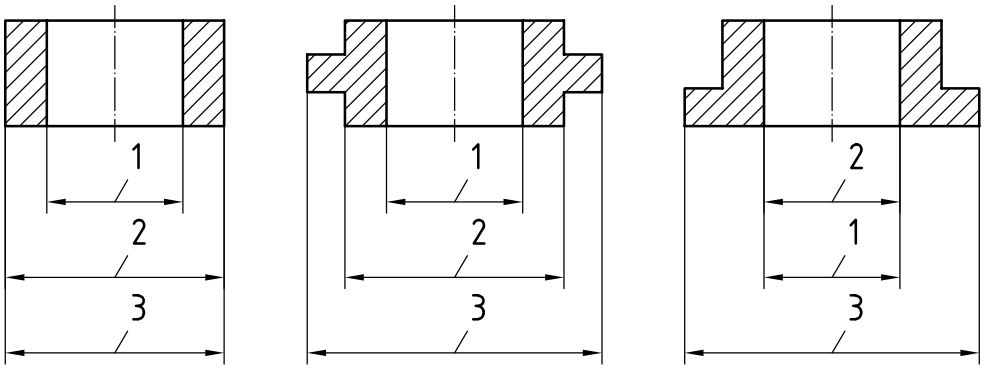
See Figure 2.

3.25
intra-annular sewing ring
sewing ring designed to secure the heart valve wholly or mostly within the patient's tissue annulus

See Figure 2. See also 3.24, 3.66 and 3.70.

3.26
intrasupra-annular sewing ring
sewing ring designed to secure a portion of the valve or sewing ring above the patient's tissue annulus and also some portion of the valve within the patient's tissue annulus

See Figure 2. See also 3.24, 3.66 and 3.70.



intra-annular **intrasupra-annular** **supra-annular**

Key
1 IOA
2 TAD
3 ESRD

Figure 2 — Designation of dimensions of heart valve substitute sewing ring configurations

3.27
isolated (aortic or mitral) heart valve substitute
implantation of single heart valve substitute excluding patients who have a second heart valve substitute in a different anatomical position

NOTE Concomitant procedures, including valve repair, coronary artery bypass, and ascending aortic aneurysm repair, are not relevant to this definition. See 7.4.4.

3.28
leakage volume
component of the regurgitant volume which is associated with leakage through the closed valve during a single cycle

NOTE 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).

3.29
linearized rate
linearized rate for a complication is the total number of events divided by the total time under evaluation

NOTE Generally, the rate is expressed in terms of percent per patient year.

3.30
long term follow-up
continued (after regulatory approval) periodic assessment of patients who have received the heart valve substitute during the clinical evaluation

3.31
manufacturer
organization with responsibility for the design, manufacture, packaging or labelling of a medical device, assembling a system, or adapting a medical device before it is placed on the market, regardless of whether these operations are carried out by the organization or on their behalf by a third party

3.32
mean arterial pressure
time-averaged arithmetic mean value of the arterial pressure during one cycle

3.33
mean pressure difference
time-averaged arithmetic mean value of the pressure difference across a heart valve substitute during the forward-flow phase of the cycle

NOTE The use of “mean pressure gradient” for this term is deprecated.

3.34
nonstructural dysfunction
abnormality resulting in stenosis or regurgitation of the heart valve substitute that is not intrinsic to the valve itself

NOTE This dysfunction is exclusive of valve thrombosis, systemic embolus or infection diagnosed at re-operation, autopsy or *in vivo* investigation. Examples include entrapment by pannus or suture, paravalvular leak, inappropriate sizing, and significant haemolytic anaemia.

3.35
occluder
component(s) of a heart valve substitute, such as rigid or flexible leaflets, discs, and balls, that move(s) to inhibit backflow

NOTE The occluders of flexible heart valve substitutes are typically called “leaflets” or “cusps”.

3.36
operative mortality
death from any cause during operation or within 30 d of the operation

3.37
outflow tract profile height
maximum distance that the valve 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 side) of the patient's annulus

3.38
pannus
ingrowth of tissue into the heart valve substitute which may interfere with normal functioning

3.39
paravalvular leak
clinically or haemodynamically detectable defect between the heart valve substitute and the patient's annulus

NOTE The term “perivalvular” is deprecated.

3.40
probability
statistical likelihood that a specific event will occur

3.41
process validation
establishing, by objective evidence, that a process consistently produces a result or product that meets its predetermined specifications

3.42
profile height
maximal axial dimension of a heart valve substitute in the open or closed position, whichever is greater

3.43
prosthetic valve endocarditis
infection involving a heart valve substitute

NOTE Diagnosis is based on customary clinical criteria, including an appropriate combination of positive blood cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly, systemic embolus or immunopathologic lesions) and/or histologic confirmation of endocarditis at reoperation or autopsy. Morbidity associated with active infection such as valve thrombosis, embolus or paravalvular leak is included under this category and is not included in other categories of morbidity.

3.44
quasi-real time durability testing
long-term durability testing performed at a cycle rate between normal and high normal (up to 200 cycles/min)

3.45
reference valve
heart valve substitute used to assess the conditions established in the *in vitro* tests used to evaluate the test heart valve substitute

NOTE The reference valve should approximate the test heart valve substitute in type, configuration and tissue annulus diameter; it may be an earlier model of the same valve, if it fulfills the necessary conditions. The characteristics of the reference valve should be well documented with clinical data.

3.46
regurgitant fraction
regurgitant volume expressed as a percentage of the stroke volume

3.47
regurgitant volume
volume of fluid that flows through a heart valve substitute in the reverse direction during one cycle and is the sum of the closing volume and the leakage volume

See Figure 1.

3.48
rigid heart valve substitute
heart valve substitute wherein the occluder(s) and orifice ring are non-flexible under physiological conditions

NOTE This category was previously known as mechanical heart valve substitute. Materials of construction of the rigid components of rigid heart valve substitutes have historically been metals, pyrolytic carbon and polymers.

3.49
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999 [14], definition 3.2]

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

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definition 3.10.

3.51
risk assessment
overall process comprising a risk analysis and a risk evaluation

[ISO/IEC Guide 51:1999 [14], definition 3.12]

3.52
risk control
process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels

3.53
risk estimation
process used to assign values to the probability and consequences of a risk

3.54
risk evaluation
judgment, on the basis of risk analysis, of whether an acceptable level of risk has been achieved in a given context based on the current values of society

NOTE Adapted from ISO/IEC Guide 51:1999 [14], definitions 3.7 and 3.11.

3.55
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk

3.56
root mean square forward flow
RMS forward flow
square root of the integral of the volume flow waveform squared

NOTE 1 This is calculated using Equation (1).

$$q_{v\,RMS} = \sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 \mathrm{d}t}{t_2 - t_1}} \tag{1}$$

where

$q_{v\,RMS}$ is root mean square forward flow;
$q(t)$ is instantaneous flow at time t;
t_1 is time at start of forward flow;
t_2 is time at end of forward flow.

NOTE 2 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.

3.57
safety
freedom from unacceptable risk

[ISO/IEC Guide 51:1999 [14], definition 3.1]

3.58
severity
measure of the possible consequences of a hazard

3.59
simulated cardiac output
net fluid volume forward flow per minute, through a test heart valve substitute

3.60
special processes
those processes for which the product cannot be fully verified by inspection or test

3.61
sterile
free from viable micro-organisms

3.62
sterility assurance level
SAL
probability of a viable micro-organism being present on a product after sterilization

3.63
sterilization
validated process used to render a product free from all forms of viable micro-organisms

3.64
stroke volume
volume of fluid moved through a test heart valve substitute in the forward direction during one cycle

3.65
structural deterioration
change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation