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Implants for surgery — Active implantable medical devices —

Part 5: Circulatory support devices

Implants chirurgicaux — Dispositifs médicaux implantables actifs —

Partie 5: Appareils annexes circulatoires

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 14708-5 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 6, *Active implants*.

ISO 14708 consists of the following parts, under the general title *Implants for surgery — Active implantable medical devices*:

— *Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

— *Part 2: Cardiac pacemakers*

— *Part 3: Implantable neurostimulators*

— *Part 4: Implantable infusion pumps*

— *Part 5: Circulatory support devices*

— *Part 6: Particular requirements for active implantable medical devices intended to treat tachyarrhythmia (including implantable defibrillators)*

Introduction

This part of ISO 14708 specifies requirements for safety and performance of active implantable circulatory support devices. It is not intended to be used for extracorporeal perfusion devices, cardiomyoplasty, heart restraint devices, and counter-pulsation devices such as extra- or intra-aortic balloon pumps. It amends and supplements ISO 14708-1:2000, hereinafter referred to as ISO 14708-1. The requirements of this part of ISO 14708 take priority over those of ISO 14708-1.

Heart failure (HF) is a major public health problem. It is estimated that worldwide more than 5 million people die per year due to heart failure. The number of newly diagnosed cases is more than 550 000 per year in the USA alone (AHA[13]). In 2001, nearly 53 000 patients in the United States died of HF as a primary cause. Further, heart failure is implicated as a contributing factor in more than 250 000 deaths each year in the USA alone (Yusuf[29]). Particularly at a higher risk for heart failure are the elderly (> 60 years), who account for 70 % of heart failure patients (Haldeman et al[18]), and for whom congestive heart failure is the leading cause of hospitalization. From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810 000 to over 1 million for HF as a primary diagnosis and from 2,4 million to 3,6 million for HF as a primary or secondary diagnosis (Koelling TM et al,[30]). The economic costs are enormous. It has been estimated that in 2005, the total direct and indirect cost of HF in the United States is equal to $27,9 billion (AHA[13]). Worldwide, it is estimated that over $900 billion per year is spent and almost one third of patients are younger than 60. Heart transplantation in recent years has become an effective treatment for end-stage heart failure. Unfortunately the number of donor hearts is limited to just about 3 000 worldwide, available only to a small fraction of patients who need heart transplants. Future drug discoveries and/or biological therapies such as cell regeneration and gene therapy hold promise for the future in the treatment of chronic heart failure. However, as of today, mechanical circulatory devices remain the only alternative to heart transplantation and will continue to be a viable treatment for end-stage heart failure for the foreseeable future.

Within this part of ISO 14708, the following terms are used to amend and supplement ISO 14708-1:

“Replacement”: the clause of ISO 14708-1 is replaced completely by the text of this particular part of ISO 14708.

“Addition”: the text of this particular part is additional to the requirements of ISO 14708-1.

“Amendment”: the clause of ISO 14708-1 is amended as indicated by the text of this particular part of ISO 14708.

“Not used”: the clause of ISO 14708-1 is not applied in this particular part of ISO 14708.

Subclauses, figures, or tables that are additional to those of ISO 14708-1 are numbered starting from 101; additional annexes are lettered AA, BB, etc.

Implants for surgery — Active implantable medical devices —

Part 5: Circulatory support devices

1 Scope

This part of ISO 14708 specifies requirements for safety and performance of active implantable circulatory support devices. It is not applicable to extracorporeal perfusion devices, cardiomyoplasty, heart restraint devices and counter-pulsation devices, such as extra- or intra-aortic balloon pumps.

This part of ISO 14708 specifies type tests, animal studies and clinical evaluation requirements.

NOTE The device that is commonly referred to as an active implantable medical device can in fact be a single device, a combination of devices, or a combination of a device or devices and one or more accessories. Not all of these parts are required to be either partially or totally implantable, but there is a need to specify main requirements of non-implantable parts and accessories if they could affect the safety or performance of the implantable device.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 5198, *Centrifugal, mixed flow and axial pumps — Code for hydraulic performance tests — Precision grade*

ISO 5840, *Cardiovascular implants — Cardiac valve prostheses*

ISO 7198, *Cardiovascular implants —Tubular vascular prostheses*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 14155[1)], *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14708-1, *Implants for surgery — Active implantable medical devices — Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

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

IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 60601-1-1, *Medical electrical equipment — Part 1-1: General requirements for safety — Collateral standard: Safety requirements for medical electrical systems*

1) To be published. (Revision of ISO 14155-1 and ISO 14155-2)

IEC 60601-1-2, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 60601-1-8, *Medical electrical equipment — Part 1-8: General requirements for basic safety and essential performance — Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*

IEC 62304, *Medical device software — Software life cycle processes*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 14708-1 and ISO 14971 and the following apply.

3.101
accessory device
separate part of a circulatory support system that is not essential to the primary function of the circulatory support system

NOTE Examples are programming units, monitoring units and alternative power supply units.

3.102
artificial valve
prosthetic valve
component of the circulatory support system that directs the unidirectional flow of the blood into and out of the pump

3.103
atrial cuff
connector between the right or left atrial ring after resection of the natural ventricle and the inlet of the right or left blood pump in total artificial heart replacement

3.104
cavitation
sudden formation and collapse of low pressure bubbles in the blood by means of mechanical forces

3.105
clinical study
evaluation of a device in humans

3.106
conduit
component of the circulatory support system that connects the pump to the patient's circulation

3.107
controller
component of the circulatory support system that contains the logic, circuitry and/or software to control the driving mechanism that enables the system to perform its primary function

3.108
diastolic pressure
arithmetic average of diastolic blood pressure (when the left ventricle is not contracting), over a sufficient number of cycles to filter out cyclic variation, of the minimum aortic pressures in a pulsatile pressure waveform

3.109
dp/dt
time derivative of pressure giving the rate of change of pressure with respect to time

NOTE dp/dt is expressed in millimetres of mercury per second, mmHg/s (kiloPascal per second [kPa/s] in SI units).

3.110
dQ/dt
time derivative of flow giving the rate of change of flow with respect to time

NOTE dQ/dt is expressed in units of litres per minute per second.

3.111
drive line
tube and/or cable that connects a driver or energy source to the pump

EXAMPLE The tube that connects a pneumatic console to a pneumatically driven pump.

3.112
durability
ability of an item to perform a required function under given conditions of use and maintenance, until a limiting state is reached

NOTE A limiting state of an item should be characterized by the end of the useful life, unsuitability for any economic or technological reasons, or other relevant factors.

3.113
ejection/fill
E/F
ratio between the ejection time period and the filling time period of the blood pump cycle

NOTE E/F is identical to S/D (systolic/diastolic) when related to the natural heart.

3.114
extracorporeal component
component or subsystem of the circulatory support system that is kept external to the patient (outside of the body)

3.115
failure
termination of the ability of an item to perform a required function

NOTE 1 After failure, the item has a fault.

NOTE 2 “Failure” is an event, as distinguished from “fault”, which is a state.

NOTE 3 This concept as defined does not apply to items consisting of software only.

3.116
fault
state of an item characterized by inability to perform a required function, excluding the inability during preventive maintenance or other planned actions, or due to lack of external resources

NOTE A fault is often the result of a failure of the item itself, but might exist without prior failure.

3.117
fully implantable
implanted circulatory support system with no skin penetrations (i.e. percutaneous lead)

3.118
hazard analysis
identification of hazards and their initiating causes

3.119
labelling
marking
any written, printed, or graphical matter affixed to a medical device or any of its containers or wrappers, or accompanying the medical device related to identification, technical description and use, but excluding shipping documents

3.120
monitor
component of the circulatory support system that allows data pertaining to the operation of the system to be displayed

3.121
peak flow
maximum flow rate during ejection of blood from a pump into the host circulatory system

3.122
peak pressure
maximum pressure generated by the circulatory support system

3.123
percutaneous lead
lead (electrical or otherwise) that crosses the patient's skin to connect implantable parts of a circulatory support system to extracorporeal parts of the system

3.124
power supply
source of energy

3.125
pulsatile flow
characteristic of the output of a pump where the flow is time-dependent (flow varies with time during one beat)

3.126
pump fill
filling phase of a volume displacement pump

NOTE Diastole is used to describe only the filling phase of the host's native ventricle(s).

3.127
pump output
performance measure for a circulatory support system indicating the volume of blood pumped into the host circulatory system per minute

NOTE The pump output is expressed in litres per minute or its equivalent in other units.

3.128
pump/pulse rate
performance measure for a circulatory support system indicating the number of complete pump cycles per minute

NOTE The pump rate is expressed in beats per minute.

3.129
pump stroke volume
performance measure for a circulatory support system indicating the volume pumped into the host circulatory system per beat by a pump with pulsatile flow

NOTE The pump stroke volume is expressed in millilitres.

3.130
pump volume
volumetric capacity of the pump

3.131
pump displacement
volume displacement
pump that imparts its pumping action by changing the volume of the pumping chamber

EXAMPLE By displacement of a diaphragm or pusher plate.

3.132
reliability
probability that an item can perform a required function under given conditions for a given time interval (t1, t2)

NOTE 1 It is generally assumed that the item is in a state to perform this required function at the beginning of the time interval.

NOTE 2 The term “reliability” is also used to denote the reliability performance quantified by this probability [see 191-02-06 of IEC 60050-191 definition of reliability (performance)].

3.133
remote access device
component of the circulatory support system that allows modification and/or monitoring of the controller and the operation of the system

3.134
rotary pump
pump that imparts its pumping action directly on the blood by a rotating mechanism

3.135
safe and effective
reasonable assurance that a device will not induce harm to the recipient and that it will provide clinical benefit for the recipient for its conditions of use

3.136
safety
freedom from unacceptable risk

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

3.137
safety hazard
potentially detrimental effect on the patient, other persons, animals, or the surroundings, arising directly from the circulatory support system

3.138
sales packaging
packaging that protects and identifies the device during storage and handling by the purchaser

NOTE The sales packaging should be enclosed in further packaging, for example a “shipping package”, for delivery.

3.139
stroke volume
amount of blood pumped by the ventricle of the heart in one contraction

3.140
systolic pressure
arithmetic average, over a sufficient number of cycles to filter out cyclic variation, of the peak aortic pressures in a pulsatile pressure waveform

3.141
transcutaneous energy transmission system
TETS
system used to send electrical energy wirelessly into a device implanted inside the body

3.142
total artificial heart
TAH
circulatory support system that replaces the pumping function of a patient's native heart

3.143
ventricular assist system
ventricular assist device
VAS/VAD
circulatory support system that augments the function of either one or both ventricles of the patient's native heart by capturing blood from the atrium(a) or ventricle(s) and providing work to pump blood into the pulmonary and/or systemic circulation

4 Symbols and abbreviated terms

This clause of ISO 14708-1 applies.

5 General requirements for non-implantable parts

This clause of ISO 14708-1 applies.

6 Requirements for particular active implantable medical devices

Addition

6.101 Intended clinical use/indications

The intended use and indications for the device system shall be described. The intended use describes what the device system does (e.g. provides circulatory support) and where it may be used safely (e.g. hospital, home, ground and/or air transport vehicles). The indications are the disease(s) or condition(s) the device will diagnose, treat, prevent, cure, or mitigate and a description of the target population for which the device is intended without causing unreasonable risk of illness or injury associated with use of the device.

6.102 System description

6.102.1 General

A comprehensive description of the system should be documented, including discussions on the principle(s) of operation, design consideration(s), system configuration(s), system component(s), and system performance and operating limits.

Design specifications for the complete system include the full range of system operating limits for each parameter (e.g. beat rates, E/F ratio, rotation speeds, power), system operational modes (e.g. manual, automatic), system component configurations (e.g. hospital, home, power sources, optional display, optional subsystems, optional console), alarm thresholds, and all associated tolerances on each of these parameters.

6.102.2 Principle of operation

A discussion of the operating principle of the system should include the blood pumping mechanism, connections to the cardiovascular system, power system, and control mechanisms.

6.102.3 Design consideration

The rationale for key design choices should be given. This should include, but is not limited to, approaches taken to minimize blood component damage, methods for thermal management, choice of drive mechanisms, a power management scheme, reliability considerations, adequacy of anatomic fit, and patient interaction.

6.102.4 System configuration

A detailed physical description of the system shall be given including implantation sites of various implantable components, external wearable units, and external consoles. Size, shape, weight, and volume of the components should be given, as well as the different configurations of system components that can be used to provide support.

6.102.5 System performance and operating limits

The entire performance range of the system shall be given, even if some operation conditions are not expected to be used clinically or might cause the system to malfunction.

6.103 Design analysis

A comprehensive analysis should be performed for the integrated system, the various component configurations, as well as for each system component for all safety and effectiveness issues, including human factors. The *in vitro*, *in vivo*, and clinical testing performed to address each issue should be identified.

6.104 Risk analysis

Risk analysis, part of the risk management process, should be performed on the system. The risk analysis should include a top-down analysis (such as a hazard analysis or fault tree analysis, FTA), a bottom up analysis (such as failure mode, effects, and criticality analysis, FMECA), as well as an analysis for potential use or user error (human factors analysis). The risk analysis should utilize a method to classify the severity of failure modes, the probability of occurrence, the risk priority number, and the detection method. The analysis should include discussion of methods used to mitigate the criticality of the failure modes (see 19.2).

NOTE For further information on risk analysis, see ISO 14971.

6.105 Human factors

Human factors evaluation should consist of both integrated system testing and subsystem testing. The user interface, both hardware and software, should be designed to be understandable and compatible with the intended users' anticipated capabilities (e.g. physical, mental, or sensory) to reduce the likelihood of error and/or confusion. Further, appropriate alarms and warnings are necessary and shall be designed to warn users of system or subsystem failures. Guidance for human factors can be found in IEC 62366.

6.106 *In vitro* design evaluation and system performance testing

6.106.1 Objective

In vitro testing shall include design characterization of the integrated system and its individual system subcomponents against all of its system design specifications. Test set-ups should be reasonably representative of the intended patient population in which pressures, compliances and flow should be at appropriate values. A description of the *in vitro* testing systems, including all pressures, compliances, and the location of all measurement equipment, as well as the rationale for the test set-up, shall be provided.

In both a volume displacement pump and a rotary pump VAD system, this testing includes the characterization of all time dependent parameters as they operate with (or as a replacement for) the native heart in a pulsatile environment. In this way the simulated performance effects of the system on the patient and the patient on the system can be understood.

6.106.2 Initial design evaluation of the pump system

6.106.2.1 Pump performance test

The pump performance test shall evaluate the ability of its design to meet the specification. The test shall be conducted using blood or a blood analogue solution that mimics critical characteristics of blood, such as viscosity, temperature and density as they might affect pump performance of the particular devices.

6.106.2.2 Fluid dynamic analysis

A fluid dynamic characterization of the device should be conducted and its results should be discussed in terms of how these characteristics relate to the design specification and the results of other *in vitro* and *in vivo* design evaluations including hemolysis, cavitation, and thrombus formation. Such studies include computational fluid dynamics (CFD) or flow visualization study (see Annex DD.4). These study results should be used for justification of design improvement of the device.

6.106.2.3 Vibration measurement

A vibration test shall be conducted over the entire range of operating speed to ensure that critical speed resonance (induced either mechanically or by magnetic bearing control systems) will not cause unacceptable mechanical instability. It might be necessary to positively restrict the operating speed range to avoid critical speeds.

NOTE For further information on vibration testing, see ISO 14708-1.

6.106.2.4 Cavitation observation

Because cavitation can have highly damaging effects on both the device material surfaces and on the formed elements of the blood and small bubbles are capable of embolising to distal organs, it is essential that cavitation be avoided under all designed operating conditions. Potential cavitation phenomena should be investigated in the laboratory and/or via computational fluid dynamics (CFD) simulation. The critical cavitation conditions, NPSHR (net positive suction head required) shall be provided for rotary devices and dynamic cavitation potential in pulsatile devices (particularly in the prosthetic valves) should be investigated.

NOTE For further information on cavitation in rotary devices, see ISO 5198.

Characteristics of the test fluid might have a significant effect on cavitation behaviour. Justification for the test fluid in terms of its cavitation potential compared to blood should be documented.

6.106.3 System characterization

6.106.3.1 General

In vitro system characterization testing is a complete evaluation of the final system design in the simulated use environment.

6.106.3.2 Test set-up

All applicable parameters should be documented and reported.

The testing should simulate the effects of changes in system performance on the patient and the effects of patient changes on system performance. The effects of extremes of operation on both the device and the patient (i.e., test set-up) should be determined. The extremes of operation include the minimum blood flow and maximum blood flow, hypertension, hypotension, responses to changes in flow, pressure and possible inflow/outflow restrictions.

Ventricular assist device (VAD) and total artificial heart (TAH) system performance (e.g. alarms, back-up systems, information displayed, measurement accuracy and precision, and failures) should be monitored and reported as specified in ISO 14708-1 and with alarms conforming to IEC 60601-1-8.

6.106.3.3 Test articles

6.106.3.3.1 General

At least one clinically representative device system shall be characterized. A complete system is comprised of all system components required for that system to be operational in its intended environment. If clinical operation of the device can utilize multiple configurations of components and accessories, then testing of each configuration is required. Where the design analysis demonstrates that critical components/sub-assemblies at the extremes of their specifications might impact overall device performance, test articles will be used which characterize that variability.

6.106.3.3.2 Substitution of device components

If a device component (e.g. biological prosthetic valves, vascular graft or atrial cuff) is substituted by its alternative, justification shall be provided.

6.106.3.4 Test equipment

6.106.3.4.1 General

Test equipment required for *in vitro* system characterization testing of the complete device system shall include a mock circulatory loop and all test measurement equipment.

6.106.3.4.2 Mock circulatory loop

In vitro models used to appropriately simulate the natural heart, as appropriate, and the vascular compliance and resistance, shall be documented, and justified as to the necessary physiological limits prescribed.

6.106.3.4.3 Physiological limits

Mock circulatory loops shall be appropriate to the intended diseased patient population, and not limited to those ranges found within the “normal” population. For those devices used in conjunction with a patient's native heart, the *in vitro* performance testing shall account for native heart rates, and systolic/diastolic pressures and flows.

6.106.3.4.4 Blood analogue fluid

Fluids used to simulate the properties of human blood shall be described. Fluids used may be Newtonian. Characteristics of the fluid and its chemical composition shall be given. Justification for necessary blood-matching trade-offs shall be given (e.g. viscosity, temperature, salinity and pH).