List of Titles

Technical Information Report

AAMI TIR26:2000

Ventricular assist and heart replacement systems

AAMI Association for the Advancement of Medical Instrumentation

Ventricular assist and heart replacement systems

Approved 16 October 2000
Association for the Advancement of Medical Instrumentation

Abstract: Provides guidance for gathering data and information to demonstrate the safety and effectiveness of ventricular assist and heart replacement systems for patients with heart dysfunction.

Keywords: electromedical device, ventricular assist device, artificial heart, implants

AAMI Technical Information Report

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Comments on this technical information report are invited and should be sent to AAMI, Attn: Standards Dept., 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

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List of Titles

Contents

List of Titles

Annexes

Tables

Committee representation

Association for the Advancement of Medical Instrumentation

Mechanical Circulatory Support Systems Committee

This technical information report (TIR) was developed by the Mechanical Circulatory Support Systems Committee of the Association for the Advancement of Medical Instrumentation. Committee approval of the TIR does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Mechanical Circulatory Support Systems Committee** had the following members:

Cochairs:	Robert T.V. Kung
	John T. Watson
Members:	Edwin F. Bjoro, Quality Assurance/Reliability Consulting Specialist, Fairfax, VA
	O.H. Frazier, MD, Texas Heart Institute
	Leonard A.R. Golding, MD, Cleveland Clinic Foundation
	Robert T.V. Kung, PhD, Abiomed Inc.
	James Lee, World Heart Corporation
	William T. Maloney, MD, American Association for Thoracic Surgery
	Jean E. Rinaldi, U.S. Food and Drug Administration
	Gerson Rosenberg, PhD, M.S. Hershey Medical Center
	Rhona B. Shanker, Medical Device Auditing & Consulting
	Richard G. Smith, Cardiowest Technologies Inc.
	James J. Thompson, Arrow International Inc.
	John T. Watson, PhD, NIH, National Heart, Lung, and Blood Institute
Alternates:	Francisco Arabia, MD, Cardiowest Technologies Inc.
	Alan S. Berson, PhD, NIH, National Heart, Lung, and Blood Institute
	Jal S. Jassawalla, World Heart Corporation
	Jeffrey P. Lewis, Arrow International Inc.

NOTE—Participation by federal agency representatives in the development of this TIR does not necessarily constitute endorsement by the federal government or any of its agencies.

Foreword

This technical information report (TIR) was developed by the Mechanical Circulatory Support Systems Committee of the Association for the Advancement of Medical Instrumentation (AAMI) in cooperation with the American Society for Artificial Internal Organs and the Society of Thoracic Surgeons. In addition, representatives of many other medical and technical organizations, as well as representatives of government agencies, contributed to this effort.

This TIR reflects the conscientious efforts of concerned physicians and clinical engineers, in consultation with device manufacturers, to develop a guidance document for those performance levels that could be reasonably achieved as of this writing.

Ventricular assist devices and total artificial hearts require extensive validation information. This document covers the documentation required to evaluate both the pump and the console for these devices. Manufacturers are encouraged to apply this document according to the unique characteristics of their system or component. For example, recommendations may be modified or omitted for appropriate application to a particular system or component if appropriate scientific justification is provided. Although this document was developed to meet the needs of an expanding body of knowledge and is based on current technology, the committee will periodically revise the criteria to keep them current.

Suggestions for improving this TIR are invited. Comments and suggested revisions should be sent to AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

Introduction

Heart failure is a major public health problem. According to recent statistics from the American Heart Association, 4.8 million Americans have heart failure, and, in 1996, more than 43,000 Americans died of this disease. The number of new cases is around 400,000 per year (Schocken 1992). Further, heart failure is implicated as a contributing factor in more than 250,000 deaths each year (Yusuf 1992). Overall, hospital admissions for heart failure have increased 10-fold since 1970 (Lorell 1994). Particularly at risk for heart failure are the elderly (≥ 60 years), who account for 70 % of heart failure patients (Haldeman *et al* 1998), and for whom congestive heart failure is the leading cause of hospitalization. Heart failure is the largest diagnosis-related group (DRG) for Medicare payments. However, although the prevalence of heart failure increases with age, almost one-third of patients—1.6 million Americans—contract the disease before the age of 60. The economic costs are enormous; $21 billion is the estimated U.S. cost for treating this condition (American Heart Association 1999). There is a poor prognosis for the Medicare population; about 17 % of men and 24 % of women survive 6 years after their first hospitalization for heart failure (Croft 1999).

Despite recent developments of pharmacologic agents developed specifically to treat advancing heart failure, the prognosis for 1-year survival for patients with class IV heart failure is between 40 % and 50 % (AHA 2000) and about 25 % at 2 years. For the vast majority of these patients, cardiac replacement therapy in the form of cardiac transplantation is the only viable treatment option. According to recent statistics provided by the United Network for Organ Sharing (UNOS), cardiac transplant patients have an in-hospital mortality of less than 5 %, a 1-year actuarial survival rate approaching 85 %, and 5-year survival rates of greater than 70 %. Yet the success of cardiac transplantation remains limited by the complications of chronic immunosuppressive therapy, by the development of accelerated allograft atherosclerosis, and, most important, by the continuing serious shortage of donor organs. An enormous difference remains between the number of Americans annually who might benefit from cardiac transplantation (~15,000–70,000) versus those who actually receive transplants (2,427 in 1997; UNOS). And, because the number of cardiac transplants is not expected to increase appreciably in the foreseeable future, there is considerable interest in developing new therapies for patients suffering from end-stage heart failure.

The Institute of Medicine evaluated the Artificial Heart Program of the National Heart, Lung, and Blood Institute in 1991 (Hogness 1991). The panel concluded that by the year 2010, there could be an annual pool of 35,000 to 70,000 candidates for mechanical circulatory support or some other form of treatment. Surgical procedures such as left ventriculectomy and myoplasty have not led to clinical benefit in most patients. Xenotransplantation using nonhuman hearts is under active investigation. Areas of concern include immunologic response of the host, inadequate performance of the non-human heart, and the possibility of transferring infectious organisms to the host. These agents sometimes have long incubation periods (10–20 years) as seen with human immunodeficiency virus and acquired immune deficiency syndrome (HIV–AIDS). An additional patient group with acutely failing hearts numbering in the tens to 100,000 annually may benefit from artificial heart therapy.

For the foreseeable future, the need for mechanical circulatory support is well defined and growing. This guidance document is intended to assist research teams and manufacturers in producing highly reliable ventricular assist devices and artificial hearts—at a reasonable cost to society—that will provide a good quality of life for patients with heart failure during their remaining lifetimes.

Ventricular assist and heart replacement systems

1 Scope

This document is intended to be a guideline for gathering data and information to demonstrate the safety and effectiveness of ventricular assist and heart replacement systems for patients with heart dysfunction. Manufacturers are encouraged to apply this document according to the unique characteristics of their system or component. For example, some of the evaluations may be modified or omitted if appropriate scientific justification is provided.

This document identifies the preclinical *in vitro*, *in vivo*, and clinical evaluations that should be performed to meet the requirements of the scope of this document.

NOTE—This technical report is considered "informative," and use of the terms "shall," "should," and so forth should be considered within the context of this technical report only. That is, if the decision is made to use these guidelines, then the guidelines should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical report.

2 References

The following documents contain provisions that, through reference in this text, constitute provisions of this technical information report (TIR). At the time of publication, the editions indicated were valid. All documents are subject to revision, and parties to agreements based on this Association for the Advancement of Medical Instrumentation (AAMI) TIR are encouraged to investigate the possibility of applying the *most recent editions* of the documents listed below. The Association for the Advancement of Medical Instrumentation maintains a register of currently valid AAMI/American National Standards.

2.1 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI). *Cardiovascular implants—Vascular graft prostheses*. ANSI/AAMI VP20:1994. Arlington (Vir.): AAMI, 1994. American National Standard.

2.2 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI). *Biological evaluation of medical devices—Part 1: Evaluation and testing*. ANSI/AAMI/ISO 10993-1:1997. Arlington (Vir.): AAMI, 1997. American National Standard.

2.3 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI). *Quality systems—Medical devices—Particular requirements for the application of ISO 9001*. ANSI/AAMI/ISO 13485:1996. Arlington (Vir.): AAMI, 1996. American National Standard.

2.4 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI). *Medical devices—Symbols to be used with medical device labels, labeling, and information to be supplied*. ANSI/AAMI/ISO 15223:2000. Arlington (Vir.): AAMI, 2000. American National Standard.

2.5 AMERICAN SOCIETY FOR ARTIFICIAL INTERNAL ORGANS (ASAIO). *Long term mechanical circulatory support system reliability recommendation*. *ASAIO J.* 1998. 44:108–14.

2.6 CODE OF FEDERAL REGULATIONS. *Investigational device exemptions*. 21 CFR Part 812. And *Pre-market approval of medical devices*. 21 CFR Part 814.

2.7 CODE OF FEDERAL REGULATIONS. *Federal Food, Drug, and Cosmetic Act*, as amended in February 1998, and related regulations. 21 CFR Parts 800–899.

2.8 INTERNATIONAL ELECTROTECHNICAL COMMISSION. *Medical electrical equipment. Part 1: General requirements for safety, second edition*. IEC 60601-1:1988. Geneva: IEC, 1988.

2.9 INTERNATIONAL ELECTROTECHNICAL COMMISSION. *Medical electrical equipment, Part 1: General requirements for safety—2. Collateral standard: Electromagnetic compatibility—Requirements and texts*. IEC 60601-1-2:1993. Geneva: IEC, 1993.

2.10 INTERNATIONAL ELECTROTECHNICAL COMMISSION. *Electromagnetic compatibility for industrial-process measurement and control equipment. Part 1: General introduction*. IEC 60801-1:1984. Geneva: IEC, 1984.

2.11 INTERNATIONAL ORGANIZATION FOR STANDARDIZATION (ISO). *Active implantable medical devices, Part 1: General requirements for safety, marking, and information to be provided by the manufacturer*. ISO 14708:2000. Geneva: ISO, 2000.

2.12 INTERNATIONAL SPECIAL COMMITTEE ON RADIO INTERFERENCE (CISPR). Limits and methods of measurement of radio-interface characteristics of industrial, scientific, and medical (ISM) equipment. CISPR 11:1997. Geneva: IEC, 1997

2.13 SOCIETY OF THORACIC SURGEONS (STS). Report on Bethesda Conference. Ann Thorac Surg. 1998. 66:1452–65.

2.14 U.S. FOOD AND DRUG ADMINISTRATION. Guideline on General Principles of Process Validation. Document 425: 1 May 1987.

2.15 U.S. FOOD AND DRUG ADMINISTRATION. Contract Sterilizers. Compliance Program Guidance Manual: Program 7382.830B. 1 October 1989.

2.16 U.S. FOOD AND DRUG ADMINISTRATION. Sterilization of Medical Devices.Compliance Program Guidance Manual: Program 7382.830A. 1 October 1989.

2.17 U.S. FOOD AND DRUG ADMINISTRATION. Guidance for Preparation of PMA Manufacturing Information. Document 448: 1 August 1992.

2.18 U.S. FOOD AND DRUG ADMINISTRATION. Blue Book Memorandum. 1 May 1995.

2.19 U.S. FOOD AND DRUG ADMINISTRATION. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. 29 May 1998.

3 Definitions and abbreviations

For the purposes of this technical information report, the following definitions and abbreviations apply:

3.1 accessory device: Separate part of a circulatory support system that is not essential to the primary function of the circulatory support system. Examples would be programming units, monitoring units, alternative power supply units, and so forth.

3.2 CCU: Coronary care unit.

3.3 clinical study: Evaluation of a device in humans.

3.4 clinical utility: Figure of merit for a medical device that includes consideration of all factors that lead to the decision of a medical practitioner to select the device. The factors would include safety, effectiveness, performance, ease of use, cost effectiveness, and other practical considerations.

NOTE—Clinical utility is defined in the working draft of IEC601-1-2. It is only relevant with respect to interference and degradation of performance.

3.5 conduit: Component of the circulatory support system that connects the pump to the patient's circulation, the implanted or external components of the system to each other, or both.

NOTE—The term conduit is generally used interchangeably with the term cannula. The specific definition for cannula is: Connection to and from the patient's circulation and the device.

3.6 continuous flow: Characteristic of the output of a pump in which the flow is not time dependent.

3.7 controller: Component of the circulatory support system containing the circuitry, the software, or both to control the driving mechanism that allows the system to perform its primary function.

3.8 diastolic arterial pressure: Arithmetic average, over a sufficient number of cycles to filter out cyclic variation, of the minimum aortic pressures in a pulsatile pressure waveform.

3.9 displacement pump: Pump that imparts its pumping action by changing the volume of the pumping chamber, e.g., by displacement of a diaphragm or pusher plate.

3.10 dP/dt: Time derivative of pressure giving the rate of change of pressure with respect to time. dP/dt has the units of millimeters of mercury per second, mmHg/sec (kiloPascal per second [kPa/s] in SI units).

3.11 drive line: Conduit that connects a driver to the pump (e.g., 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—A limiting state of an item may be characterized by the end of the useful life, unsuitability for any economic or technological reasons, or other relevant factors.

3.13 dynamic stroke volume: Performance measure for a circulatory support system indicating the volume pumped into the host circulatory system per beat by a pump with pulsatile flow. The dynamic stroke volume has the units of milliliters. Dynamic stroke volume is not relevant to nonpulsatile pumps.

3.14 extracorporeal component: Component or subsystem of the circulatory support system that is kept external to the patient.

3.15 failure: Termination of the ability of an item to perform a required function.

NOTE 1—After failure, the item has a fault.

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

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

3.16 fault: State of an item characterized by inability to perform a required function, excluding the inability during preventive maintenance or other planned actions, or because of lack of external resources.

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

3.17 filling pressure: Arithmetic average pressure required during filling of a displacement pump.

3.18 fully implantable: Implanted long-term circulatory support system with no skin penetrations (i.e., percutaneous lead).

3.19 GLP: Refers to the Code of Federal Regulation, title 21, part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. Sets requirements for the conduct and reporting of laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

3.20 hazard analysis: Identification of hazards and their initiating causes.

3.21 ICU: Intensive care unit.

3.22 IDE: Refers to the Code of Federal Regulation, title 21, part 812, Investigational Device Exemptions. Provides procedures for the conduct of clinical investigations of devices in the United States.

3.23 implanted component: Component or subsystem of the circulatory support system that is placed internal to the patient.

3.24 *in vitro*: Outside the living body and in an artificial environment.

3.25 *in vitro* test simulator: Also known as a mock loop. A fixture that is used in laboratory testing to simulate human circulation for testing the performance of a circulatory support system.

3.26 *in vivo*: In the living body of an animal.

3.27 *in vivo* study: Evaluation of a device using an animal model.

3.28 labeling (marking): Any written, printed, or graphical matter affixed to a medical device or any of its containers or wrappers, or accompanying the medical device, related to identification, technical description, and use, but excluding shipping documents.

3.29 long term circulatory support system: Device that augments or replaces the function of a patient's heart by pumping the patient's blood and relieving in part or in total the work load of the native heart and that is intended to be used for 30 days or longer.

3.30 mean aortic pressure: Arithmetic average of pressure in the aorta throughout the cardiac cycle. Mean aortic pressure has the units of millimeters of mercury, mmHg (120 mmHg is equal to 16 kiloPascal [kPa] in SI units).

3.31 monitor: Component of the circulatory support system that allows data pertaining to the operation of the system to be evaluated.

3.32 OR: Operating room.

3.33 peak flow: Maximum flow rate during ejection of blood from a pump into the host circulatory system.

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

3.35 PMA: Refers to the Code of Federal Regulation, title 21, part 814, Premarket Approval of Medical Devices. Provides procedures for premarket approval of medical devices intended for human use that have been shown to be safe and effective and that otherwise meet the statutory criteria for approval. The code ensures the disapproval of PMAs for devices that have not been shown to be safe and effective or that do not otherwise meet the statutory criteria for approval.

3.36 power supply: Source of electrical energy.

3.37 primary component: Parts of the device that are essential to the primary function of the device. Examples would be the blood pump, the drive source, the valves, the conduits, etc.

3.38 primary function: Main function of a device. For a long-term circulatory support system, the primary function would be to pump blood to relieve in total or in part the work load of the native heart for a period of 30 days or longer.

3.39 programmer: Component of the circulatory support system that allows modification to the control of the operation of the system.

3.40 pulsatile flow: Characteristic of the output of a pump in which the flow is time dependent.

3.41 pump ejection: Term used to describe the ejection phase of a pump with pulsatile flow.

NOTE—Systole is used to describe only the pumping phase of the host's native ventricle(s).

3.42 pump fill: Term used to describe the filling phase of the pump with pulsatile flow.

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

3.43 pump output: Performance measure for a circulatory support system indicating the volume of blood pumped into the host circulatory system per minute. The pump output has the units of liters per minute.

3.44 pump rate: Performance measure for a circulatory support system indicating the number of complete pump cycles per minute required to produce a pulsatile flow. The pump rate has the units of beats per minute. Pump rate is not relevant to nonpulsatile pumps.

3.45 pump volume: Volumetric capacity of the pump. The pump volume has the units of milliliters.

3.46 quality system: System of procedures developed in accordance with a quality system regulation such as CFR 21, part 820, or ISO 9001.

3.47 reliability: Probability that an item can perform a required function under given conditions for a given time interval (t1, t2).

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

NOTE 2—The term "reliability" is also used to denote the reliability performance quantified by this probability [see 191-02-06 of IEC50(191) definition of reliability (performance)].

3.48 risk: Probable rate of occurrence of a hazard causing harm, and the degree of severity of the harm.

3.49 risk analysis: Investigation of available information to identify hazards and to estimate risks.

3.50 rotary pump: Pump that imparts its pumping action by hydrodynamic forces, imparted by a rotating impeller.

3.51 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 (Code of Federal Regulation, title 21, part 860 section 860.7, Determination of safety and effectiveness).

3.52 safety: Freedom from unacceptable risk.

3.53 safety hazard: Potentially detrimental effect on the patient, other persons, animals, or the surroundings, arising directly from the circulatory support system.

3.54 sales packaging: Packaging that protects and identifies the device during storage and handling by the purchaser.

NOTE—The sales packaging may be enclosed in further packaging, e.g., a "shipping package" for delivery.

3.55 secondary component: Parts of the device that are not essential to the primary function of the device. Examples would be a monitoring circuit, alarm subsystems, back-up power supply, etc.

3.56 secondary function: Additional functions of a device that add to the usefulness of the device. An example of a secondary function is monitoring and alarms.

3.57 short-term circulatory support system: Device that augments or replaces the function of a patient's heart by pumping the patient's blood and relieving in part or in total the work load of the native heart and that is intended to be used for fewer than 30 days.

3.58 SQA: Software quality assurance.

3.59 systolic aortic pressure: Arithmetic average—over a sufficient number of cycles to filter out cyclic variation—of the peak aortic pressures in a pulsatile pressure waveform.

3.60 total artificial heart: Long-term circulatory support system that replaces a patient's native ventricles and pumps blood in both the pulmonary and the systemic circulation.

3.61 valve: Component of the circulatory support system that directs the flow of the blood into and out of the pump.

3.62 ventricular assist system: Circulatory support system that augments the function of either one or both ventricles of the native heart of a patient by capturing blood from the atrium(a) or ventricle(s) and by providing work to pump blood into the pulmonary or the systemic circulation, or both.

4 Intended clinical use and indications

The intended use and indications for the system shall be described. The intended use describes what the 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 system will diagnose, treat, prevent, cure, or mitigate and a description of the target population for which the system is intended without causing unreasonable risk of illness or injury associated with use of the system.

5 System description

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

5.1 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.

5.2 Design consideration

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

5.3 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.

5.4 System performance and operating limits

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

5.5 Design analysis

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

5.6 Risk analysis

Risk analysis, which is 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)), and an analysis for potential use or user error (human factors analysis). The risk analysis should use a method to classify the severity of failure modes and the probability of occurrence. The analysis should include discussion of methods used to mitigate the criticality of the failure modes.

5.7 Human factors

5.7.1 General

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, confusion, or both. Further, appropriate alarms and warnings are necessary and should be designed to warn users of system or subsystem failures.

5.7.2 Specific human factors considerations

Specific human factors considerations include the following:

a) Connectors are designed to preclude critical misconnections.

b) Leads can be connected easily and securely by the intended users.

c) Alarms are sufficient for critical failure conditions (e.g., low batteries or disconnects) and there are status indicators for critical device functions (e.g., alarms and warnings are timely, understandable, conspicuous, and distinctive).

d) Operating procedures and sequences are clear (e.g., not confusing or counterintuitive).

e) External batteries are designed for easy installation. External batteries (e.g., primary and secondary) are distinctly different and identifiable as to their designed purpose and use.

f) Problems and hazards associated with bathing, portable use, sleeping, etc. have been considered in the design.

g) User population characteristics (e.g., visual acuity, color blindness, hearing loss, and finger dexterity) have been considered in the design.

h) Human factors analyses and tests have been conducted. Tests have emphasized the performance (e.g., errors and observed problems) of actual users under actual or simulated use conditions, including different device configurations and use of important components and connections.

6 *In vitro* design evaluation

In vitro testing includes design characterization of the integrated system and its individual system subcomponents, as well as reliability. Such testing incorporates the characteristics of the intended patient population, the engineering principles associated with the system, and human factors.

6.1 *In vitro* test setup

An *in vitro* test setup should be used to test the system to evaluate the ability of the design to meet its specifications. Test setups should be representative of the intended patient population. 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 setup, should be provided. *In vitro* test setup considerations are as follows:

a) The system should be evaluated for all modes of operation under the full range of steady-state conditions according to the design specifications. The testing should simulate the effects of changes in system performance on the patient and the effects of patient changes on system performance.

b) The effects of extremes of operation on both the device and the patient (i.e., test setup) should be determined. The extremes of operation include the minimum blood flow and maximum blood flow, hypertension, hypotension, responses to changes in flow and in pressure, and possible inflow and outflow restriction and obstruction.

c) All applicable parameters (e.g., device output, output pressure, filling pressures and volumes, drive pressure, power, and speed) should be measured and reported.

d) System performance (e.g., alarms, backup systems, information displayed, measurement accuracy and precision, and failures) should be monitored and reported.

6.2 "Worst-case" operating conditions

System characterization data should be evaluated to determine the worst-case modes of operation. A discussion should provide the rationale for the selection of the conditions determined to be worst case and should be used for reliability testing (see clause 8) and for what effect it may have on the device.

6.3 Fluid dynamics

A fluid dynamic characterization of the device should be presented. It should discuss how these characteristics relate to the design specification.

6.4 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 should be well documented and controlled. Software information should be provided as recommended in the ODE Guidance for the Content of Premarket Submissions for Medical Devices Containing Software (draft document).

6.5 Electrical qualification

Electrical or electronic subsystems of the circulatory support system may be required for a particular circulatory support system. The electrical or electronic subsystems are qualified by design analysis and testing. The design analysis provides a theoretical rationale for the design. Additionally, specifications essential for proper operation of the subsystems should be established and then verified with tests.

6.5.1 Electromagnetic compatibility

Electromagnetic compatibility (EMC) testing should be conducted for all devices that contain 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). When EMC standards are used for these evaluations, the test levels used shall be justified as to their appropriateness to the intended use environment (e.g., hospital, home, and ambulance).

The test plan for EMC testing should include test protocols and test levels appropriate for the device in its intended environment of use. IEC 60601-1-2 may be a starting point for testing EMC emissions and immunity.

6.5.2 Electrical safety

Electrical safety testing should be conducted for all devices that contain electrical components, electronic components, or both to demonstrate that the system will perform per design specification. When electrical safety standards are used for these evaluations, the test levels used shall be justified as to their appropriateness to the intended use environment (e.g., hospital, home, and ambulance).

6.6 Power sources

The power systems, which provide the energy required to sustain the pumping function of a circulatory support system, may come from a number of different sources. For a particular circulatory support system, the power system specifications should be defined and then verified with testing.

6.6.1 Transcutaneous energy transmission systems

A transcutaneous energy transmission system sends power across the 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 may include parameters such as efficiency, input power, output power, maximum power, voltage range, effect of primary and secondary coil alignment, power dissipation, and so forth.

6.6.2 Batteries

A circulatory support system may be battery powered. The battery power may be a nonrechargeable primary battery or a rechargeable secondary battery. The following considerations may be important 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 backup procedure if the battery fails;

f) recharge specifications; charge current, end of charge determination, recharge time, and so forth;

g) method to measure battery depletion; and

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

6.7 Mechanical qualification

Mechanical qualification testing of individual components or subassemblies is necessary to ensure that 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 to characterize failure modes, or it may be representative of anticipated normal use (accelerated or real time) to show freedom from failure.

6.7.1 Connections and connectors

6.7.1.1 Electrical

Electrical connections to and from all power supplies, batteries, controllers, and blood pumps should be subjected to pull strength, torsion, flex, drop, and vibration tests. The connection should be tested for electrical and mechanical integrity, resistance to corrosion, proper connector mating, and conductivity and resistance both before and after each of the appropriate tests to ensure that design specifications are met.

6.7.1.2 Pneumatic/gas

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 with 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.

6.7.1.3 Blood/conduits

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 environmental (body fluid) testing. Following this testing, the junctions of the inflow and outflow conduits at the blood pump should be examined for damage and leakage. The whole pathway should be evaluated for any changes that would result in the conduits not complying with design specifications.

6.7.2 Vascular grafts

All vascular grafts should be evaluated for conformance with specifications in accordance with ANSI/AAMI VP20:1994, *Cardiovascular implants—Vascular graft prostheses*. This evaluation may be conducted by the supplier of the grafts or by the manufacturer of the blood pump. Grafts that are custom made for the device may need to be qualified independently of the blood pump.

6.7.3 Valves

If possible, blood pathway 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 clinical valve design cannot be evaluated with the final device configuration, it should be qualified independently of the system, and a justification should be provided.

6.7.4 Materials qualification

The selection of materials for engineering components and devices depends on knowledge of material properties and behavior 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: oxidation, corrosion, diffusion, and leaching; and

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

6.8 Biocompatibility

All blood-contacting and tissue-contacting surfaces should be biocompatible as defined in ANSI/AAMI/ISO 10993-1 (as modified by the U.S. FDA Blue Book Memorandum, 1 May 1995).

NOTE—Compliance with ANSI/AAMI/ISO 10993-1 encompasses the application of the appropriate parts of the 10993 series of standards.

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.

6.9 Environmental testing

Environmental testing should be conducted to demonstrate that the system will perform according to its design specification. When 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, and ambulance).

Environmental testing should include consideration for EMC; drop and shock; vibration; temperature and humidity; fluid ingress; and shipping, handling, and storage.

See annex B for a fictitious example of test specifications.

7 *In vivo* design evaluation

The *in vivo* testing plan or protocol should include a rationale for each of the following elements: purpose and scope of the *in vivo* testing, animal model, sample size, test duration, the study endpoint(s), and data collection and analysis.

7.1 *In vivo* study plan

The *in vivo* study plan should be structured around the intended use of the device in the specified patient population. The study should verify that the design could support a living system. The plan should describe what system designs require *in vivo* verification beyond planned *in vitro* studies, what pertinent tests are to be conducted, and how the tests are to be performed. Success or failure of a study should be defined in objective terms or measurable quantities.

7.2 *In vivo* protocol

On the basis of the study plan, an *in vivo* protocol should be developed that describes what and how the experiments will be conducted. The protocol(s) should include standard procedures, such as:

a) preoperative animal management;

b) implant procedures;

c) postoperative animal management;

d) physiologic and hemodynamic measurements;

e) exercise studies;

f) battery cycling, if applicable;

g) necropsy; and

h) device retrieval analysis.

Protocol(s) should include standard clinical measures such as blood chemistry and hematology, anesthesia dosages, fluid management, anticoagulation therapy, and other relevant parameters. Adverse events should be defined and recorded. Attrition caused by animal complications should be discussed. Special biologic, hematologic, or physiologic tests, if planned, should be described and justified.

7.3 *In vivo* analysis plan

The *in vivo* analysis plan should include analysis of all data collected according to the *in vivo* protocol. The pathology and histology findings should be discussed in relation to the intended use. Explanted devices should be subjected to a full evaluation. Typical items to consider are blood- and tissue-contacting surfaces, thrombus and infection, corrosion and wear, cables and connectors, and hermetic integrity. Reference scales should be developed for subjective rankings.

8 Reliability

System reliability is defined as the probability of a system to perform its function for a specified period of time under stated conditions. Important considerations are the following:

a) Numeric reliability specifications (percent reliability) with confidence intervals (percent confidence) shall be defined for performance testing over the desired life of the system. (For example, the demonstrated reliability of the heart replacement system shall be *X* with at least *Y* confidence for a *Z* year mission life.)

b) Each system should be comprised of components of quality and reliability that are appropriate for their application in the system. Some components may require separate testing or analysis to demonstrate appropriate reliability for use in the total system.

c) The number of systems to be tested under controlled *in vitro* conditions should be statistically justified to demonstrate that the stated reliability specifications are met.

d) Statistical methods to be used in the analysis of the reliability test results should be described.

e) The definition of failure of the system under test should be clinically relevant (e.g., flow rate for a specified duration that results in irreversible organ damage).

f) 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 should be documented.

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

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

i) The *in vitro* reliability study may identify wear-out failures (durability). The wear-out failures identified should be included in a preventive maintenance plan.

9 Clinical trial considerations

This section provides guidance for design of a clinical study of ventricular assist and total artificial heart systems. A new system may need to be evaluated for safety in humans in a small pilot study to minimize the number of people exposed to unknown risks with a new system before commencement of a pivotal clinical trial to demonstrate safety and efficacy. The pilot study data should be used to assess system safety and to support the design of the pivotal trial.

The following guidance is intended to assist in the design of a clinical study of ventricular assist and total artificial heart systems.

a) Provide a clear statement of the scientific and clinical questions that are to be investigated in the study design.

b) Include the general and specific objectives, the study hypothesis(es), and the specific study endpoints that will be used to assess the safety and efficacy, including clinical utility, of the system. The endpoints should be measurable with clearly defined variables relevant to the hypothesis(es) and objectives of the study.

c) Specify and provide the statistical rationale for the number of patients and the number of institutions to be included in the study.

d) Describe the patient clinical enrollment criteria. Provide a list of patient inclusion and exclusion criteria. Sex, age, medical and physical condition, and other demographic characteristics should be considered when developing the enrollment criteria.

e) Describe the control group and how the investigators ensure that it is similar to the study group.

f) Describe the enrollment process used to minimize the potential for bias. As appropriate, include discussions related to stratification and intention to treat.

g) Relate the data to be collected to the study endpoints used to determine safety and efficacy. Include well-defined data collection procedures in the protocol to ensure that each participating institution is collecting data in the same manner and is using the same criteria for reporting clinical events. The case report forms should provide for the collection of all data specified in the clinical protocol.

h) Include a detailed plan that analyzes the data and that identifies all the questions to be addressed by the study, as well as the statistical methods that will be used for each analysis.

i) Develop definitions for all anticipated adverse events, along with guidance and procedures, for consistent interpretation among physicians and centers. The definitions for anticipated adverse events were developed at the 1998 Society of Thoracic Surgeons conference in Bethesda, Maryland, on clinical study designs for ventricular assist devices. Every clinical investigator should agree to use the definitions in the study.

j) Specify and discuss the expected rate of anticipated 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 to justify the study.

k) Include criteria for stopping the study in the event of excessive rates of adverse events (including system failures) or in the event of lack of clinical benefit.

l) Include a detailed clinical plan for patient management and follow-up.

m) Include criteria for study success and study failure that are related to the study hypothesis(es).

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

o) Include a retrieval and analysis protocol for implanted system component(s) for uniform data collection at each center to ensure uniform data collection across all participating centers.

p) Include an autopsy protocol for uniform collection of data at each investigative site. An independent pathologist should evaluate all autopsy results.

q) Provide a plan for ensuring the completeness and quality of data collection. The plan should include which monitoring procedure to use, how frequent site visits will be, and how adherence to the protocol will be evaluated. The plan should also identify the individual responsible for monitoring the study.

10 Labeling

10.1 General

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

Table 1—General labeling guidelines

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

All labeling should be legible and durable.

10.2 Instructions for use

10.2.1 General

When placed on the market, each device should be accompanied by instructions for use and should provide additional information as needed, such as the following:

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 correctly use the device, its accessories, and software, as well as information on the nature, scope, and times for operating controls and trials and, where appropriate, information on maintenance measures;

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

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

NOTE—Any special operating instructions, warnings, and cautions should be given. The manufacturer should decide the type and level of information required, taking into consideration factors such as the assumed technical knowledge and skill of the intended user and any novel or unfamiliar features or mode of operation that may not be self-evident. Internationally recognized symbols may be used.

f) Information regarding risks of reciprocal interference in connection with the presence of the device during specific investigations or treatment;

g) Necessary instructions in the event of the sterile pack being damaged and, where appropriate, details of the appropriate methods of sterilization;

h) If the device is reusable, information on the appropriate processes to allow reuse—including how to clean, disinfect, package, and, where appropriate, what method of sterilization to use for the device to be resterilized—and any restriction on the number of reuses;

When devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization should be such that, if correctly followed, the device will still comply with the performance requirements.

NOTE—This requirement relates only to devices intended by the manufacturer to be reusable. It does not relate to devices which a user may decide to reuse outside the manufacturer's recommendations (e.g., those devices marked as "single use").

i) Details of any further treatment or handling needed before use (e.g., sterilization, final assembly, etc.);

j) Detailed information, if appropriate, on the nature of any emitted radiation from the devices, any means of protecting the patient and users, and any ways of avoiding misuse and of eliminating the risks inherent in installation.

10.2.2 Contra-indications and associated precautions

When placed on the market, an instruction leaflet should be included to provide details that allow the physician to brief the patient on the known contra-indications and about the associated precautions to be taken. These details should cover, in particular, the following:

a) information allowing the lifetime of the energy source to be established;

b) precautions to be taken should changes occur in the device's performance;

c) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, accelerations, and so forth;

d) adequate information regarding the medicinal products that the device in question is designed to administer, where appropriate;

e) instructions for use must be included in the packaging for every device;

NOTE—By way of exception, no such instructions for use are needed for devices in Class I or Class IIa if they can be used safely without any such instructions.

f) precautions to be taken against any special, unusual risks related to the disposal of the device;

g) medicinal substances incorporated into the device as an integral part, if appropriate; and

h) degree of accuracy claimed for devices with a measuring function.

10.2.3 Human factors considerations

The following are important human factors considerations:

a) Font style and size should facilitate easy reading. If the population of device users is anticipated to have problems with vision, this factor should be considered in the preparation of labeling materials.

b) Cautions and warnings should be presented so that attention is focused on them (e.g., bolding the caution or warning statement, indenting, or surrounding the statement with extra white space).

c) Manuals should include space for the user to write important information such as phone numbers for emergency contacts, battery replacement dates, etc.

d) Quality considerations should be presented.

e) Labeling should not confuse readers with multiple definitions, synonymous terms or phrases, or vague or incomplete descriptions.

f) Reading level of material, particularly patient manuals, should be appropriate for the general public (approximately 6th-grade level).

g) Technical terms should be used as infrequently as possible without sacrificing understanding of the text. To the extent possible, technical terms should be defined when first used in the text. If it makes more sense to define them in the context of later sections, that section should be referred to when the term is first used.

Annex A

Rationale for the development and provisions of this technical information report

The field of mechanical circulatory support is growing and changing at a fast pace. Initial designs, each with its own characteristics for providing circulatory support, were pulsatile pumps. Some pumps were implanted and tethered to external power sources, whereas other pumps were extracorporeal with implanted cannulae. All of them provided a physiologic stroke volume at natural beat rates. On the basis of this initial experience, newer designs are being developed that use different blood-pumping techniques.

All of these systems, whether they are current or future designs, involve a multitude of engineering technologies and present a variety of biological and medical issues. There is no document describing the evaluations that may be appropriate to validate all of the different engineering, biological, and medical aspects of these diverse systems. This document is intended to assist developers and manufacturers in identifying the evaluations that should be performed to demonstrate that their system is suitable for its intended use. The document also identifies issues that should be taken into consideration in designing test procedures. No standard acceptance criteria in this document are caused by the diverse nature of the system designs and their intended uses. Therefore, it is incumbent on device developers and manufacturers to develop acceptance criteria for each evaluation according to predictive risk and benefit. The collective results of all evaluations should be subjected to a risk and benefit analysis to establish whether the benefits of the design in the intended patient population outweigh the risks posed by use of the system.

Annex B

Example environmental testing matrix

Environmental testing should be performed to a plan that includes a list of the environmental stresses applied, the level of the stresses, the test conditions, and a rationale for selecting the stress types and levels chosen, all of which should be based on the intended use environments.

A particular system may consist of different parts that may be categorized as implantable parts, wearable (or handheld) parts, portable (or tabletop) parts, or floor-standing equipment. The environmental stress levels applied may be different for the different parts.

For tests in which the circulatory support system is operating, the operating conditions should be chosen so that all functions are exercised and monitored.

When a mock loop is used, the test protocol should describe the mock loop in detail and should include the rationale describing why the mock loop is appropriate for the test being performed.

The following table provides a matrix for shock, vibration, temperature, and humidity with fictitious test levels and applicability.

Table B.1—Test levels and conditions

Test description	Implantable parts	Wearable (handheld) parts	Portable (tabletop) parts	Floor-standing equipment
Drop/shock	20-cm drop onto hardwood nonoperating	1-m drop onto hardwood nonoperating	50-mm drop onto hardwood nonoperating	N/A
Vibration, random	N/A	0.002 g^2/Hz operating	0.02 g^2/Hz operating	N/A
Temperature and humidity, operating	35 °C to 40 °C, immersed in 9 g/L saline solution	–20 °C to 50 °C, 10 % to 95 % RH, noncondensing	5 °C to 40 °C, 10 % to 95 % RH, noncondensing	5 °C to 40 °C, 10 % to 95 % RH, noncondensing
Temperature and humidity, storage	0 °C to 40 °C, 10 % to 95 % RH, noncondensing	–40 °C to 70 °C, 10 % to 95 % RH, noncondensing	–40 °C to 70 °C, 10 % to 95 % RH, noncondensing	–40 °C to 70 °C, 10 % to 95 % RH, noncondensing
Shipping and handling	ASTM D4169 Assurance level II	ASTM D4169 Assurance level II	ASTM D4169 Assurance level II	ASTM D4169 Assurance level II
Fluid spill	N/A	400-mL spill, 9 g/L saline solution	400-mL spill, 9 g/L saline solution	1-L spill, 9 g/L saline solution

NOTE 1—N/A indicates not applicable. RH indicates relative humidity.

NOTE 2—This next table provides a matrix for electromagnetic compatibility (EMC) testing with fictitious test levels and applicability.

Table B.2—EMC test levels

Test type	Test level		Test method
	Hospital environment	General environment	
Emissions	Class A	Class B	CISPR 11
Immunity			
Electrostatic discharge (ESD)	6 kV contact, 8 kV air	6 kV contact, 8 kV air	IEC 1000-4-2
Radiated	3 V/m 80 MHz to 800 MHz, 10 V/m 800 MHz to 1 GHz	20 V/m 80 MHz to 1 GHz	IEC 1000-4-3
Power frequency magnetic	3 A/m	3 A/m	IEC 1000-4-8
Conducted Electrical Fast Transient/Burst (EFT)	2 kV for power supply lines, 1 kV for input/output lines > 3 m	2 kV for power supply lines, 1 kV for input/output lines > 3 m	IEC 1000-4-4
Conducted surge	1 kV differential mode, 2 kV common mode	1 kV differential mode, 2 kV common mode	IEC 1000-4-5
Voltage dips, short interruptions and voltage variations on power supply input lines	0 % U_T for 0.5 cycle, 40 % U_T for 5 cycles, 70 % U_T for 25 cycles, 0 % U_T for 5 sec	0 % U_T for 0.5 cycle, 40 % U_T for 5 cycles, 70 % U_T for 25 cycles, 0 % U_T for 5 sec	IEC 1000-4-11

NOTE—U_T is the a.c. mains voltage prior to application of the test level.

Annex C

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