List of Titles

American National Standard

ANSI/AAMI/ISO 5840:1996

Cardiovascular implants—Cardiac valve prostheses

AAMI Association for the Advancement of Medical Instrumentation

List of Titles

Association for the Advancement of Medical Instrumentation
1110 N. Glebe Rd., Suite 220
Arlington, VA 22201-4795

Copyright and Permissions

5840 Cardiovascular implants—Cardiac valve prostheses

ANSI/AAMI/ISO 5840—1996
(Revision of ANSI/AAMI/ISO 5840—1991)

Cardiovascular implants—Cardiac valve prostheses

Developed by
Association for the Advancement of Medical Instrumentation

Approved 8 April 1996 by
American National Standards Institute, Inc.

Abstract:

This standard specifies types of tests, test methods and/or requirements for test apparatus, and requires disclosure of test methods and results. The areas with which this 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.

Committee representation

Association for the Advancement of Medical Instrumentation

The adoption of ISO 5840:1996 as a revision of ANSI/AAMI/ISO 5840-1991 was initiated by the AAMI Cardiac Valve Prostheses Committee, which also functions as a U.S. Technical Advisory Sub-Group to the relevant work in the International Organization for Standardization (ISO).

The **AAMI Cardiac Valve Prostheses Committee** has the following members:

Cochairs:
David J. Myers, MA
Stanton P. Nolan, MD

Members:
Steve Anderson, St. Jude Medical, Inc. , St. Paul, MN
Arthur C. Beall Jr., MD, VA Medical Center, Houston, TX
Richard W. Bianco, University of Minnesota, Minneapolis, MN
Lawrence Burr, MD, Standards Council of Canada, Vancouver, BC
Richard E. Clark, MD, Allegheny General Hospital, Pittsburgh, PA
Robert W. M. Frater, MD, Montefiore Medical Center, Bronx, NY
Warren D. Hancock, Hancock Jaffe Labs, Irvine, CA
Richard D. Jones, PhD, St. Luke Med. Ctr., Cleveland, OH
Chris Kingsbury, BS, MBA, Baxter Healthcare Corp., Irvine, CA
Stanton P. Nolan, MD, U. of Va. Hlth. Sciences, Charlottesville, VA
William F. Regnault, FDA/CDRH, Rockville, MD
Gerald J. Richard, Carbomedics Inc., Austin, TX
Diana Salditt, Medtronic Inc., Minneapolis, MN
Daniel Schickele, Consultant, San Diego, CA

Ajit P. Yoganathan, PhD, Georgia Inst. of Tech., Atlanta. GA

Alternate: Louis Arin, FDA Winchester Engr. & Analyt. Ctr., Winchester, MA
Andrew K. Balo, St. Jude Medical, Inc., St. Paul, MN
Edward Mueller, FDA/CDRH, Rockville, MD
David J. Myers, MA, Medtronic Inc., Irvine, CA
Stefan G. Schreck, PhD, Baxter Healthcare Corp., Irvine, CA

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 5840:1996

Cardiac valve prostheses

As indicated in the foreword to the main body of this document (page vi), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of the standard for cardiac valve prostheses.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication. AAMI also encourages its committees to harmonize their work with international standards as much as possible.

This standard was prepared by ISO/TC 150/SC 2, Implants for surgery—Cardiovascular implants, in cooperation with CEN/TC 285, with the intention to eventually harmonize the International and European Standard in the near future. The AAMI Cardiac Valve Prostheses Committee (U.S. Technical Advisory Sub-Group for ISO/TC 150/SC 2) supports such international harmonization of standards and recommended in 1995 that AAMI initiate parallel adoption of ISO 5840 in the United States as a revision of the American National Standard ANSI/AAMI/ISO 5840-1991.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201.

NOTE—Beginning with the ISO foreword on page vi, this American National Standard is identical to ISO 5840:1996.

Foreword

The International Organization for Standardization (ISO) 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.

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

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 labeling 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.

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 program.

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

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

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

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.*

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 hemorrhage: 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.

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).

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 volume 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.

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.

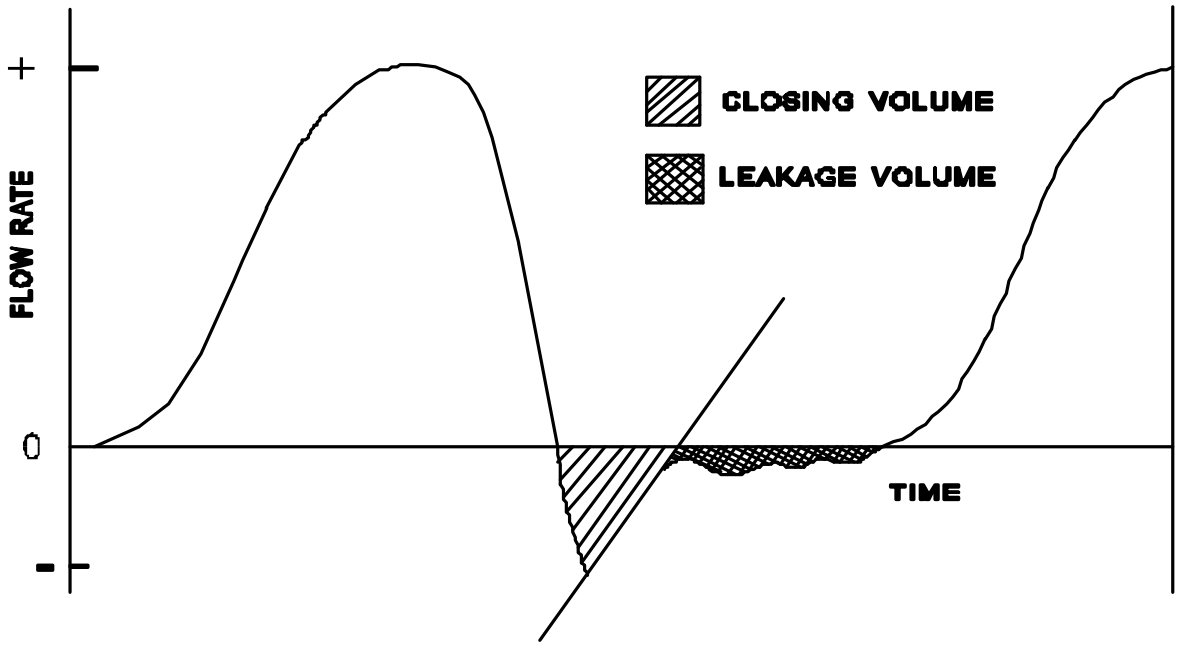

Figure 1—Example of flow waveform and regurgitant volumes for one cycle

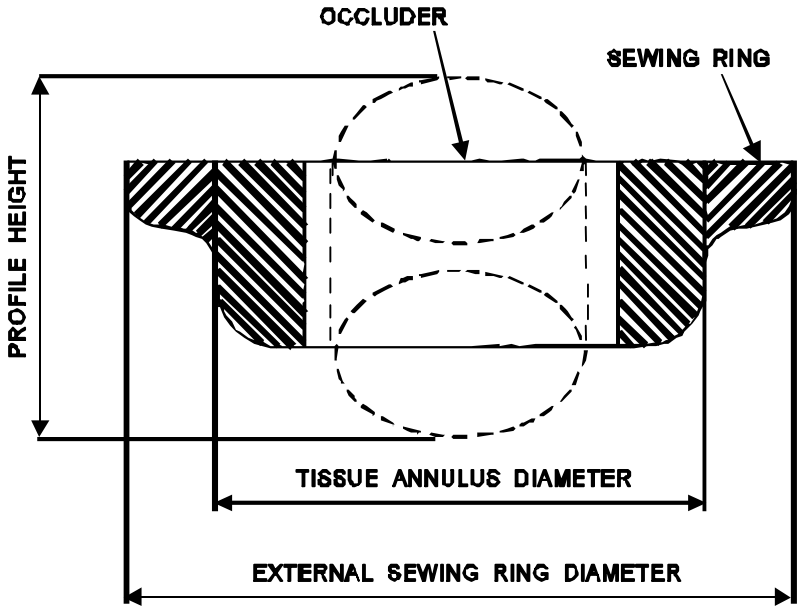

Figure 2—Designation of dimensions of heart valve substitutes

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 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 hemolytic anemia.

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.

3.20 reference valve: Heart valve substitute used to assess the conditions established in the tests employed 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 both *in vitro* and clinical data available in the literature.

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 hemorrhage) 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)

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.

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 test 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) 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 help guide the reader in the use of tables 1 and 2.

5.5.2 Valve assembly testing

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

5.6 Test report

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.

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

Clause reference (annex C)	Physical and chemical properties	Component Material				
		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.

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	

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 modeling		
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)		

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 the 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 kilopascals (kPa) (±1 millimeters mercury (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.

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.

6.3.3 Test procedure

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 liters per minute;

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

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

EXAMPLE, based on the Carnot equation**:**

$$EOA = \frac{A}{1 + \sqrt{\frac{2\,DR}{r\,n^2}}}$$

where

EOA is the effective orifice area;

A is the cross-sectional area of the tube;

ΔR is the mean pressure difference across heart valve substitute;

ν is the cross-sectional average velocity in the tube;

ρ is the density of testing fluid.

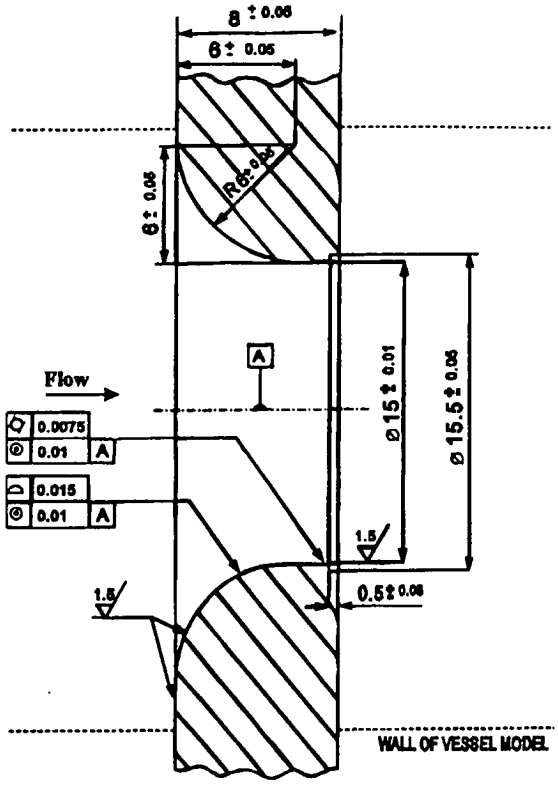

Figure 3—Standard nozzle

a) Forward flow

Dimensions in millimeters—Surface roughners values in micrometers

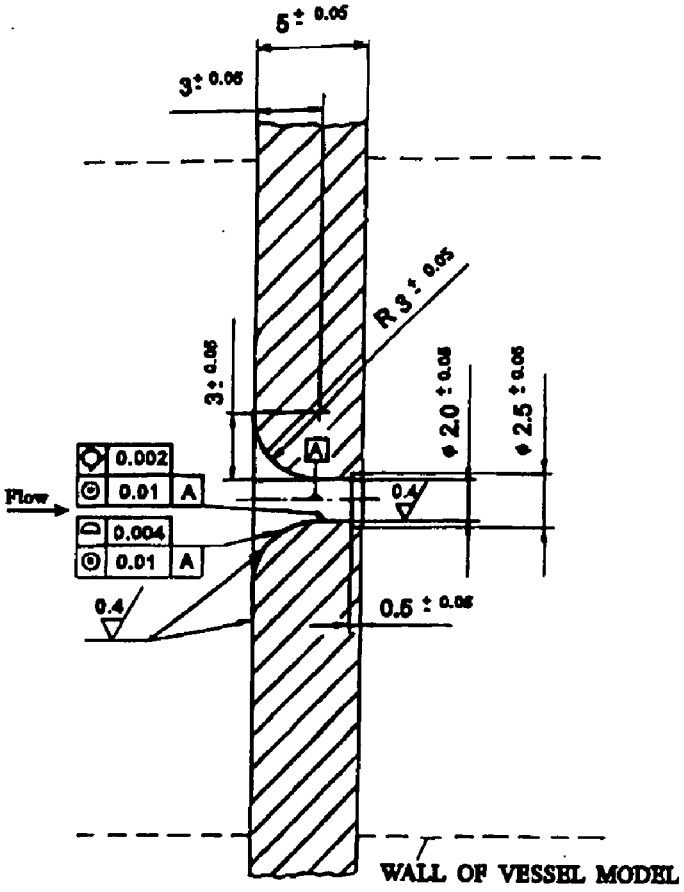

Figure 3—Standard nozzle

b) Back flow

Dimensions in millimeters—Surface roughners values in micrometers

6.4 Steady back-flow leakage testing

6.4.1 Measuring equipment accuracy and testing fluid

6.4.1.1 Regurgitant volume measurements shall have a measurement accuracy of at least ±1 ml.

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

6.4.1.3 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.

6.4.2 Test apparatus requirements

6.4.2.1 The steady back-flow leakage testing shall be conducted in an apparatus that is capable of generating constant back-pressures in the range of 5.2 kPa to 26 kPa (40 mmHg to 200 mmHg).

6.4.2.2 The heart valve substitute shall be mounted in a manner to prevent leakage around and through the sewing ring.

6.4.2.3 A standard nozzle, in accordance with figure 3 b), shall be used to characterize the back pressure, leakage volume flowrate and pressure-measuring equipment.

6.4.3 Test procedure

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

6.4.3.2 Measure the static leakage across the test valve and the standard nozzle at five equidistant back-pressures in the range of 5.2 kPa (40 mmHg) to 26 kPa (200 mmHg). Collect at least five measurements at each condition.

6.4.4 Test report

6.4.4.1 The steady back flow test report shall include:

a) a description of the fluid used for 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 6.4.2;

c) details of the mean, range and standard deviation of the performance test variables, at each simulated condition for each test heart valve substitute and standard nozzle, presented in tabular or graphic form; i.e. static leakage volume flowrate, expressed in liters per minute, as a function of back-pressure, expressed in kilopascals.

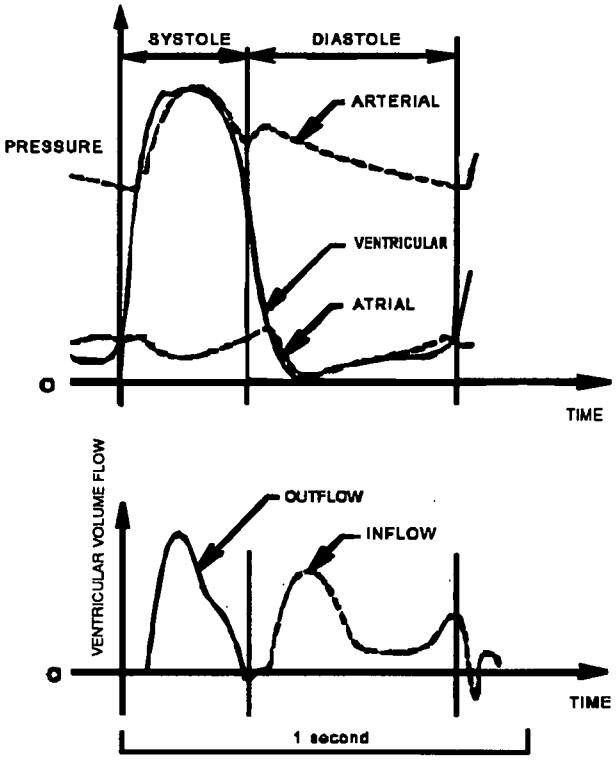

Figure 4—Diagrams of hemodynamic waveforms simulating those of healthy humans

6.5 Pulsatile-flow testing

6.5.1 Measuring equipment accuracy and testing fluids

6.5.1.1 The pressure measurement system shall have a natural frequency of at least 20 Hz and a measurement accuracy of at least ±0.26 kPa (±2 mmHg).

6.5.1.2 Regurgitant volume measurements shall have a measurement accuracy of at least ±2 ml.

6.5.1.3 All measuring equipment other than that specified in 6.5.1.1 and 6.5.1.2 shall have a measurement accuracy of at least ± 5% of the full scale reading.

6.5.1.4 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.

6.5.2 Test apparatus requirements

6.5.2.1 The pulsatile-flow testing shall be conducted in a pulse duplicator which produces pressure and flow waveforms that approximate physiological conditions (see figure 4).

6.5.2.2 The pulse duplicator shall have had its properties and performance established by means of testing reference valve(s).

6.5.2.3 The pulse duplicator shall have a variable stroke volume in the range of 30 ml to 100 ml or greater.

6.5.2.4 The pulse duplicator shall have a cycle rate range of 40 cycles/min to 120 cycles/min or greater.

6.5.2.5 The pulse duplicator shall be an equivalent hydrodynamic model of the systemic circulation, incorporating components that are analogous to systemic vascular resistance and to systemic vascular compliance.

6.5.2.6 The pulse duplicator shall permit measurement of time-dependent pressures and flows.

6.5.2.7 The system shall simulate a mean arterial pressure of at least 13 kPa ±0.65 kPa (100 mmHg ±5 mmHg), with an arterial peak systolic pressure of between 14.3 kPa and 19.5 kPa (110 mmHg and 150 mmHg) and an arterial diastolic pressure between 7.8 kPa and 11.7 kPa (60 mmHg and 90 mmHg), depending on valve size and cardiac output.

6.5.2.8 The systolic forward flow shall account for 35% ±5% of the total cycle time at a cycle rate of 70 cycles/min ±10 cycles/min.

6.5.2.9 Relevant dimensions of the cardiac chambers and vessels shall be simulated. The relevant compliance should also be simulated when testing nonstented biological heart valve substitutes.

6.5.2.10 The chamber shall allow the observer to view and photograph the test heart valve substitute at all stages of the cycle.

6.5.3 Test procedure

6.5.3.1 Carry out the test on at least three heart valve substitutes of each tissue annulus diameter and one reference valve in the position in which they are intended to be used.

6.5.3.2 Include qualitative assessments over a flow volume range corresponding to simulated cardiac outputs from 2 l/min to at least 7 l/min.

6.5.3.3 Examine at least simulated cardiac outputs.

6.5.3.4 Make at least ten measurements of each variable obtained from either consecutive or randomly-selected cycles.

6.5.3.5 Qualitatively assess the opening and closing action of each heart valve substitute.

6.5.3.6 If appropriate, qualitatively assess the flow field in the immediate vicinity of the heart valve substitute.

6.5.3.7 Record or measure:

a) mean pressure difference across the test heart valve substitute;

b) mean and r.m.s. flowrates through the test heart valve substitute;

c) stroke volume;

d) cycle rate;

e) mean arterial pressure over the whole cycle;

f) duration of forward flow through the test heart valve substitute, as a percentage of cycle time;

g) regurgitant volume at three cycle rates, including the closing volume, the leakage volume (see figure 1) and the corresponding mean pressure difference across the closed valve.

6.5.4 Test report

6.5.4.1 The pulsatile-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 pulse duplicator, as specified in 6.5.2, and its major components and associated apparatus, including a schematic diagram of the system giving the relevant chamber dimensions, details of the location of the pressure-measuring sites relative to the midplane of the heart valve substitute sewing ring, pressure measurement instrumentation frequency response, and the appropriate representative pressure and flow waveforms at approximately 70 cycles/min, cardiac output of 5 l/min and mean arterial pressure of 13 kPa (100 mmHg);

c) an assessment, including appropriate documentation, of the opening and closing action of a test heart valve substitute and, if appropriate, its adjacent flow field under stated conditions;

d) a permanent recording of at least ten consecutive cycles of the time-dependent simultaneous pressures, proximal and distal to the heart valve substitute, and the volume flow through it.

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

e) simulated cardiac output, expressed in liters per minute;

f) cycle rate, expressed in cycles per minute;

g) duration of forward-flow phase, expressed as a percentage of the cycle time;

h) stroke volume, expressed in cubic centimeters;

i) mean and r.m.s. flowrates, expressed in liters per minute;

j) mean pressure difference, expressed in kilopascals and in millimeters mercury;

k) effective orifice area (provide formula used), expressed in square centimeters;

l) regurgitant volume, expressed in cubic centimeters, regurgitant fraction, expressed as a percentage, closing volume, leakage volume and the corresponding mean pressure difference across the closed valve, expressed in kilopascals and in millimeters mercury;

m) mean arterial pressure over the whole cycle, expressed in kilopascals and in millimeters mercury.

7 Durability testing (See A.2 for rationale)

7.1 Principle

Information on durability and failure modes experienced *in vitro* is provided which can be compared to a reference valve.

7.2 General

All heart valve substitutes to be tested shall be of the 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.

7.3 Measuring equipment accuracy and testing fluid

7.3.1 The pressure-measuring system shall have a natural frequency of at least 1 000 Hz and a measurement accuracy of at least ±0.65 kPa (±5 mmHg).

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

7.3.3 The fluid used for the test shall be appropriate for the purpose of the test.

7.3.4 Most mechanical and biological heart valve substitutes may be tested at room temperature, but mechanical heart valve substitutes using flexible polymer leaflets or containing coatings shall be tested at 37° C.

7.4 Test apparatus requirements

7.4.1 The apparatus shall produce a minimum peak pressure difference of 11.7 kPa (90 mmHg) across closed aortic valves, and a minimum peak pressure difference of 15.6 kPa (120 mmHg) across closed mitral valves. These pressure differences shall be maintained for 95% of all of the test cycles.

7.4.2 The apparatus shall produce full valve opening and closing during each cycle.

7.5 Test procedure

7.5.1 Conduct the test on at least three each of the largest, medium, and smallest sizes of each type (aortic and mitral) heart valve substitute. Test one equivalent-size reference valve under identical conditions, although it may be tested in a separate testing machine. If the aortic and mitral heart valve substitutes are identical in configuration except for the sewing ring, then test only in the mitral position.

7.5.2 During the test, examine each heart valve substitute at least every 50×10^6 cycles.

7.5.3 Continue the test until failure occurs or until at least 380×10^6 cycles (mechanical heart valve substitute) or 200×10^6 cycles (biological heart valve substitute) have been completed.

7.5.4 If failure occurs, describe and document the modes of failure and their most probable cause(s).

NOTE—Failures are characterized by structural damage and/or functional impairment. Examples of structural deterioration include holes, tears, gross delamination, fraying, incomplete coaptation, fracture, excessive deformation, failure of any individual component, other mechanical breakdown and/or wear. Examples of functional impairment include increased regurgitation and/or increased forward pressure difference across the valve.

7.6 Test report

The durability test report shall include:

a) a description of the fluid used for the test, including biological origin or chemical components,

temperature, viscosity, and specific gravity under the test conditions;

b) a description and specification of the test and associated apparatus, including a schematic diagram of the system;

c) the cycle rate (cycles/min);

d) a validation of the test method, by documentation of the pressure difference, expressed in kilopascals and in millimeters mercury across the heart valve substitute and across a reference valve of a corresponding size, as described by pressure/time waveforms, and appropriate visual recording of the opening and closing of at least one heart valve substitute of each tissue annulus diameter studied and of at least one reference valve;

e) a detailed description of the appearance of the heart valve substitute at the completion of the test, or upon the development of structural change and/or failure. Any damage shall be characterized using the appropriate means, e.g. histology or surface characterization. It shall be indicated if the valves were intact for the length of the evaluation.

8 Pre-clinical *in vivo* evaluation (See A.3 for rationale)

8.1 Principle

Data are obtained pertaining to the claimed performance and unanticipated side effects of a heart valve substitute *in vivo*.

8.2 Method

8.2.1 General requirements

a) The test heart valve substitute shall be evaluated in at least one of the anatomical positions for which it is intended;

b) the heart valve substitutes shall be of clinical quality, and of the same design and size; all reference valves shall be of identical design and size;

c) the same surgical techniques shall be used for the implantation of all of the heart valve substitutes (e.g. suture technique, anatomical location and orientation);

d) animal welfare shall be addressed in accordance with the principles given in ISO 10993-2.

8.2.2 Test procedure

Implant animals of the same species, and preferably of the same sex and age, with test heart valve substitutes so that at least six animals shall have survived a minimum of 20 weeks after implantation.

Implant at least two animals with a reference valve to serve as concurrent controls. Subject each animal in which a heart valve substitute has been implanted to a postmortem examination. Thus, the data shall include that obtained from all animals; those that do and those that do not survive this 20-week period.

The assessment shall provide at least the following:

a) any pathological consequences to the major organs;

b) the hematological consequences of implantation;

c) an evaluation of hemodynamic performance during or after the 20-week implantation period, including measurements of the pressure difference across the heart valve substitute at a cardiac index of approximately 3 l/(min•m^2), the cardiac output and an assessment of regurgitation;

d) any structural change of the heart valve substitute (e.g. macroscopic damage, degeneration of materials, deformation, and calcification).

8.3 Test report

The test report shall contain:

a) a gross and microscopic pathology report on each animal in which a heart valve substitute was implanted, including any animal that did not survive for the minimum post-implantation period. This report shall include visual records of the heart valve substitute *in situ* and the results of any thromboembolism of the major organs.;the cause of death shall be given if the animal was not sacrificed;

b) the description and results of all blood studies performed, including a statement of the time elapsed between implantation and these studies; blood studies shall include at least an evaluation of hemolysis, hematology and blood chemistry;

c) the post-operative hemodynamic performance of the heart valve substitute, including the pressure difference across the heart valve substitute expressed in kilopascals and in millimeters mercury, cardiac output measurements expressed in liters per minute, a quantitative assessment of regurgitation, and visualization of occluder or leaflet motion;

d) the appearance of the explanted heart valve substitute, including a visual record and an assessment of structural changes (e.g. macroscopic damage, degeneration of the materials, deformation, and calcification); if appropriate, the functional status of the heart valve substitute shall be assessed by hydrodynamic testing as described in clause 6;

e) a detailed description of the animal model used, the rationale for its use, and the pretest health assessment of each animal; this shall include documentation of the age of the animal at implantation;

f) the name and dose of medication(s) received by the animal during the survival period (e.g. antibiotics or drugs which alter hemostasis);

g) an assessment of the difficulty in surgical handling of the valve and accessories, including any unusual or unique characteristics;

h) operative procedure, including suture technique, test heart valve substitute orientation and operative complications;

i) the names of the investigators and their institutions.

9 Clinical evaluation (See A.4 for rationale)

9.1 Principle

Where a clinical evaluation is deemed appropriate, data are obtained on the safety and performance of heart valve substitutes under normal conditions of use, and the side effects and related risks of heart valve substitute implantation in humans are determined.

9.2 General

For new heart valve designs, a clinical evaluation shall be carried out. For modifications of an existing valve, the need for a clinical evaluation shall be considered and the rationale for any decision documented.

A rationale shall be provided for deviation from any specified requirement of this section.

The clinical study shall be conducted in accordance with ISO 14155.

9.3 Number of institutions

The clinical evaluation shall be conducted at a minimum of five institutions. The minimum number of heart valve substitutes implanted at any institution shall be 20 of each type being evaluated.

NOTE—Each valve type (e.g. aortic or mitral) should be implanted in as broad a distribution of tissue annulus diameters as possible.

9.4 Number of patients

A minimum of 150 recipients of isolated aortic heart valve substitutes and a minimum of 150 recipients of isolated mitral heart valve substitutes shall be evaluated. If the heart valve substitute is intended for implantation in only one position, a minimum of 150 heart valve substitutes shall be evaluated in that position.

NOTE—The term "isolated" refers to recipients who have only one heart valve substitute.

9.5 Duration of the study

The study shall be continued for a minimum of 12 months after implantation of the last heart valve substitute.

9.6 Clinical data

9.6.1. General

Clinical data specified in 9.6.2 to 9.6.5 shall be reported for all patients receiving the test heart valve substitute at the institutions referred to in 9.3. For operative and postoperative assessments only, blood studies and hemodynamic evaluations should employ similar testing methods and protocols at each of the evaluating institutions.

9.6.2 Identifying data

The following identifying data shall be collected:

a) patient's sex, date of birth and race (optional);

b) investigator's name;

c) name of institution.

9.6.3 Preoperative data

The following preoperative data shall be collected:

a) diagnosis and coexisting diseases;

b) New York Heart Association functional class[3];

c) previous cardiovascular operations;

d) hemodynamic evaluation (invasive and/or non-invasive);

e) blood studies, including coagulation profile and tests for hemolysis;

f) body surface area.

9.6.4 Operative data

The following operative data shall be collected:

a) diagnosis;

b) procedure(s);

c) date of operation;

d) heart valve substitute model, type, size and serial number;

e) heart valve substitute tissue annulus diameter;

f) suture technique;

g) heart valve substitute positioning in relation to tissue annulus (e.g. supra-annular, sub-annular);

h) heart valve substitute disc/leaflet orientation;

i) complications, including operative mortality.

9.6.5 Follow-up data

Follow-up data shall be collected within 3 months of implantation of the heart valve substitute, at 1 year and, with the exception of 9.6.5c), annually thereafter for the duration of the study (see 9.5).

NOTE—Structural deterioration or nonstructural dysfunction may not occur in the early years after implantation; it is recommended that annual or biennial follow-up be extended to collect long-term data.

The following follow-up data shall be collected:

a) date and method of follow-up (e.g. telephone, letter or personal visit);

b) New York Heart Association functional class;

c) hemodynamic evaluation by Doppler echocardiography (see A.5 for rationale) or alternative acceptable method;

d) blood studies, including coagulation profile and test for hemolysis;

e) dates of initiation and discontinuation of anticoagulant and/or antiplatelet therapy (type(s) of therapy shall be specified);

f) incidence of systemic embolism and thrombotic dysfunction of the heart valve substitute;

g) complications, to include prosthetic valve endocarditis, structural deterioration and nonstructural dysfunction of the heart valve substitute including paravalvular leak and hemolysis, intracardiac thrombus, anticoagulant-related hemorrhage, systemic embolus, and thrombotic dysfunction;

h) reports of electrocardiograms, chest X-rays and cardiac catheterization, if performed;

i) reoperation report(s);

j) explant analysis when available;

k) date and cause of death;

l) autopsy report when available.

9.7 Clinical evaluation report (See A.6 for rationale)

9.7.1 General

The report shall tabulate the data collected in 9.6 and shall include:

a) the names of the investigators and institutions;

b) an analysis of patient population by age, sex, and race (optional);

c) comparison of pre-operative and post-operative New York Heart Association functional class;

d) pre-operative diagnosis of valvar and co-existing diseases, operative diagnoses, operative procedures including suture technique, operative complications;

e) the model, type, size, and tissue annulus diameter of the heart valve substitute;

f) the number of months since implantation and type of follow-up;

g) results of hemodynamic evaluation [see 9.6.5 c)];

h) results of blood studies and therapy [see 9.6.5 d) and 9.6.5 e)];

i) an analysis of complications [see 9.6.4 i)];

j) analysis of reoperation reports, explant results, cause and date of death, and autopsy reports.

9.7.2 Method

The method of reporting shall conform to the "*Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations*" [4] and shall include:

a) an analysis of survival rates and freedom from complication rates using actuarial techniques;

b) all deaths and complications, with appropriate analyses and rationale for the analyses used;

c) results in terms of

1) overall survival;

2) survival without complications;

3) survival without specific complications, including but not limited to valve thrombosis, systemic embolism, anticoagulant-related hemorrhage, prosthetic valve endocarditis, structural deterioration of the heart valve substitute, nonstructural dysfunction of the heart valve substitute, and reoperation.

10 Packaging, labeling and instructions

10.1 Principle

Packaging, labeling and instructions shall be designed to ensure that the user is provided with the following:

a) a heart valve substitute whose characteristics and performance are unaltered by transit or storage;

b) information on handling and inserting the heart valve substitute;

c) a patient identification registration form.

10.2 Packaging

10.2.1 General

The packaging shall maintain the characteristics and performance of the package contents under all conditions of handling, transit and storage, and shall permit the contents to be presented for use in an aseptic manner.

10.2.2 Unit container

The heart valve substitute shall be packaged in a unit container which shall be designed so that any damage to the unit container seal is readily apparent.

10.2.3 Outer container

The unit container shall be packaged in an outer container (sales package) to protect the unit container.

10.2.4 Sterility

Heart valve substitutes shall be supplied sterile within at least the unit container. Sterilization shall occur by an

appropriate method and shall be validated per internationally-recognized criteria, as given in ISO 11134, ISO 11135, and ISO 11137. If the manufacturer states that the heart valve substitute can be resterilized prior to implantation, instructions shall be provided by the manufacturer.

10.3 Labeling

10.3.1 Unit-container labeling

Each unit container shall be marked with word(s), phrase(s) or symbol(s) for:

a) the contents;

b) the name or tradename of the heart valve substitute;

c) the model, size and type of heart valve substitute;

d) the name/tradename and address of the manufacturer and/or distributor;

e) the batch code (lot or serial number);

f) sterile;

g) single use;

h) the method of sterilization;

i) the “Use before“ date (year expressed in four digits and month expressed in two digits as specified in ISO 8601:1988, subclause 5.2.1.2);

j) a warning against use of the device if the unit container has been opened or damaged.

10.3.2 Outer-container labeling

Each outer container shall be marked with all the information specified in 10.3.1 as well as any applicable storage instructions.

10.4 Instruction leaflet

Each heart valve substitute shall be accompanied by an instruction leaflet that shall include at least:

a) the information contained in 10.3.1 except e) batch code and i) the “Use before“ date;

b) the internal orifice area in square millimeters (see 3.10), the tissue annulus diameter expressed in millimeters (see 3.28), the external sewing ring diameter expressed in millimeters (see 3.7), and the profile height expressed in mm (see 3.18);

c) the indications for use and any known contraindications;

d) any warnings regarding handling or implanting the heart valve substitute;

e) the details of any precautions to be observed, including concomitant procedures or devices (e.g. placing catheters across the valve);

f) a statement concerning the risk of magnetic resonance imaging and any precautions to be observed for patients who have the heart valve substitute;

g) an account of techniques/instructions for handling or implanting the heart valve substitute;

h) a list of potential complications associated with implanted heart valve substitutes;

i) a description of any accessories required and instructions for their use;

j) any recommendations for storage;

k) the instructions for re-sterilization (if applicable), including the maximum number of resterilization cycles;

l) any information or instructions which are intended to be communicated from the physician to the patient;

m) the manufacturer's name, address, telephone number and facsimile number.

10.5 Patient registration form

The manufacturer shall provide with each heart valve substitute a form or card which enables transfer of patient information to the appropriate registries. This form shall contain or make provision for recording at least:

a) the patient's name or ID code, or hospital file number;

b) the name and address of the hospital;

c) the name of the implanting surgeon;

d) the name, address and telephone number of the physician in charge of post-operative care and medical follow-up;

e) the date of implantation;

f) the position of the heart valve substitute;

g) the model, size, type and serial number of the heart valve substitute;

h) the name, address, telephone number, and facsimile number of the manufacturer.

Annex A
(informative)
Rationale for the provisions of this International Standard

A.1 Rationale for material, component and valve assembly testing (see clause 5)

The assessment of materials stability is a critical step for achieving long-term reliability/performance of heart valve substitutes. This standard identifies a series of performance tests which serve as quantitative and qualitative indicators of the stability of materials and/or components used in heart valve substitutes. Some tests are designed to indicate component lifetime, through a fatigue or fracture mechanics approach. Another test objective is to quantify the functional and safety aspects of heart valve substitutes and to look for potential failure modes. It is the responsibility of the manufacturer to conduct all appropriate material and/or component tests to reasonably ensure the safety of the heart valve substitute.

A.2 Rationale for *in vitro* testing (see clauses 6 and 7)

In vitro testing of heart valve substitutes and/or their components provides important information on the fluid-mechanical performance, design and durability of these devices under well-controlled test conditions. Such information is necessary to assure that basic safety and efficacy issues have been addressed prior to evaluation in clinical studies. However, the direct translation of these results to *in vivo* performance is currently not possible. As with all *in vitro* tests, knowledge of the limitations of the test is of paramount importance in analyzing any results obtained from such tests.

A.3 Rationale for preclinical *in vivo* evaluation (see clause 8)

The objective of preclinical testing is to aid in the evaluation of the performance characteristics of the heart valve substitute which are not assessable by *in vitro* testing. Thus, while it is not feasible to assess the long-term

durability of a heart valve substitute by using an animal model, valuable data on hemodynamic and certain aspects of biological performance can be obtained by implantation in an animal. It is recognized that no uniformly acceptable animal model has been established. Therefore the animal model selected should be based on the characteristics of the heart valve substitute and the experience of the investigators.

A.4 Rationale for clinical evaluation (see clause 9)

Data obtained from *in vitro* and preclinical *in vivo* evaluation cannot replace the evaluation of heart valve substitute performance in human patients, where physiologic and metabolic factors can contribute to long-term survival and freedom from complications. The objective of clinical evaluation is to obtain data on the safety and performance of the heart valve substitute in humans. The clinical evaluation described in this International Standard represents a first phase that involves a small number of patients and short duration of follow-up to detect early valve-related problems without unduly delaying the general availability of new heart valve substitutes. Larger numbers of patients followed for a longer period will be necessary for detailed statistical analysis of the incidence of complications. The potential for late complications warrants long-term follow-up of the initial patient population. Acceptance of a heart valve substitute after this first phase of clinical studies should be contingent upon a commitment to prospective, comprehensive, long-term monitoring.

A.5 Rationale for Doppler echocardiographic assessment (see 9.6.5c)

Two-dimensional echocardiography and Doppler echocardiography are presently accepted as practical and available methods for evaluating human cardiac function and the function of heart valve substitutes. The accuracy of these diagnostic procedures depends upon the skill of the operator. Major efforts are being made to develop standardized calibration techniques for the equipment and clinical protocols to assess the function of heart valve substitutes. This is an area of intense scientific effort, but as yet there is no consensus. It is recommended that all investigating institutions involved in the clinical evaluation of a specific heart valve substitute employ the same echocardiographic protocol.

A.6 Rationale for clinical evaluation reporting (see 9.7)

The *"*Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations*"* has evolved by international consensus, and has been accepted as guidelines to publication by the *Annals of Thoracic Surgery,* the *European Journal of Cardiothoracic Surgery,* and the *Journal of Cardiovascular and Thoracic Surgery.* The purpose of these guidelines is to facilitate the analysis and reporting of results of operations on diseased cardiac valves. The definitions and recommendations are designed to facilitate comparisons between different surgeons, cohorts, techniques, and materials.

Annex B
(informative)

Materials related to heart valve substitutes (see clause 4)

This list is of materials is not intended to be comprehensive or to imply the material is "approved" for use. This list is provided for reference only.

B.1 Synthetic polymers

epoxides

fluorocarbons

polyamides

polyesters

polyacetals

polysulfones

polyurethanes

silicones

B.2 Biological materials

bovine pericardium

bovine heart valve

porcine heart valve

collagen

B.3 Metals

cobalt/chrome alloys

nickel/chrome alloys

stainless steels

tantalum

titanium and titanium alloys

B.4 Ceramics

alumina

barium sulfate

barium chloride

titanium oxide

zirconia

graphites

low temperature isotropic pyrolytic carbon

monolithic

composite

ultra-low temperature isotropic pyrolytic carbon

glassy carbon

B.5 Textiles

polyester

knit

woven

velour knit

velour woven

multifilament

polytetrafluoroethylene

knit

woven

expanded

perfluoroethylenepropylene

polypropylene

B.6 Coatings

passive

chemical or physical vapor-deposited material, e.g. carbon

hydrophobic polymers

hydrophilic polymers

active

anticoagulants

antimicrobials

negative surface charge

thrombolytics

B.7 Composites

carbon/carbon

carbon/polymers

Annex C
(informative)

Physical and material properties of heart valve substitutes and their components
(see clause 5)

C.1 General

This annex provides a description of the physical and material properties which may be relevant to characterize a heart valve substitute and/or its components. All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication. These properties should be evaluated when appropriate.

C.2 Bulk physical properties

C.2.1 Chemical composition

A measurement of the chemical composition and purity, including any processing aids.

C.2.2 Density

A measurement of the mass per unit volume,. i.e. the compactness of a material.

C.2.3 Liquid diffusivity (porosity and permeability)

A measurement of the ability of a material to absorb or adsorb biological components from the surrounding tissues and fluid environments.

NOTE—This biological property may cause calcification and premature failure under certain stresses.

C.2.4 Material hardness

A measurement of resistance to scratching or plastic deformation by indentation (generally related to wear resistance).

C.2.5 Microstructure/morphology

A measurement of the size and shape of the grains, defects, voids, etc. of which the material is composed. For tissue valves, this should include the cellular or collagen morphology.

C.2.6 Tear strength

A measurement of the force needed to initiate or continue tearing a sheet of fabric.

C.2.7 Young's modulus

A measurement of the mechanical stiffness of a material.

NOTE—As a tensile or compressive stress is exerted on a piece of material, it tends to elongate or contract. The ratio of the applied stress to the percentage change in length (strain) is defined as Young's modulus. Young's modulus is needed in theoretical modeling of both the static and dynamic stress distributions anticipated in completed devices.

C.2.8 Poisson's ratio

A measurement of the ratio of change in dimensions in the transverse direction to the longitudinal direction.

NOTE—When a piece of material is stretched or compressed longitudinally under a uniaxial load, it changes shape transversely. As with Young's modulus, Poisson's ratio is needed to model the mechanical behavior of completed devices.

C.2.9 Dynamic moduli

A measurement of the complex moduli (storage and loss moduli) that describe the mechanical behavior of viscoelastic materials.

C.2.10 Coefficient of thermal expansion

A measurement of the change in physical dimension with temperature.

NOTE—This property is generally important only for composite parts such as pyrolytic carbon-coated graphite occluders. As the part cools from the deposition temperature of 1300 °C to room temperature, the coating acquires a residual stress, the size and magnitude of which depends on the difference in thermal expansion between the substrate and the coating. This residual stress could affect the strength of the material, the critical flaw size, and crack propagation rates.

C.2.11 Glass transition temperature

A measurement of the characteristic temperature of a polymer system below which long-chain mobility no longer exists.

C.2.12 Melt index

The number of grams of thermoplastic resin at a specified temperature that can be forced through a specified orifice in an allotted time by a specified pressure.

C.2.13 Melting point

A measurement of the temperature at which a solid material turns liquid.

C.2.14 Hydraulic expansion

A measurement of the dimensions of the material before and after exposure to water.

C.2.15 Biostability

A measurement of the change in chemical composition of a material after exposure to a physiologic-fluid environment.

C.2.16 Film thickness

A measurement of the thickness of a film deposited on a substrate, averaged over the surface of the film.

NOTE—Techniques for measuring thin-film thickness include profilometry and ellipsometry. In some cases, Auger depth profiling can be used.

C.2.17 Percent elemental composition of a film

A measurement of the elemental composition of a film expressed as a percentage.

C.3 Surface physical properties

C.3.1 General

All measurements should be performed on materials or components as they would be found in the finished product. This includes all subsequent treatments after fabrication, e.g. sterilization.

C.3.2 Critical surface tension

A measurement of the surface morphology of a biological implant.

NOTE—Surface roughness and chemical composition play a key role in how an implant interacts with the biological host. Critical surface tension is a useful attribute for characterizing the surface of a solid material. The measurement is affected by surface topology, chemistry and cleanliness. The measurements are related to the surface free energy of the material.

C.3.3 Surface roughness

A measurement of the microtopology of the component surface.

C.3.4 Surface chemical composition

A measurement of the material composition within a few atomic layers of the surface.

NOTE—Variations in the chemicals present at the surface could affect how a material will react with the host. The chemical constituents of the surface can be altered by manufacturing processes such as grinding, polishing, cleaning, sterilizing and handling.

C.3.5 Surface charge and surface charge density

A measurement of the type of charge (positive or negative) and the amount that can be bound to the surface of a material.

NOTE—It has been suggested that surface charge can play an important role in the biocompatibility of materials.

C.3.6 Surface resistance, *R*

A measurement of the ratio of the bulk resistivity and film thickness:

$$R_{sheet} = r/t$$

where:

ρ is the bulk resistivity expressed in ohm-centimeters;

t is the sample thickness expressed in centimeters.

NOTE—A typical method for determining the sheet resistance is the "four-point probe" method. Such measurements should be done at several places on the surface of the film to obtain an average sheet resistance value.

C.4 Mechanical and chemical engineering properties

C.4.1. General

The following are the materials engineering properties that can be evaluated to assess the ability of a material or a component to function in the intended site.

C.4.2 Wear resistance

A measurement of the rate of the systematic removal of material as two surfaces move past one another.

C.4.3 Coefficient of friction

A measurement of the energy expended in moving two components past one another that are in intimate contact.

C.4.4 Peel strength

A measurement of the adhesion between different layers of a material, usually a lamellar composite.

NOTE—Lamellae could include thin surface layers used to change the chemical boundary conditions of a material.

C.4.5 Flexural strength

A measurement of the stress level required to cause fracture in bending.

NOTE—There usually is considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

C.4.6 Compressive strength

A measurement of the stress level required to cause fracture in compression.

NOTE—There usually is considerable variation in the measured strength among specimens in these tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

C.4.7 Tensile strength

A measurement of the stress level required to cause fracture in tension.

NOTE—There usually is considerable variation in the measured strength among specimens in these types of tests. To ensure that the data are representative of the true strength of the material, the results should be reported using an appropriate statistical method.

C.4.8 Tensile strain to failure (elongation)

A measurement of the amount of strain or elongation that a material can tolerate just prior to fracture.

C.4.9 Strain energy to failure

A measurement of the energy needed to deform a material to the breaking point.

NOTE—Strain energy is a measure of the toughness of a material, generally in the absence of a fatigue mechanism.

C.4.10 Residual stress

A measurement of the stresses that remain in a material after it has been fabricated.

C.4.11 Stress relaxation

A measurement of the gradual change in stress needed to produce a specified elongation or deformation.

C.4.12 Creep

A measurement of the nonrecoverable change in dimension of a material under a prescribed mechanical loading condition.

C.4.13 Fracture toughness

A measurement of the resistance of a material to crack growth.

NOTE—It is the stress intensity at which unstable crack growth will proceed.

C.4.14 Crack growth velocity

A measurement of the speed and load conditions under which a crack will propagate through a material once it has been initiated.

NOTE—The rates can be influenced by the residual stresses in the material.

C.4.15 Fatigue life

A measurement of the number of times a material can be subjected to a load without fracturing.

NOTE—In general, there are two independent time components to fatigue failure. First is the crack initiation phase, when repeated loading cycles weaken a material, usually through a defect coalescence process at a flaw site, until a critical flaw size is reached and fracture occurs. Once a crack is initiated, the crack growth phase of fatigue begins. The crack continues to grow under repeated loading conditions until the stress loading exceeds the fracture toughness, resulting in total failure.

C.4.16 Stress corrosion potential

A measurement of the corrosion that could occur or become accelerated as a result of sustained stress, either residual or applied.

C.4.17 Galvanic corrosion potential

A measurement of the corrosion that might occur between two dissimilar materials.

NOTE—An example would be the reaction between a pyrolytic carbon housing and a titanium stiffening ring.

C.4.18 Fretting corrosion potential

A measurement of the surface damage that occurs between two surfaces that are in close contact, under pressure, and are subjected to slight relative motions.

C.4.19 Void concentration

A measurement of the number of voids in a film (areas where the film did not cover the substrate) per unit area.

NOTE—The void concentration is specific to the void size or range of sizes (e.g. a void concentration may be 100 voids of diameter 1 µor less per square centimeter).

C.5 Valve design parameters

C.5.1 Computer modeling

A computer method for determining the maximum stress to which a part will be subjected.

NOTE—This method should take into consideration the peak loads that are expected, including dynamic effects.

C.5.2 Tissue annulus diameter and internal orifice area measurements

Measurement of the tissue annulus diameter (see 3.6) and internal orifice area (see 3.5).

C.5.3 Valve impact and fatigue life

A measurement of the tolerance of the heart valve substitute to damage caused by the repeated cycling of the occluder.

C.5.4 Static pressure; "burst" test

A measurement of the hydrostatic load at which failure, e.g. leaflet or orifice fracture or leaflet escape, occurs.

C.5.5 Orifice deflection

A measurement of the diametric and/or axial load on the orifice required to cause leaflet/occluder escape or bind-up.

C.5.6 Sewing ring push-off

A measurement of the strength of the sewing ring attachment to the heart valve substitute.

NOTE—Particular attention should be paid to the potential for the attachment mechanism to be damaged on insertion.

C.5.7 Sewing ring torque

A measurement of the torque required to rotate the valve within the sewing ring.

C.5.8 Suture retention strength

A measurement of the holding strength of an attachment suture in the sewing ring.

C.5.9 Calcification (*in vivo* model)

A measurement of the rate and degree of calcification of the heart valve substitution *in vivo*.

Annex D
(informative)

Standards applicable to the testing of materials and components of heart valve substitutes
(see clause 5)

D.1 Metals

Specifications for materials for metal surgical implants:

ISO 5832-1:1987, *Implants for surgery—Metallic materials–Part 1: Wrought stainless steel*

ISO 5832-2:1993, *Implants for surgery–Metallic materials–Part 2: Unalloyed titanium*

ISO 5832-3:1990, *Implants for surgery–Metallic materials–Part 3: Wrought titanium 6-aluminium 4-vanadium alloy*

ISO 5832-4:1978, *Implants for surgery–Metallic materials–Part 4: Cobalt-chromium-molybdenum casting alloy*

ISO 5832-5:1993, *Implants for surgery–Metallic materials–Part 5: Wrought cobalt-chromium-tungsten-nickel alloy*

ISO 5832-6:1980, *Implants for surgery–Metallic materials –Part 6: Wrought cobalt-nickel-chromium-molybdenum alloy*

ISO 5832-7:1994, *Implants for surgery–Metallic materials–Part 7: Forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy*

ISO 5832-8:1987, *Implants for surgery–Metallic materials–Part 8: Wrought cobalt-nickel-chromium-molybdenum-tung-iron alloy*

Tensile test with extensometer to failure

ASTM E8-95, *Test Methods for Tension Testing of Metallic Materials*

ASTM E111-88, *Test Method for Young's Modulus, Tangent Modulus, and Chord Modulus*

Poisson's ratio

ASTM E132-92, *Test Method for Poisson's Ratio at Room Temperature*

Fatigue crack initiation and endurance limit; S-N curves

ASTME466-82, *Practice for Conducting Constant Amplitude Axial Fatigue Test of Metallic Materials*

ASTM E468-90, *Practice for Presentation of Constant Amplitude Fatigue est Results for Metallic Materials*

ASTM E739-91, *Practice for Statistical Analysis or Linearized Stress-Life (S-N) and Strain-Life (O-N) Fatigue Data*

Fatigue crack growth rate; crack growth velocity

ASTM E647-95, *Test Method for Measurement of Fatigue Crack Growth Rates*

Hardness

ASTM E18-94, *Test Methods for Rockwell Hardness and Rockwell Superficial Hardness of Metallic Materials*

ASTM E92-82, *Test Method for Vickers Hardness of Metallic Materials*

Microstructure

ASTM E3-95, *Methods of Preparation of Metallographic Specimens*

ASTM E112-88, *Test Methods for Determining the Average Grain Size*

Thermal expansion (heat-shrink stiffening ring)

ASTM E228-85, *Test Method for Linear Thermal Expansion of Solid Materials with a Vitreous Silica Dilatometer*

Fracture toughness

ASTM E399-90, *Test Method for Plane-Strain Fracture Toughness of Metallic Materials*

ASTM E813-89, *Test Method for a Measure of Fracture Toughness*

Fatigue life

ASTM E466-82, *Practice for Conducting Constant Amplitude Axial Fatigue Test of Metallic Materials*

ASTM E468-90, *Practice for Presentation of Constant Amplitude Fatigue Test Results for Metallic Materials*

ASTM E739-91, *Practice for Statistical Analysis or Linearized Stress-Life (S-N) and Strain-Life (O-N) Fatigue Data*

ASTM E648-94a, *Test Method for Critical Radiant Flux of Floor-Covering Systems Using a Radiant Heat Energy Source*

D.2 Polymers

Viscosimetry

ASTM D20-91, *Test Method for Distillation of Road Tars*

ISO 61:1976 *Plastics–Determination of apparent density of moulding material that cannot be poured from a specified funnel*

Melt flow index

ASTM D1238-94a, *Test Method for Flow Rates of Thermoplastics by Extrusion Plastometer*

Specifications for high molecular mass polyethylene

ISO 3834-1:1994, *Quality requirements for welding–Fusion welding of metallic materials–Part 1: Guidelines for selection and use*

ISO 3834-2:1994, *Quality requirements for welding–Fusion welding of metallic materials–Part 2: Comprehensive quality requirements*

ISO 3834-3:1994, *Quality requirements for welding–Fusion welding of metallic materials–Part 3: Standards quality requirements*

ISO 3834-4:1994, *Quality requirements for welding–Fusion welding of metallic materials–Part 4: Elementary quality requirements*

Determination of breaking strength under static load

ISO 5081:1977, *Textiles–Woven fabrics–Determination of breaking strength and elongation (Strip method)*

Tensile test with extensometer to failure (if possible)

ASTM D638-94b, *Test Method for Tensile Properties of Plastics*

Tensile properties

ISO/R 527:1966, *Plastics–Determination of tensile properties*

Poisson's ratio

ASTM E132-92, *Test Method for Poisson's Ratio at Room Temperature*

Determination of dynamic mechanical properties

ISO 6721-1:1994, *Plastics–Determination of dynamic mechanical properties–Part 1: General principles*

ISO 6721-2:1994, *Plastics–Determination of Dynamic mechanical properties–Part 2: Torsion-pendulum method*

Resistance to surface wear

ISO 4586-2:1995, *High-pressure decorative laminates–Sheets made from thermosetting resins–Part 2: Determination of properties*

Resistance to scratch

ISO 1518:1992, *Paints and varnishes–Scratch test*

BS 3962-6:1980, *Method of test for finished wooden furniture–Assessment of resistance to mechanical damage*

Flexural properties; determination of breaking strength under dynamic bending load

ISO 178:1993, *Plastics–Determination of flexural properties*

Fatigue crack initiation and endurance limit; S-N curves

ASTM E466-82, *Practice for Conducting Constant Amplitude Axial Fatigue Test of Metallic Materials*

ASTM E468-90, *Practice for Presentation of Constant Amplitude Fatigue Test Results for Metallic Materials*

Fatigue crack growth rate

ASTM E647-95, *Test Method for Measurement of Fatigue Crack Growth Rates*

Determination of compressive properties

ISO 604:1993, *Plastics–Determination of compressive properties*

Specification of surgical implants made from high-density silicone elastomer

BS 7253-3:1990, *Non-metallic materials for surgical implants–Specification for surgical implants made of heat-vulcanized silicone elastomer*

Density

ASTM E792-95, *Guide for Selection of a Clinical Laboratory Information Management System*

Liquid diffusivity (porosity and permeability; water absorption)

ASTM D570-81, *Test Method for Water Absorption of Plastics*

Hardness

ASTM D785-93, *Test Method for Rockwell Hardness of Plastics and Electrical Insulating Materials*

Wear resistance

ASTM D1044-94, *Test Method for Resistance of Transparent Plastics to Surface Abrasion*

ASTM D4060-90, *Test Method for Abrasion Resistance of Organic Coatings by the Taber Abraser*

Creep

ASTM D2990-93a, *Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics*

Fracture toughness

ASTM E399-90, *Test Method for Plane-Strain Fracture Toughness of Metallic Materials*

ASTM E813-89, *Test Method for a Measure of Fracture Toughness*

Hydraulic expansion

ASTM F1087-88, *Test Method for Linear Dimensional Stability of a Gasket Material to Moisture*

D.3 Ceramics and carbons

Physical and chemical properties

ISO 6474:1994, *Implants for surgery–Ceramic materials based on high purity alumina*

Fatigue crack growth rate

ASTM E647-95, *Test Method for Measurement of Fatigue Crack Growth Rates*

Hardness

ASTM E92-82, *Test Method for Vickers Hardness of Metallic Materials*

Thermal expansion

ASTM E228-85, *Test Method for Linear Thermal Expansion of Solid Materials with a Vitreous Silica Dilatometer*

Fracture toughness

ASTM E399-90, *Test Method for Plane-Strain Fracture Toughness of Metallic Materials*

D.4 Biological materials

Possible adaptation of tensile properties

ISO 527 (all parts), *Plastics–Determination of tensile properties*

D.5 Textiles

Determination of tear-out resistance

DIN 53859-2:1979, *Tear growth testing of textile fabrics–Leg tear growth test*

Determination of water absorption

DIN 53923:1978, *Testing of textiles–Determination of water absorption of textile fabrics*

Annex E
(informative)

Definitions of components of a heart valve substitute (see clauses 4 and 5 and figure E.1)

E.1 coating: Any thin-film material that is applied to an element of a heart valve substitute to modify its physical or chemical properties.

E.2 component-joining material: Material, such as a suture, adhesive or welding compound, used to assemble the components of a heart valve substitute, thereby becoming part of the implant device.

E.3 covering: Any element applied to coat or enclose any other element of the heart valve substitute.

E.4 occluder retention mechanism: Component(s) of a heart valve substitute that support(s) or retain(s) the occluder(s).

NOTE—These parts have also been called struts, posts, commissures, retainers or cages.

E.5 orifice ring; housing: Component of a heart valve substitute that houses the occluder(s) of a mechanical heart valve.

E.6 sewing ring; cuff: Component of a heart valve substitute by which it can be attached to the heart.

E.7 sewing-ring filler: Any material within the confines of the sewing ring which provides it with bulk and shape.

E.8 sewing-ring retaining material: Material used to prevent separation of the sewing ring from the orifice ring or frame.

E.9 stent; frame; body: Component of a heart valve substitute that houses the occluder(s) of a flexible leaflet device (i.e. biologic or mechanical valve).

E.10 stiffening element: Component which reduces deformation of the orifice ring or stent.

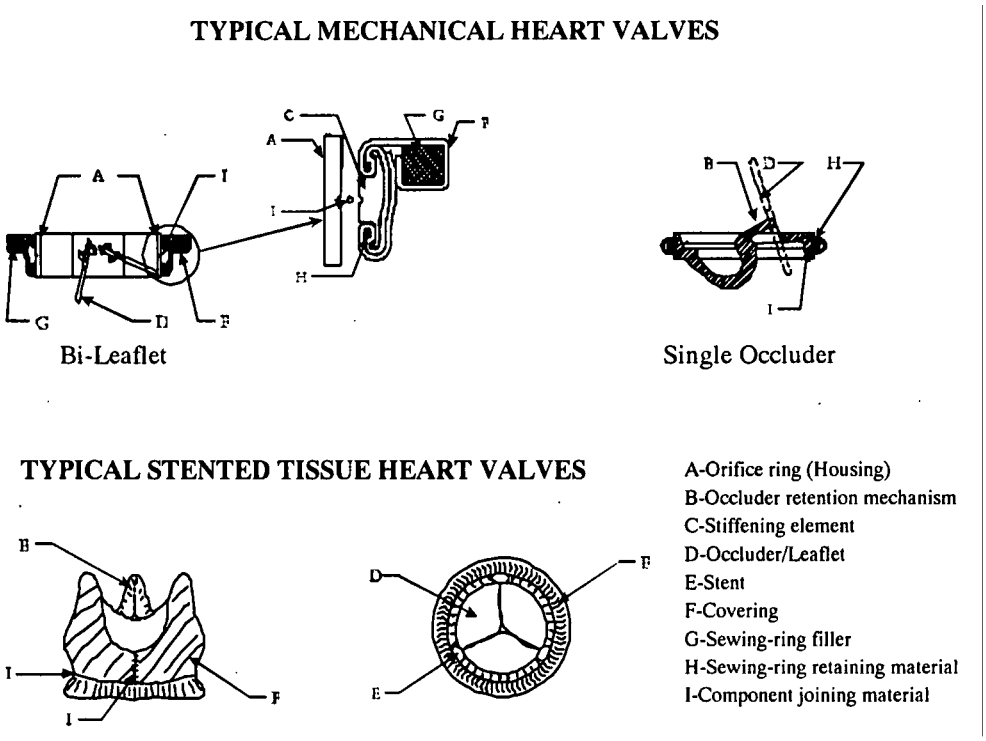

Figure E.1—Cutaway drawings showing the apparent location of various components of four generic heart valve substitutes

Annex F
(informative)

Valve description

F.1 Description of a heart valve substitute

The heart valve substitute may be classified according to the scheme in table F.1.

Table F.1—Determination of major classes of heart valve substitute

Major heart valve substitute class	Animal source	Anatomic site of origin	Occluders		Intended implant position
			number	material	
Stented Bioprosthesis				n.a.	
Nonstented Bioprosthesis				n.a.	
Mechanical Prosthesis	n.a.	n.a.			

NOTE—n.a. = not applicable

Examples of heart valve substitutes described according to the scheme in table F.1 might be:

a) stented bioprosthesis, porcine, aortic valve, 3, n.a., mitral;
b) nonstented bioprosthesis, bovine, pericardium, 3, n.a., aortic;
c) mechanical, n.a., n.a., 2, pyrolytic carbon, aortic, or mitral;
d) mechanical, n.a., n.a., 1, ceramic, tricuspid;
e) mechanical, n.a., n.a., 3, polyurethane, aortic, or mitral.

F.2 Components of heart valve substitute

F.2.1 Component description

The material composition of the components used in a heart valve substitute (e.g. housing, occluders, sewing ring) may be classified according to the scheme in table F.2.

F.2.2 Component material

All of the major components applicable to a particular heart valve substitute as shown in figure E.1 may be identified by the materials they are made of, and these materials may be classified under one of the major material categories defined in annex B.

Table F.2—Heart valve substitute component material classification

Component	Material class				
	Biological	**Synthetic polymers**	**Metals**	**Ceramics**	**Textiles**
Orifice ring (housing)					
Occluder retention mechanism					
Stiffening element					
Occluder					
Stent					
Covering					
Sewing-ring filler					
Sewing-ring retaining material					
Component joining material					

Annotations from 5840.pdf

Page 6

Annotation 1; Label: AAMI; Date: 10/02/2000 10:22:39 AM
1) To be published. (Revision of ISO 10993-1:1992)

Annotation 2; Label: AAMI; Date: 10/02/2000 10:23:20 AM
2) To be published.

Page 22

Annotation 1; Label: AAMI; Date: 10/02/2000 10:25:39 AM
3)For further information see Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. The Criteria Committee of the New York Heart Association, 8th ed. Little, Brown; Boston, 1979.

Page 24

Annotation 1; Label: AAMI; Date: 10/02/2000 10:35:27 AM
4)Edmunds L.H. Jr., Cohn L.H., and Weisel R.D. Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operation. Ann. Thorac. Surg. 62(3), 1996, pp 932-935.