5 General requirements for non-implantable parts

This clause of ISO 14708-1 applies.

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., provide 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.

6.2 System description

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

6.2.1 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.

6.2.2 Design consideration

The rationale for key design choices should be given. This should include approaches taken to minimize blood component damage, methods for thermal management, choice of drive mechanisms, power management scheme, reliability considerations, adequacy of anatomic fit, and patient interaction.

6.2.3 System configuration

A detailed physical description of the system should 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.

6.2.4 System performance and operating limits

The performance range of the system should be given, especially all operating limits which may restrict the physiologic capabilities of a patient, or which may result in system malfunction.

6.3 Design analysis

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

6.4 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 as well as the probability of occurrence. The analysis should include discussion of methods used to mitigate the criticality of the failure modes.

6.5 Human factors

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 should be designed to warn users of system or subsystem failures. Guidance for human factors can be found in IEC 60601-1-6.

6.6 In Vitro design evaluation and system performance testing

6.6.1 Objective
In vitro system performance testing is a complete evaluation of the final system design against all of its system design specifications. Test set-ups should be reasonably representative of the intended patient population in which pressures, compliances and flows should be at values appropriate for the disease condition of the patients. 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.

This testing includes the characterization of all time dependent parameters in either pulsatile or continuous flow systems as both types of circulatory assist devices can operate with the natural 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.

6.6.2 System design specifications
Design specifications for the complete system include the full range of system operating limits (e.g. beat rates, S/D 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 these specifications. All applicable parameters should be measured 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) system performance (e.g., alarms, back-up systems, information displayed, measurement accuracy and precision, and failures) should be monitored and reported as per ISO 14708-1 and with alarms conforming to IEC 60601-1-8.

6.6.3 Test articles
One complete device system is to be characterized. A complete system consists of all system components to be used. These should include such articles as: cannulae, blood pump, valves, percutaneous leads, transcutaneous energy transmission devices, drivers, controllers, power sources including the batteries, monitoring devices, programming devices, telemetry devices, backup driving devices, and accessories. Test various system configurations of the above listed components.

6.6.4 Test equipment
Test equipment required for in vitro system performance testing of the complete device system will include all test measurement equipment and circulatory simulation models.

6.6.4.1 Test measurement equipment

6.6.4.1.1 Transducers
All transducers used for the measurement of system parameters will be specified. Transducers will be appropriate for measuring time dependent waveforms so that any subsequent ensemble averaging to produce representative waveforms can be achieved and any cycle to cycle variation can be measured. All transducer characteristics, including amplifier devices (e.g., range, resolution, error, frequency response), must be given. Calibration schedules and calibration methods used for all transducers are required as well.

6.6.4.1.2 Data handling
Systems used for data acquisition, manipulation, display, and storage need to be described in detail. Data acquisition methods and equipment used must 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. Characteristics for the display will be provided (e.g. accuracy, precision, error). Storage information regarding data handling becomes important with respect to trade-offs required and justifications to be made for the overall experimental system.

6.6.4.1.3 Use of the device system itself

Many device systems are capable of measuring, acquiring, manipulating, displaying, and storing desired parameters to be measured. The device system transducers and data handling systems must be fully described as given in sections 3.1.1 and 3.1.2 and must be independently characterized using external measurement verification techniques.

6.6.4.1.4 Substitution of device components

There are times when it is impossible to use the actual device components in an in vitro test due to the inherent nature of their design. This often happens with implantable elements such as bioprosthetic valves, cannulae (vascular grafts), or cuffs. Explanations are necessary to allow for substitution of the unsuitable components and justifications must be provided for alternate components used.

6.6.4.2 Circulatory simulation models

In vitro models used to appropriately simulate the natural heart and its associated vasculature need to be fully described, simplified through testing, and justified as to the necessary physiologic limits proscribed. These in vitro circulatory simulation models are known generally as "mock circulatory loops."

6.6.4.2.1 Physiologic limits

Mock circulatory loop limits on systolic and diastolic pressures and flows, natural heart beat rates and S/D ratios, and vascular compliances and resistances must be appropriate to the intended diseased patient population and not limited to those ranges found within "normal" human patients.

6.6.4.2.2 Blood analog fluid

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

6.6.5 Data collection

A matrix of test conditions will be generated so that system performance over the full range of design operational limits using all possible component configurations can be compared to the design specifications for the product. This will result in the need to collect data on the mock circulatory loop, the blood pump, and the drive system. The relevant parameters used to define the performance of the system should be selected according to the type of system under test (e.g. pulsatile or continuous flow, total artificial heart or ventricular assist system). These parameters could include, but are not necessarily limited to the following:

(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 current use
(k) Blood pump voltage
(l) Blood pump speed
(m) Blood pump input power
(n) Mock natural heart left and/or right ventricular pressures
(o) Mock natural heart left and/or right cardiac output
(p) Mock natural heart cycle time
(q) Mock natural heart systolic duration
(r) Mock circulatory loop temperature
(s) Mock circulatory loop fluid viscosity
(t) Mock circulatory loop flow

(u)System alarm behavior

6.6.5.1 Determined aarameters
From the measured parameters obtained above under data collection, the following parameters need to be determined depending upon the nature of the blood pump design:

(a) Blood pump outlet pressure waveform
(b) Blood pump outlet flow waveform
(c) Average outflow pressure from the pump
(d) Average inflow pressure to the pump
(e) Average pump outflow
(f) Maximum achievable operating limits

6.6.6 Data analysis
Data analysis is necessary to graphically show the system performance with respect to the design specifications for the system. This can 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 needs to be provided.

6.7 "Worst case" operating conditions
System characterization data should be evaluated to determine the worst-case modes of operation *(battery life, power input, outflow, pressures)* within the design input specification. A discussion should provide the rationale for the selection of the conditions determined to be worst case, and used for reliability testing (See Reliability section) and what effect it might have on the device.

6.8 Pump hydraulic performance test
Tests shall be carried out in blood or a blood analogue solution that mimics critical characteristics of blood such as viscosity, temperature and density as they relate to the particular device. The pump will be deemed to have passed this test if pump performance meets the envelope of performance specified in system design specifications (6.6.2).

6.8.1 Pulsatile devices
Pulsatile devices should have pump performance validated in terms of physiologically relevant parameters to include: flow rate as a function preload and afterload, power, and efficiency. Test conditions and data collection will be carried out with steady physiologic pressure preload and simulated arterial compliance and resistance that produces physiologic mean and pulse pressures under each flow condition.

Output from these tests should 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)

6.8.2 Rotary devices

VADs based on rotary technology shall have pump performance validated in terms of physiologically relevant parameters to include: flow rate, head, power, and efficiency. ISO 5198 "Centrifugal, Mixed Flow and Axial Flow Pumps - Code for Hydraulic Performance Tests –Precision Class" provides the basis for such tests. Flow characteristics should be determined over the full operating range and shall also include negative flow data which results from pump shutoff pressures (at given speeds) being lower than envisaged physiological pressure gradients

across the device. Retrograde flow data at representative physiological pressures shall also be presented in the case of pump stoppage.

Test conditions and data collection should be carried out during steady flow.

Output from these tests should include:

a) Graphic H-Q curves which should extend into negative flow quadrants

b) Graphic power curves against flow rates

c) Graphic flow and pressure waveforms

6.8.2.1 Rotary devices - critical speed tests

Vibration measurements shall be made over the entire operating speed range to ensure that critical speed resonance (induced either mechanically or by magnetic bearing control systems) will not cause unacceptable mechanical instability. It may be necessary to positively restrict the operating speed range to avoid critical speeds.

6.8.3 Pulsatile and rotary devices - cavitation tests

Because cavitation can have highly damaging effects 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 via Computational Fluid Dynamics (CFD) simulation. The critical cavitation conditions, NPSHR (net positive suction head required) must be provided for rotary devices and dynamic cavitation potential in pulsatile devices (particularly in the prosthetic valves) should be investigated.

For rotary devices, ISO 5198 provides guidance for these tests.

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 provided.

6.9 Hemodynamic flow pattern testing

6.9.1 Test circuit

6.9.1.1 Requirements

a) Test circuit should simulate not only a normal case of human circulation but also failing heart conditions that cannot be tested in patients.

b) Three kinds of circuits, (i) for the right heart circulation, (ii) left heart circulation, and (iii) combined circulation of both sides of the heart, should be prepared according to the device objectives.

c) Test circuit should be at least composed of inlet reservoir and compliance, outlet compliance and resistance.

6.9.1.2 Parameters to be variable

a) Inlet pressure to the device should be governed by the simulated natural heart. The inlet pressure to the simulated natural heart should model as closely as possible the expected pulsatile waveform characteristics found in the intended patient population.

b) Outlet resistance should be based upon expected circulatory resistance values for both the right and left sides as found in the intended patient population.

6.9.1.3 Pump connections

Inlet and outlet tube diameter should be selected appropriately to match the resistance expected with the clinical use of the device, based upon expected values found in the intended patient population.

6.9.2 Test fluid

a) Test fluid should be a blood analog fluid. Matching the fluid properties of blood with respect to (viscosity)/(density) is generally adequate but other system parameters should be described.

b) The type and temperature of test fluid used for hemodynamic testing should be documented.

6.9.3 Measurement apparatus

a) Transducers selected for dynamic pressure and flow waveforms should have the appropriate frequency response characteristic for the waveforms expected.

b) Dynamic flow waveform: electro-magnetic flow meter, ultrasonic flow meter, etc

c) Dynamic pressure waveform: semiconductor pressure sensor, piezo-electric pressure sensor, etc.

6.9.3.1 Flow characterization of the blood flow path

a) Particle: micro resin powder, metallic flakes, dyes, etc. It should be noted that neutrally buoyant particles are necessary. Particle size and specific gravity should be described.

b) Lighting: slitted Xenon lamp, laser beam, etc. Imaging planes and imaging volumes should be specified as well.

c) Recording apparatus: high-speed camera, high-speed video camera, normal-speed video camera, etc.

6.9.4 Testing

a) Relationship between pump output, inlet and outlet pressure, and driving parameters

b) Driving parameters:
   (i) Continuous flow pump: motor revolution number
   (ii) Pulsatile pump: pulse rate, S/D ratio and wave form
   (iii) Pneumatic driven pump: driving air pressure, pulse rate, S/D ratio

c) Analysis of stagnation points and excessive turbulent flow regions in the blood pump through flow visualization study.

d) Analysis of rise time and peak value of pressure and flow waveform in the case of pulsatile flow.

6.10 Software verification and validation

Every software product should possess a basic level of reliability through analysis, design, implementation, system testing, quality assurance, and maintenance of the software product, all of which shall be documented and controlled. Guidance for software design and validation can be found in IEC 62304.

6.11 External applied forces

Bearing systems and other components of implanted systems must be able to withstand clinically expected external loads.

6.11.1 Vibration

Vibration testing should be conducted to a level that ensures that the test article will experience regular instantaneous accelerations. No failures or incipient failures should occur as a result of testing.

6.11.2 Angular acceleration

Whole-body rotations of 1 revolution per second (2π rad/s) are a likely maximum to be experienced during normal daily activities. This rotation is most likely experienced about the longitudinal (cephlo-caudal) axis of the body. The operating implanted device should withstand rotation at 2π rad/s in three mutually orthogonal directions for a period of 30 minutes each without failure or incipient failure (e.g. evidence of abnormal wear).

6.12 Electromagnetic compatibility

Electromagnetic compatibility (EMC) testing should be conducted for all devices containing electrical and/or electronic components to demonstrate that the system (1) will not adversely affect the operation/performance of other equipment used in the same environment (emissions), and (2) will perform per design specification in the presence of other equipment (immunity). Testing to IEC 60601-1-2 for Life Supporting equipment should be met.

6.12.1 Transcutaneous energy transmission systems

Transcutaneous energy transmission systems send power across the intact skin to an implanted system without use of wires or tubes that penetrate the skin. Qualification of the energy system should include a theoretical analysis as well as testing. Specifications for the system should be established and then verified by testing. Specifications should include parameters such as local temperature rise, efficiency, input power, output power, maximum power, voltage range, effect of primary/secondary coil alignment, power dissipation, effect of nearby large metal objects, etc.

6.12.2 Batteries

A circulatory support system should be battery powered. The implanted battery power should be a rechargeable primary battery or a rechargeable secondary battery. Batteries should be internal and/or external. The following should be considered in battery selection, specification, and qualification:

a) Battery voltage from full capacity to depleted

b) Effect of current (load) on battery performance (voltage and capacity)

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; charge current, end of charge determination, recharge time, etc.

g) Method to measure battery depletion

h) Method to control hazard from potential gasses 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) Audible warning alarms in the event of battery depletion

k) Appropriateness of parallel redundancy for battery sources

l) Method to measure/identify high discharge temperatures

6.13 Mechanical qualification

Mechanical qualification testing of individual components or subassemblies is necessary to ensure design specifications for those components or subassemblies are met. The testing examines the suitability of components, subassemblies, and materials in different environments. The environment may be more abusive than expected

clinically in order to characterize failure modes, or it may be representative of anticipated normal use (accelerated or real time) in order to show freedom from failure.

6.14 Connections and connectors

6.14.1 Electrical

Electrical connections to and from all power supplies, batteries, controllers, and blood pumps should be subjected to pull strength, torsion, flex, drop, permeation test and vibration tests. The connection should be tested for electrical/mechanical integrity, resistance to corrosion, proper connector mating, connector connect/disconnect cycling, and conductivity/resistance both before and after each of the appropriate tests to ensure design specifications are met. Conformance to ISO 14708 will be deemed sufficient.

6.14.2 Pneumatic/gas drivers

For systems with pneumatic drives, all drive lines to and from the pneumatic supply and the blood pump (the entire gas pathway) should be evaluated for pull strength, torsion, drop, vibration, kink (bend radius), and abrasion. Following this testing, the drive lines should be tested for damage, leakage, and any changes in pressure drop in accordance with design specifications.

6.14.3 Vascular grafts, cannulae, blood conduits and atrial cuff

All blood conduits should be evaluated for conformance with ISO 7198.

Inflow conduits and their connectors used with rotary and some pulsatile devices need to withstand significant negative pressures without collapse or entrainment of air. Tests to establish satisfactory performance should be conducted in excess of the maximum negative pressure capable of being generated by the device.

All connections to and from the blood pump and the blood pathway should be evaluated for conformance with specifications with tests such as pull strength, torsion, vibration, kink (bend radius), and seal integrity. Connection interfaces should avoid gaps and steps in the flow path that could generate unacceptable levels of microemboli, as assessed by design analysis and in animal trials.

6.14.4 Artificial/prosthetic valves

If possible, prosthetic valves within the device should be tested as part of the durability and reliability sections described in this document and assessed in the final device configuration in that manner. If the valve design cannot be evaluated in the final device configuration, the valve may be qualified independent of the system according to ISO 5840 and a justification shall be provided.

6.15 Materials qualification

The selection of materials for components and devices depends upon knowledge of material properties and behaviour in particular environmental states. Although a criterion for the choice of material in critically designed parts relates to the performance in a field test, it is usual in preliminary design to use appropriate data obtained from standardized tests. All testing should take into account all intended use environments of the system. The following considerations are important in material selection and qualification:

a) Elastic Properties: stiffness and rigidity.

b) Plastic Properties: yield conditions, stress-strain relations, and hysteresis.

c) Time-dependent Properties: elastic properties, creep, relaxation, and strain-rate effect.

d) Fracture Phenomena: crack propagation, fatigue, and ductile-to-brittle transition.

e) Thermal Properties: thermal expansion, thermal conductivity, and specific heat.

f) Chemical Interactions with the Environment: swelling due to hydration, oxidation, corrosion, diffusion, and leaching and exposure to pharmacologic agents.

g) Surface characteristics: all specialized blood-contacting surface characteristics, any particular surface treatments within the device used to improve material strength, hardness, fatigue life, lubrication, and/or heat dissipation should be described.

6.16 Biocompatibility

All blood contacting and tissue contacting surfaces should be biocompatible as defined in ISO 10993-1.

Detailed protocols, raw data, observations, and discussion and interpretation of the results with respect to the intended use of the system and patient safety should be documented.

For assessment of potential damage to blood cells, *in vitro* heamolysis testing of continuous flow devices according to ASTM F1841-97 is recommended if exposure to high shear and/or small gaps in the blood flow path occurs. Suitable control test pumps for this assessment could be devices with acceptable haemolysis (e.g., previous model).

6.17 Environmental testing

Environmental testing to ISO 14708 shall be conducted to demonstrate that the system will perform according to its design specification. If other environmental test standards are used for these evaluations, the test levels used should be justified as to their appropriateness to the intended use environment (e.g., hospital, home, aircraft and ambulance).

6.18 *In vivo* evaluation

6.18.1 Objective

The objective of an animal study is to perform a pre-clinical validation of the final device by obtaining safety and performance data in a living animal, supporting the suitability of the system prior to first human use. Suitability of the device will be corroborated by safety and performance data.

6.18.1.1 Safety

The purpose is to evaluate biocompatibility of the device in an appropriate animal model. Safety will be assessed based on thrombogenicity, hemolysis, calcification, end organ dysfunction, and other biocompatibility evaluations compared to clinically acceptable limits.

6.18.1.2 Performance

Performance will be assessed based on ability of the device to maintain hemodynamics such as blood pressures and blood flow at clinically acceptable flow rates.

6.18.2 Definition of success

Success is defined as animal survival with:

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

b) Maintenance of clinically acceptable flow rates throughout the duration of the study, which are appropriate for the intended use of the device.

c) No clinically unacceptable levels of major organ dysfunction or hemolysis, defined as:

i) renal dysfunction, marked by creatinine 3 times upper limit of normal individual animal baseline value.

ii) hepatic dysfunction, marked by liver enzymes (GOT, GPT, LDH) > 3 times higher than normal individual animal baseline values, 14 days postoperatively. During recovery, liver enzymes may be elevated due to the surgery.

iii) hemolysis, plasma free hemoglobin > 40 mg/dl. This 40 mg/dl value was published as the clinically relevant, upper limit for plasma free haemoglobin [**add citation**]. However, the target value of plasma free hemoglobin should be less than 10 mg/dl in the chronic animal model after the recovery phase.

d) No severe thromboembolism that is considered to arise from the device. "Severe" is defined generally to include events that are life threatening or causing animal suffering. A severe thromboembolism is one that is confirmed by standard clinical and laboratory testing to cause clinically unacceptable levels of renal or hepatic dysfunction, as defined above; pain that cannot be controlled by pain medication or other pain interventions; or immobility that causes animal suffering and requires intervention. Thromboembolism will not be deemed a failure if it is of an etiology that is determined to be non-device related by both clinical symptoms and autopsy. For example, if it is due to accidental injury of the vasculature or device thrombosis caused by accidental stoppage beyond the reasonable controls of the sponsor or study site (e.g., due to earthquake/fire, chewing of percutaneous cable by the animal, etc.).

Should the pump stop, the sponsor must define the duration of stoppage to safely restart the pump without thromboembolic consequences based upon well defined laboratory studies.

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 intravenous anti-microbial treatment is instituted with positive blood culture (excluding routine prophylactic treatment) and cannot be corrected. 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 symptoms and autopsy to be of an etiology unrelated to the device (e.g., environmental causes such as water pollution, accidental microbial contamination of intravenous solutions, etc.) will not be deemed device failures. All infections regardless of etiology shall 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 will not be deemed failures.

6.18.3 Test articles

The device shall be representative of the final clinical device. The test records will refer to information that describes the system details and processes used to assemble these devices. All items are identical to the clinical model except where described and justification provided i.e. external battery.

6.18.4 Test system

6.18.4.1 Test animals

Animal species, quantity, strain and gender, weight, animal supplier name and address shall be recorded. Animal identification, the individual number that corresponds to an ear tag, cage label or equivalent, shall be recorded so that the history of each individual animal is accurate.

6.18.4.1.1 Choice of animal model

Studies of ventricular assist systems require an intact animal with a functional circulatory system and active hematological, inflammatory, immunological and coagulation responses. Animal model selection shall include the following considerations:

a) Non-mammalian species are not appropriate for comparison with human implant conditions for these devices.

b) The size of the heart and the dimension of the major blood vessels of the selected species must be close and similar to those of a human.

c) The blood coagulation response of the chosen animal model must be reasonably comparable to that of humans. Anticoagulation used during the evaluation should be carefully documented and assessed for comparison to the patient population.

d) Calf, sheep, goat, dog and pig models have been widely used for cardiovascular device studies and current researchers have a significant knowledge concerning anatomy, physiology, coagulation, histology and animal management for these animals.

6.18.4.1.2 Sample size

Sample size shall be suitable for demonstrating the safety of the device within a biological system (chronic testing).

In addition to chronic tests, other studies (acute testing) must be performed to assess performance of the device under a full range of physiologic conditions. This should also be an animal study in order to best simulate hemodynamic conditions that may occur clinically.

6.18.4.1.3 Implantation period

The implantation period should be appropriate for the intended use of the device. For a device intended for chronic use(> 30 days), an implantation period at least three times longer than 30 days (at least 90 days) is appropriate. Even when the device is intended for longer than 90 days, the information that can be obtained from this animal model is complete within 90 days.

6.18.4.2 Control

Each animal's baseline vital signs and blood measurements will be used to assess the changes to the animal's condition. The animal's measured postoperative parameters are compared to preoperative values.

6.18.5 Test equipment

The test report shall provide detailed equipment information.

6.18.6 Preoperative animal care

The testing laboratory shall provide animal care protocols for approval that include at least the following topics:

a) Primary procedure and activities of receiving materials: Record of animal species, strain, gender, supply dealer, and quantity shall be confirmed, and an identification number assigned.

b) Examination procedure.

c) Quarantine/acclimation period, according to each institutions' procedure.

d) Record keeping of medicine administration.

e) Blood Sampling: Minimum of two blood measurement samples are obtained during quarantine/acclimation period. Samples are used for control information.

f) Test subject selection criteria: Only healthy animals, with blood parameters within normal range are to be selected for the study.

g) Room Conditions: Ambient temperature range, Humidity Range, Ventilation cycles, Lighting time per day, Luminous intensity

h) Description of animal identification method.

i) Record keeping of feeding description, frequency.

k) Monitoring of fluid intake.

l) Animal fasting prior to the operation, according to each test sites' procedure.

6.18.7 Surgical procedure for device implantation

a) Anesthesia and Surgical protocols shall be recorded.

b) Device specific implantation methods shall be described.

c) Monitoring and animal management shall be described.

6.18.8 Special instructions for early termination

When the following conditions occur, the surgical operation is considered a failure and another animal is added to the test.

a) Bleeding that cannot be controlled by transfusion or re-operation.

b) The animal does not recover from intra-operative cardiac arrest and cardiac defibrillator fails to resuscitate the animal.

c) The animal experiences a cardiac arrest within twenty-four (24) hours, when it is confirmed that the cause is unrelated to the device.

d) In the case that the animal cannot recuperate from the surgery, the animal will be euthanized. For example, if the animal doesn't stand on its own feet after 24 hours. Should any control measures fail to resolve the animal's health problem, device functional problem, or blood measurements exceed acceptable limits, the animal will be euthanized as soon as possible to minimize the animal suffering.

Animals that fail to thrive due to conditions unrelated to device function or circumstances beyond the reasonable controls will not be deemed failures and will be excluded from the total number of animals qualified for the study.

The animal is autopsied for histopathological examination of major organs. The device is explanted for gross assessment, histological examination and engineering analysis. All findings are recorded, including observations and conclusions regarding the early termination of the animal study.

6.18.9 Post operative care

The test laboratory shall provide standard protocols for approval that outline the following topics:

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 post operatively according to each institutions' procedure.

d) Anticoagulation management, if used, is monitored closely and fully documented. Use of anticoagulants must be justified with respect to the intended use of the device and the pharmacological effect of the anticoagulant on the animal.

e) If an injury is observed by examination of the physical condition of the animal, it will be recorded.

f) All cares and administrations must be recorded on the forms.

g) Exercise protocol shall be provided and exercise routines for the animals will be recorded.

6.18.10 Adverse events

Possible adverse events associated with the device include death, device/system failures, bleeding, infection, hemolysis, neurological dysfunction, thromboembolic events, pulmonary dysfunction, hepatic dysfunction, renal dysfunction, and cardiovascular dysfunction (arrhythmia, myocardial infarction, hypertension, hypotension).

a) All adverse events will be fully documented.

b) All low flow conditions will be documented for starting and stopping time of these events.

c) If the device stops performing as indicated and cannot be corrected without a serious impact on the animal's condition, the animal will be kept as comfortable as possible and euthanized at the earliest opportunity. An autopsy will be performed to greater identify the contributing factors of the event.

6.18.11 System performance

In order to characterize system performance in vivo, the system parameters shall be measured during the course of the experiment.

6.18.12 Measurement of physiologic parameters

The condition of the postoperative animal is recorded every day. In order to reduce the possibility of infection /complication associated with indwelling catheters and wiring for the measurements in the chronic animal study, no "invasive" monitoring of physiologic pressures (arterial pressure, central venous pressure, pulmonary artery pressure, left atrial pressure), or cardiac output is preferable. Physiologic parameters include:

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) Fluid intake and output is monitored.

6.18.13 Blood measurements

6.18.13.1 Timing

Timing of blood collection shall be provided during following periods:

a) Pre-operatively: minimum of 3 samples

(note: These samples are used to determine the animals baseline values)

b) Intra-operative/recovery blood chemistry analysis

At the discretion of the surgical staff, anticoagulation monitoring and blood gases during the surgery and recovery period for monitoring pulmonary health and anesthesia responses will be performed. All measurements shall be recorded in the surgical records.

c) Post-operative blood sampling: in accordance with the standard practices of each site.

Two samples during the first week, then at least once every two weeks.

d) When infection is suspected, blood culture samples (2 samples, drawn 6 hours apart) are analyzed for aerobic bacteria, anaerobic bacteria and fungi.

6.18.13.2 Analysis

For documentation at each time point, four (4) test samples will be drawn according to laboratory standard procedures for the following analyses:

1) Hematology:

i) White blood cell (WBC)

ii) percentage of leukocyte fraction (or WBC Differential)

iii) Red blood cell (RBC)

iv) Hemoglobin (Hb)

v) hematocrit (Hct)

vi) Platelet (PLT)

vii) Blood gas (pO_2, pCO_2, pH)

2) Serum biochemistry:

i) Glutamic oxaloacetic transaminase (GOT/ AST)

ii) glutamic pyruvic transaminase (GPT/ ALT)

iii) gamma-glutamyl transpeptidase (γ-GTP) GGT

iv) Lactate dehydrogenase (LDH) and its fraction,

v) Blood urea nitrogen (BUN),

vi) Creatinine

vii) Creatinine phosphokinase (CK),

viii) glucose (GLC)

ix) calcium(Ca)

x) sodium (Na)

xi) chloride (Cl)

xii) potassium (K)

xiii) Total bilirubin (TB),

xiv) Total protein (TP),

xv) Albumin (ALB),

xvi) Albumin/Globulin (A/G) ratio

3) Plasma free hemoglobin

4) Blood coagulation:

i) prothrombin time (PT)

ii) activated partial thromboplastin time (aPTT)

iii) Fibrinogen

iv) International Normalized Ratio (INR)

v) Activated Clotting Time (ACT)

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

6.18.14 Preparation for necropsy and device retrieval

a) Ensure that the animal is fasted prior to being sacrificed.

b) In case of premature animal death, perform the autopsy examination and retrieve device as soon as possible.

c) Prepare solution and equipment for device retrieval. Use 2.5-5% of phosphate buffered gluteraldehyde, or acceptable alternative, for a fixative of the device.

6.18.15 Euthanasia and device explantation procedure

a) In-situ photographs are taken during the device explantation procedure, according to the macroscopic examination section, at the discretion of the investigator, to monitor the general condition of the animal.

b) Heparin is intravenously administered in order to prevent secondary clot formation after animal's circulation is ceased.

c) The animal is euthanized (according to appropriate methods that regard the welfare of the animal).

d) Device retrieval protocol shall be described. The device is gently rinsed with heparinized saline to remove residual blood.

6.18.16 Macroscopic examination

The test animals will be subjected to full, detailed gross necropsy, which includes careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents.

a) The brain, lungs, heart, liver, diaphragm and kidneys, will be weighed and examined grossly.

b) The spleen, pancreas, adrenals, small and large bowel and bladder of the test animals will be examined grossly.

In situ photographic documentation will be made of the device and major organs. The device is scrutinized for obvious mechanical changes, infective vegetations; thrombus; and tissue reaction to the system. Further device analysis is described in later section of this protocol.

6.18.17 Histological examination

After fixation with a standard fixative 10% buffered formaldehyde, the following organs and all gross lesions will be analyzed: brain, heart (with implantation site), lungs, spleen, kidneys, liver, and implantation sites (aorta and tissues surrounding graft and pocket lining).

Each tissue sample will be embedded in paraffin, sectioned (3µm thickness), stained with hematoxylin-eosin, and analyzed for histological changes under light microscopy. If necessary, other stains may be used.

6.18.18 Explanted device analysis

a) An integrated program of disassembly of the device that facilitates electrical analysis, haemocompatibility analysis (including gross/microscopic inspection and photography and SEM assessment of blood-contacting surfaces) along with mechanical assessment of parts should be implemented.

b) During disassembly seals and connections should be assessed. Seals should be examined for integrity and connections in the blood path should be examined for presence of thrombus. Electrical connections should be tested, inspected for corrosion, and shielding should be assessed for integrity.

c) The cables, electrical and mechanical connections, device components and other devices of the system are also inspected for evidence of damage, wear, degradation, corrosion or other anomalies.

6.18.19 Study file report

The study file will contain the following information:

a) Signed protocol

b) Original completed data forms

i) Preoperative records (fluid/drug administration, vital sign measurements)

ii) Surgical and anesthesia records

iii) Post operation record (fluid/drug administration, other medical therapies, vital sign measurements general condition etc.)

c) Tabulated data

d) Test articles ID, with reference to the detailed design and manufacturing information.

e) Study animal ID and records (species/strain used, age and sex, body weight, etc.)

f) Blood measurement records

g) Device system data records

h) Major organ function analysis

i) Anomalous performance

j) Instrumentation ID and reference to calibration records and procedures.

k) Hemodynamic / physiologic evaluation

l) Pathology analysis

m) Device retrieval and Engineering analysis

n) Statistical analysis of results, where appropriate

o) Experimental summary

6.18.20 Preservation of materials

All materials obtained in this study are preserved after the examinations in accordance with GLP requirements.

6.19 Reliability

System reliability is defined as the probability of a system to perform its function for a specified period of time under stated conditions. (For example, the demonstrated reliability of the VAD system shall be X with at least Y confidence for a Z year mission life.)

6.19.1 It is desirable to test as much of the integrated system as possible in a test. However, not all system components may be suitable for long term life cycle testing (such as tissue valves) and these components must be independently life-cycle tested. In this respect, the study document must make clear what items of the system are being evaluated in a particular life cycle study.

6.19.2 Each system shall be comprised of components of quality and reliability that is appropriate for their application in the system.

6.19.3 VAD systems used for reliability testing shall be sterilized the maximum number of times permitted for normal use prior to in vitro reliability testing.

6.19.4 All implanted components shall be tested in a physiological environment (such as a pH buffered, temperature controlled, saline filled tank) and operated within a pulsatile mock circulatory loop. If a pulsatile mock loop is not to be used, a justification must be provided that lack of pulsatility will not invalidate the test.

6.19.5 Numeric reliability specifications (percent reliability) with confidence intervals (percent confidence) shall be defined for performance testing over the desired life of the system.

6.19.6 The number of systems to be tested under controlled *in vitro* conditions shall be statistically justified to demonstrate that the stated reliability specifications are met. Statistical methods to be employed in the analysis of the reliability test results shall be described. An example of such a statistical justification is a Weibull calculation (see Nelson 1985)[7].

6.19.7 Risk analyses based upon Failure Modes Effects and Criticality Analysis (FMECA) and Fault Tree Analysis (as per ISO 14971) will suggest some of the most important modes of failure associated with the implantation and use of the system. These identified failure modes shall be examined in the reliability test.

6.19.8 Definitions of failure events should be based on the termination of the ability of any implanted item to perform a required function (British Standard 4778) or the inability of the implanted components to meet minimum performance specifications (21CFR 820.162).

6.19.9 Failure definitions shall include cases of incipient failure such as breach of hermetic seals, production of significant particulate debris or ongoing corrosion which would ultimately lead to implanted component failure.

6.19.10 Important test parameters (such as flow rate) shall be continuously monitored to enable identification of failure incidents.

6.19.11 The results of all failure analyses (including component failures that do not result in system failures) shall be documented. All decisions and rationales regarding corrective actions shall be documented.

6.19.12 All failures shall be classified (as per Pantalos, 1998)[6]

6.19.13 Test documentation should describe the type and frequency of collection of test data necessary for assessing the reliability and maintainability. The rationale for the data to be collected shall be documented.

6.19.14 As part of the concept of Total Product Lifecycle, reliability data accumulated during clinical trials may require that a parallel life test be initiated should unexpected failure mode be discovered and/or redesign be performed. Such a parallel test may require different operating parameters and/or revised test articles

6.19.15 All design changes resulting from failure analyses should be justified and assessed as to their effect on system reliability.

6.19.16 The *in vitro* reliability study may identify wear-out failures and their precursors. The identified wear-out failures and predictive events should be included in a preventative maintenance or device replacement plan.

6.19.17 Tests on VAD systems designed to operate from a mains power supply or from batteries should include a schedule of battery/mains operation, based on expected usage.

6.19.18 The *in vitro* test conditions should be designed to replicate physiological conditions. Exceptions should be made if a justification can be provided. For example: a more rigorous test of blood immersed contact bearings should be performed using a low viscosity fluid. One example of foreseeable physiological conditions for a left ventricular assist device is:

Pulse rate:	40-140 beats per minute (BPM)
Systolic to Diastolic Ratio:	40:60 (at 72 BPM)
System temperature:	35°C - 40°C
Salt Concentration	0.9 % NaCl
pH	7.15 – 7.5
Blood Analogue Fluid Viscosity:	3.5 mPa.s +/- 0.3mPa.s
Flow-rate range:	2.5 L/min to 8 L/min

6.19.19 Cycling of VAD operating conditions is required to simulate physiological states (such as sleeping, normal activity and exercise – see Pantalos 1998)[6] and to operate the device at the extremes of its design specifications. Values of these parameters will depend on design input specifications.

6.20 Clinical evaluation

This section provides guidance for clinical evaluation of mechanical circulatory support devices. Clinical evaluation can generally begin once sufficient in vitro and in vivo data has been obtained to support the overall safety and efficacy of the device. Clinical evaluation of a new system should begin with a small feasibility study (approximately 5-10 recipients) to minimize the number of people exposed to unknown risks with a new system. Upon successful completion of the feasibility study, a pivotal clinical trial with a statistically significant number of recipients should be conducted, in order to demonstrate the safety and clinical efficacy in a given patient population.

6.20.1 Clinical study protocols

The clinical study protocols shall provide a clear statement of the scientific and clinical questions that are to be investigated in the study design including, but not limited to:

a) A clearly stated study hypothesis(es), with specific study goals to be achieved that will be used to assess the overall outcome of the trial (i.e. successful study or unsuccessful study). These studies should be directly related to predetermined endpoints which are measurable and relevant to the hypothesis(es) and overall objectives of the study.

b) The study design and rationale for a specific approach. Note there are now an increasing number of potential study designs, each with specific pros and cons in a given patient population. A clear rationale should be provided on why a certain design approach was selected, and the associated limitations with the proposed approach.

c) A description of the control group methodology (concurrent, historical, prospective, computer matched, etc.). What data elements will be analyzed to ensure the groups are comparable. Detailed description of the treatment of cross-over patients, if allowed. Discussion regarding access to new treatments or drugs, especially in the control group for multi-year studies.

d) Description of statistical methods and other rationale utilized to determine sample size, endpoints, study length, and number of centers.

e) The patient selection methodology, including detailed clearly measurable inclusion and exclusion criteria.

f) A description of the enrollment process used to minimize the potential for bias. As appropriate, include discussions related to stratification and intention to treat. If randomization is utilized, the randomization methods (such as blocking, etc.) should also be described.

g) A list of data to be collected. Outline the data collection procedures to assure that each participating institution is collecting data in the same manner and using the same criteria for reporting clinical events. Provide the data collection forms and detailed adverse event descriptions.

h) A detailed plan for data analysis that identifies each of the data analyses to be conducted and as well as the statistical methods to be used for each.

i) The patient consent forms, which include the expected rates of adverse events, including system failures, during the study. If these rates exceed those experienced with standard therapy, a detailed discussion of the risks and benefits must be presented in clear language to ensure patient comprehension.

j) A detailed clinical plan for patient management and follow-up.

k) A plan for training investigators and other appropriate staff in the implementation of the study protocol, including procedures for system use, system management, patient management, and data collection.

l) A retrieval and analysis protocol for implanted system component(s) to ensure uniform collection of data at each investigative site.

m) An autopsy protocol to ensure uniform collection of data at each investigative site.

n) Membership and schedule of meetings for an Independent Data Safety Monitoring Board. Detailed predetermined criteria for stopping the study in the event of excessive adverse event rates (including system failures) or lack of clinical benefit.

o) A plan for assuring the completeness and quality of data collection. The plan should include the monitoring procedure that will be used, the frequency of site visits, how adherence to the protocol will be evaluated, and the individual(s) responsible for monitoring the study.

7 General arrangement of the packaging

This clause of ISO 14708-1 applies

8 General markings for active implantable medical devices

8.1 General

The labelling should provide the health care provider with sufficient information on the safety, use, indications, and performance of the system, as well as traceability information. The following table shows information that should be included on the external package, sterile package, and the device accessories, where applicable.

Table 1 — General labelling guidelines

		External Package	Sterile Package	Device/Accessories
1	Name / trademark	è	è	è
2	Address of manufacturer or distributor	è	è	
3	Description of device	è	è	
4	Intended use of device	è		
5	Relevant characteristics	è		
6	Transport/storage requirements	è		
7	Model designation	è	è	è
8	Lot or serial number			è
9	Month/year of manufacture	è	è	
10	Use before date	è	è	
11	Method of sterilization		è	
12	Sterile condition declaration	è		
13	STERILE marking		è	
14	Special purpose (custom-made, exclusive for investigational use)	è	è	
15	Identify connection with other devices		è	
16	Identify package content	è	è	
17	Instructions for opening package		è	
18	Internal power source ID without surgical op.			è
19	Power source identification			è
20	Self evident visual indications			è

All labeling should be legible and durable.

8.2 Instructions for use

8.2.1 When placed on the market, each device should be accompanied by Instructions for Use providing additional information as needed:

a) Any warnings, instructions for use and limitations of use.

b) Information allowing the physician to select a suitable device and the corresponding software and accessories.

c) Information constituting the instruction for use allowing the physician and, where appropriate, the patient to use the device, its accessories and software, correctly, as well as information on the nature, scope and times for operating controls and trials and, where appropriate, maintenance measures.

d) Information allowing, if appropriate, certain risks in connection with implantation of the device to be avoided.

e) Information regarding alarm conditions and subsequent corrective action, instruction for restricted activity, and device performance characteristics.

NOTE Any special operating instructions, any warnings and/or cautions should be given. The manufacturer should decide the type and level of information required taking into consideration such factors as the assumed technical knowledge and skill of the intended user and