TC 150

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Implants for surgery — Cardiovascular implants — Cardiac valve prostheses

Implants chirurgicaux — Implants cardiovasculaires — Prothèses valvulaires

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Every 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.

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.

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Implants for surgery — Cardiovascular implants — Cardiac valve prostheses

0 Introduction

Twenty years of intensive and continuous research and development has failed to result in the ideal valve replacement. Indeed, at the time of writing, many would argue that not even a particular type of valve can be singled out as nearest the optimum. This is due to many conflicting factors in valve design. For example, a prosthesis with excellent hydraulic characteristics may have a poor record of thromboembolic complication; a second valve, satisfactory from the haemodynamic point of view, may have limited durability; and a third may be too noisy for the patient to tolerate. Thus there is no clear-cut choice for the surgeon.

This International Standard has been prepared by a group well aware of the problems associated with prosthetic heart valves and their development. In several areas, this International Standard has deliberately been left open, for there was no wish to inhibit valve improvement. It intentionally makes no attempt to specify minimum performance requirements for the finished product, since standard performance criteria do not exist and, in fact, may vary according to the needs of a specific patient.

The areas with which this International Standard is concerned are thus intended to be those which will aid the surgeon in his choice of valve and ensure that the prosthesis will be presented in a convenient form at the operating table. Emphasis has therefore been placed on labelling and packaging aspects of the device and on the reporting of *in vitro* hydraulic and durability data.

With regard to testing and reporting, the document has been restricted to cover the important pulsatile hydraulic characteristics of the valve; because various test methods in current use are also in a state of evolution and improvement, the exact method of test has not been specified. Similarly, in the case of accelerated fatigue testing, only a description of the method of test and the results obtained are required.

It is recognized that this International Standard is incomplete, but it is intended that it be updated as knowledge and techniques in prosthetic heart valve technology improve.

1 Scope and field of application

This International Standard specifies basic requirements for test reporting, packaging, labelling and terminology for prosthetic heart valves (aortic/pulmonary and mitral/tricuspid).

2 Definitions

2.1 arterial diastolic pressure: Minimum value on the central aortic pressure wave form during the diastolic phase.

2.2 arterial systolic pressure: Maximum value on the central aortic pressure wave form during the systolic phase.

2.3 ball valve: A prosthetic heart valve which employs an occluder of spherical shape constrained in such a manner that fluid forces move the sphere away from the orifice area such that forward fluid flow is permitted, and conversely, fluid forces in the opposite direction move the sphere to occlude the orifice, thereby preventing fluid flow in the reverse direction.

2.4 cardiac valve prosthesis: Prosthetic device used to replace or supplement natural valves of the heart as follows:

a) arterial outflow valves (aortic/pulmonary);

b) ventricular inflow valves (mitral/tricuspid).

2.5 cycle rate: Number of complete cycles per unit time, usually expressed in terms of number of cycles per second (f) (or cycles per minute).

2.6 cycle time: Time, in seconds, during which a complete cycle is performed

$$T = \frac{1}{f}$$

where

T is the cycle time in seconds;

f is the cycle rate in cycles per second.

2.7 disc valve: The same as a ball valve except that the occluder element is disc-shaped.

2.8 external annulus diameter: (Also know as *mounting diameter*.) The diameter of the prosthetic valve where it is intended to mate with the smallest diameter of host tissue.

2.9 frustum: (Also known as *secondary valve orifice*.) The minimum built-in area available for flow other than at the primary valve orifice.

2.10 hinged disc prosthetic heart valve: (Also known as *pivoted disc prosthetic heart valve*.) Prosthetic heart valve in which flow and occlusion are controlled by one or more hinged rigid occluders.

2.11 leaflet prosthetic heart valve: A prosthetic heart valve consisting of one or more flexible leaflets attached to a ring in such a manner that fluid forces will cause them to flex between the open and closed positions, allowing flow in one direction and restricting it in the other.

2.12 mean flow rate: Mean (average) rate of flow across the valve being tested either during the systolic ejection phase (outflow valve) or during the diastolic filling phase (inflow valve).

2.13 mean pressure difference (deprecated term: *mean pressure gradient*): Mean (average) value of the pressure difference wave form across a valve under test during the whole of the systolic ejection phase (outflow valve) or diastolic filling phase (inflow valve).

2.14 mounting diameter: [See 2.8, *external annular diameter*.]

2.15 occluder: The components of a prosthetic valve that move to inhibit retrograde flow, either totally or partially.

2.16 pivoted disc prosthetic heart valve: [See 2.10, *hinged disc prosthetic heart valve*.]

2.17 primary valve orifice: Space available through open valve at narrowest point of valve inlet.

2.18 regurgitant fraction: That proportion of the stroke volume which flows in a retrogade manner across the test valve.

2.19 secondary valve orifice: [See 2.9, *frustum*.]

2.20 stroke volume: Volume of blood ejected from the ventricle during one systolic ejection flow phase or entering the ventricle during one diastolic filling flow phase. In test rigs the stroke volume usually refers to the volume moved across the test valve, it being assumed that no leakage occurs at the other valve.

2.21 systolic ejection flow phase (deprecated term: *systolic ejection phase*): That phase of a cycle during which forward flow occurs across the test outflow valve.

NOTE — The term "systolic ejection phase" has been commonly used to denote both systolic ejection flow phase and systolic ejection pressure phase but these are not equivalent. The use of the term "systolic ejection phase" without further qualification is consequently to be deprecated. Similarly the term "diastolic filling phase" is deprecated.

2.22 systolic ejection pressure phase (deprecated term: *systolic ejection phase*): That phase of a cycle during which the ventricular pressure exceeds that on the opposite side of the test outflow valve. See also note to 2.21.

2.23 systolic phase: That phase of a cycle during which a force is applied to drive the ventricle, including the stage during which the force builds up.

2.24 tilting disc prosthetic heart valve: A prosthetic heart valve in which flow and occlusion are controlled by the tilting of a disc.

2.25 transvalvular pressure difference: Indirect measure of the energy lost in transporting the test fluid across the valve. Depending on the method of use (see below) and the particular measure used, this should always be specified.

2.26 ventricular (cardiac) output: Net forward flow during one minute. It is defined as:

stroke volume × (1 − regurgitant fraction) × cycle rate

or

(stroke volume − regurgitant volume) × cycle rate

3 Materials, design and manufacture

3.1 The size of the prosthetic heart valve shall be designated by the mounting diameter of the heart valve where it is intended to mate with the host tissue, expressed in millimetres.

3.2 Materials used in the construction of prosthetic heart valves shall be corrosion resistant and of adequate mechanical strength, and, in the finally processed condition, not be incompatible with the human tissue with which they are intended to be used.

3.3 All construction processes and techniques shall be performed in accordance with good manufacturing practice. (An example is provided as annex B.) In addition, all construction processes shall be adequately qualified by *in vitro* and/or *in vivo* testing as applicable with respect to mechanical or corrosion resistant properties of the material.

4 Methods of test or inspection

4.1 *In vitro* haemodynamic testing

4.1.1 Principle

In vitro haemodynamic testing is conducted to assess the performance of prosthetic heart valves.

4.1.2 Apparatus

4.1.2.1 The test apparatus shall be a prosthetic heart valve pulse duplicator system which is a simplified analogue of the human circulatory system. An ideal analogue of the human circulatory system cannot be realized because of the pulsatile nature of flow in a constantly varying geometry of both the mounting of the natural valve and the inflow/outflow tracts.

4.1.2.2 The pulse duplicator system should simulate pertinent variables of the human circulatory system such as mean cardiac output, normal heart rate, pertinent chamber and vascular dimensions, systolic and diastolic blood pressures and durations. The system should also permit basic haemodynamic measurements such as pressure and flow as dependent variables of time.

4.1.3 Procedure

4.1.3.1 At least four conveniently spaced measurement points shall be chosen covering the intended range of flow rates and cyclic rates.

4.1.3.2 The test shall be conducted at 37 ± 2 °C.

4.1.3.3 The density of the test liquid shall be 1,100 ± 0,1 kg/l at the temperature specified in 4.1.3.2.

4.1.3.4 The test liquid viscosity shall be in the range of 0,7 to 4 cP at the temperature specified in 4.1.3.2.

4.1.3.5 The systolic duration shall be between 30 and 50 % of the simulated cardiac cycle.

4.1.3.6 The volume displacement wave form shall have a configuration between and including a rectangular wave and sine wave.

4.1.4 Test report

The test report shall include the following information:

4.1.4.1 Specifications of the valve tested, including:

a) valve type (ball, caged-disc, pivoting/tilting disc, leaflet, other) and designation;

b) mounting diameter, primary orifice area, and secondary orifice area, and methods of determination;

c) density, weight and travel of occluder, if applicable;

d) materials of valve body and occluder or leaflet.

4.1.4.2 Specific description of the pulse duplicator and major components of the test loop and associated apparatus, including a schematic diagram of the system.

4.1.4.3 Specific description of the test conditions.

4.1.4.4 Specific description of instrumentation used for all measurements during the testing.

4.1.4.5 The following haemodynamic quantities at the four measurement points chosen in 4.1.3.1:

a) cyclic rate;

b) systolic duration as a percentage of the simulated cardiac cycle;

c) forward stroke volume;

d) simultaneous pulsatile pressure versus time graphs on both sides of the valve;

e) simultaneous pulsatile flow rate through the valve and pulsatile pressure drop across the valve versus time graphs;

f) regurgitant fraction;

g) regurgitant volume per stroke.

With regard to d) and e) above the measurement points shall show variation of mean pulsatile pressure difference (in conventional millimetres of mercury) with variation of mean pulsatile flow rate (in millilitres per second) and may be presented in either graphic or tabular form. The mean pulsatile pressure difference measurements shall be corrected to the density of blood as follows:

$$\bar{P}_{dc} = \frac{1{,}055 \times \bar{P}_d}{\varrho}$$

where

$\bar{P}_{dc}$ is the density corrected mean pressure drop, in kilopascals (or in conventional millimetres of mercury);

$\bar{P}_d$ is the measured mean pressure drop, in kilopascals (or in conventional millimetres of mercury), using liquid of density ϱ, in grams per millilitre;

1,055 is the density, in grams per millilitre, of blood at 37 °C.

The test liquid, its temperature, density and viscosity shall be stated.

4.2 Accelerated wear testing

4.2.1 Principle

Accelerated wear testing is conducted to facilitate assessment of prosthetic heart valve durability.

4.2.2 Apparatus

Any test apparatus capable of meeting the requirements of 4.2.3 may be used.

4.2.3 Procedure

4.2.3.1 The accelerated wear test shall be conducted by means of the *in vitro* cycling of a prosthetic heart valve at rates substantially greater than 72 cycles per minute.

4.2.3.2 The manufacturer shall test the opening and closing mechanism for 380 million cycles or to failure, whichever occurs first, and report the results in accordance with 4.2.4.

4.2.3.3 The maximum speed at which these tests can be performed will vary with different valve configurations and materials. The fluid used in the test apparatus will affect results. Although wear per cycle may change with increased speed, present knowledge does not allow an exact correction factor to be applied.

4.2.3.4 In view of these variables, and to make results obtained by one investigator readily comparable with others, the test results shall be reported in accordance with 4.2.4.

4.2.4 Test report

The test report shall include the following information:

4.2.4.1. Specifications of the valve tested, including:

a) valve type (ball, caged-disc, pivoting/tilting disc, leaflet, other) and designation;

b) mounting diameter, primary orifice area, and, if applicable, secondary orifice area, and methods of determination;

c) density, weight and travel of occluder, if applicable;

d) materials of valve body and occluder or leaflet.

4.2.4.2 Test speed in cycles per minute.

4.2.4.3 The gas or liquid in which the test was performed, and its temperature, viscosity and density.

4.2.4.4 Specific description of the accelerated wear test and associated apparatus, including a schematic diagram of the system.

4.2.4.5 Specific description of the test conditions.

4.2.4.6 Specific description of instrumentation used for all measurements during the testing.

4.2.4.7 Total number of cycles. The total reported should not exceed the number at which valve function is impaired.

4.2.4.8 Degradation description.

5 Sterility

5.1 The manufacturer may dispatch heart valves in a sterile or non-sterile condition as specified by the purchaser.

5.2 The method of sterilization employed or recommended by the manufacturer shall not produce changes that will render the product incompatible with human tissue or cause detectable deterioration in mechanical or other properties.

5.3 Where the prosthetic heart valve may be sterilized or re-sterilized by the user, the manufacturer shall supply full details of the recommended procedures for sterilization of the valve, including the maximum number of cycles which may be undertaken by the user.

6 Packaging, labelling and marking

6.1 Packaging

6.1.1 The prosthetic heart valve shall be individually packaged in a suitable unit container.

6.1.2 Where the prosthetic heart valve may be sterilized or re-sterilized by the user, the unit container shall permit sterilization of the contents *in situ*, and shall provide adequate physical protection against mechanical damage to the prosthesis during sterilization.

6.1.3 The packaging material within the unit container shall not cause significant particulate contamination of the prosthesis.

6.1.4 The unit container shall be sealed in such a way that once the container is opened it is obvious that the seal has been broken.

6.1.5 The unit container shall be so designed as to permit the prosthesis to be presented for use in an aseptic manner.

6.1.6 The unit container shall be packaged within an individual outer container or containers which shall be sufficiently robust to protect the unit container from damage during normal conditions of handling, transit or storage.

6.1.7 Where the prosthesis is dispatched in a sterile condition, the package system (which comprises the unit container packed within one or more outer containers) shall be designed to maintain sterility of the prosthesis under normal conditions of handling, transit and storage.

6.2 Labelling

6.2.1 Unit container

Each unit container shall display the following:

a) description of contents including name, type, model and serial number of prosthetic heart valve and the size of the valve in accordance with 4.1.4.1;

b) the words "contents sterile" or "contents not sterile";

c) date of sterilization (year and month) and/or expiration date (year and month) where applicable;

d) the name and place of business of the manufacturer or distributor and country of origin.

6.2.2 Package insert

Each unit container shall be accompained by a product information text which includes the following items, where applicable:

a) concept/description;

b) indications for use;

c) contraindications;

d) warnings;

e) precautions;

f) complications;

g) technique/directions for use;

h) accessories;

j) how supplied;

k) storage;

m) sterilization (or re-sterilization);

n) patient identification system (see 6.2.3 and annex C);

p) references;

q) the common and/or chemical names of all materials which come into contact with blood or tissue.

6.2.3 *Patient identification system*

The manufacturer shall supply a system of identification for the hospital, surgeon, manufacturer and patient. An example of a patient identification system is provided as annex C.

Annex A

Rationale for the provisions of this International Standard

(This annex does not form part of the standard.)

A.1 Rationale for *in vitro* haemodynamic testing

Among the primary considerations in the performance of prothestic heart valves are

a) haemodynamics;

b) thrombogenicity;

c) durability.

A valve with less than optimum haemodynamic properties may not require long-term anti-coagulant regimes and may thus be the valve of choice for a particular patient; however, some patient conditions may require that emphasis be placed on optimum haemodynamics at the expense of continuing anti-coagulation.

Any attempt to set minimum performance requirements at this time would involve one of two courses. The first alternative would be to specify the minimum level of success, for each performance objective, that must be achieved by all currently available prosthetic valves. The other alternative would be to specify average or "desirable" levels of success for each performance objective.

If the first alternative were adopted, prosthetic heart valves could then be manufactured which, while meeting the requirements in all respects, would still be significantly less effective clinically than the devices now available.

With respect to the second alternative, many clinically effective valves in current use might not comply with at least one of the performance requirements and consequently be unavailable to the physician, thereby restricting his use of the valve of choice for a particular patient.

Neither course, if implemented at this time, would be beneficial to either the medical profession or the patient population.

It was the initial intention of the committee to develop standardized performance testing of prosthetic heart valves, so that reasonable levels of safety and efficacy could be established. It soon became apparent that due to the limitations of the test methods and the lack of sufficient data, a consensus could only be established for parametric ranges of test conditions.

A.2 Rationale for accelerated wear testing

Accelerated testing has been found to be extremely useful to prosthetic heart valve developers, because significant amounts of valve cycling data relating to durability can be accumulated in a reasonable length of time. This type of test shows its primary value in the identification of faulty valve designs and inferior materials early in the development process. Accelerated testing is also useful for ongoing evaluations of current valves by highlighting the effects of manufacturing process changes and minor design modifications on wear. It may also assist in clinical testing of new valve designs.

Several methods of accelerated testing have been used, including pneumatic cycling, variations of mechanical cycling, hydraulic cycling, and combinations of all of these. While pneumatic and mechanical cycling methods provide useful data on special tests, hydraulic cycling is the primary method of assessing durability of the finished prosthetic heart valve.

Most difficulties encountered in accelerated cycle testing are related to the interpretation of results in terms of clinical application. Early wear rates, for example, can be high, but then level off once the mating parts have seated. Failure criteria are difficult to quantify; thus, projection of valve "life" based on wear rate projections would not be appropriate if structural fatigue were the limiting factor. Accelerated testing inherently imposes unrealistically severe conditions because of

a) the inability to achieve adequate system damping;

b) high frequencies causing stresses that are not found at lower rates.

Incompatibility of the test fluid with the tissue further complicates the problem. All of these factors must be considered both in the design of the test system and in the subsequent evaluation of the results. As with all *in vitro* tests, knowledge of the limitations of the test is of paramount importance in analyzing the results.

Annex B

Example of good manufacturing practice for prosthetic heart valves

(This annex does not form part of the standard.)

B.1 Introduction

These guidelines set forth basic principles and minimum requirements in the manufacture of prosthetic heart valves to ensure that such products meet the requirements indicated by the manufacturer's specification and government regulations. The purpose of these guidelines is to promote the consistent meeting of such requirements once established for a given product.

B.2 Applicability

This document applies to the manufacture of prosthetic heart valves.

B.3 Facilities

B.3.1 Manufacturing facilities shall be suitably maintained and shall be of a size, construction and location as to facilitate cleaning, maintenance and proper operation in the manufacture, processing, reworking, packaging, labelling, storage and distribution, thereby meeting the manufacturer's specification, and applicable government standards and regulations.

B.3.2 Facilities shall provide space for:

a) orderly storage of equipment and materials;

b) receipt and storage of materials pending release or otherwise;

c) holding of nonconforming materials, and manufacturing and processing rejects;

d) packaging and/or labelling operations;

e) storage of finished products;

f) material evaluation operations.

Lighting, ventilation, screening and changing rooms shall be adequate for intended production or control purposes. When necessary to meet process requirements, control systems for pressure, microbiological conditions, dust, humidity and temperature shall be provided.

B.4 Equipment

Equipment used for the manufacture, processing, packaging, labelling, holding, inspection or control of devices shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction and location to facilitate cleaning, maintenance and operation for its intended purpose. Test equipment used to verify the conformance of parts, processes and manufactured products to the product specifications shall be controlled, maintained and calibrated on a regular basis. Calibration records shall be maintained, to verify that the test equipment is of sufficent accuracy to ensure that the requirements of the material, part, or product specification are met. Such equipment or processes shall not alter the product beyond the requirements of the specifications, nor make them unsuitable for the intended use.

B.5 Personnel

B.5.1 All personnel shall have

a) capabilities commensurate with their assigned functions;

b) the necessary training or experience;

c) a thorough understanding of the manufacturing or control operations that they perform;

d) a general understanding of their function and its significance to functions performed by others and to the final product application.

B.5.2 To ensure that the device is manufactured according to written procedures, the personnel responsible for directing its manufacture and control shall have appropriate education, training, and experience, or combination thereof.

B.5.3 All new employees involved in the manufacture or control of the devices shall be given formal training on current good manufacturing practice; training on this subject shall be continued on a regular basis.

B.5.4 Personnel directly responsible for quality control shall not also be directly responsible for production.

B.6 Product and process specifications

B.6.1 Each product shall have a specification, procedure, formula, or drawing which includes or makes reference to the manufacturing, processing, and testing details, and inspection parameters; this need not necessarily be in the form of a single document in one place.

B.6.2 A procedure shall be established to document any revisions to the specifications, formulae, or drawings, to ensure that revisions are authorized only by the person(s) assigned such responsibilities.

B.6.3 Nonconforming critical material shall be identified and separated; it shall not be used in the manufacture of devices except as authorized by a material review board.

B.6.4 Nonconforming subassemblies or devices shall not be used or shipped without the approval of a material review

board. Records shall be maintained detailing conclusions and decisions about these devices.

B.6.5 The complete specification, formula, or drawing should include:

a) the name of the product, a description, and a specimen or copy of each label required by law and all other labelling immediately associated with the retail or bulk unit, including copies of such labelling signed or initialled and dated by the person or persons responsible for approval of such labelling;

b) a complete list of material designated by names or codes sufficiently specific to indicate any special quality characteristics;

c) a description of any specific or special containers, closures, and packaging and finishing material used in the manufacture of the product;

d) manufacturing and control or inspection instructions, procedures, specifications, special notations, and precautions to be followed.

B.7 Material

B.7.1 Material used in the manufacture, processing, and packaging of devices shall be stored and handled in a systematic and controlled manner. This should provide that, prior to use or when indicated, incoming lots of material shall be subject to inspection which may include the examination of samples. Material shall be identified, handled and stored to guard against damage, deterioration, mix-up, or contamination. Nonconforming material shall be identified and kept separate pending a final decision as to its use.

B.7.2 Records of inspections performed and decisions on material shall be maintained. This shall include the identity and quantity of the material, the name of the supplier, and the date of receipt.

B.8 Operations

B.8.1 Production

Production operations shall be designed and controlled to ensure that the product conforms to applicable product and process specifications and/or mandatory standards established by law.

Each significant step in the process shall be perfomed by a competent and responsible individual and, if such steps in the processing are controlled by precision, automatic, mechanical, or electronic equipment, the proper performance of such equipment shall be periodically checked or calibrated. Where appropriate, ongoing monitoring of production and quality shall be carried out so as to ensure the uniformity and integrity of the product.

Where appropriate, all containers, lines, and production equipment used during the manufacture of a device shall be identified as to contents and/or stage of production, including removal of previous product or batch identification.

Production and control records shall be prepared to document manufacturing and control or inspection operations. (There shall be production and control records concerning the number of units produced, date(s) of production and relevant specification or standards at the time of production).

B.8.2 Traceability

Production records shall include documentation that the devices produced have the performance characteristics, identity and quality required by specification. Such records shall include:

a) documentation for each lot indicating that specified operations were performed and inspected;

b) an indication to relate the lot or control number of the device to the manufacturing procedures and engineering drawings used in its production;

c) an indication to relate the lot or control number of the devices to batches of materials or components where such batch control is specified in the manufacturing procedures or engineering drawings. Such specifications shall be required where material or component batch control could have an effect on fitness for use not readily confirmable by inspection or test of the finished parts or products.

B.8.3 Quality assurance

The manufacturer shall have a quality assurance programme for finished products. It shall provide for inspection of representative samples of finished products after packaging and labelling to safeguard against any faults in the finished product and to prevent distribution until specified requirements have been met.

Where appropriate, data indicating compliance with specified requirements shall be recorded and maintained. This data shall be recorded at the time of measurement and be initialled by the individual performing the test or measurement.

If modification, repairs, or replacements are required after finished product inspection and prior to distribution, reinspection and/or retesting of any characteristics affected shall be carried out.

B.8.4 Packaging and labelling

Packaging and labelling operations shall be controlled to ensure that only those devices that have met established requirements shall be distributed. Packaging and labelling controls shall include the following:

a) packaging and labelling operations shall be controlled by written procedures to ensure that only correct labels and packaging materials are used;

b) there shall be controls to prevent mix-ups between devices during the packaging and labelling operations, to ensure that correct labels and labelling are used for the device and to provide for the identification of the finished product by a lot or control number;

c) containers, closures and other component parts of device packages shall provide protection and prevent contamination of the device during handling and shipping, and