INTERNATIONAL STANDARD

ISO 5840

Third edition
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Cardiovascular implants — Cardiac valve prostheses

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Implants cardiovasculaires — Prothèses valvulaires

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Contents

iTeh STANDARD PREVIEW
(standards.iteh.ai)
ISO 5840:1996
https://standards.iteh.ai/catalog/standards/sist/2b6c979d-8b3e-48d3-bce3-dea705fa0c7/iso-5840-1996

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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.

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.

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International Standard ISO 5840 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommitte SC 2, *Cardiovascular implants*.

ISO 5840:1996
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This third edition cancels and replaces the second edition (ISO 5840:1989), which has been technically revised. Additions include testing of materials and components and a scheme for classification of heart valve substitutes and their components.

Annexes A to F of this International Standard are for information only.

Introduction

There is, as yet, no heart valve substitute which 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. For these reasons, this International Standard intentionally does not attempt to specify performance requirements for finished products. It does specify types of tests, test methods and/or requirements for test apparatus, and requires disclosure of test methods and results. The areas with which this International Standard is concerned are those which will 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 subsequent problems.

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ISO 5840:1996
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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 accelerated fatigue characteristics of heart valve substitutes. The exact test methods for hydrodynamic and accelerated fatigue testing have not been specified, but requirements 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.

Cardiovascular implants — Cardiac valve prostheses

1 Scope

1.1 This International Standard specifies tests to be performed and requirements for test apparatus to be used in determining the physical, biological and mechanical properties of heart valve substitutes of all types, and of the materials and components of which they are made.

1.2 Requirements are provided for preclinical *in vivo* evaluation, for clinical evaluation, and for reporting the results of all types of testing and evaluation covered in this International Standard. These requirements do not purport to comprise a complete test programme.

1.3 Specifications are also given for packaging and labelling of heart valve substitutes.

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1.4 This International Standard is not applicable to heart valve substitutes comprised in whole or in part of human tissue.

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

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2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 8601:1988, *Data elements and interchange formats — Information interchange — Representation of dates and times.*

ISO 10993-1:—[1], *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 10993-3:1992, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.*

ISO 10993-4:1992, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood.*

ISO 10993-5:1992, *Biological evaluation of medical devices — Part 5: Tests for cytotoxicity: in vitro methods.*

ISO 10993-6:1994, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.*

ISO 10993-7:1995, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.*

ISO/TR 10993-9:1994, *Biological evaluation of medical devices — Part 9: Degradation of materials related to biological testing.*

1) To be published. (Revision of ISO 10993-1:1992)

ISO 10993-10:1995, *Biological evaluation of medical devices — Part 10: Tests for irritation and sensitization.*

ISO 10993-11:1993, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity.*

ISO 10993-12:—[2], *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.*

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 14155:1996, *Clinical investigation of medical devices.*

3 Definitions

For the purposes of this International Standard, the following definitions apply.

3.1 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.

3.2 arterial diastolic pressure: Minimum value of the arterial pressure during diastole.

3.3 arterial peak systolic pressure: Maximum value of the arterial pressure during systole.

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3.4 closing volume: Component of the regurgitant volume that is associated with the dynamics of valve closure during a single cycle (see figure 1).

ISO 5840:1996
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3.5 cycle: One complete sequence in the action of a test heart valve substitute under pulsatile flow conditions.

3.6 cycle rate: Number of complete cycles per unit of time, usually expressed as cycles per minute (cycles/min).

3.7 external sewing ring diameter: Maximum external diameter of a heart valve substitute, including the sewing ring (see figure 2).

3.8 forward-flow phase: Portion of the cycle time during which forward flow occurs through a test heart valve substitute.

3.9 heart valve substitute: Device used to replace or supplement a natural valve of the heart, categorized according to the position in which it is intended to be used (valve type).

3.9.1 mechanical heart valve substitute: Heart valve substitute composed wholly of synthetic materials.

3.9.2 biological heart valve substitute: Heart valve substitute composed wholly or partly of animal tissue.

3.10 internal orifice area: Minimum projected area normal to the plane of the heart valve substitute, excluding the occluder(s).

3.11 leakage volume: Component of the regurgitant volume that is associated with leakage through the closed valve during a single cycle (see figure 1).

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).

3.12 mean arterial pressure: Time-averaged arithmetic mean value of the arterial pressure during one cycle.

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2) To be published.

3.13 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 usage of "mean pressure gradient" for this term is deprecated.

3.14 mean volume flow: Time-averaged arithmetic mean value of the flow across a heart valve substitute during the forward-flow phase of the cycle.

3.15 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 by reoperation, autopsy or *in vivo* investigation. Examples include entrapment by pannus or suture, paravalvular leak, inappropriate sizing, and significant haemolytic anaemia.

3.16 occluder: Component(s) of a heart valve substitute that move(s) to inhibit reflux.

3.17 operative mortality: Death from any cause during operation or within 30 days after operation.

3.18 profile height: Maximum axial dimension of a heart valve substitute in the open or closed position, whichever is greater (see figure 2).

3.19 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.

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ISO 5840:1996
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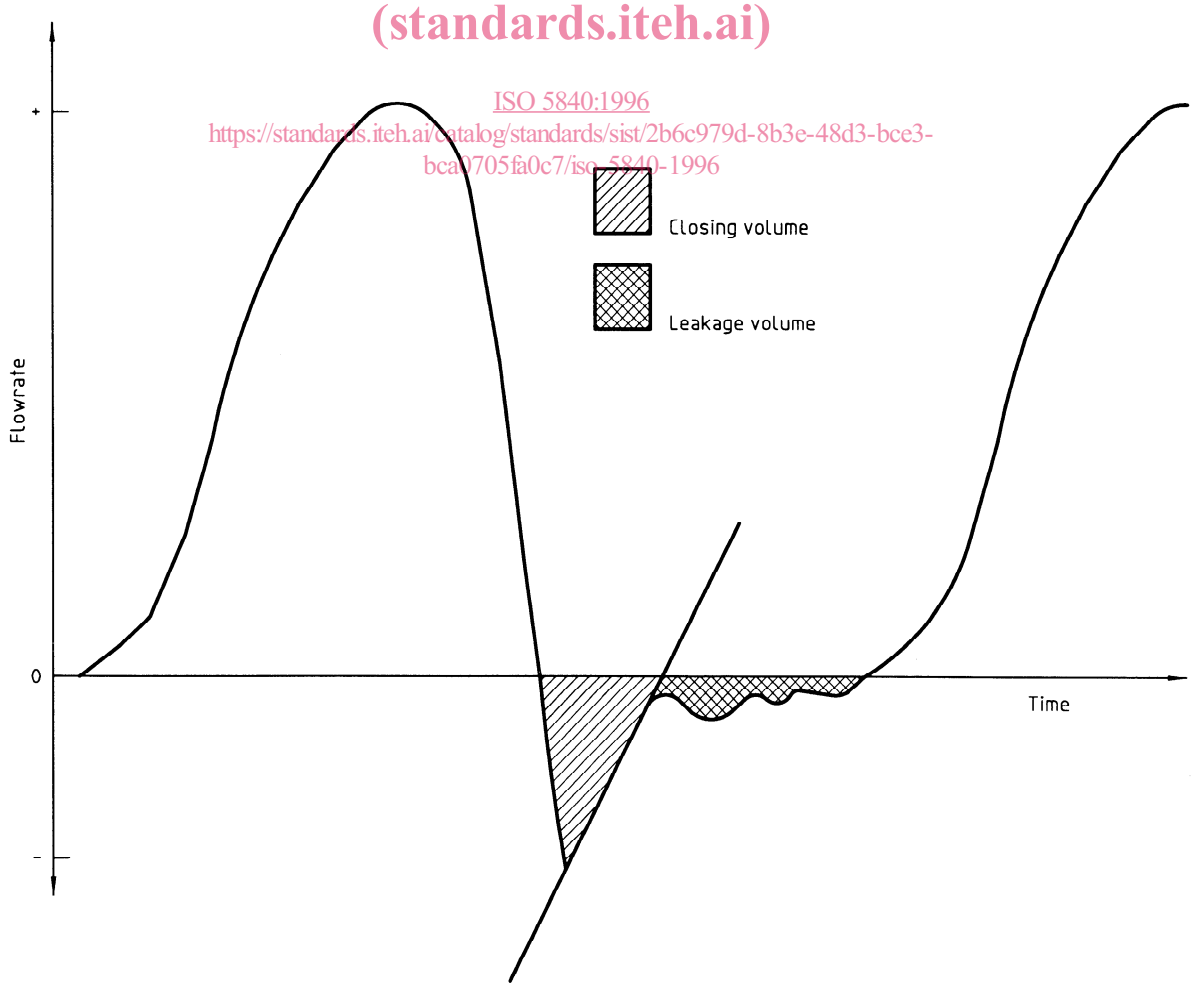

Figure 1 — Example of flow waveform and regurgitant volumes for one cycle

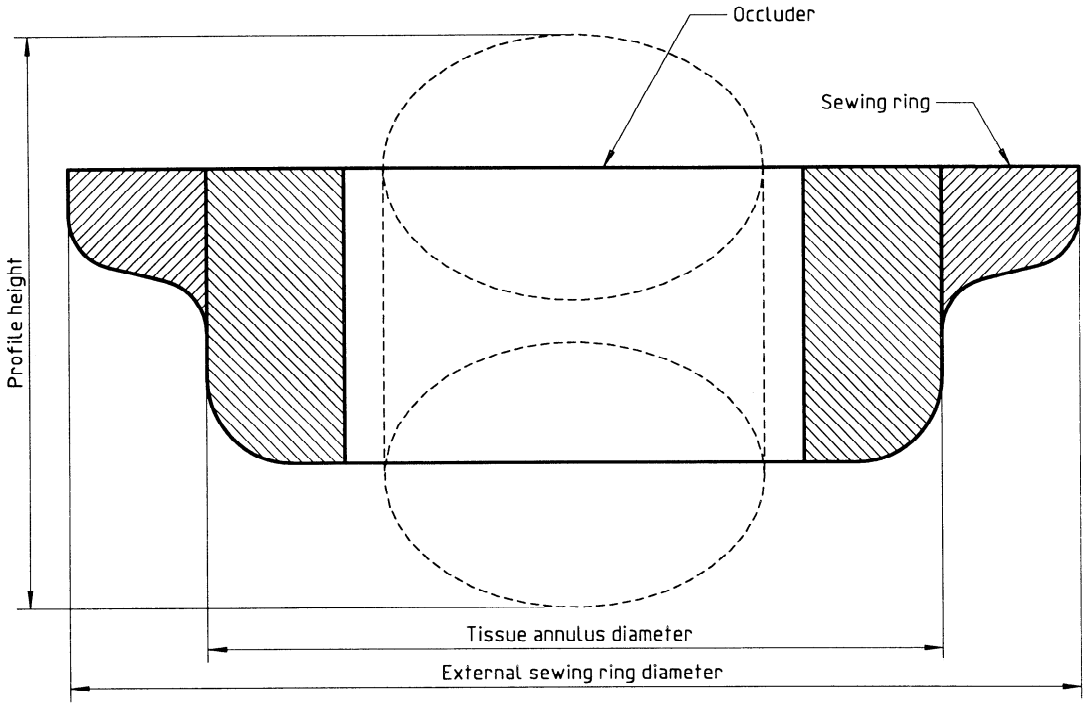

Figure 2 — Designation of dimensions of heart valve substitutes

3.20 reference valve: Heart valve substitute used to assess the conditions established in the tests employed to evaluate the test heart valve substitute.

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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 both *in vitro* and clinical data available in the literature.

ISO 5840:1996
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3.21 regurgitant fraction: Regurgitant volume expressed as a percentage of the stroke volume.

3.22 regurgitant volume: Volume of fluid that flows through a test heart valve substitute in the reverse direction during one cycle; it is the sum of the closing volume and the leakage volume (see figure 1).

3.23 root mean square (r.m.s.) volume flow: Square root of the time-averaged arithmetic mean square value of the volume flow through a test heart valve substitute during the forward-flow phase of the cycle.

3.24 simulated cardiac output: Net fluid volume flowing forward through a test heart valve substitute per minute.

3.25 stroke volume: Volume of fluid moved through a test heart valve substitute in the forward direction during one cycle.

3.26 structural deterioration: Change in the function of a heart valve substitute resulting from an intrinsic abnormality that causes stenosis or regurgitation.

NOTE — This definition excludes infection or thrombosis of the heart valve substitute as determined by reoperation, autopsy or *in vivo* investigation. It includes intrinsic changes such as wear, stress fracture, occluder escape, calcification, leaflet tear and stent creep.

3.27 systemic embolism: Clot or other particulate matter, not associated with infection, originating on or near the heart valve substitute and transported to another part of the body.

NOTE — Diagnosis may be indicated by a new, permanent or transient, focal or global neurologic deficit (exclusive of haemorrhage) or by any peripheral arterial embolus unless proved to have resulted from another cause (e.g. atrial myxoma). Patients who do not awaken post-operatively or who awaken with a stroke or myocardial infarction are excluded. Acute myocardial infarction that occurs *after* operation is arbitrarily defined as an embolic event in patients with known normal coronary arteries or who are less than 40 years of age.

3.28 tissue annulus diameter: External diameter of a heart valve substitute, including any covering where it is intended to mate with the smallest diameter of host tissue (see figure 2).

NOTE — The usage of "mounting diameter" for this term is deprecated.

3.29 valve size: Manufacturer's designation of the dimensions of the heart valve substitute.

3.30 valve thrombosis: Blood clot, not associated with infection, causing dysfunction of the heart valve substitute.

NOTE — Diagnosis may be proved by operation, autopsy, or clinical investigation (e.g. echocardiography, angiocardiography or magnetic resonance imaging).

4 Valve description

A complete description of the heart valve substitute, its components, materials and processes of construction shall be provided.

NOTES

1 See annex E for definitions of terms that can be used to identify the heart valve substitute components.

2 Relevant construction processes may include anticalcification treatment or carbon coating of sewing rings (see annex F).

5 Material, component and valve assembly testing (see A.1 for rationale)

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5.1 Principle

Physical testing of the materials and components of heart valve substitutes is performed to assure that the valve or components will withstand the rigors imposed by the host over the lifetime of the device. Test selection is based on a matrix criterion that accounts for the materials and components used in the heart valve substitute and the site of use.

ISO 5840:1996
https://standards.iteh.ai/catalog/standards/sist/2b6c979d-8b3e-48d3-bce3-bca0705fa0c7/iso-5840-1996

5.2 General

The test specimens chosen for evaluation shall emulate, as closely as possible, the condition of the finished product as supplied for clinical use.

5.3 Testing fluid and temperature

Where emulation of *in vivo* conditions is applicable, testing shall be performed using a testing fluid of isotonic saline, blood or a blood-equivalent fluid whose physical properties (e.g. specific gravity, viscosity at working temperature) shall be stated. The tests shall be conducted at 37 °C unless an acceptable scientific/engineering rationale allows for other conditions.

NOTE — Mechanical properties and degradation properties can vary with temperature.

5.4 Biocompatibility

The biocompatibility of the materials and components used in heart valve substitutes shall be determined in accordance with the appropriate part(s) of ISO 10993.

5.5 Physical and material testing

5.5.1 Materials and component testing

Properties of heart valve substitutes and their components shall be evaluated, where applicable to the design of the valve, according to tables 1 and 2. A rationale for the selection of properties evaluated shall be provided.

NOTE — See annexes C, D, E and F for references and a description of possible materials and component testing of heart valve substitutes. These annexes are provided to guide the reader in the use of tables 1 and 2.

Table 1 — Physical and chemical properties for evaluation of heart valve substitute components

Clause reference (annex C)	Physical and chemical properties	Component[1)]				
		Synthetic polymer	Biological	Metal	Ceramic	Textile
C.2.	**Bulk physical properties**					
2.1	Chemical composition	ABCDEFGHIJ	J	ABCDEHJ	ABDJ	FGI
2.2	Density	ABCDEFGHIJ		ABCDEHJ	ABDJ	
2.3	Liquid diffusivity	ABCDEFGHI			ABD	
2.4	Hardness	ABCDEFGHJ		ABCDEHJ	ABDJ	
2.5	Microstructure/morphology		ABCDEFGHI	ABCDEHJ	ABDJ	
2.6	Tear strength	DI	ABCDEFGHI			
2.7	Young's modulus	ABCDEH		ABCDEH	ABD	
2.8	Poisson's ratio	ABCDEFGHI		ABCDEH	ABD	
2.9	Dynamic moduli	BDE	ABCDEFGHI			
2.10	Coefficient of thermal expansion	ABCDE		ABDH	ABD	
2.11	Glass transition temperature	ABCDEFI				FGI
2.12	Melt index	ABCDEHI				
2.13	Melting point	ABCDEFI				FGI
2.14	Hydraulic expansion	ABCDEFHIJ		J	J	
2.15	Biostability	ABCDEFGHI				
2.16	Film thickness	J		J	J	
2.17	% Elemental composition of a film	J		J	J	
C.3.	**Surface physical properties**					
3.2	Critical surface tension	ABDEJ	J	ABCDJ	ABDJ	
3.3	Surface roughness	ABDEJ	J	ABCDJ	ABDJ	
3.4	Surface chemical composition	ABDEJ	J	ABCDJ	ABDJ	
3.5	Surface charge and charge density	ABDEJ	J	ABCDJ	ABDJ	
3.6	Surface resistance	J		J	J	
C.4.	**Mechanical and chemical properties**					
4.2	Wear resistance	ABCDJ		ABDHJ	ABDJ	
4.3	Coefficient of friction	ABDE		ABDH	ABD	
4.4	Peel strength	DE				
4.5	Flexural strength	BDE		E	ABD	
4.6	Compressive strength	ABCE			ABD	
4.7	Tensile strength	DEI	ABCDE	ABCDEH	ABD	
4.8	Tensile strain to failure (elongation)	DEIJ	ABCDE	ABCDEHJ	ABDJ	
4.9	Strain energy to failure	EI		C	ABD	
4.10	Residual stress	ABCDEFGH		ABCDEH	ABD	
4.11	Stress relaxation	ABCDEFGH	ABCDE			
4.12	Creep	ABCDEH				
4.13	Fracture toughness			ABCDEH	ABD	
4.14	Crack growth velocity			ABCDEH	ABD	
4.15	Fatigue life	ABCDEHI		ABCDEH	ABD	
4.16	Stress corrosion potential			ABDH		
4.17	Galvanic corrosion potential			ABCDH		
4.18	Fretting corrosion potential			ABDH		
4.19	Void concentration	J		J	J	

NOTE — See figure E.1 and annex E for description of components A to J.

1) A Orifice ring (housing) D Occluder/leaflet G Sewing ring filler J Coating
B Occluder retention mechanism E Stent H Sewing ring retaining material
C Stiffening element F Covering I Component joining material

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ISO 5840:1996
https://standards.iteh.ai/catalog/standards/sist/2b6c979d-8b3e-48d3-bce3-bea0705fa0c7/iso-5840-1996

Table 2 — Physical and chemical properties for application to design of heart valve substitutes and their components

Clause reference (annex C)	Physical and chemical properties tests	Appropriate for current design	
		Yes	No
C.5.	**Valve design parameter**		
5.1	Computer modelling		
5.2	Tissue annulus diameter and internal orifice area measurements		
5.3	Valve impact and fatigue life		
5.4	Static pressure; "burst" test		
5.5	Orifice deflection		
5.6	Sewing ring push-off		
5.7	Sewing ring torque		
5.8	Suture retention strength		
5.9	Calcification (*in vivo* model)		

5.5.2 Valve assembly testing

The physical and chemical properties relating to valve design, listed in table 2, shall be evaluated on heart valve substitutes, subassemblies or components as applicable.

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5.6 Test report

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Each test report shall include:

a) rationale for the test;

b) identity of the material tested (e.g. generic chemical name or biological source) or a description of the item(s) tested;

c) identification of the sample tested (e.g. batch number);

d) number of specimens tested;

e) test method used and, where a test method other than a test specified in an International Standard is used, full details of the test procedure;

f) test results.

6 Hydrodynamic testing (see A.2 for rationale)

6.1 Principle

Hydrodynamic testing provides *in vitro* information on the fluid mechanical performance of the heart valve substitute under steady and pulsatile flow conditions.

6.2 General

All heart valve substitutes to be tested shall be of quality suitable for human implantation. Before testing, each heart valve substitute shall have been sterilized by the process used or intended to be used by the manufacturer during production. If a heart valve substitute can be resterilized prior to implantation, it shall also be subjected to the recommended maximum number of resterilization cycles, using the method stated by the manufacturer.

6.3 Steady forward-flow testing

6.3.1 Measuring equipment accuracy and testing fluid

6.3.1.1 The pressure measurement system shall have a measurement accuracy of at least ± 0,13 kPa (± 1 mmHg).

6.3.1.2 All measuring equipment shall have a measurement accuracy of at least ± 5 % of the full-scale reading.

6.3.1.3 The fluid used for the test shall be isotonic saline, blood or a blood-equivalent fluid whose physical properties (e.g. specific gravity, viscosity at working temperature) shall be stated.

6.3.2 Test apparatus requirements

6.3.2.1 Steady-flow testing for aortic and mitral heart valve substitutes shall be conducted in a straight tube having an internal diameter of 35 mm.

6.3.2.2 The test system shall be capable of generating flowrates of at least 30 l/min.

6.3.2.3 Flow entering the test chamber shall be relatively nondisturbed, which can be achieved with a flow straightener upstream of the heart valve substitute.

6.3.2.4 Pressure taps shall be located one tube-diameter upstream and three tube-diameters downstream from the midplane of the heart valve substitute sewing ring. If sufficient data can be provided to demonstrate comparable results, other pressure tap configurations may be used.

6.3.2.5 The pressure taps shall be flush with the inner wall of the tube.

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6.3.2.6 A standard nozzle in accordance with figure 3 a) shall be used to characterize the forward-flow pressure and flow-measuring equipment.

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6.3.3 Test procedure

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6.3.3.1 Carry out the test on at least three heart valve substitutes of each tissue annulus diameter.

6.3.3.2 Measure the pressure difference across the test valve and the standard nozzle over a flowrate range of 5 l/min to 30 l/min, in 5 l/min increments.

6.3.4 Test report

The steady-flow test report shall include:

a) a description of the fluid used for the test, including its biological origin or chemical components, temperature, viscosity and specific gravity under the test conditions;

b) a description of the steady-flow apparatus, as specified in 6.3.2.

Details of the mean, range and standard deviation of the following performance test variables, at each simulated condition for each test heart valve substitute and standard nozzle, shall be presented in tabular or graphic form:

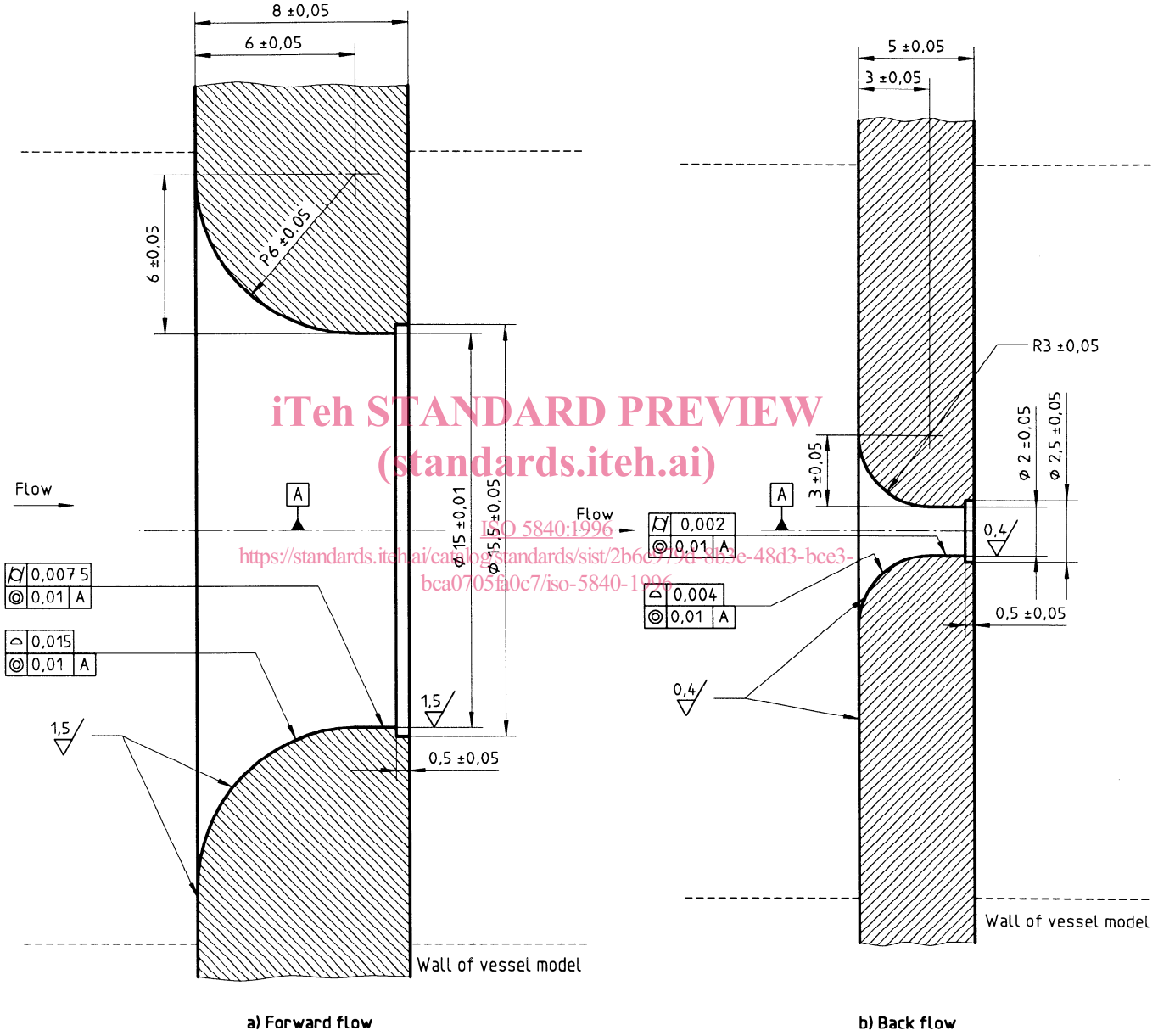
c) steady flowrate, expressed in litres per minute;

d) pressure differences, expressed in kilopascals and in millimetres mercury;

e) effective orifice area, expressed in square centimetres, calculated taking into account the pressure recovery downstream from the test heart valve substitute.

Dimensions in millimetres

Surface roughners values in micrometres



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ISO 5840:1996
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Figure 3 — Standard nozzle