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Implants for surgery — Active implantable medical devices —

Part 5: Circulatory support devices

Implants chirurgicaux — Dispositifs médicaux implantables actifs — Partie 5: Dispositifs d'assistance circulatoire

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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

This second edition cancels and replaces the first edition (ISO 14708-5:2010), which has been technically revised. The main change compared to the previous edition is as follows:

— alignment to the revised ISO 14708-1:2014.

A list of all parts in the ISO 14708 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document specifies requirements for safety and performance of active implantable circulatory support devices. It amends and supplements ISO 14708-1:2014, hereinafter referred to as ISO 14708-1. The requirements of this document take priority over those of ISO 14708-1.

Heart failure is a major public health problem. It is estimated that worldwide more than 5 million people die per year due to heart failure. In addition, it accounts for a large portion of health care expenditure and rehospitalisation (see Reference [35]). Circulatory support devices are needed for promoting myocardial recovery following acute heart failure as well as long-term support until eventual transplantation or permanent therapy. Circulatory support devices may be fully implanted, partially implanted, or delivered by percutaneous approach. The growth of heart failure is expected to increase with the aging population (see Reference [30]).

The requirements of this document supplement or modify those of ISO 14708-1.

In this document, terms printed in italics are used as defined in Clause 3. Where a defined term is used as a qualifier in another term, it is not printed in italics unless the concept thus qualified is also defined.

Information is also provided in Annex A that explains the relationship between ISO/TR 14283, ISO 14708-1 and this document.

Notes on this document are provided in Annex B for information.

Annex C provides guidance on pre-clinical in vitro and in silico evaluation. Annex D provides information device hazards, associated failure modes, and evaluation methods. All annexes are informative.

Implants for surgery — Active implantable medical devices —

Part 5: Circulatory support devices

1 Scope

This document specifies requirements for safety and performance of active implantable circulatory support devices, including 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.

The tests that are specified in this document are type tests and are to be carried out on a sample of a device to assess device behavioural responses and are not intended to be used for the routine testing of manufactured products.

Included in the scope of this document are:

— ventricular assist devices (VAD), left or right heart support;

— total artificial hearts (TAH);

— biventricular assist devices (biVAD);

— percutaneous assist devices;

— paediatric assist devices.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 10993-1:2018, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 14708-1:2014, *Implants for surgery — Active implantable medical devices — Part 1: General requirements for safety, marking and for information to be provided by the manufacturer*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

IEC 60068-1:2013, *Environmental testing — Part 1: General and guidance*

IEC 60068-2-27:2008, *Environmental testing — Part 2-27: Tests — Test Ea and guidance: shock*

IEC 60068-2-31:2008, *Environmental testing — Part 2-31: Tests — Test Ec: rough handling shocks, primarily for equipment-type specimens*

IEC 60068-2-64:2008, *Environmental testing — Part 2-64: Tests — Test Fh: vibration, broadband random and guidance*

IEC 60601-1:2018, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 60601-1-2:2014, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 60601-1-6:2010, *Medical electrical equipment — Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability*

IEC 60601-1-10:2007, *Medical electrical equipment — Part 1-10: General requirements for basic safety and essential performance — Collateral standard: Requirements for the development of physiologic closed-loop controllers*

IEC 60601-1-11:2015, *Medical electrical equipment — Part 1-11: General requirements for basic safety and essential performance — Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment*

IEC 62304:2006, *Medical device software — Software life cycle processes*

IEC 62366-1:2015, *Medical devices — Part 1: Application of usability engineering to medical devices*

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.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
accessory device
separate part of a circulatory support system that is not essential to the primary function of the circulatory support system

Note 1 to entry: Examples are programming units, monitoring units and alternative *power source* (3.18) units.

3.2
artificial valve
prosthetic valve
component of the circulatory support system that directs the unidirectional flow of the blood into and out of the pump

3.3
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* (3.31) replacement

3.4
biVAD
biventricular assist device
configuration in which two VADs are used to support both ventricles respectively

3.5
cavitation
sudden formation and collapse of low-pressure bubbles in the blood by means of mechanical forces

3.6
circulatory support device
electromechanical device that is used to partially or completely replace the left and/or right ventricular function of a failing heart

3.7
conduit
component of the circulatory support system that connects the pump to the patient's circulation

3.8
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

3.9
diastolic pressure
arithmetic average of minimum pressures in a pulsatile pressure waveform over a sufficient number of cycles to filter out cyclic variation

3.10
display
component of the circulatory support system that allows data pertaining to the operation of the system to be observed

3.11
driveline
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.

3.12
durability
ability of an item to perform a required function under given conditions of use and maintenance, until a limiting state is reached

Note 1 to entry: 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.

3.13
DUT
device under test

3.14
ejection/fill
E/F
ratio between the ejection time period and the filling time period of the blood pump cycle

Note 1 to entry: E/F is identical to S/D (systolic/diastolic) when related to the natural heart.

3.15
failure
termination of the ability of an item to perform a required function

Note 1 to entry: After failure, the item has a *fault* (3.16).

Note 2 to entry: "Failure" is an event, as distinguished from "fault", which is a state.

Note 3 to entry: This concept as defined does not apply to items consisting of software only.

3.16
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 1 to entry: A fault is often the result of a *failure* (3.15) of the item itself but might exist without prior *failure*.

3.17
labelling
marking
any written, printed, electronic information, 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

3.18
power source
source of energy (battery, mains)

3.19
pulsatile flow
characteristic of the output of a pump where the flow is time dependent

3.20
pulse pressure
difference between the systolic and *diastolic pressure* (3.9) readings

Note 1 to entry: It represents the force that the heart generates each time it contracts.

3.21
pump output
performance measure for a circulatory support system indicating the volume of blood pumped into the host circulatory system per minute

Note 1 to entry: The pump output is expressed in litres per minute or its equivalent in other units.

3.22
volume displacement
pump displacement
pump that imparts its pumping action by changing the volume of the pumping chamber

EXAMPLE By displacement of a diaphragm or pusher plate.

3.23
reliability
probability that an item can perform a required function under given conditions for a given time interval (t1, t2) for a specified confidence level

Note 1 to entry: 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 to entry: The term "reliability" is also used to denote the reliability performance quantified by this probability[11].

3.24
rotary pump
pump that imparts its pumping action directly on the blood by a rotating mechanism

3.25
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

3.26
safety
freedom from unacceptable risk

Note 1 to entry: See ISO/IEC Guide 51.

3.27
sales packaging
packaging that protects and identifies the device during storage and handling by the purchaser

Note 1 to entry: The sales packaging should be enclosed in further packaging, for example a "shipping package", for delivery.

3.28
service life
period after implantation when the circulatory support system remains within stated specifications and characteristics

Note 1 to entry: The service life of the components of the system can vary (implanted components might have longer lifetimes versus the peripheral components which are replaceable).

3.29
stroke volume
amount of blood pumped by the ventricle of the heart in one contraction

3.30
transcutaneous energy transmission system
TETS
system used to send electrical energy wirelessly into a device implanted inside the body

3.31
total artificial heart
TAH
circulatory support system that replaces the pumping function of a patient's native heart

3.32
ventricular assist device
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 abbreviations

The text in ISO 14708-1:2014, Clause 4 applies.

5 General requirements for active implantable medical devices

5.1 General requirements for non-implantable parts

The text in ISO 14708-1:2014, 5.1 applies.

5.2 General requirements for software

The text in ISO 14708-1:2014, 5.2 applies.

5.3 Usability of non-implantable parts

The text in ISO 14708-1:2014, 5.3 applies.

5.4 Data security and protection from harm caused by unauthorized information tampering

The text in ISO 14708-1:2014, 5.4 applies.

5.5 General requirements for risk management

The text in ISO 14708-1:2014, 5.5 applies.

5.6 Misconnection of parts of the active implantable medical device

The text in ISO 14708-1:2014, 5.6 applies.

5.7 Wireless coexistence and wireless quality of service

When communication with any part of an active implantable medical device is provided through wireless communication channels, the manufacturer shall evaluate wireless coexistence and wireless quality of service through the risk management process and apply the appropriate risk control measures to protect the patient from harm (see 27.6).

Testing of wireless communication channels, for EMC, is performed in accordance with IEC 60601-1-2:2014.

Compliance is checked by the inspection of the risk management file.

6 Requirements for particular active implantable medical devices

6.1 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), where it may be used safely (e.g. hospital, home, ground and/or air transport vehicles), and the intended duration of use. 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.

Compliance is checked by the inspection of the manufacturer's documentation.

6.2 System description

6.2.1 General

A comprehensive description of the system shall be documented, including discussions on the principles of operation, rationale for key design choices, system configurations, system components, and system performance and operating limits.

Compliance is checked by the inspection of the manufacturer's documentation.

The rationale for key design choices, for example:

— approaches taken to minimize blood component damage;

— methods for thermal management;

— choice of drive mechanisms;

— power management scheme;

— choice of connectors to prevent misuse;

— reliability considerations;

— adequacy of anatomic fit;

— electromagnetic compatibility (EMC)/ interference;

— driveline damage resistance;

— exposure to environmental conditions;

— human factors.

Design specifications for the complete system include the full range of system operating limits for each parameter, for example:

— beat rates;

— E/F ratio;

— rotation speeds;

— power consumption;

— flow rate as a function of pressure head (with varying pump rotational speed or beat rate).

Required system components, for example:

— hydrodynamic bearings;

— magnetic bearings.

System operational modes, for example:

— manual;

— automatic.

System component configurations, for example:

— hospital;

— home;

— power sources;

— optional display;

— optional subsystems;

— optional console.

Alarm thresholds, and all associated tolerances on each of these parameters.

Principle(s) of operation, for example:

— blood pumping mechanism;

— connections to the cardiovascular system;

— power system;

— control mechanisms.

6.6.2.4.4.2 Use of the device system as test measurement equipment

Many device systems are capable of measuring, acquiring, manipulating, displaying, and storing desired parameters to be measured. The device system measurement and data handling systems shall be documented and validated against calibrated instruments for accuracy.

6.6.2.4.4.3 Data handling

Systems used for data acquisition, manipulation, display, and storage shall be documented. Data acquisition methods and equipment used shall be specified (e.g. real time, triggering methods, sampling rate, filters, amplification). If any data manipulation (e.g. averaging, smoothing) is performed prior to display and storage of final information, this should be clearly explained, including the algorithms used and documenting evidence of system consistency. Characteristics for the display shall be documented (e.g. accuracy, precision, and error).

6.6.2.5 Test conditions

A matrix of test conditions should be generated in order to characterize the system over the full range of operational limits using all possible component configurations against all of the design specifications of the device. The VAD system algorithms, if configurable by the clinician, should also be tested in the ON and OFF states to demonstrate they meet their specifications. 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 (e.g. 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.

The relevant conditions used to characterize the system should be selected according to the type of the system (e.g. volume displacement or continuous flow, total artificial heart or ventricular assist system). See Annex C for more information.

6.6.2.6 Parameters to be measured

The pump should be characterized over the full operating range with the following parameters as appropriate (see Annex C for more information):

a) blood pump inlet and outlet pressure waveforms;

b) blood pump outlet flow waveform;

c) average outlet pressure from the pump;

d) average inlet pressure to the pump;

e) average pump outlet flow.

6.6.2.7 Data analysis

Data analysis shall be performed to show that the system performance meets the design specifications for the system. This shall include statistical significance calculations comparing actual in vitro system performance to the expected design specification. Further, data analysis of system performance and the expected clinical effects of the system, based upon a review of the literature, should be provided.

6.6.2.8 "Worst case" operating conditions

System characterization data should be evaluated to determine the worst-case modes of operation (e.g. power input, pump flow, pressures, battery life) within the design input specification. A discussion should provide the rationale for the selection of the conditions determined to be worst case and what effect they might have on the device.

6.6.3 Subsystem component testing

6.6.3.1 Design evaluation of the pump subsystem

6.6.3.2 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 haemolysis, cavitation, and thrombus formation. Such studies include computational fluid dynamics (CFD) or experimental flow characterization (see Annex C). These study results should be used for justification of design improvement of the device. The contribution of the native heart to the total pump flow should be considered during the analysis or test method development.

6.6.3.3 Cavitation

The device shall not exhibit cavitation under any operating conditions. As applicable, the critical cavitation conditions [e.g. net positive suction head required (NPSHR)] should be provided.

Compliance is checked by the inspection of the design verification record.

6.6.3.4 Control and drive units

6.6.3.4.1 External units

Blood pump controlling and driving units that are carried by patients shall be tested against the design requirement specifications. At a minimum, these units should be qualified by verifying the following requirements.

a) Electrical input (voltage range, ripple, current range, and power requirements).

b) Electrical and/or mechanical output (e.g. voltage, current, power, torque, and pressure).

c) Electrical safety requirements, as specified in IEC 60601-1:2018 shall be met.

d) Software used in the controlling and driving units shall be verified as specified in IEC 62304:2006.

e) The unit alarms should meet the requirements of IEC 60601-1-8 and include multiple types of alarms (e.g. auditory, visual, and vibratory).

f) The external control and drive unit qualification shall also include testing as specified in the following documents:

   1) IEC 60068-1:2013;

   2) IEC 60068-2-64:2008;

   3) IEC 60068-2-27:2008;

   4) IEC 60068-2-31:2008;

   4) IEC 60601-1-10:2007 (for closed-loop controller);

   5) IEC 60601-1-11:2015.

g) Unit enclosure temperature shall be as specified in IEC 60601-1:2018.

h) Biocompatibility of materials that might be in contact with the patient's skin shall also be verified according to the biocompatibility documents within ISO 10993-1:2018.

This list of documents is not all-inclusive, and others may be used as applicable.

6.6.3.4.2 Implantable controllers and drivers

Implantable devices shall comply with the safety, marking and supplied information requirements specified in ISO 14708-1.

6.6.3.4.3 Programming and monitoring units

Peripheral/accessory devices are for the programming of the system, collecting, storing and displaying information in hospitals and/or home environment. As a part of the circulatory support system, programming and monitoring units shall be tested as described in 6.6.3.4.1 External units. Where appropriate, the test levels shall be documented for the intended use environment (e.g. hospital, home, and air/ground transport). See ISO 14708-1. If testing is not to be performed (e.g. the use of qualified off-the-shelf laptops), an equivalency rationale shall be provided.

6.6.3.4.4 Power supplies

Power supplies (including battery chargers) for the circulatory support devices shall meet safety requirements for medical devices as specified in IEC 60601-1:2018, such that at no time is there total loss of power. Electrical input and output (voltage range, ripple, current, and power) as well as overload capabilities and protection shall be verified.

Where appropriate, the test levels shall be documented for the intended use environment (e.g. hospital, home, and air/ground transport).

6.6.3.4.5 Batteries

Battery-powered circulatory support systems should be considered for testing the following:

a) battery voltage from full capacity to the depleted state;

b) effect of current (load) on battery performance (voltage, capacity, and case temperature);

c) effect of time, temperature, load, and cycles on the battery's capacity (aging);

d) battery preventive maintenance and replacement schedule (based on cycles or time);

e) emergency back-up procedure if the battery fails;

f) recharge specifications, for example, charge current, end of charge determination, and recharge time;

g) method to measure battery depletion;

h) method to control hazard from potential gases produced while charging;

i) battery status indicator that gives advance warning of battery depletion. The manufacturer shall define the time interval between the activation of this indicator and the point at which the battery will cease to support the normal operation of the device;

j) auditory, visual, and vibratory warning alarms in the event of battery depletion;

k) appropriateness of parallel redundancy for battery sources;

l) method to measure/identify high discharge temperatures;

m) protection against battery explosion or burst;

n) ease of battery exchange process especially if the battery is implanted.

6.6.3.5 Connectors and driveline

6.6.3.5.1 Electrical and pneumatic connectors

Electrical and pneumatic connectors to and from all power supplies, batteries, controllers, and blood pumps shall be designed to satisfy the pre-conditioning requirements (see 6.6.2.3.2) and following tests, as appropriate:

— connector connect/disconnect cycling;

— connector misalignment;

— fluid and solid contamination ingress.

Conductivity/resistance/pressure shall be measured as appropriate after each of the appropriate tests to ensure design specifications are met.

6.6.3.5.2 Pneumatic driveline

For systems with pneumatic drives, all drivelines to and from the pneumatic supply and the blood pump (the entire gas pathway) shall be pre-conditioned (see 6.6.2.3.2) and then required to maintain pneumatic pressure or alarm while subjected to the following tests:

— tension;

— torsion;

— kink (bend radius);

— pinch;

— jerk;

— vibration;

— flex testing of pneumatic tubing and strain relief(s);

— abrasion;

— aging;

— UV exposure;

— crush resistance;

— cut resistance.

Following subjecting the pneumatic driveline to the insults listed above, the driveline should be:

— visually examined for damage with photographic evidence;

— leak test after insults per manufacturer's acceptance specification.

6.6.3.5.3 Electrical cable

Electrical cables to and from all power supplies, batteries, controllers, and blood pumps shall be pre-conditioned (see 6.6.2.3.2). Following subjecting the electrical cable to the insults listed below, the electrical cable should be visually examined for damage with photographic evidence and evaluated for any change in electrical continuity/resistance according to the manufacturer's acceptance specifications.

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
5.8.4.1 Implants intended to emit ionizing radiation must be designed and manufactured in such a way as to ensure that, where reasonably practicable, the quantity, geometry and energy distribution (or quality) of radiation emitted can be varied and controlled taking into account the intended use.	—	—
5.8.4.2 Implants emitting ionizing radiation intended for diagnostic radiology must be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose while minimising radiation exposure of the patient and user.	—	—
5.8.4.3 Implants emitting ionizing radiation, intended for therapeutic radiology must be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the energy distribution of the radiation beam.	—	—
5.9 Implants that incorporate software		
5.9.1 Implants incorporating electronic programmable systems, including software must be designed to ensure repeatability, reliability and performance according to the intended use. In the event of a single fault condition, appropriate means must be adopted to eliminate or reduce as far as reasonably practicable and appropriate consequent risks.	5.2 Requires implants to be designed according to software life cycle process activities compliant with IEC 62304:2006 and validated.	* retained 6.6.3.4 additional requirements
	19.3 Requires a design analysis and defines the methodology for the analysis.	* retained 6.3 additional requirements
5.9.2 For implants which incorporate software, the software must be validated according to the state of the art taking into account the principles of life-cycle development, risk management, verification and validation.	5.2 Requires implants to be designed according to software life cycle process activities compliant with IEC 62304:2006 and validated.	* retained 6.6.3.4 additional requirements
5.10 Active implants and devices connected to them		
5.10.1 For active implants, in the event of a single fault condition, appropriate means must be adopted to eliminate or reduce as far as reasonably practicable and appropriate consequent risks.	19.3 Defines methodology to ensure single fault conditions are not a hazard.	* retained
5.10.2 Implants where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	19.2 Requires power source depletion indicator.	* retained 19.7, 19.8 additional requirements
5.10.3 Implants where the safety of the patients depends on an external power supply must include an electronic alarm system to signal any power failure by way of an external device used in association with the implant.	5.1 Applies IEC 60601–1 to the non-implantable parts of the active implantable medical device that are connected to or equipped with an electrical power source.	* retained 6.6.3.4, 6.6.3.5 additional requirements
5.10.4 Implants intended to monitor one or more clinical parameters of a patient must be equipped with appropriate electronic alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health by way of an external device used in association with the implant.	5.1 Applies IEC 60601–1 to the non-implantable parts of the ACTIVE IMPLANTABLE MEDICAL DEVICE that are connected to or equipped with an electrical power source.	* retained additional requirements

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
15.12 Protection against the risks posed to the patient by energy supplies or substances		
5.12.1 Implants for supplying the patient with energy or substances must be designed and constructed in such a way that the delivered amount can be set and maintained accurately enough to guarantee the safety of the patient and of the user.	19.3 Requires a design analysis and defines the methodology for the analysis.	* retained 6.3 additional requirements
	5.1 Applies IEC 60601–1 to the non-implantable parts of the active implantable medical device that are connected to or equipped with an electrical power source.	* retained
5.12.2 Implants must be fitted with the means of preventing and/or indicating any inadequacies in the delivered amount which could pose a danger. Implants must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy or substances from an energy and/or substance source.	5.1 Applies IEC 60601–1 to the non-implantable parts of the active implantable medical device that are connected to or equipped with an electrical power source.	* retained
5.12.3 The function of the controls and indicators must be clearly specified on the implants or associated devices. Where an implant or associated device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user.	13.4 Specifies on-device markings.	* retained 13.5 additional requirements
5.13 Label and instruction for use		
5.13.1 General principles		
This subclause describes the general principles that apply equally to all implants. The primary purpose of labelling is to identify the implant and its manufacturer and communicate safety and performance related information to the user, professional or other person, as appropriate. Such information can appear on the implant itself, on packaging or as instructions for use. The following principles are recommended.		
The medium, format, content, legibility, and location of the label and instructions for use must be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use must be written in terms readily understood by the intended user and, where appropriate, supplemented with drawings and diagrams.	4 Allows use of symbols, abbreviations, and identification colours	* retained
The information required on the label, might be provided on the implant itself. If this is not practicable or appropriate, some or all of the information can appear on the packaging for each unit, and/or on the packaging of multiple implants.	12.3 Requirement that any markings shall be indelible.	* retained
	13.2 Requires implantable parts to be marked with sufficient information to allow for positive identification at the time of implantation.	* retained
Where the manufacturer supplies multiple implants to a single user and/or location, it might be sufficient to provide only a single copy of the instructions for use. In these circumstances, the manufacturer must provide further copies upon request.	—	—
Instructions for use might not be needed or might be abbreviated for implants if they can be used safely and as intended by the manufacturer without any such instructions for use.	—	—

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
b) The details strictly necessary for a user to identify the implant and its use.	9.3 Requires description of device and model designation on the sales pack.	* retained
	9.4 Requires marking with characteristics sufficient to identify device.	* retained
	9.8 Requires sales pack to bear information about accessories provided.	* retained
	9.10 Requires supplementary description, if 9.3 and 9.4 are inadequate to declare purpose.	* retained
	11.6 Requires description of device and mode designation on the sterile pack.	* retained
	11.7 Requires identification of contents of sterile pack.	* retained
c) The name and address of the manufacturer in a format that is recognizable and allows the location of the manufacturer to be established.	9.2 Requires name and address of manufacturer on the sales pack.	* retained Clause 28 additional requirements
d) For imported implants, the name and postal address of the authorized representative, or importer or distributor established within the importing country/jurisdiction might be required. This information can be added by the authorized representative, importer, or distributor within the country of import, rather than be provided by the manufacturer, in which case, the additional label must not obscure any of the manufacturer's labels.	9.2 Requires name and address of manufacturer on the sales pack.	* retained Clause 28 additional requirements
e) Where appropriate, an indication that the implant contains or incorporates a medicinal or biological substance, e.g. bone cement containing an antibiotic for use in orthopaedics.	28.7 Requires information about medicinal products which the device is designed to administer	* retained
	28.28 Requires an indication that the device contains medicinal substance derived from human blood or human plasma	* retained
f) The batch code/lot number or the serial number of the implant preceded by the word LOT or SERIAL NUMBER or an equivalent symbol, as appropriate, to allow post-market action to be taken if there is a need to trace or recall the implant.	9.3 Requires batch code or serial number on the sales pack.	* retained
	11.6 Requires batch code or serial number on the sterile pack.	* retained
g) An unambiguous indication of the date until when the implant can be used safely, expressed at least as the year and month (e.g. on implants supplied sterile), where this is relevant.	9.7 Requires marking of a "use-before" date.	* retained
	11.5 Requires marking of a "use-by" date.	* retained
h) Where there is no indication of the date until when it can be used safely, the year of manufacture. This year of manufacture can be included as part of the batch or serial number, provided the date is clearly identifiable.	9.7 Requires marking and defines format.	* retained
	11.4 Requires marking and defines format.	* retained
i) An indication of any special storage and/or handling condition that applies.	9.11 Requires marking and defines format.	* retained

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
j) If the implant is supplied sterile, an indication of its sterile state and, where appropriate, the sterilization method.	11.2 Requires method of sterilization to be marked.	* retained
k) Warnings or precautions to be taken that need to be brought to the immediate attention of the user of the implant as relevant, and to any other person where appropriate (e.g. "THIS IMPLANT CONTAINS LATEX"). This information can be kept to a minimum in which case more detailed information must appear in the instructions for use.	8.1 Requires warnings to be prominent.	* retained
	28.12 Requirement for warning notices.	* retained
l) If the implant is intended for single use, an indication of that fact.	28.18 Requires and defines warning notice about reuse of the device.	* retained Clause 28 additional requirements
m) If the implant is for use by a single individual and has been manufactured according to a written prescription or pattern (i.e. it is custom made), an indication of that fact.	9.13 Requires marking of special purpose.	* retained
	11.3 Requires marking of special purpose.	* retained
n) If the implant is intended for premarket clinical investigation only, an indication of that fact.	9.13 Requires marking of special purpose.	* retained
	11.3 Requires marking of special purpose.	* retained
o) If the implant is intended for non-clinical research, teaching or testing purposes only, an indication of that fact.	9.13 Requires marking of special purpose.	* retained
	11.3 Requires marking of special purpose.	* retained
p) If the implant is intended for presentation or demonstration purposes only, an indication of that fact.	9.13 Requires marking of special purpose.	* retained
	11.3 Requires marking of special purpose.	* retained
5.13.3 Content of the instructions for use		
The instructions for use must contain the following particulars: a) The name or trade name of the implant.	28.1 Requires name and address of manufacturer.	*retained Clause 28 additional requirements
b) The name and address of the manufacturer in a format that is recognizable and allows the location of the manufacturer to be established, together with a telephone number and/or fax number and/or website address to obtain technical assistance.	28.1 Requires name and address of manufacturer.	* replacement
c) The implant's intended use/purpose including the intended user (e.g. professional), as appropriate.	28.8 Requires information describing the intended use.	* replacement
d) The performance of the implant intended by the manufacturer.	28.8 Requires information describing the intended use.	* replacement
e) Where the manufacturer has included clinical investigations as part of premarket conformity assessment to demonstrate conformity to the essential principles, a summary of the investigation, outcome data and clinical safety information, or a reference as to where such information can be accessed.	19.4 Requires investigation of unintended effects caused by the device.	* retained

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
f) Any residual risks, contraindications and any expected and foreseeable side effects, including information to be conveyed to the patient in this regard.	28.12 Requires warning notices on hazards arising from interaction.	* replacement
g) Specifications the user requires to use the implant appropriately, for example, if the implant has a measuring function, the degree of accuracy claimed for it.	5.1 Applies IEC 60601–1 to the non-implantable parts of the active implantable medical device.	* retained
h) If the implant contains, or incorporates, a medicinal substance and/or material of biological origin, identification of that substance or material, as appropriate.	28.7 Requires information about medicinal products which the device is designed to administer.	* retained
	28.28 Requires an indication that the device contains medicinal substance derived from human blood or human plasma.	* retained
i) Details of any required preparatory treatment or handling of the implant before it is ready for use (e.g. checking, cleaning, disinfection, drying, packaging, sterilization, final assembly, calibration). NOTE 1 The principle in i) is in addition to information given in the previous edition of this document, and in addition to information given in Global Harmonization Task Force guidance documents.	(Not applicable to active implantable medical devices.)	
j) Any requirements for special facilities, or special training, or particular qualifications of the implant user and/or third parties.	(Not applicable to active implantable medical devices.)	
k) The information needed to verify whether the implant is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant:	(Not applicable to active implantable medical devices.)	
— details of the nature, and frequency, of preventative and regular maintenance, and of any preparatory cleaning or disinfection; — identification of any consumable components and how to replace them; — information on any necessary calibration to ensure that the implant operates properly and safely during its intended life span; — methods of eliminating the risks encountered by persons involved in installing, calibrating or servicing the implants.		

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
l) An indication of any special storage and/or handling condition that applies.	7.2 Requires sterile pack to be protected by sales packaging.	* retained
	10.1 Requires packaging to be durable.	* retained
	10.2 Requires packaging to be protected against the effects of humidity.	* retained
	10.3 Requires markings on sales packaging to be indelible.	* retained
	10.4 Requires accompanying documentation to be physically associated with the device.	* retained
	12.3 Requires markings on sales packaging to be indelible.	* retained
	26.2 Requires device to be protected against the effect of temperature changes.	* retained
m) If the implant is supplied sterile, instructions in the event of the sterile packaging being damaged before use.	28.17 Requires instructions on dealing with the contents if the sterile pack has been opened or damaged.	* retained
n) If the implant is supplied non-sterile, the appropriate instructions for sterilization. NOTE 2 Further information is provided in ISO 17664.	(Not applicable because 14.1 requires that active implantable medical device be provided sterile.)	
o) If the implant is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of re-sterilization. Information must be provided to identify when the implant must no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses.	(Not applicable to active implantable medical devices.)	
p) For implants intended for use together with other implants, medical devices and/or general-purpose equipment:	28.4 Requires information on connector specifications, assembly instructions, and connector performance.	* retained
— information to identify such implants, medical devices or equipment, in order to obtain a safe combination and/or; — information on any known restrictions to combinations of implants, medical devices and equipment.	28.5 Requires provision of information on accessories that might be required to facilitate the intended use of the device.	* retained
NOTE 3 Medical devices and equipment intended for use together with the implant include both those designed and manufactured by the implant manufacturer (e.g. associated instruments) and those designed and manufactured by others (e.g. general-purpose equipment).	28.9 Requires information to allow selection of device, accessories and related devices.	* retained
q) If the implant emits hazardous, or potentially hazardous levels of radiation for medical purposes:	9.1 Requires markings warning of any radioactive substances.	* retained

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
— detailed information as to the nature, type and where appropriate, the intensity and distribution of the emitted radiation; — the means of protecting the patient, user, or third party from unintended radiation during use of the implant;	28.2 Requires information to be provided about radioactive substances.	* retained
r) Information that allows the user and/or patient to be informed of any warnings, precautions, measures to be taken and limitations of use regarding the implant. This information must cover, where appropriate:	28.22 Requires warnings on precautions to avoid adverse environments.	* retained
	28.12 Requires warning regarding known hazards by reciprocal interference.	* replacement
— warnings, precautions and/or measures to be taken in the event of malfunction of the implant, or malfunction of devices used in association with the implant, or changes in implant performance that can affect safety; — warnings, precautions and/or measures to be taken with regards to the exposure to reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, or temperature; — warnings, precautions and/or measures to be taken with regards to the risks of interference posed by the reasonably foreseeable presence of the implant during specific diagnostic investigations, evaluations, therapeutic treatment or use (e.g. electromagnetic interference emitted by the implant affecting other equipment); — if the implant administers medicinal or biological products, any limitations or incompatibility in the choice of substances to be delivered; — warnings, precautions and/or limitations related to the medicinal substance or biological material that is incorporated into the implant as an integral part of the implant; — precautions related to materials incorporated into the implant that are carcinogenic, mutagenic or toxic, or could result in sensitization or allergic reaction of the patient or user.	14.3 Requires investigation of biocompatibility.	* retained

Table A.1 *(continued)*

Essential principles from ISO/TR 14283	Clauses of ISO 14708-1:2014	Clauses of ISO 14708-5 and aspects covered
s) Warnings or precautions to be taken related to the disposal of the implant, its accessories and the consumables used with it, if any. This information must cover, where appropriate:	28.29 Requires instructions for proper removal and disposal.	* retained
— infection or microbial hazards (e.g. explants, needles or surgical equipment contaminated with potentially infectious substances of human origin); — environmental hazards (e.g. batteries or materials that emit potentially hazardous levels of radiation); — physical hazards (e.g. from sharps).		
t) Date of issue or latest revision of the instructions for use and, where appropriate, an identification number.	28.25 Requires the date of issue or an indication of last revision.	* retained
5.14 Clinical evaluation		
5.14.1 For all implants, the demonstration of conformity with essential principles must include a clinical evaluation. The clinical evaluation must review clinical data in the form of any — clinical investigation reports, — literature reports/reviews, and — clinical experience, to establish that a favourable benefit-risk ratio exists for the implant.	19.4 Requires investigation of unintended effects caused by the device.	* retained
5.14.2 Clinical investigations on human subjects must be carried out in accordance with the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results. In addition, some countries might have specific regulatory requirements for pre-study protocol review or informed consent.	19.4 Requires that any clinical investigations are conducted according to ISO 14155.	* retained

Annex B
(informative)

Rationale

B.1 General

The following notes on some of the provisions of document are provided as an aid to understanding. The notes in this annex carry the numbers of the relevant clauses of this document, therefore, paragraph numbering in this annex is not consecutive.

B.2 Notes on specific clauses and subclauses

Note on 6.6.2.4.2

Mock circulatory loops shall be able to simulate the intended diseased patient population or specific adverse events, and not be 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.

Table B.1 below shows the expected pulsatile physiological conditions that a circulatory device would experience during left ventricle usage in adult patients. Table B.1 is intended to provide reference for the operating ranges of the mock loop.

Table B.1 — Physiological conditions

Parameter	Range
Systolic to diastolic ratio, at 72 BPM:	2:3
Body temperature, °C:	35 to 40
Salt concentration, % NaCl:	0,9
Blood pH:	7,15 to 7,5
Haematocrit, %:	20 to 50
Blood fluid viscosity[a], mPa*s:	2,3 to 3,4
Flow-rate range, L/min:	2,5 to 8
Mean arterial pressure, mmHg:	55 to 110
Pulse Pressure, mmHg:	2,5 to 55
Heart rate, BPM:	55 to 125

[a] Blood fluid viscosity, not a routinely measured clinical variable, is strongly related to haematocrit. In a mock physiological loop, glycerol or ethylene glycol are commonly used in blood analogue solutions for which haematocrit is not germane, but viscosity is. A range of clinically possible haematocrit (e.g. 20 % to 50 %) can thus be simulated by a corresponding range of blood analogue viscosity (2,3 to 3,4 mPa*s per Reference [36]). Note that since viscosity is also a function of temperature, adjustments might be necessary if the blood analogue is not at body temperature. Justification for parameter selection should be documented.

Note on 6.6.3.5.5

Certain *circulatory support devices* incorporate valves to reduce backflow. In most cases, these are prosthetic heart valves that have already been approved for human implant. The issue is that valves in these support devices are exposed to peak loading and rates of loading greater than in the clinical environment. This non-clinical loading does cause wear not seen in the clinical environment. As a result, the ISO 5840 series on heart valves is specifically intended to exclude valves to be used in circulatory support.

However, one option available to investigators testing *circulatory support devices* is to evaluate the valves during the overall *durability* assessment of the whole device. When testing valves in the whole device, information relevant to testing can be used from the ISO 5840 family of heart valve documents.

As a general guideline there should be an assessment of tears, creep or wear on stents and occluders. Pre- and post-inspections, profilometry or hydrodynamic performance should be considered.

Note on 6.11

The random vibration spectrum specified in ISO 14708-1:2014 is excessively strict for devices implanted where viscoelastic damping is significant, such as in the abdomen or thoracic cavity. Dupuis et al.[47] have shown that even when undertaking extreme physical activities such as running, horse riding and athletic long jump, the peak accelerations experienced at the subject's head is never greater than 5,7 g (running 3,6 g, riding 3,6 g, long jump 5,7 g).

Note on 6.12.2

Success is defined as animal survival with:

a) No device *failures* of implanted components that cannot be resolved without surgical intervention, excluding repairs or component replacement that can be performed without serious surgical complications.

b) Maintenance of prespecified pump flow rates throughout the duration of the study, which are appropriate for the intended use of the device within the manufacturer's specified flow tolerance limit.

c) No clinically unacceptable levels of major organ dysfunction or haemolysis, such as:

   1) renal dysfunction, marked by creatinine three times the upper limit of normal individual animal baseline value;

   2) hepatic dysfunction, marked by any two of the hepatic laboratory values (AST, ALT, total bilirubin) >3 times higher than normal individual animal baseline values beyond 14 days post-implant;

   3) haemolysis, marked by plasma free haemoglobin >20 mg/dl occurring after the first 72 h post-implant (see References [36] and [45]). Haemolysis is excluded from this definition when defined as non-device related (e.g. transfusion or drug).

d) No clinical manifestations of thromboembolism that are considered to arise from the device during *in vivo* observations. Clinical signs that are related to thromboembolism can be diagnosed by a combination of a thorough physical examination that includes neurological evaluation, radiography, ECG and clinical pathology analysis; pain that cannot be controlled by analgesics or other pain interventions; or immobility that causes animal suffering and requires intervention. *In vivo* and post-mortem (macroscopic/gross and microscopic/histopathological) diagnosis of thromboembolism will not be deemed a *failure* if it is of an etiology that is determined to be non-device related. For example, if it is due to accidental injury of the vasculature or caused by accidental device function stoppage beyond the reasonable controls of the sponsor or study site (e.g. chewing of percutaneous cable by the animal; facility power supply *failure*).

   Should the pump stop, the sponsor should define the duration of stoppage to safely restart the pump without thromboembolic and/ or other animal *safety* consequences based on the approved animal study protocol.

e) No severe infection that is considered to arise from the device. With respect to infection, both systemic and local infections can be deemed "severe" under the following conditions: for systemic infections, a severe infection is one in which anti-microbial treatment is instituted due to a positive blood culture (excluding routine prophylactic antimicrobial treatment) and cannot be corrected in spite of appropriate antibiotic use resulting from antibiotic sensitivity tests. A local infection at the exit site of the percutaneous cable is not considered "severe" unless there is evidence of a resultant

systemic infection. Infections that are determined by both clinical signs and necropsy to be of an etiology unrelated to the device (e.g. environmental causes such as water pollution) should not be deemed device *failures*. All infections regardless of etiology should be recorded.

f) Animals that fail to thrive due to conditions unrelated to device function or any circumstance beyond the reasonable controls of the sponsor or study site should not be deemed *failures*. Additionally, humane endpoints, such as failure to thrive, shall be clearly defined and justified in the animal study protocol.

g) No significant bleeding (defined in terms of volume per time in the *in vivo* protocol of the manufacturer) due to either the implant surgery or, subsequently, to the device remaining implanted.

Note on 6.12.6

The following items may be included in preoperative animal care:

a) primary procedure and activities of receiving animals: record of animal species, strain, age, gender, vendor, and quantity should be confirmed, and an identification number assigned;

b) thorough physical examination by the clinical veterinarian;

c) quarantine/acclimation period, according to each institution's procedure;

d) record keeping of medicine administration;

e) blood sampling used for control information;

f) test subject selection criteria;

g) room conditions;

h) description of animal identification method;

i) record keeping of feeding description, frequency;

j) monitoring of fluid intake;

k) animal fasting prior to the operation, according to each institution's procedure.

Note on 6.12.10

The following items may be included in postoperative animal care.

a) Postoperatively, the animal is closely monitored for the duration of the study.

b) The chest drainage tube is removed when fluid loss is diminished.

c) An antibiotic is administered postoperatively according to the institution's procedure.

d) If an injury and/or abnormal finding is observed upon physical examination or routine daily observation, it shall be documented and immediately reported to the clinical veterinarian.

e) All cares and administrations should be recorded on the forms.

f) Exercise protocol should be provided and exercise routines for the animals will be recorded.

Note on 6.12.12

Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS), see Reference [45].

Note on 6.12.14

The following physiological parameters may be included for measurements, but are not limited to:

a) respiratory rate;

b) heart rate;

c) temperature (routinely recorded for the duration of the study);

d) the animal's general condition and observations, recorded daily;

e) food and water intake; defecation and urination.

Note on 6.12.15.2

Blood parameters may include the following, but are not limited to:

a) haematology:

   1) white blood cell (WBC),

   2) percentage of leukocyte fraction (or WBC Differential),

   3) red blood cell (RBC),

   4) haemoglobin (Hb),

   5) haematocrit (Hct),

   6) platelet (PLT),

   7) blood gas (pO_2, pCO_2, pH);

b) blood chemistry:

   1) serum glutamic oxaloacetic transaminase (SGOT) or aspartate transaminase (AST),

   2) serum glutamic pyruvic transaminase (SGPT) or alanine transaminase (ALT),

   3) gamma-glutamyl transpeptidase (γ-GTP) GGT,

   4) lactate dehydrogenase (LDH) and its fraction,

   5) blood urea nitrogen (BUN),

   6) creatinine,

   7) creatinine phosphokinase (CK),

   8) glucose (GLC),

   9) calcium (Ca),

   10) sodium (Na),

   11) chloride (Cl),

   12) potassium (K),

   13) total bilirubin (TB),

   14) total protein (TP),

   15) albumin (ALB),

16) albumin/globulin (A/G) ratio;

c) plasma free haemoglobin;

d) blood coagulation:

1) prothrombin time (PT),

2) activated partial thromboplastin time (aPTT),

3) fibrinogen,

4) International normalized ratio (INR),

5) Activated clotting time (ACT).

Additional blood tests may be requested for diagnostic or other research purposes.

Note on 6.13

Since *circulatory support devices* provide an ongoing life support function in patients with end stage heart *failure*, *circulatory support devices* should be designed to be highly reliable without introduction of risk from poor design and manufacturing, or inappropriately specified parts and components. Systems should therefore be comprised of components of quality and *reliability* that are appropriate for their application. Some components should require separate testing and/or analysis to demonstrate appropriate *reliability* for use in the total system. This would include the *failure* analysis of prototype laboratory devices and those which malfunction in part or in whole during the animal testing phase of design qualification and proving.

It is important that the statistical methods employed in the analysis of the *reliability* test results be adequately described within design documentation.

The definition of *failure* of the system under test should be clinically relevant.

EXAMPLE Flow rate for a specified duration that results in irreversible organ damage.

Note on 27.2.1

An active implantable medical device is expected to maintain its intended use during routine daily living and not present an unacceptable risk when exposed to the everyday EM environment. The tests and test levels used within this clause are intended to simulate routine, everyday, general public EM exposure conditions. These are levels typical of a home environment, power mains, transportation, common areas (school, retail, office, and hospital), and modern communication systems, including mobile phones, Wi-Fi, and Bluetooth.

The risk assessment process, performed in accordance with ISO 14971:2019, will result in hazardous situations being identified (see ISO 14971:2019, Figure C.1). Since actual risk cannot be observed during testing, it will be necessary to observe the performance of the device to see if any hazardous situations occur.

Note on 27.4

The level of 50 mT (500 Gauss), although seldom encountered, is a possibility for the general public. Static magnetic field strengths, right on the surface of common household magnets (e.g. refrigerator magnets, loud speakers) and from magnets supplied from medical device manufacturers, are typically on the order of 50 mT (magnetic fields fall off rapidly, so field strengths just a few centimetres away are usually insignificant). Therefore, devices are expected to not suffer any permanent damage or change of state after exposure to these field levels.

Note on 27.5

The radiated magnetic field test from 1 kHz to 140 kHz is intended to assure that no damage will occur from high field levels that could be present in the patient environment.

Note on 28.31

This requirement relates only to devices intended by the manufacturer to be reusable. It does not relate to devices which a user might decide to reuse outside the manufacturer's recommendations, for example. those devices marked as 'single use'.

Annex C
(informative)

Pre-clinical *in vitro*/*in silico* evaluation

C.1 Experimental flow characterization

C.1.1 General

The purpose of an experimental flow characterization is to determine stagnation, high shear, flow separation, and turbulent flow regions in the blood pump. It can also be used to validate the CFD models.

C.1.2 Test methods

a) Methodology: The experimental flow characterization method may be selected depending on the purpose. These may include, but are not limited to, qualitative flow visualization, quantitative particle image velocimetry, and quantitative laser Doppler velocimetry.

b) Particle, for example, micro resin powder, metallic flakes, and dyes. Neutrally buoyant particles are necessary. Particle size and specific gravity should be provided.

c) Lighting, for example, slitted Xenon lamp, and laser beam. Imaging planes and imaging volumes should be defined.

d) Recording apparatus, for example, film camera, video camera, and charged coupled device.

C.1.3 Examples of test variables

a) Pump output, inlet and outlet pressures;

b) Specific parameters:

   1) continuous flow pump: motor rotational speed,

   2) pulsatile pump: pulse rate, E/F ratio (see 3.15 *ejection/fill*) and waveform,

   3) pneumatic driven pump: driving air pressure, pulse rate, E/F ratio (see 3.15 *ejection/fill*);

c) Rise time and peak value of pressure and flow waveform in the case of *pulsatile flow*.

C.2 Examples of the test conditions used to characterize the system

Examples include:

a) inlet pressure to the blood pump;

b) outlet pressure from the blood pump;

c) internal blood pump chamber pressure;

d) inflow to the pump;

e) outflow from the blood pump;

f) retrograde pump flow;

g) blood pump cycle time;

h) blood pump systolic duration;

i) blood pump drive pressure;

j) blood pump motor current;

k) blood pump voltage;

l) blood pump rotational speed/pulse rate;

m) blood pump input power;

n) mock heart left and/or right ventricular pressures;

o) mock heart left and/or right cardiac output;

p) mock heart cycle time;

q) mock heart systolic duration;

r) mock circulatory loop temperature;

s) mock circulatory loop fluid description including chemical composition, density, and viscosity;

t) mock circulatory loop flow;

u) system alarm behaviour.

C.3 Examples of measurement for *volume displacement* and rotary devices

C.3.1 Volume displacement devices

Volume displacement devices have pump performance validated in terms of physiologically relevant parameters to include: flow rate as a function of preload and afterload, power, and efficiency. Test conditions and data collection are carried out with pulsatile physiological pressure preload and simulated arterial compliance and resistance that produces physiological mean and *pulse pressures* under each flow condition.

Output from these tests include:

a) mean flow vs. preload and afterload;

b) drive pressures (for pneumatic devices);

c) power curves against flow rates and afterloads;

d) output flow and pressure waveforms;

e) current draw (for electrical devices).

C.3.2 Rotary devices

Rotary technology has pump performance validated in terms of physiologically relevant parameters to include: flow rate, pump pressure, input and output power, and efficiency. ISO 5198 provides the basis for such tests. Flow characteristics are determined over the full operating range and also include negative flow data that result from pump shutoff pressures (at given speeds) being lower than envisaged physiological pressure gradients across the device. Retrograde flow data at representative physiological pressures are also presented in the event of pump stoppage.

Test conditions and data collection are carried out during *pulsatile flow*.

Output from these tests include:

a) pressure vs. flow curves that extend into negative flow quadrants;

b) power vs. flow curves;

c) flow and pressure waveforms.

C.4 Application of computational fluid dynamic analysis

C.4.1 General

CFD can be used to assess hydraulic performance, flow patterns, shear stress distributions, risk of *cavitation*, or risk of haemolysis/thrombus formation. However, the use of CFD should be limited to the design stage and to assessing relative performance metrics, unless CFD predictions of absolute performance metrics are justified and rigorously validated (see Reference [33]).

C.4.2 Design and performance metrics to be evaluated with computational fluid dynamic analysis

The CFD analysis can be applied to any section of the device to evaluate the following items.

a) Device hydraulic performance: this analysis evaluates if a device design is adequate for producing specified hydraulic output with acceptable efficiency.

b) Risk of haemolysis or thrombus formation:

   — this analysis evaluates shear stress, exposure time, and their history for blood cells inside the device that could cause blood trauma;

   — this analysis provides information of velocity, pressure, or stress distributions; separation and stagnation zones are to be analysed when associated with an elevated risk of thrombus formation.

c) Risk of *cavitation*: the risk of air emboli, blood cell damage, and blood-contacting surface damage associated with possible low-pressure zones inside the device can be evaluated. Because *cavitation* can have highly damaging effects on both the device material surfaces and on the formed elements of the blood, potential *cavitation* phenomena should be investigated in the laboratory and/or via CFD simulation. Dynamic *cavitation* potential in pulsatile devices (particularly in mechanical *artificial valves*) should be investigated. 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.

C.4.3 Computational fluid dynamics procedural considerations

The use of a CFD analysis requires validation[33]. The results of a CFD analysis should be accompanied by the following information:

a) Pre-processing:

   1) Geometry and material inputs;

   2) physiological inputs;

   3) fluid-solid interactions;

   4) mesh/grid generation;

5) mathematical model assumptions.

b) Analysis:

1) boundary and initial conditions;

2) flow solution (e.g. velocity, pressure and shear stress, and turbulence intensity);

3) numerical methods;

4) simulation parameters, including type of numerical method used, solver settings, and convergence criteria.

c) Verification, validation, and uncertainty quantification:

1) validation (code verification and solution verification);

2) error analysis (uncertainty quantification);

3) sensitivity analysis: demonstrate sensitivity of CFD outputs to changes in the values of significant input parameters (e.g. fluid density and viscosity, initial conditions like velocities and pressures).

Annex D
(informative)

Active implantable medical device hazards, associated failure modes, and evaluation methods

Typical hazards, examples of their associated *failure* modes, and possible evaluation methods are given in Table D.1. This list is not intended to be all-inclusive but representative of hazards and *failure* modes that are applicable to active implantable medical devices.

For guidance on how to identify and assess potential device-related use errors, and extensive information about use-related hazards, *failure* modes, and evaluation methods, see IEC 62366-1:2015, which includes a figure of a comparison of the risk management process (ISO 14971:2019) and the usability engineering process (IEC 62366-1:2015). IEC/TR 62366-2 contains an informative annex on categories of user action and an informative annex on examples of use errors, abnormal use and possible causes.

Table D.1 — Active implantable medical device hazards, associated *failure* modes, and evaluation methods

Potential harm	Possible hazard(s)	Possible evaluation method(s)
Thrombosis	Material or mechanical factors that cause flow stasis or adverse blood-material interaction.	Material characterization, fluid dynamic analysis, in vitro system performance testing, blood-material interaction characterization, pre-clinical *in vivo* evaluation, clinical evaluation.
Haemolysis	Material or mechanical factors that cause elevated shear stresses and turbulence	Fluid dynamic analysis, in vitro whole blood studies in bench models, pre-clinical *in vivo* evaluation, clinical evaluation, Biocompatibility testing per ISO 10993-1:2018, dynamic haemolysis testing (see 6.10) over the operating range.
Bleeding	Device housing seams and/or interface between graft and device blood flow port(s) improperly sealed	Leak testing with device and delivery system, pressure pulsatility, pre-clinical *in vivo* evaluation, clinical evaluation.
Infection	Device sterility compromised, excessive contamination of *driveline* exit site	Sterilization/packaging studies, pre-clinical *in vivo* evaluation, clinical evaluation.
Systemic toxicity	Local or systemic toxicity, inappropriate tissue response or effect on coagulation, material degradation, leaching of toxic compounds	Biocompatibility testing per ISO 10993-1:2018. Animal studies.
Compromised intended hemodynamic support	Use error in mating connectors, connector/receptacle interface wear or corrosion, suction, loss of *driveline* integrity, power supply *failure*, *controller* malfunction, device repositioning, outflow graft disconnection, anatomic malposition.	Usability assessment of representative intended users, wear/*durability* testing, corrosion testing, *driveline durability* and integrity testing, environmental conditioning, usability assessment of representative intended users conducting the implant procedure, *controller* power management testing (e.g. battery charge/ discharge testing, runtime testing, and battery software validation).
Additional generic *failure* modes:		
Controller misreporting information	Sensor malfunction, inappropriate memory allocation, incorrect software behaviour	Compliance testing to IEC 62304:2006.

Table D.1 *(continued)*

Potential harm	Possible hazard(s)	Possible evaluation method(s)
Alarm misinterpretation	Alarm/information system complexity, excessive number of alarms	Usability assessment of representative intended users in emergency situations reacting to alarms.

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