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INTERNATIONAL STANDARD

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Cardiovascular implants — Cardiac valve prostheses

Implants cardiovasculaires — Prothèses valvulaires

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Contents

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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 approval before their acceptance as International Standards by the ISO Council. They are approved in accordance with ISO procedures requiring at least 75 % approval by the member bodies voting.

International Standard ISO 5840 was prepared by Technical Committee ISO/TC 150, *Implants for surgery.*

This second edition cancels and replaces the first edition (ISO 5840 : 1984), of which it constitutes a technical revision.

Annexes A and B 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 deliberately been left open as there was 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 thus intended to be those which will facilitate quality assurance, aid the surgeon in his choice of heart valve substitute, and ensure that the device will be presented in a convenient form at the operating table. Emphasis has therefore been placed on specifying types of *in vitro* testing, on *in vivo* animal and clinical evaluation, on reporting of all *in vitro*, *in vivo* and clinical studies, and on the labelling and packaging aspects of the device. Such a process involving *in vitro*, *in vivo* and clinical studies is intended to clarify the procedure prior to market release and enable prompt identification and notification 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 hydraulic and accelerated fatigue characteristics of heart valve substitutes. The exact test methods have not been specified for hydrodynamic and accelerated fatigue testing, but the requirements of the test apparatus are given.

This International Standard is incomplete in several areas, but it is intended that it will be revised and updated, and/or addenda will be published as knowledge and techniques in heart valve substitute technology improve.

Cardiovascular implants — Cardiac valve prostheses

1 Scope

This International Standard specifies a number of test methods and makes recommendations regarding the performance characteristics of equipment to be used for determining the biological and mechanical properties of heart valve substitutes of all types and the materials of which they are made.

Recommendations are also made for *in vivo* testing and clinical evaluation and for the reporting of results of all types of testing and evaluation covered in this International Standard. These recommendations do not purport to comprise a complete test programme.

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

This International Standard excludes consideration of heart valve substitutes comprised in whole, or in part, of tissue of human origin.

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

2 Definitions

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

2.1 heart valve substitutes; cardiac valve prostheses: Devices used to replace or supplement the natural valves of the heart; these are categorized according to the position in which they are intended to be used (valve type).

2.1.1 mechanical heart valve substitute: Heart valve substitute wholly of synthetic origin.

2.1.2 biological heart valve substitute: Heart valve substitute consisting wholly or partly of tissue obtained from animal sources.

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

2.3 mounting 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 1).

2.4 external sewing ring diameter: Maximum external diameter of a heart valve substitute, including the sewing ring or flange (see figure 1).

2.5 profile height: Maximum axial dimension of a heart valve substitute in the open or closed position, whichever is the greater (see figure 1).

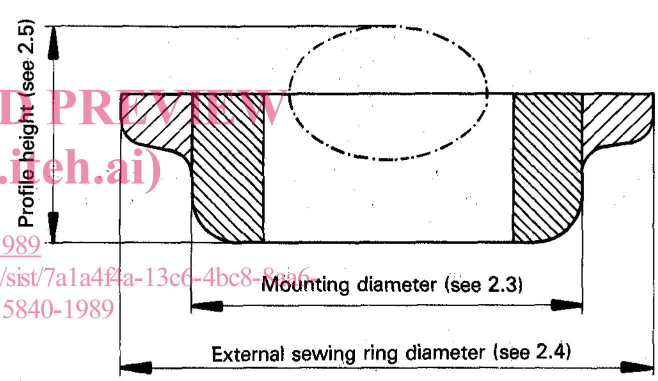

Figure 1 — Designation of dimensions of heart valve substitutes

2.6 cycle: One complete sequence in the action of a test heart valve substitute under pulsatile flow conditions.

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

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

2.9 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 2).

2.9.1 closing volume: That component of the regurgitant volume which is associated with the dynamics of valve closure (see figure 2).

2.9.2 leakage volume: That component of the regurgitant volume which is associated with leakage through the closed valve (see figure 2).

2.9.3 regurgitant fraction: Regurgitant volume expressed as a percentage of the stroke volume.

2.10 forward flow phase: That portion of the cycle time during which forward flow occurs through a test heart valve substitute.

2.11 root mean square volume flow; 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.

2.12 mean volume flow: Time-averaged arithmetic mean volume flow through a test heart valve substitute during the forward flow phase of the cycle.

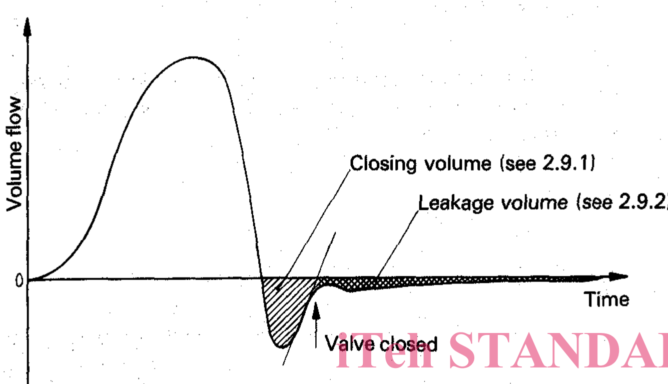

Figure 2 — Simulated flow wave-form showing regurgitant volume (closing volume plus leakage volume) for one cycle

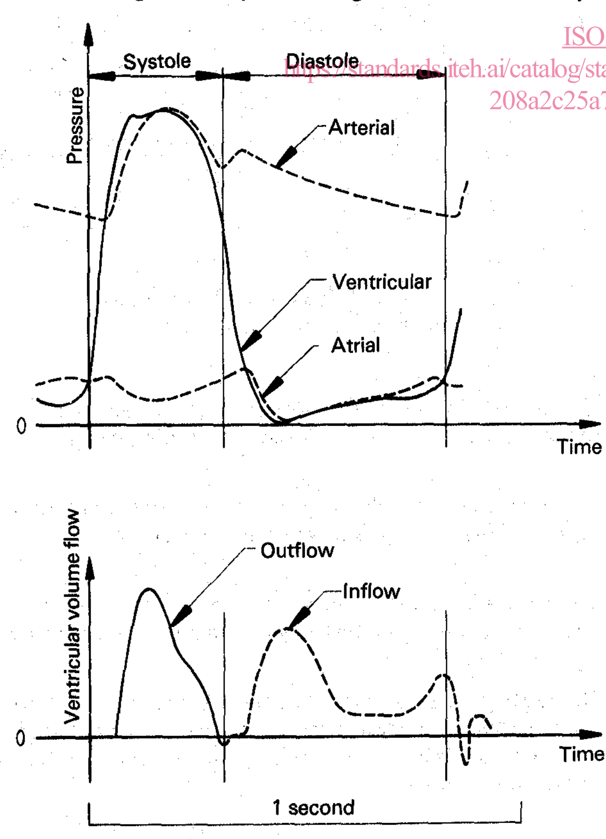

Figure 3 — Diagrams of haemodynamic wave-forms simulating those of healthy humans

2.13 mean pressure difference; (deprecated: **mean pressure gradient**)**:** Time-averaged arithmetic mean value of the pressure difference across a heart valve substitute during the forward flow phase of the cycle.

2.14 arterial peak systolic pressure: Maximum value of the arterial pressure.

2.15 arterial diastolic pressure: Minimum value of the arterial pressure.

2.16 mean arterial pressure: Time-averaged arithmetic mean arterial pressure during one cycle.

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

2.18 reference valve: Heart valve substitute which is used to assess the conditions established in the test device employed to evaluate the test heart valve substitute.

NOTE — The reference valve should approximate to the test valve in its type, configuration and mounting diameter; it could be an earlier model of the same valve, if it fulfils the necessary conditions. The characteristics of the reference valve should preferably be well documented with both *in vitro* and clinical data available in the literature.

3 Testing of materials

3.1 Requirements and procedures

All materials used shall have been identified and characteristics specified: the methods of identification and of specifying characteristics shall be relevant to the materials under test (see annex A). Evaluation for biological safety and compatibility shall be made according to generally accepted principles and methods for materials intended for long-term implantation. The test results shall be reported.

3.2 Test report

Each test report shall include the following information:

a) the rationale for the test;

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

c) sample identification (e.g. batch number);

d) the number of specimens tested;

e) the 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.

4 Testing of components

4.1 Requirements and procedures

Samples of the heart valve components shall have been tested for biological compatibility, durability and mechanical characteristics, and the results reported. Testing of the complete heart valve substitute may satisfy the requirements for component testing.

4.2 Test reports

Each test report shall include the following information:

a) the rationale for the test;

b) a description of the item(s) tested;

c) the number of specimens tested;

d) details of the test method used;

e) test results.

5 Testing of heart valve substitutes

5.1 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 for production purposes. In the case of a heart valve substitute that may be re-sterilized by the user, it shall also be subjected to the recommended maximum number of re-sterilization cycles using the method stated by the manufacturer to be the worst case procedure.

5.2 Description

Details of each test heart valve substitute and reference valve, including their identity, type (e.g. aortic or mitral), mounting diameter, external sewing ring diameter and profile height shall be provided.

Details of each test heart valve substitute, including the materials of which it is made, and, if appropriate, the specific gravity, mass and travel of the occluder shall be provided.

5.3 Hydrodynamic testing (see clause B.1 for rationale)

5.3.1 Test apparatus and fluids

5.3.1.1 Pulse duplicator for pulsatile flow testing of heart valve substitutes

The pulse duplicator shall

a) produce pressure and flow wave-forms that approximate to those found in healthy adult humans (for an example, see figure 3);

b) have a variable stroke volume up to at least 100 ml;

c) have a variable cycle rate up to at least 150 cycles/min;

d) have a forward flow phase that accounts for 35 % ± 5 % of the total cycle time at a cycle rate of 70 cycles/min ± 10 cycles/min;

e) simulate the relevant cardiac chamber and vascular dimensions;

f) include an equivalent hydrodynamic model of the systemic circulation which incorporates both resistive and compliant components;

g) simulate an arterial peak systolic pressure of at least 16 kPa ± 1 kPa (120 mmHg ± 7,5 mmHg) and an arterial diastolic pressure of 10,7 kPa ± 0,5 kPa (80 mmHg ± 3,8 mmHg);

h) permit the measurement of time-dependent pressures and flows;

i) allow the observer to view and photograph the test valve at all stages of the cycle;

j) have had its properties and performance established by means of testing reference valve(s), and these characteristics shall be monitored by means of regular tests using a reference valve.

5.3.1.2 Measuring equipment accuracy

5.3.1.2.1 The pressure-measuring system shall have a natural frequency of at least 20 Hz and a measurement accuracy of at least ± 0,15 kPa (approximately ± 1 mmHg).

5.3.1.2.2 All flow-measuring equipment used to measure regurgitant volume shall have a measurement accuracy of at least ± 1 ml.

5.3.1.2.3 All other measuring equipment used shall have a measurement accuracy of ± 5 % of the full scale reading.

5.3.1.3 Test fluid

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

5.3.2 Test method

5.3.2.1 Aim

The aim of the test procedure is to generate information on the fluid mechanical performance of the heart valve substitute during one complete cycle.

5.3.2.2 Procedure

Test at least three heart valve substitutes of each mounting diameter in the position in which they are intended to be used. Carry out all measurements and qualitative assessments over a volume flow range corresponding to simulated cardiac outputs from 2 l/min to at least 7 l/min. Use at least four simulated cardiac outputs. Carry out at least ten measurements of each variable, and calculate the mean and standard deviation. These ten measurements shall be obtained from either consecutive or randomly selected cycles. Assess qualitatively and document the opening and closing action of each heart valve substitute. If possible, qualitatively investigate the flow field in the immediate vicinity of the heart valve substitute. Determine the following parameters:

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

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

c) the stroke volume;

d) the cycle rate;

e) the mean arterial pressure over the whole cycle;

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

g) the regurgitant volume at three cycle rates, including the closing volume, the leakage volume (see figure 2) and the corresponding mean pressure difference across the closed valve.

5.3.3 Test report

The test report shall include the following information:

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

b) a description of the pulse duplicator, as specified in 5.3.1.1, and major components of the test loop 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 mid-plane of the valve sewing ring and a representative pressure and flow wave-form at approximately 70 cycles/min;

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

d) details of the following performance test variables (mean, range and standard deviation) at each simulated cardiac output for each test heart valve substitute and reference valve, presenting the data in tabular or graphic form, as appropriate:

1) the simulated cardiac output,

2) the cycle rate,

3) the duration of forward flow phase as a percentage of the cycle time,

4) the stroke volume,

5) the mean and r.m.s. volume flows,

6) the mean pressure difference (see 2.13),

7) the regurgitant volume, regurgitant fraction, closing volume, leakage volume and the corresponding mean pressure difference across the closed valve,

8) the mean arterial pressure over the whole cycle (for aortic valve substitutes only);

e) 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.

5.4 Durability testing (see clause B.1 for rationale)

5.4.1 Aim

The aim of the test procedure is to provide information on the change of form and durability *in vitro* of heart valve substitutes; this procedure is normally undertaken at an accelerated cycle rate chosen so that the conditions specified in 5.4.2.1a) and b) are achieved.

5.4.2 Test apparatus and fluids

5.4.2.1 Test apparatus

The test apparatus shall:

a) produce a pressure difference across the closed heart valve substitute of at least 10 kPa (75 mmHg) and shall maintain it for all test cycle rates;

b) produce full valve opening and closing during each cycle;

c) allow objective evaluation of the opening and closing action of the heart valve substitute under test.

5.4.2.2 Measuring equipment accuracy

5.4.2.2.1 The pressure-measuring system shall have a natural frequency of at least 20 Hz and a measurement accuracy of at least ± 0,15 kPa (approximately ± 1 mmHg).

5.4.2.2.2 All flow-measuring equipment used to measure regurgitant volume shall have a measurement accuracy of at least ± 1 ml.

5.4.2.2.3 All other measuring equipment used shall have a measurement accuracy of ± 5 % of the full scale reading.

5.4.2.3 Test fluid

The test fluid shall be appropriate for the conditions set by the test apparatus (see 5.4.2.1).

5.4.3 Procedure

Test at least three heart valve substitutes of each of the largest, medium and smallest mounting diameters as well as at least one valve of all intermediate mounting diameters. Monitor the performance of the test apparatus by performing comparative tests on at least one reference valve [see 5.4.4d)]. Continue the test until either valve failure occurs or until at least 380 $\times$ 10^6 cycles have been completed. During the test, examine each heart valve substitute at least every 38 $\times$ 10^6 cycles. If failure occurs, the modes of failure and its most probable cause shall be defined and documented.

NOTE — Structural damage and/or functional impairment may occur during testing. Examples of structural damage may include holes, tears, gross delamination, fraying, coaptation problems, fracture, excessive deformation of the valve, failure of any individual component, other mechanical breakdown and/or wear. Examples of functional impairment may include excessive regurgitation and/or excessive pressure drop across the valve.

5.4.4 Test report

The test report shall include the following information:

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

b) a description and the specification of the test and associated apparatus (see 5.4.2.1), including a schematic diagram of the system;

c) the cycle rate;

d) a validation of the test method, by means of documentation of the pressure difference across each heart valve substitute and reference valve, as described by pressure/time wave-forms, and appropriate visual recording of the opening and closing characteristics of at least one heart valve substitute of each mounting diameter and 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 appearance of structural change and/or failure — any damage should be fully characterized by using the appropriate means, e.g. histology or surface characterization.

5.5 Animal tests (see clause B.2 for rationale)

5.5.1 Aim

The aims of animal testing are to provide data pertaining to the function of a heart valve substitute *in vivo* and to the host response in at least five animals of the same species that have survived for at least three months after implantation. The data shall also include those obtained from animals that do not survive this three-month period. Thus each animal in which a heart valve substitute has been implanted is to be subjected to a post-mortem examination.

Animal testing shall provide at least the following information:

a) an evaluation of haemodynamic performance during or after the third month following implantation: this shall include measurements of the pressure difference across the heart valve substitute, the cardiac output and an assessment of regurgitation;

b) an assessment of any structural change of the heart valve substitute;

c) an assessment of the haematological consequences of implantation;

d) an assessment of any pathological consequences to the major organs.

5.5.2 Test report

The test report shall contain the following information:

a) a detailed description of the animal model used, the rationale for its use and the pre-test clinical assessment of each animal;

b) 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 period post-implantation: this report should include visual records of the heart valve substitute *in situ* and the results of macroscopic examination including visual records of any thromboembolism of the major organs — the cause of death shall be given if the animal was not sacrificed;

c) the name and dose of the medications received by the animal during the survival period, especially of those drugs altering haemostasis;

d) a description and results of any blood studies performed, including a statement of the time elapsed between implantation and these studies;

e) a report on the post-operative haemodynamic performance of the heart valve substitute, including the pressure difference across the heart valve substitute, cardiac output measurements and an assessment of regurgitation;

f) a report on 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 should be assessed, e.g. by hydrodynamic testing as described in 5.3.

5.6 Clinical evaluation (see clause B.3 for rationale)

5.6.1 Aim

The aim of the clinical evaluation is to obtain data on the performance of the heart valve substitute in humans under monitored conditions.