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Medical devices — Application of risk management to medical devices

Dispositifs médicaux — Application de la gestion des risques aux dispositifs médicaux

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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Contents

Page

Foreword

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

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

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

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

International Standard ISO 14971 was prepared by ISO/TC 210, *Quality management and corresponding general aspects for medical devices*, and Subcommittee IEC/SC 62A, *Common aspects of electrical equipment used in medical practice*. Annex H, "Guidance on risk management for *in vitro* diagnostic medical devices", was prepared by ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

This second edition cancels and replaces the first edition (ISO 14971:2000) as well as the amendment ISO 14971:2000/Amd.1:2003.

For purposes of future IEC maintenance, Subcommittee 62A has decided that the contents of this publication will remain unchanged until the maintenance result date[1] indicated on the IEC web site under http://webstore.iec.ch in the data related to the specific publication. At this date, the publication will be

— reconfirmed,

— withdrawn,

— replaced by a revised edition or

— amended.

This corrected version of ISO 14971:2007 incorporates the following correction:

— a corrected version of Figure 1 on page 6.

1) IEC National Committees are requested to note that for this publication the maintenance result date is 2014.

Introduction

The requirements contained in this International Standard provide manufacturers with a framework within which experience, insight and judgment are applied systematically to manage the risks associated with the use of medical devices.

This International Standard was developed specifically for medical device/system manufacturers using established principles of risk management. For other manufacturers, e.g., in other healthcare industries, this International Standard could be used as informative guidance in developing and maintaining a risk management system and process.

This International Standard deals with processes for managing risks, primarily to the patient, but also to the operator, other persons, other equipment and the environment.

As a general concept, activities in which an individual, organization or government is involved can expose those or other stakeholders to hazards which can cause loss of or damage to something they value. Risk management is a complex subject because each stakeholder places a different value on the probability of harm occurring and its severity.

It is accepted that the concept of risk has two components:

a) the probability of occurrence of harm;

b) the consequences of that harm, that is, how severe it might be.

The concepts of risk management are particularly important in relation to medical devices because of the variety of stakeholders including medical practitioners, the organizations providing health care, governments, industry, patients and members of the public.

All stakeholders need to understand that the use of a medical device entails some degree of risk. The acceptability of a risk to a stakeholder is influenced by the components listed above and by the stakeholder's perception of the risk. Each stakeholder's perception of the risk can vary greatly depending upon their cultural background, the socio-economic and educational background of the society concerned, the actual and perceived state of health of the patient, and many other factors. The way a risk is perceived also takes into account, for example, whether exposure to the hazard seems to be involuntary, avoidable, from a man-made source, due to negligence, arising from a poorly understood cause, or directed at a vulnerable group within society. The decision to use a medical device in the context of a particular clinical procedure requires the residual risks to be balanced against the anticipated benefits of the procedure. Such judgments should take into account the intended use, performance and risks associated with the medical device, as well as the risks and benefits associated with the clinical procedure or the circumstances of use. Some of these judgments can be made only by a qualified medical practitioner with knowledge of the state of health of an individual patient or the patient's own opinion.

As one of the stakeholders, the manufacturer makes judgments relating to safety of a medical device, including the acceptability of risks, taking into account the generally accepted state of the art, in order to determine the suitability of a medical device to be placed on the market for its intended use. This International Standard specifies a process through which the manufacturer of a medical device can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of that control.

For any particular medical device, other International Standards could require the application of specific methods for managing risk.

Medical devices — Application of risk management to medical devices

1 Scope

This International Standard specifies a process for a manufacturer to identify the hazards associated with medical devices, including *in vitro* diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.

The requirements of this International Standard are applicable to all stages of the life-cycle of a medical device.

This International Standard does not apply to clinical decision making.

This International Standard does not specify acceptable risk levels.

This International Standard does not require that the manufacturer have a quality management system in place. However, risk management can be an integral part of a quality management system.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply:

2.1
accompanying document
document accompanying a medical device and containing information for those accountable for the installation, use and maintenance of the medical device, the operator or the user, particularly regarding safety

NOTE Adapted from IEC 60601-1:2005, definition 3.4.

2.2
harm
physical injury or damage to the health of people, or damage to property or the environment

[ISO/IEC Guide 51:1999, definition 3.3]

2.3
hazard
potential source of harm

[ISO/IEC Guide 51:1999, definition 3.5]

2.4
hazardous situation
circumstance in which people, property, or the environment are exposed to one or more hazard(s)

[ISO/IEC Guide 51:1999, definition 3.6]

NOTE See Annex E for an explanation of the relationship between “hazard” and “hazardous situation”.

2.5
intended use
intended purpose
use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer

2.6
***in vitro* diagnostic medical device**
IVD medical device
medical device intended by the manufacturer for the examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes

EXAMPLES Reagents, calibrators, specimen collection and storage devices, control materials and related instruments, apparatus or articles.

NOTE 1 Can be used alone or in combination with accessories or other medical devices.

NOTE 2 Adapted from ISO 18113-1:—, definition 3.29.

2.7
life-cycle
all phases in the life of a medical device, from the initial conception to final decommissioning and disposal

2.8
manufacturer
natural or legal person with responsibility for the design, manufacture, packaging, or labelling of a medical device, assembling a system, or adapting a medical device before it is placed on the market or put into service, regardless of whether these operations are carried out by that person or on that person's behalf by a third party

NOTE 1 Attention is drawn to the fact that the provisions of national or regional regulations can apply to the definition of manufacturer.

NOTE 2 For a definition of labelling, see ISO 13485:2003, definition 3.6.

2.9
medical device
any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

— investigation, replacement, modification, or support of the anatomy or of a physiological process,

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body,

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

NOTE 1 This definition has been developed by the Global Harmonization Task Force (GHTF). See bibliographic reference [38].

[ISO 13485:2003, definition 3.7]

NOTE 2 Products, which could be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach, are:

— aids for disabled/handicapped people,

— devices for the treatment/diagnosis of diseases and injuries in animals,

— accessories for medical devices (see Note 3),

— disinfection substances,

— devices incorporating animal and human tissues which can meet the requirements of the above definition but are subject to different controls.

NOTE 3 Accessories intended specifically by manufacturers to be used together with a "parent" medical device to enable that medical device to achieve its intended purpose, should be subject to this International Standard.

2.10
objective evidence
data supporting the existence or verity of something

NOTE Objective evidence can be obtained through observation, measurement, testing or other means.

[ISO 9000:2005, definition 3.8.1]

2.11
post-production
part of the life-cycle of the product after the design has been completed and the medical device has been manufactured

EXAMPLES transportation, storage, installation, product use, maintenance, repair, product changes, decommissioning and disposal.

2.12
procedure
specified way to carry out an activity or a process

[ISO 9000:2005, definition 3.4.5]

2.13
process
set of interrelated or interacting activities which transforms inputs into outputs

[ISO 9000:2005, definition 3.4.1]

2.14
record
document stating results achieved or providing evidence of activities performed

[ISO 9000:2005, definition 3.7.6]

2.15
residual risk
risk remaining after risk control measures have been taken

NOTE 1 Adapted from ISO/IEC Guide 51:1999, definition 3.9.

NOTE 2 ISO/IEC Guide 51:1999, definition 3.9 uses the term "protective measures" rather than "risk control measures." However, in the context of this International Standard, "protective measures" are only one option for controlling risk as described in 6.2.

2.16
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, definition 3.2]

2.17
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[ISO/IEC Guide 51:1999, definition 3.10]

NOTE Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm. See Annex E.

2.18
risk assessment
overall process comprising a risk analysis and a risk evaluation

[ISO/IEC Guide 51:1999, definition 3.12]

2.19
risk control
process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

2.20
risk estimation
process used to assign values to the probability of occurrence of harm and the severity of that harm

2.21
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

2.22
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

2.23
risk management file
set of records and other documents that are produced by risk management

2.24
safety
freedom from unacceptable risk

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

2.25
severity
measure of the possible consequences of a hazard

2.26
top management
person or group of people who direct(s) and control(s) a manufacturer at the highest level

NOTE Adapted from ISO 9000:2005, definition 3.2.7.

2.27
use error
act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

NOTE 1 Use error includes slips, lapses and mistakes.

NOTE 2 See also IEC 62366:—, Annexes B and D.1.3.

NOTE 3 An unexpected physiological response of the patient is not by itself considered use error.

[IEC 62366:— [2)], definition 2.12]

2.28
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

NOTE 1 The term "verified" is used to designate the corresponding status.

NOTE 2 Confirmation can comprise activities such as:

— performing alternative calculations;

— comparing a new design specification with a similar proven design specification;

— undertaking tests and demonstrations;

— reviewing documents prior to issue.

[ISO 9000:2005, definition 3.8.4]

3 General requirements for risk management

3.1 Risk management process

The manufacturer shall establish, document and maintain throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process shall include the following elements:

— risk analysis;

— risk evaluation;

— risk control;

— production and post-production information.

Where a documented product realization process exists, such as that described in Clause 7 of ISO 13485:2003[8], it shall incorporate the appropriate parts of the risk management process.

NOTE 1 A documented quality management system process can be used to deal with safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in complex medical devices and systems.

2) To be published.

NOTE 2 A schematic representation of the risk management process is shown in Figure 1. Depending on the specific life-cycle phase, individual elements of risk management can have varying emphasis. Also, risk management activities can be performed iteratively or in multiple steps as appropriate to the medical device. Annex B contains a more detailed overview of the steps in the risk management process.

Compliance is checked by inspection of appropriate documents.

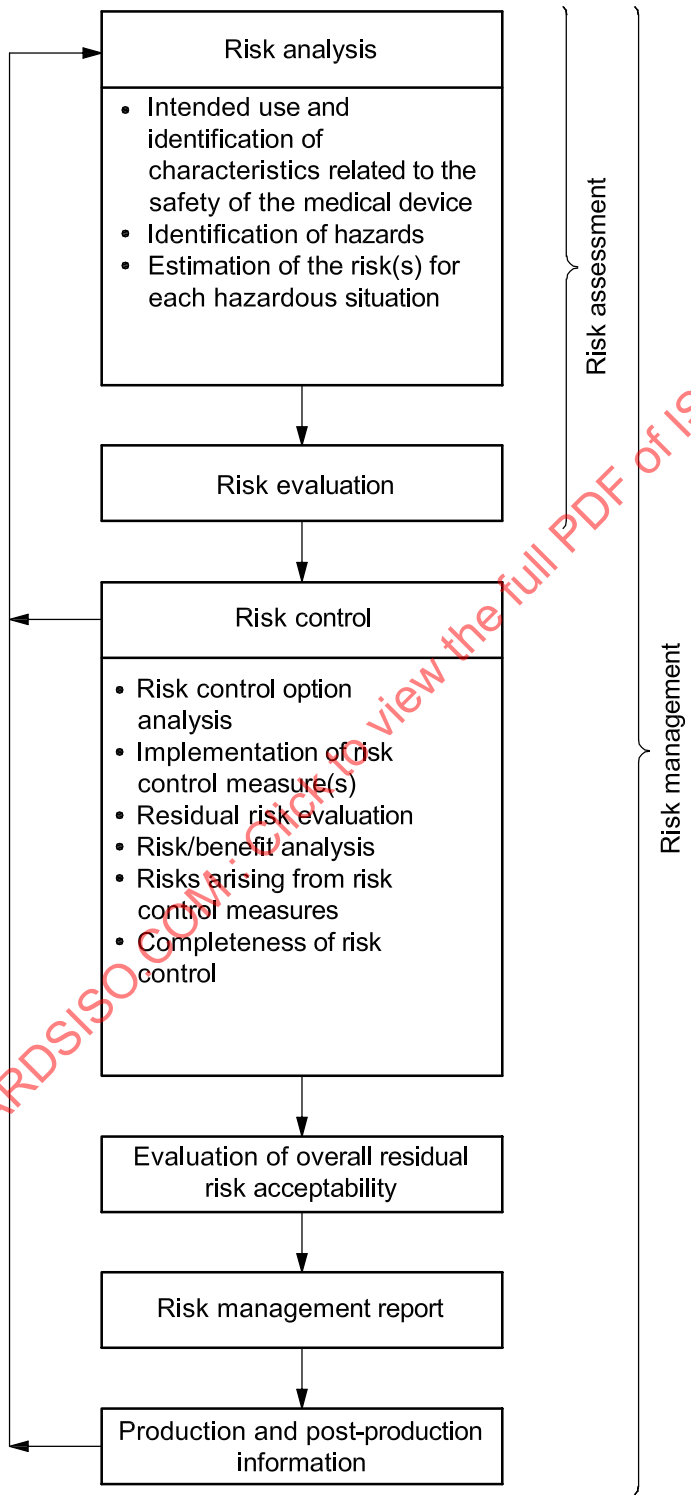


Figure 1 — A schematic representation of the risk management process

3.2 Management responsibilities

Top management shall provide evidence of its commitment to the risk management process by:

— ensuring the provision of adequate resources

and

— ensuring the assignment of qualified personnel (see 3.3) for risk management.

Top management shall:

— define and document the policy for determining criteria for risk acceptability; this policy shall ensure that criteria are based upon applicable national or regional regulations and relevant International Standards, and take into account available information such as the generally accepted state of the art and known stakeholder concerns;

— review the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and document any decisions and actions taken; if the manufacturer has a quality management system in place, this review may be part of the quality management system review.

NOTE The documents can be incorporated within the documents produced by the manufacturer's quality management system and these documents can be referenced in the risk management file.

Compliance is checked by inspection of the appropriate documents.

3.3 Qualification of personnel

Persons performing risk management tasks shall have the knowledge and experience appropriate to the tasks assigned to them. These shall include, where appropriate, knowledge and experience of the particular medical device (or similar medical devices) and its use, the technologies involved or risk management techniques. Appropriate qualification records shall be maintained.

NOTE Risk management tasks can be performed by representatives of several functions, each contributing their specialist knowledge.

Compliance is checked by inspection of the appropriate records.

3.4 Risk management plan

Risk management activities shall be planned. Therefore, for the particular medical device being considered, the manufacturer shall establish and document a risk management plan in accordance with the risk management process. The risk management plan shall be part of the risk management file.

This plan shall include at least the following:

a) the scope of the planned risk management activities, identifying and describing the medical device and the life-cycle phases for which each element of the plan is applicable;

b) assignment of responsibilities and authorities;

c) requirements for review of risk management activities;

d) criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated;

e) verification activities;

f) activities related to collection and review of relevant production and post-production information.

NOTE 1 Refer to Annex F for guidance on developing a risk management plan.

NOTE 2 Not all parts of the plan need to be created at the same time. The plan or parts of it can be developed over time.

NOTE 3 The criteria for risk acceptability are essential for the ultimate effectiveness of the risk management process. For each risk management plan the manufacturer should choose appropriate risk acceptability criteria.

Options could include, among others:

— indicating in a matrix, such as Figures D.4 and D.5, which combinations of probability of harm and severity of harm are acceptable or unacceptable;

— further subdividing the matrix (e.g., negligible, acceptable with risk minimization) and requiring that risks first be made as low as reasonably practicable before determining that they are acceptable (see D.8).

Whichever option is chosen, it should be determined according to the manufacturer's policy for determining criteria for risk acceptability and thus be based upon applicable national or regional regulations and relevant International Standards, and take into account available information such as the generally accepted state of the art and known stakeholder concerns (see 3.2). Refer to D.4 for guidance on establishing such criteria.

If the plan changes during the life-cycle of the medical device, a record of the changes shall be maintained in the risk management file.

Compliance is checked by inspection of the risk management file.

3.5 Risk management file

For the particular medical device being considered, the manufacturer shall establish and maintain a risk management file. In addition to the requirements of other clauses of this International Standard, the risk management file shall provide traceability for each identified hazard to:

— the risk analysis;

— the risk evaluation;

— the implementation and verification of the risk control measures;

— the assessment of the acceptability of any residual risk(s).

NOTE 1 The records and other documents that make up the risk management file can form part of other documents and files required, for example, by a manufacturer's quality management system. The risk management file need not physically contain all the records and other documents; however, it should contain at least references or pointers to all required documentation. The manufacturer should be able to assemble the information referenced in the risk management file in a timely fashion.

NOTE 2 The risk management file can be in any form or type of medium.

4 Risk analysis

4.1 Risk analysis process

Risk analysis shall be performed for the particular medical device as described in 4.2 to 4.4. The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded in the risk management file.

NOTE 1 If a risk analysis, or other relevant information, is available for a similar medical device, that analysis or information can be used as a starting point for the new analysis. The degree of relevance depends on the differences between the devices and whether these introduce new hazards or significant differences in outputs, characteristics, performance or results. The extent of use of an existing analysis is also based on a systematic evaluation of the effects the changes have on the development of hazardous situations.

NOTE 2 Some risk analysis techniques are described in Annex G.

NOTE 3 Additional guidance on risk analysis techniques for *in vitro* diagnostic medical devices is given in Annex H.

NOTE 4 Additional guidance on risk analysis techniques for toxicological hazards is given in Annex I.

In addition to the records required in 4.2 to 4.4, the documentation of the conduct and results of the risk analysis shall include at least the following:

a) a description and identification of the medical device that was analysed;

b) identification of the person(s) and organization who carried out the risk analysis;

c) scope and date of the risk analysis.

NOTE 5 The scope of the risk analysis can be very broad (as for the development of a new device with which a manufacturer has little or no experience) or the scope can be limited (as for analysing the impact of a change to an existing device for which much information already exists in the manufacturer's files).

Compliance is checked by inspection of the risk management file.

4.2 Intended use and identification of characteristics related to the safety of the medical device

For the particular medical device being considered, the manufacturer shall document the intended use and reasonably foreseeable misuse. The manufacturer shall identify and document those qualitative and quantitative characteristics that could affect the safety of the medical device and, where appropriate, their defined limits. This documentation shall be maintained in the risk management file.

NOTE 1 In this context, misuse is intended to mean incorrect or improper use of the medical device.

NOTE 2 Annex C contains questions such as those relating to use that can serve as a useful guide in identifying medical device characteristics that could have an impact on safety.

Compliance is checked by inspection of the risk management file.

4.3 Identification of hazards

The manufacturer shall compile documentation on known and foreseeable hazards associated with the medical device in both normal and fault conditions.

This documentation shall be maintained in the risk management file.

NOTE The examples of possible hazards in E.2 and H.2.4 can be used as guidance by the manufacturer to initiate hazard identification.

Compliance is checked by inspection of the risk management file.

4.4 Estimation of the risk(s) for each hazardous situation

Reasonably foreseeable sequences or combinations of events that can result in a hazardous situation shall be considered and the resulting hazardous situation(s) shall be recorded.

NOTE 1 To identify hazardous situations not previously recognised, systematic methods covering the specific situation can be used (see Annex G).

NOTE 2 Examples of hazardous situations are provided in H.2.4.5 and E.4.

NOTE 3 Hazardous situations can arise from slips, lapses and mistakes.

For each identified hazardous situation, the associated risk(s) shall be estimated using available information or data. For hazardous situations for which the probability of the occurrence of harm cannot be estimated, the possible consequences shall be listed for use in risk evaluation and risk control. The results of these activities shall be recorded in the risk management file.

Any system used for qualitative or quantitative categorization of probability of occurrence of harm or severity of harm shall be recorded in the risk management file.

NOTE 4 Risk estimation incorporates an analysis of the probability of occurrence and the consequences. Depending on the application, only certain elements of the risk estimation process might need to be considered. For example, in some instances it will not be necessary to go beyond an initial hazard and consequence analysis. See also D.3.

NOTE 5 Risk estimation can be quantitative or qualitative. Methods of risk estimation, including those resulting from systematic faults, are described in Annex D. Annex H gives information useful for estimating risks for *in vitro* diagnostic medical devices.

NOTE 6 Information or data for estimating risks can be obtained, for example, from:

a) published standards;

b) scientific technical data;

c) field data from similar medical devices already in use, including published reported incidents;

d) usability tests employing typical users;

e) clinical evidence;

f) results of appropriate investigations;

g) expert opinion;

h) external quality assessment schemes.

Compliance is checked by inspection of the risk management file.

5 Risk evaluation

For each identified hazardous situation, the manufacturer shall decide, using the criteria defined in the risk management plan, if risk reduction is required. If risk reduction is not required, the requirements given in 6.2 to 6.6 do not apply for this hazardous situation (i.e., proceed to 6.7). The results of this risk evaluation shall be recorded in the risk management file.

NOTE 1 Guidance for deciding on risk acceptability is given in D.4.

NOTE 2 Application of relevant standards, as part of the medical device design criteria, might constitute risk control activities, thus meeting the requirements given in 6.3 to 6.6.

Compliance is checked by inspection of the risk management file.

6 Risk control

6.1 Risk reduction

When risk reduction is required, risk control activities, as described in 6.2 to 6.7, shall be performed.

6.2 Risk control option analysis

The manufacturer shall identify risk control measure(s) that are appropriate for reducing the risk(s) to an acceptable level.

The manufacturer shall use one or more of the following risk control options in the priority order listed:

a) inherent safety by design;

b) protective measures in the medical device itself or in the manufacturing process;

c) information for safety.

NOTE 1 If implementing option b) or c), manufacturers can follow a process where reasonably practicable risk control measures are considered and the option providing the appropriate reduction in risk is chosen before determining whether the risk is acceptable.

NOTE 2 Risk control measures can reduce the severity of the harm or reduce the probability of occurrence of the harm, or both.

NOTE 3 Many standards address inherent safety, protective measures, and information for safety for medical devices. In addition, many other medical device standards have integrated elements of the risk management process (e.g. electromagnetic compatibility, usability, biocompatibility). Relevant standards should be applied as part of the risk control option analysis.

NOTE 4 For risks for which the probability of occurrence of harm cannot be estimated, see D.3.2.3.

NOTE 5 Guidance on information for safety is provided in Annex J.

The risk control measures selected shall be recorded in the risk management file.

If, during risk control option analysis, the manufacturer determines that required risk reduction is not practicable, the manufacturer shall conduct a risk/benefit analysis of the residual risk (proceed to 6.5).

Compliance is checked by inspection of the risk management file.

6.3 Implementation of risk control measure(s)

The manufacturer shall implement the risk control measure(s) selected in 6.2.

Implementation of each risk control measure shall be verified. This verification shall be recorded in the risk management file.

The effectiveness of the risk control measure(s) shall be verified and the results shall be recorded in the risk management file.

NOTE The verification of effectiveness can include validation activities.

Compliance is checked by inspection of the risk management file.

6.4 Residual risk evaluation

After the risk control measures are applied, any residual risk shall be evaluated using the criteria defined in the risk management plan. The results of this evaluation shall be recorded in the risk management file.

If the residual risk is not judged acceptable using these criteria, further risk control measures shall be applied (see 6.2).

For residual risks that are judged acceptable, the manufacturer shall decide which residual risks to disclose and what information is necessary to include in the accompanying documents in order to disclose those residual risks.

NOTE Guidance on how residual risk(s) can be disclosed is provided in Annex J.

Compliance is checked by inspection of the risk management file and the accompanying documents.

6.5 Risk/benefit analysis

If the residual risk is not judged acceptable using the criteria established in the risk management plan and further risk control is not practicable, the manufacturer may gather and review data and literature to determine if the medical benefits of the intended use outweigh the residual risk. If this evidence does not support the conclusion that the medical benefits outweigh the residual risk, then the risk remains unacceptable. If the medical benefits outweigh the residual risk, then proceed to 6.6.

For risks that are demonstrated to be outweighed by the benefits, the manufacturer shall decide which information for safety is necessary to disclose the residual risk.

The results of this evaluation shall be recorded in the risk management file.

NOTE See also D.6.

Compliance is checked by inspection of the risk management file.

6.6 Risks arising from risk control measures

The effects of the risk control measures shall be reviewed with regard to:

a) the introduction of new hazards or hazardous situations;

b) whether the estimated risks for previously identified hazardous situations are affected by the introduction of the risk control measures.

Any new or increased risks shall be managed in accordance with 4.4 to 6.5.

The results of this review shall be recorded in the risk management file.

Compliance is checked by inspection of the risk management file.

6.7 Completeness of risk control

The manufacturer shall ensure that the risk(s) from all identified hazardous situations have been considered. The results of this activity shall be recorded in the risk management file.

Compliance is checked by inspection of the risk management file.

7 Evaluation of overall residual risk acceptability

After all risk control measures have been implemented and verified, the manufacturer shall decide if the overall residual risk posed by the medical device is acceptable using the criteria defined in the risk management plan.

NOTE 1 For guidance on overall residual risk evaluation, see D.7.

If the overall residual risk is not judged acceptable using the criteria established in the risk management plan, the manufacturer may gather and review data and literature to determine if the medical benefits of the intended use outweigh the overall residual risk. If this evidence supports the conclusion that the medical benefits outweigh the overall residual risk, then the overall residual risk can be judged acceptable. Otherwise, the overall residual risk remains unacceptable.

For an overall residual risk that is judged acceptable, the manufacturer shall decide which information is necessary to include in the accompanying documents in order to disclose the overall residual risk.

NOTE 2 Guidance on how residual risk(s) can be disclosed is provided in Annex J.

The results of the overall residual risk evaluation shall be recorded in the risk management file.

Compliance is checked by inspection of the risk management file and the accompanying documents.

8 Risk management report

Prior to release for commercial distribution of the medical device, the manufacturer shall carry out a review of the risk management process. This review shall at least ensure that:

— the risk management plan has been appropriately implemented;

— the overall residual risk is acceptable;

— appropriate methods are in place to obtain relevant production and post-production information.

The results of this review shall be recorded as the risk management report and included in the risk management file.

The responsibility for review should be assigned in the risk management plan to persons having the appropriate authority [see 3.4 b)].

Compliance is checked by inspection of the risk management file.

9 Production and post-production information

The manufacturer shall establish, document and maintain a system to collect and review information about the medical device or similar devices in the production and the post-production phases.

When establishing a system to collect and review information about the medical device, the manufacturer should consider among other things:

a) the mechanisms by which information generated by the operator, the user, or those accountable for the installation, use and maintenance of the medical device is collected and processed;

or

b) new or revised standards.

The system should also collect and review publicly available information about similar medical devices on the market.

This information shall be evaluated for possible relevance to safety, especially the following:

— if previously unrecognised hazards or hazardous situations are present or

— if the estimated risk(s) arising from a hazardous situation is/are no longer acceptable.

If any of the above conditions occur:

1) the impact on previously implemented risk management activities shall be evaluated and shall be fed back as an input to the risk management process and

2) a review of the risk management file for the medical device shall be conducted; if there is a potential that the residual risk(s) or its acceptability has changed, the impact on previously implemented risk control measures shall be evaluated.

The results of this evaluation shall be recorded in the risk management file.

NOTE 1 Some aspects of post-production monitoring are the subject of some national regulations. In such cases, additional measures might be required (e.g., prospective post-production evaluations).

NOTE 2 See also 8.2 of ISO 13485:2003[8].

Compliance is checked by inspection of the risk management file and other appropriate documents.

Annex A
(informative)

Rationale for requirements

A.1 General

The ISO/TC 210-IEC/SC 62A Joint Working Group 1, *Application of risk management to medical devices*, developed this rationale to document its reasoning for establishing the various requirements contained in the first edition of this International Standard. During the development of this edition, this rationale was updated to take account of normative changes. Those who make future revisions to this International Standard can use this annex, along with experience gained in the use of this International Standard, to make this International Standard more useful to manufacturers, regulatory bodies and health care providers.

A standard for the application of risk management to medical devices became important largely because of the increasing recognition by regulators, that the manufacturer should apply risk management to medical devices. No medical device risk management standard existed, and this International Standard has been written to fill that gap. ISO/TC 210 Working Group 4 was formed to develop the new International Standard. Almost simultaneously, drafters of the third edition of IEC 60601-1[23] planned to have risk management included in the standard then under development. They saw the need for a separate risk management activity and formed Working Group 15 of IEC/SC 62A. Recognising that the efforts of these two working groups overlapped, IEC and ISO formed the Joint Working Group 1 (JWG 1) on risk management combining the membership of both working groups. This collaboration resulted in the publication of ISO 14971 with both an ISO and an IEC logo. ISO and IEC also recognise each other's single-logo standards as the international standards covering their respective subjects. The dual logo signifies that the standard has been developed jointly by both communities, through the ISO Member Bodies and the IEC National Committees.

When discussions began on the international risk management standard, crucial features of risk management needed to be addressed, such as the process of risk evaluation, as well as the balancing of risks and benefits for medical devices. Manufacturers, regulatory bodies, and health care providers had recognised that "absolute safety" in medical devices was not achievable. In addition, the risks that derive from the increasing diversity of medical devices and their applications cannot be completely addressed through product safety standards. The recognition of these facts and the consequent need to manage risks from medical devices throughout their life-cycle led to the decision to develop ISO 14971.

The original plan was to write the standard in several parts, each dealing with a specific aspect of risk management. ISO 14971-1, covering risk analysis, was intended as the first part of an overall risk management standard. Later, it was decided that it was better to develop a single document that would include all aspects of risk management. The main reason for this was that it was apparent that risk management would be mandated by several regulatory regimes in the world. It was therefore no longer useful or necessary to have a separate standard on risk analysis available. Also, making one risk management standard instead of having several parts would much better show the coherence between the several aspects of risk management.

This edition of ISO 14971 was developed to address the need for additional guidance on its application. Minor changes were made to the normative section, such as the addition of the requirement to plan for post-production monitoring and the removal of the requirement for traceability from the risk management report. New guidance on the relationship between hazards and hazardous situations was developed and placed in Annex E (formerly Annex D). Each use of these terms in this International Standard was reviewed to ensure consistency with this guidance.

The following text gives further information on the clauses and subclauses in ISO 14971.

A.2 Rationale for requirements in particular clauses and subclauses

A.2.1 Scope

As explained in the introduction to this International Standard, a risk management standard applying to the design and manufacturing of all medical devices is required. IVD medical devices are specifically mentioned in the scope to avoid any misunderstanding that, due to different regulations, might be excluded from this International Standard.

Risks can be introduced throughout the product life-cycle, and risks that become apparent at one point in the life-cycle can be managed by action taken at a completely different point in the life-cycle. For this reason, the standard needs to be a complete life-cycle standard. This means that the standard instructs manufacturers to apply risk management principles to a medical device from its initial conception until its ultimate decommissioning and disposal.

The scope of this International Standard does not include decisions on the use of a medical device. The decision to use a medical device in the context of a particular clinical procedure requires the residual risks to be balanced against the anticipated benefits of the procedure or the risks and anticipated benefits of alternative procedures. Such judgements should take into account the intended use, performance and risks associated with the medical device as well as the risks and benefits associated with the clinical procedure or the circumstances of use. Some of these judgements can be made only by a qualified health care professional with knowledge of the state of health of an individual patient and the patient's own opinion.

Although there has been significant debate over what constitutes an acceptable level of risk, this International Standard does not specify acceptability levels. Specifying a universal level for acceptable risk could be inappropriate. This decision is based upon the belief that:

— the wide variety of medical devices and situations covered by this International Standard would make a universal level meaningless;

— local laws, customs, values and perception of risk are more appropriate for defining risk acceptability for a particular culture or region of the world.

Because not all countries require a quality management system for medical device manufacturers, a quality management system is not a requirement of this International Standard. However, a quality management system is extremely helpful in managing risks properly. Because of this and because most medical device manufacturers do employ a quality management system, this International Standard is constructed so that it can easily be incorporated into the quality management system that they use.

A.2.2 Terms and definitions

To avoid inventing a host of new and possibly unfamiliar terms, this International Standard is intentionally built upon the wealth of risk management information both in standards and in the literature. Existing definitions have been used wherever possible. The primary sources for the definitions are:

— ISO/IEC Guide 51:1999, *Safety aspects — Guidelines for the inclusion in standards*

— ISO 9000:2005, *Quality management systems — Fundamentals and vocabulary*

— ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

Some of these definitions have a slightly different meaning in this International Standard. For example, JWG 1 intended the definition of “harm” (2.2) to include unreasonable psychological stress or unwanted pregnancy as part of “damage to the health of people.” It was known that risk management would be made mandatory, either explicitly or implicitly, in many countries and regions of the world. An attempt was therefore made to use definitions that would be widely acceptable in a regulatory sense. For example, the term, “manufacturer” (2.8), while based on the medical device directive in the EU, is consistent with the definition used in the United States. The term, “medical device” (2.9), was taken from ISO 13485[8], which adopted the definition developed by the Global Harmonization Task Force (GHTF). See bibliographic reference [38].

The definition of the term, “intended use” (2.5) combines the definition of “intended use” as used in the United States and “intended purpose,” which is the term in the European Union. These terms have essentially the same definition. It was intended that, when considering the intended use of a medical device, the manufacturer take account of the intended users of the product.

Seven other terms in ISO 14971 are not based on definitions in other standards. These are “life-cycle” (2.7), “post-production” (2.11), “risk control” (2.19), “risk evaluation” (2.21), “risk estimation” (2.20), “risk management” (2.22), and “risk management file” (2.23). The definition of “life-cycle” was necessary to make it clear that the term as used in this International Standard covers all aspects of the existence of a medical device. A definition of "post-production" was added to emphasise that the entire life-cycle of the medical device is important for risk management. The definition for “risk control” was provided to be consistent with the definitions of “risk analysis” given by ISO/IEC Guide 51[2]. In the first edition, the definition of risk evaluation used the term “current values of society”. In this edition, this reference has been removed for two reasons: one is that the definition of the term should not contain a requirement, and the other is that “current values of society” is an imprecise term. The removal of the term from the definition is compensated for by the fact that the concept is already in the introduction and by providing additional normative requirements for the risk management policy and by guidance on risk acceptability. The definition for “risk management” emphasises the use of a systematic approach and the need for management oversight. The concept of a “risk management file” was originally expressed in IEC 60601-1-4[24], but the definition was changed because the definition in IEC 60601-1-4 refers to quality records, which need not exist for compliance with ISO 14971.

The definition of “top management” (2.26) uses the definition from ISO 9000:2005[4]. It applies to the person or group at the highest level in an organization.

A.2.3 General requirements for risk management

A.2.3.1 Risk management process

Subclause 3.1 requires the manufacturer to establish a risk management process as part of the design of a medical device. This is required so that the manufacturer can systematically ensure that the required elements are in the process. Risk analysis, risk evaluation and risk control are commonly recognised as essential parts of risk management. In addition to these elements, this International Standard emphasises that the risk management process does not end with the design and production (including, as relevant, sterilization, packaging, and labelling) of a medical device, but continues on into the post-production phase. Therefore, the gathering of post-production information was identified as a required part of the risk management process. Furthermore, it was felt that when a manufacturer employs a quality management system, the risk management process should be fully integrated into that quality management system.

Although risk management activities are highly individual to the medical device being evaluated, there are basic elements that need to be included in the risk management process. This clause addresses that need. This clause also recognises that there can be some differences in regulatory approach to applying risk management to medical devices.

Subclauses 3.2 and 3.3 closely follow some requirements of quality management system standards. In some countries a quality management system is always required to market a device (unless the device is specifically exempted). In other countries manufacturers can choose whether to apply a quality management system. However, the requirements of subclauses 3.2 and 3.3 are always needed for an effective risk management process, whether or not the manufacturer operates all the other elements of a quality management system.

A.2.3.2 Management responsibilities

The commitment of top management is critical for an effective risk management process. These individuals should take responsibility for overall guidance of the risk management process and this subclause is intended to emphasise their role. In particular:

a) in the absence of adequate resources, risk management activities would be less effective, even if complying, to the letter, with the other requirements of this International Standard;

b) risk management is a specialized discipline and requires the involvement of individuals trained in risk management techniques (see A.2.3.3);

c) because this International Standard does not define acceptable risk levels, top management is required to establish a policy on how acceptable risks will be determined;

d) risk management is an evolving process and periodic review of the risk management activities is needed to ascertain whether they are being carried out correctly, to rectify any weaknesses, to implement improvements, and to adapt to changes.

A.2.3.3 Qualification of personnel

It is most important to get people with the expertise necessary to perform risk management tasks. The risk management process requires people with expertise in areas such as:

— how the medical device is constructed;

— how the medical device works;

— how the medical device is produced;

— how the medical device is actually used;

— how to apply the risk management process.

In general, this will require several representatives from various functions or disciplines, each contributing their specialist knowledge. The balance and relation between individuals performing risk management tasks should be considered.

Records of the appropriate qualifications are required to provide objective evidence. In order to avoid duplication and because of confidentiality and data protection considerations, this International Standard does not require these records to be kept in the risk management file.

A.2.3.4 Risk management plan

A risk management plan is required because:

a) an organized approach is essential for good risk management;

b) the plan provides the roadmap for risk management;

c) the plan encourages objectivity and helps prevent essential elements being forgotten.

The elements a) to f) (subclause 3.4) are required for the following reasons.

— There are two distinct elements in the scope of the plan. The first identifies the intended medical device, the other identifies the phase of the life-cycle covered by each element in the plan. By defining the scope, the manufacturer establishes the baseline on which all the risk management activities are built.

— Allocation of responsibilities and authorities are needed to ensure that no responsibility is omitted.

— Review of activities such as risk management is included as a generally recognised responsibility of management.

— The criteria for risk acceptability are fundamental to risk management and should be decided upon before risk analysis begins. This helps make the process in Clause 5 to be objective.

— Verification is an essential activity and is required by 6.3. Planning this activity helps ensure that essential resources are available when required. If verification is not planned, important parts of the verification could be neglected.

— Device specific methods for obtaining production and post-production information need to be established so that there is a formal and appropriate way to feed back production and post-production information into the risk management process.

The requirement to keep a record of changes is to facilitate audit and review of the risk management process for a particular medical device.

A.2.3.5 Risk management file

This International Standard uses this term to signify where the manufacturer can locate or find the locations of all the records and other documents applicable to risk management. This facilitates the risk management process and enables more efficient auditing to this International Standard. Traceability is necessary to demonstrate that the risk management process has been applied to each identified hazard.

Completeness is very important in risk management. An incomplete task can mean that an identified hazard is not controlled and harm to someone can be the consequence. The problem can result from incompleteness at any stage of risk management, e.g. unidentified hazards, risks not assessed, unspecified risk control measures, risk control measures not implemented or risk control measures that prove ineffective. Traceability is needed to establish completeness of the risk management process.

A.2.4 Risk analysis

A.2.4.1 Risk analysis process

The second paragraph describes how to deal with the availability of a risk analysis for a similar medical device. The note informs users of this International Standard that when adequate information already exists it can and should be applied to save time, effort and other resources. Users of this International Standard need to be careful, however, to assess systematically the previous work for applicability to the current risk analysis.

Note that details required by a), b), and c) form the basic minimum data set for ensuring traceability and are important for management reviews and for subsequent audits. The requirement in c) also helps clarify what is in the scope of the analysis and verifies completeness.

A.2.4.2 Intended use and identification of characteristics related to the safety of the medical device

This step forces the manufacturer to think about all the characteristics that could affect safety of the medical device. The manufacturer should also consider the intended user(s) of the medical device, e.g., whether a lay user or a trained medical professional will use the medical device. This analysis should consider that medical devices can also be used in situations other than those intended by the manufacturer and in situations other than those foreseen when a medical device is first conceived. Medical devices are frequently used in situations other than those intended by the manufacturer and in situations other than those foreseen when a medical device is first conceived. It is important that the manufacturer tries to look into the future to see the hazards due to potential uses of their medical device.

Annex C is intended to be helpful in describing the characteristics of the medical device and the environments in which it is used. It cannot be emphasised too strongly that this list is not exhaustive. Every manufacturer should be creative in determining the relevant safety characteristics for the medical device under investigation. The list in Annex C was originally taken from ISO 14971-1 with some additions made as a result of comments on drafts of that standard. The list ought to stimulate thinking of “where can things go wrong.” Annex H on *in vitro* diagnostic medical devices has been developed by ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems*, for use in this International Standard. Annex I on toxicological hazards has been taken from Annex B of ISO 14971-1 with only minor changes.

A.2.4.3 Identification of hazards

This step requires that the manufacturer be systematic in the identification of anticipated hazards in both normal and fault conditions. The identification should be based upon the safety characteristics identified in 4.2.

A.2.4.4 Estimation of the risk(s) for each hazardous situation

A risk can only be assessed and managed once a hazardous situation has been identified. Documenting the reasonably foreseeable sequences of events that can transform a hazard into a hazardous situation allows this to be done systematically.

Annex E is provided to help manufacturers identify hazards and hazardous situations by listing typical hazards and giving examples to demonstrate the relationships between hazards, foreseeable sequences of events, hazardous situations and associated possible harm. This is especially important when there is a sequence of events that can lead to a hazardous situation and maybe in the end to harm. The manufacturer should recognise and identify these sequences of events in order to address risk properly (see Figure E.1).

The list as given in Annex E is non-exhaustive and is not intended as a checklist, but rather to stimulate creative thinking.

This is the final step of risk analysis. The difficulty of this step is that estimation of risk is different for every hazardous situation that is under investigation as well as for every medical device. Therefore, this subclause was written generically. Because hazards can occur both when the medical device functions normally and when it malfunctions, one should look closely at both situations. In practice, both components of risk, probability and consequence, should be analysed separately. When a manufacturer uses a systematic way of categorizing the severity levels or probability of occurrence of harm, the categorization scheme should be defined and recorded in the risk management file. This enables the manufacturer to treat equivalent risks consistently and serves as evidence that the manufacturer has done so.

Some hazardous situations occur because of systematic faults or sequences of events. There is no consensus on how to calculate the probability of a systematic fault. Where the probability of occurrence of harm cannot be calculated, hazards still have to be addressed and listing resulting hazardous situations separately allows the manufacturer to focus on reducing the risks due to these hazardous situations.

Frequently, good quantitative data are not readily available. The suggestion that estimation of risk should be done only in a quantitative way has therefore been avoided.

Annex D has been provided as helpful guidance on risk analysis. The information originates from several sources, including IEC 60300-3-9[21]. This International Standard recognised the usefulness of IEC 60300-3-9[21] and extended it to apply to all medical devices and all phases of the risk management process. Although risk charts and risk matrices are used extensively in Annex D as examples, this International Standard does not require their use.

A.2.5 Risk evaluation

Decisions have to be made about the acceptability of risk. Manufacturers can use the recently estimated risks and evaluate them using the criteria for risk acceptability defined in the risk management plan. They can screen the risks to determine which ones need to be reduced. Clause 5 was carefully worded to allow the user of this International Standard to avoid unnecessary work.

A.2.6 Risk control

A.2.6.1 Risk reduction

It is intended that steps 6.2 to 6.7 make up a logical sequence of stages. This systematic approach is important since it ensures that relevant information is available when required.

A.2.6.2 Risk control option analysis

Often there will be more than one way to reduce a risk. There are three mechanisms listed:

a) inherent safety by design;

b) protective measures in the medical device itself or in the manufacturing process;

c) information for safety.

These are all standard risk reduction measures and are derived from ISO/IEC Guide 51[2]. The priority order listed is important. This principle is found in several places, including IEC/TR 60513[22] and local or regional regulations (e.g. the European Medical Device Directive[34]). If practicable, the medical device should be designed to be inherently safe. If this is not practicable, then protective measures such as barriers or alarms are appropriate. The least preferred protective measure is a written warning or contra-indication.

It is recognised that one possible result of the risk control option analysis could be that there is no practicable way of reducing the risk to acceptable levels according to the pre-established criteria for risk acceptability. For example, it could be impractical to design a life-supporting medical device with such an acceptable residual risk. In this case, a risk/benefit analysis can be carried out as described in 6.5 to determine whether the benefit of the medical device, to the patient, outweighs the residual risk. This option is included at this point in the standard to make sure that every effort was first made to reduce risks to the pre-established acceptable levels.

A.2.6.3 Implementation of risk control measures

Two distinct verifications are included. The first verification is required to make sure that the risk control measure has been implemented in the final design. The second verification is required to ensure that the measure as implemented actually reduces the risk. In some instances, a validation study can be used for verifying the effectiveness of the risk control measure.

A.2.6.4 Residual risk evaluation

A check was introduced here to determine whether the implemented measures have made the risk acceptable. If the risk is not less than the criteria established in the risk management plan, manufacturers are instructed to assess additional risk control measures. This iterative procedure should be continued until the risk is reduced to within the acceptable levels established in the risk management plan.

The user should be provided with relevant information on residual risks so that the user can make informed decisions. However, it is the manufacturer's decision as to what and how much information on residual risk should be provided. This requirement is consistent with the approach taken in many countries and regions.

A.2.6.5 Risk/benefit analysis

There will be some occasions where the risk of a medical device is greater than the manufacturer’s criteria for acceptable risk. This subclause enables the manufacturer to provide a high-risk medical device for which they have done a careful evaluation and can show that the benefit of the medical device outweighs the risk. It is important for users to be informed of significant residual risks and resulting benefits so that informed decisions can be made. See Annex J.

A.2.6.6 Risks arising from risk control measures

This subclause recognises that risk control measures alone or in combination might introduce a new and sometimes quite different hazard and that measures introduced to reduce one risk might increase another risk.

A.2.6.7 Completeness of risk control

At this stage, the risk of all the hazards should have been evaluated. This check was introduced to ensure that no hazards were left out in the intricacies of a complex risk analysis.

A.2.7 Evaluation of overall residual risk acceptability

During the process defined by Clauses 4 to 6, manufacturers identify hazards, evaluate the risks, and implement risk control measures in their design one at a time. This is the point where the manufacturer has to step back, consider the combined impact of the individual residual risks, and make a decision as to whether to proceed with the medical device. It is possible that the overall residual risk can exceed the manufacturer's criteria for acceptable risk, even though individual residual risks do not. This is particularly true for complex systems and medical devices with a large number of risks. Even if the overall residual risk exceeds the criteria in the risk management plan, the manufacturer has an opportunity to do an overall risk/benefit evaluation to determine whether a high-risk, but highly beneficial, medical device should be marketed. It is important for users to be informed of significant overall residual risks. Thus, manufacturers are instructed to include pertinent information in the accompanying documents.

A.2.8 Risk management report

The risk management report is a crucial part of the risk management file. It is intended to be a summary of the review of the final results of the risk management process. The report serves as the high level document that provides evidence that the manufacturer has ensured that the risk management plan has been satisfactorily fulfilled and results confirm that the required objective has been achieved. The first edition required that traceability be part of the risk management report. This requirement was deleted because for complex devices and analyses traceability makes the risk management report much more extensive than was originally envisioned by the Joint Working Group 1. Traceability still has to be part of the risk management file, and so 3.5 was modified to require this.

A.2.9 Production and post-production information

It cannot be emphasised too often that risk management does not stop when a medical device goes into production. Risk management often begins with an idea where there is no physical manifestation of the medical device. Risk estimates can be refined throughout the design process and made more accurate when a functioning prototype is built. Information for use in risk management can come from any source, including production or quality records. However, no amount of modelling can substitute for an actual medical device in the hands of actual users. Therefore, the manufacturers should monitor production and post-production information for data and information that can affect their risk estimates and, consequently, their risk management decisions. The manufacturer should also take into account state-of-the-art considerations and the practicability of applying them. The information should also be used to improve the risk management process. With the post-production information the risk management process truly becomes an iterative closed-loop process.

In this second edition of this International Standard, the title of this section has been changed from "Post-production information" to "Production and post production information" in recognition of the fact that important risk management information can be acquired as early as the initiation of manufacturing of a device. The requirements in the clause have also been rewritten to emphasise the sequence of steps expected of the manufacturer.

Annex B
(informative)

Overview of the risk management process for medical devices

Figure B.1 is provided to give the user of this International Standard an overview of the risk management process. It is for illustrative purposes only. As indicated in Figure B.1, the process needs to be iterative, covering each risk in turn, and returning to earlier steps if risk control measures introduce new hazards or if new information becomes available.

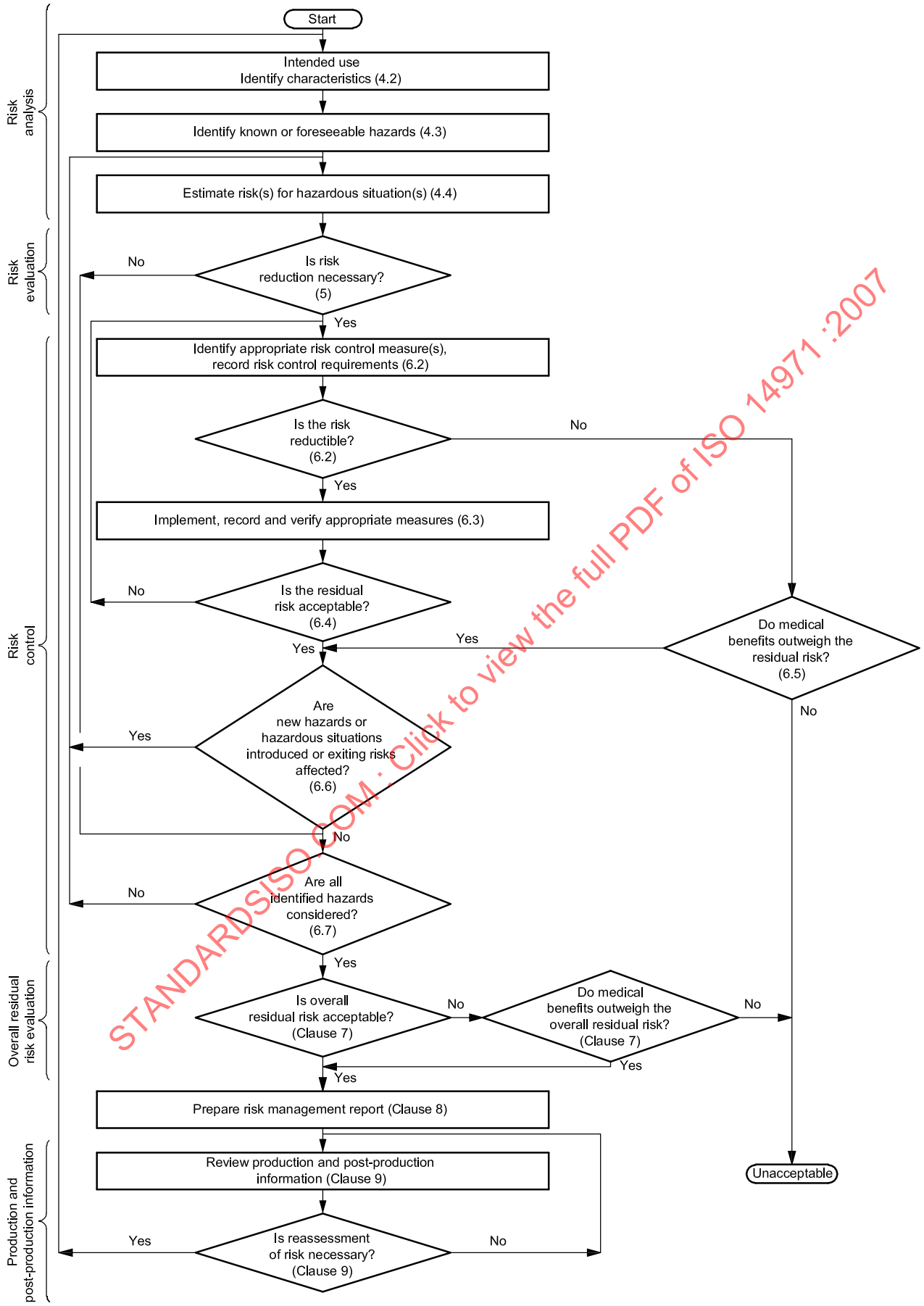


Figure B.1 — Overview of risk management activities as applied to medical devices

Annex C
(informative)

Questions that can be used to identify medical device characteristics that could impact on safety

C.1 General

Subclause 4.2 requires that the manufacturer identifiy those characteristics of the medical device that could affect safety. Consideration of these characteristics is an essential step in identifying the hazards of the medical device as required in 4.3. One way of doing this is to ask a series of questions concerning the manufacture, intended users, intended use, reasonably foreseeable misuse, and ultimate disposal of the medical device. If one asks these questions from the point of view of all the individuals involved (e.g., users, maintainers, patients, etc.), a more complete picture can emerge of where the hazards can be found. The following questions can aid the reader in identifying all the characteristics of the medical device that could affect safety. H.2.5.4 contains points to consider in estimating risk to the patient from IVD medical devices.

The list is not exhaustive, or representative of all medical devices, and the reader is advised to add questions that can have applicability to the particular medical device and to skip questions that are not relevant to the particular medical device. The reader is also advised to consider each question not only on its own but also in relation to others.

C.2 Questions

C.2.1 What is the intended use and how is the medical device to be used?

Factors that should be considered include:

- what is the medical device's role relative to
  - diagnosis, prevention, monitoring, treatment or alleviation of disease,
  - compensation for injury or handicap or
  - replacement or modification of anatomy, or control of conception?
- what are the indications for use (e.g. patient population)?
- does the medical device sustain or support life?
- is special intervention necessary in the case of failure of the medical device?

C.2.2 Is the medical device intended to be implanted?

Factors that should be considered include the location of implantation, the characteristics of the patient population, age, weight, physical activity, the effect of ageing on implant performance, the expected lifetime of the implant, the reversibility of the implantation.

C.2.3 Is the medical device intended to be in contact with the patient or other persons?

Factors that should be considered include the nature of the intended contact, i.e. surface contact, invasive contact, or implantation and, for each, the period and frequency of contact.

C.2.4 What materials or components are utilized in the medical device or are used with, or are in contact with, the medical device?

Factors that should be considered include:

— compatibility with relevant substances;

— compatibility with tissues or body fluids;

— whether characteristics relevant to safety are known;

— is the device manufactured utilizing materials of animal origin?

NOTE See Annex I and also the ISO 22442 series of standards[19].

C.2.5 Is energy delivered to or extracted from the patient?

Factors that should be considered include:

— the type of energy transferred;

— its control, quality, quantity, intensity and duration;

— whether energy levels are higher than those currently used for similar devices.

C.2.6 Are substances delivered to or extracted from the patient?

Factors that should be considered include

— whether the substance is delivered or extracted;

— whether it is a single substance or range of substances;

— the maximum and minimum transfer rates and control thereof.

C.2.7 Are biological materials processed by the medical device for subsequent re-use, transfusion or transplantation?

Factors that should be considered include the type of process and substance(s) processed (e.g. auto-transfusion, dialysis, blood component or cell therapy processing).

C.2.8 Is the medical device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?

Factors that should be considered include

— whether the medical device is intended for single use or re-use packaging;

— shelf-life issues;

— limitation on the number of re-use cycles;

— method of product sterilization;

— the impact of other sterilization methods not intended by the manufacturer.

C.2.9 Is the medical device intended to be routinely cleaned and disinfected by the user?

Factors that should be considered include the types of cleaning or disinfecting agents to be used and any limitations on the number of cleaning cycles. The design of the medical device can influence the effectiveness of routine cleaning and disinfection. In addition, consideration should be given to the effect of cleaning and disinfecting agents on the safety or performance of the device.

C.2.10 Is the medical device intended to modify the patient environment?

Factors that should be considered include:

— temperature;

— humidity;

— atmospheric gas composition;

— pressure;

— light.

C.2.11 Are measurements taken?

Factors that should be considered include the variables measured and the accuracy and the precision of the measurement results.

C.2.12 Is the medical device interpretative?

Factors that should be considered include whether conclusions are presented by the medical device from input or acquired data, the algorithms used, and confidence limits. Special attention should be given to unintended applications of the data or algorithm.

C.2.13 Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies?

Factors that should be considered include identifying any other medical devices, medicines or other medical technologies that can be involved and the potential problems associated with such interactions, as well as patient compliance with the therapy.

C.2.14 Are there unwanted outputs of energy or substances?

Energy-related factors that should be considered include noise and vibration, heat, radiation (including ionizing, non-ionizing, and ultraviolet/visible/infrared radiation), contact temperatures, leakage currents, and electric or magnetic fields.

Substance-related factors that should be considered include substances used in manufacturing, cleaning or testing having unwanted physiological effects if they remain in the product.

Other substance-related factors that should be considered include discharge of chemicals, waste products, and body fluids.

C.2.15 Is the medical device susceptible to environmental influences?

Factors that should be considered include the operational, transport and storage environments. These include light, temperature, humidity, vibrations, spillage, susceptibility to variations in power and cooling supplies, and electromagnetic interference.

C.2.16 Does the medical device influence the environment?

Factors that should be considered include:

— the effects on power and cooling supplies;

— emission of toxic materials;

— the generation of electromagnetic disturbance.

C.2.17 Are there essential consumables or accessories associated with the medical device?

Factors that should be considered include specifications for such consumables or accessories and any restrictions placed upon users in their selection of these.

C.2.18 Is maintenance or calibration necessary?

Factors that should be considered include:

— whether maintenance or calibration are to be carried out by the operator or user or by a specialist;

— are special substances or equipment necessary for proper maintenance or calibration?

C.2.19 Does the medical device contain software?

Factors that should be considered include whether software is intended to be installed, verified, modified or exchanged by the operator or user or by a specialist.

C.2.20 Does the medical device have a restricted shelf-life?

Factors that should be considered include labelling or indicators and the disposal of such medical devices when the expiration date is reached.

C.2.21 Are there any delayed or long-term use effects?

Factors that should be considered include ergonomic and cumulative effects. Examples could include pumps for saline that corrode over time, mechanical fatigue, loosening of straps and attachments, vibration effects, labels that wear or fall off, long term material degradation.

C.2.22 To what mechanical forces will the medical device be subjected?

Factors that should be considered include whether the forces to which the medical device will be subjected are under the control of the user or controlled by interaction with other persons.

C.2.23 What determines the lifetime of the medical device?

Factors that should be considered include ageing and battery depletion.

C.2.24 Is the medical device intended for single use?

Factors that should be considered include: does the medical device self-destruct after use? Is it obvious that the device has been used?

C.2.25 Is safe decommissioning or disposal of the medical device necessary?

Factors that should be considered include the waste products that are generated during the disposal of the medical device itself. For example, does it contain toxic or hazardous material, or is the material recyclable?

C.2.26 Does installation or use of the medical device require special training or special skills?

Factors that should be considered include the novelty of the medical device and the likely skill and training of the person installing the device.

C.2.27 How will information for safe use be provided?

Factors that should be considered include:

— whether information will be provided directly to the end user by the manufacturer or will it involve the participation of third parties such as installers, care providers, health care professionals or pharmacists and whether this will have implications for training;

— commissioning and handing over to the end user and whether it is likely/possible that installation can be carried out by people without the necessary skills;

— based on the expected life of the device, whether re-training or re-certification of operators or service personnel would be required.

C.2.28 Will new manufacturing processes need to be established or introduced?

Factors that should be considered include new technology or a new scale of production.

C.2.29 Is successful application of the medical device critically dependent on human factors such as the user interface?

C.2.29.1 Can the user interface design features contribute to use error?

Factors that should be considered are user interface design features that can contribute to use error. Examples of interface design features include: control and indicators, symbols used, ergonomic features, physical design and layout, hierarchy of operation, menus for software driven devices, visibility of warnings, audibility of alarms, standardization of colour coding. See IEC 60601-1-6[25] for additional guidance on usability and IEC 60601-1-8[26] for guidance on alarms.

C.2.29.2 Is the medical device used in an environment where distractions can cause use error?

Factors that should be considered include:

— the consequence of use error;

— whether the distractions are commonplace;

— whether the user can be disturbed by an infrequent distraction.

C.2.29.3 Does the medical device have connecting parts or accessories?

Factors that should be considered include the possibility of wrong connections, similarity to other products' connections, connection force, feedback on connection integrity, and over- and under-tightening.

C.2.29.4 Does the medical device have a control interface?

Factors that should be considered include spacing, coding, grouping, mapping, modes of feedback, blunders, slips, control differentiation, visibility, direction of activation or change, whether the controls are continuous or discrete, and the reversibility of settings or actions.

C.2.29.5 Does the medical device display information?

Factors that should be considered include visibility in various environments, orientation, the visual capabilities of the user, populations and perspectives, clarity of the presented information, units, colour coding, and the accessibility of critical information.

C.2.29.6 Is the medical device controlled by a menu?

Factors that should be considered include complexity and number of layers, awareness of state, location of settings, navigation method, number of steps per action, sequence clarity and memorization problems, and importance of control function relative to its accessibility and the impact of deviating from specified operating procedures.

C.2.29.7 Will the medical device be used by persons with special needs?

Factors that should be considered include the user, their mental and physical abilities, skill and training, ergonomic aspects, the use environment, installation requirements, and the patient's capability to control or influence the use of the medical device. Special attention should be paid to users with special needs, such as handicapped persons, the elderly and children. Their special needs might include assistance by another person to enable the use of a medical device. Is the medical device intended to be used by individuals with various skill levels and cultural backgrounds?

C.2.29.8 Can the user interface be used to initiate user actions?

Factors that should be considered include the possibility of initiatinig a deliberate action for the user to enter a controlled operation mode, which enlarges the risks for the patient and which creates awareness for the user for this condition.

C.2.30 Does the medical device use an alarm system?

Factors that should be considered are the risk of false alarms, missing alarms, disconnected alarm systems, unreliable remote alarm systems, and the medical staff's possibility of understanding how the alarm system works. Guidance for alarm systems is given in IEC 60601-1-8[26].

C.2.31 In what way(s) might the medical device be deliberately misused?

Factors that should be considered are incorrect use of connectors, disabling safety features or alarms, neglect of manufacturer's recommended maintenance.

C.2.32 Does the medical device hold data critical to patient care?

Factors that should be considered include the consequence of the data being modified or corrupted.

C.2.33 Is the medical device intended to be mobile or portable?

Factors that should be considered are the necessary grips, handles, wheels, brakes, mechanical stability and durability.

C.2.34 Does the use of the medical device depend on essential performance?

Factors that should be considered are, for example, the characteristics of the output of life-supporting devices or the operation of an alarm.

See IEC 60601-1[23] for a discussion of essential performance of medical electrical equipment and medical electrical systems.

Annex D
(informative)

Risk concepts applied to medical devices

D.1 General

This annex provides guidance on the following risk concepts important for managing the risks of medical devices:

— hazards and hazardous situations;

— risk estimation;

— risk acceptability;

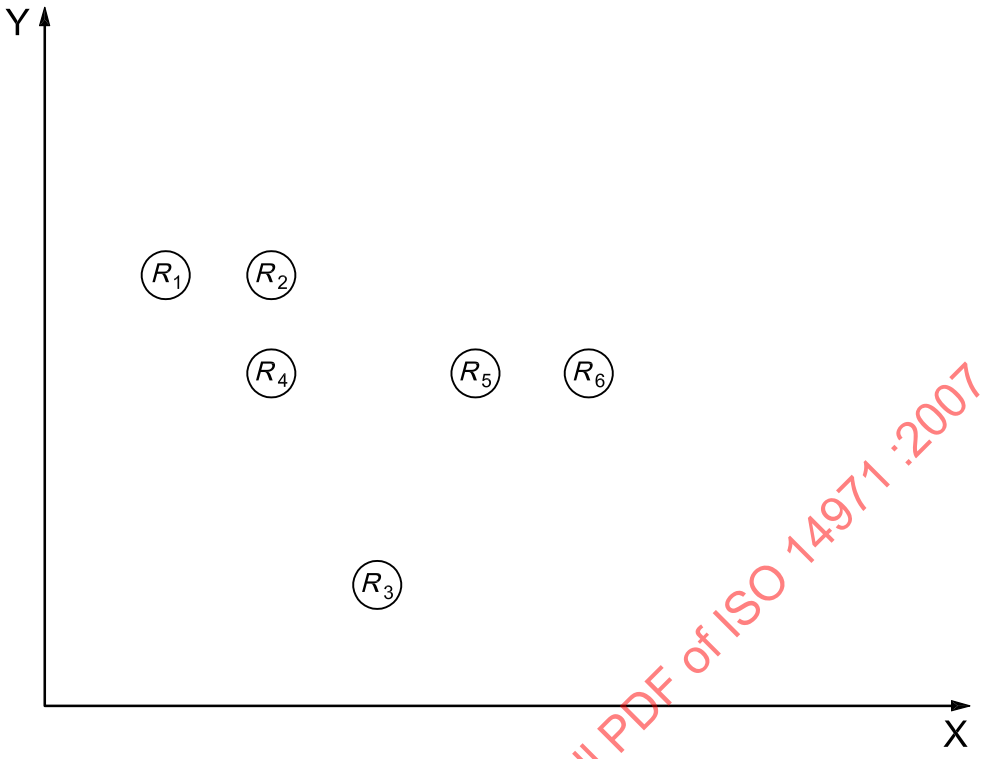
— risk control;

— risk/benefit analysis;

— overall risk evaluation.

Risk is defined in 2.16 as the combination of the probability of occurrence of harm and the severity of that harm. This does not mean that the two factors are multiplied to arrive at a risk value. One way to describe risk and to visualize the meaning of the definition could be done by a two-dimensional risk chart.

The risk chart such as shown in Figure D.1 can provide a visual representation of the severity of harm on the x-axis and the probability of occurrence of harm on the y-axis. For each hazard or hazardous situation the estimation of severity and probability of harm can be plotted as an individual point on the risk chart. In this example, the estimated risks (R_1, R_2, R_3…) are plotted on the chart.



Key

X increasing severity of harm

Y increasing probability of occurrence of harm

Figure D.1 — Example of a risk chart

D.2 Hazards and hazardous situations

D.2.1 General

Medical devices only cause harm if a sequence of events occurs, which results in a hazardous situation and which then could cause or lead to harm. A sequence of events includes both a single event and combinations of events. A hazardous situation occurs when people, property or the environment are exposed to a hazard.

Annex C provides guidance in the form of questions on characteristics of medical devices that can help in identifying hazards. Annex E provides guidance on identifying hazards and sequences of events that can lead to a hazardous situation. Annex H provides guidance on identifying hazards and sequences of events that can lead to hazardous situations and harm for *in vitro* diagnostic medical devices.

It needs to be emphasised that hazardous situations can arise even when there are no faults, i.e. in the normal condition for the medical device.

D.2.2 Hazardous situations arising from faults

D.2.2.1 General

In cases where a hazardous situation only occurs due to a fault, the probability of a fault is not the same as the probability of the occurrence of harm. A fault does not always result in a hazardous situation, and a hazardous situation does not always result in harm.

Particular attention is usually paid to hazardous situations arising from faults in the medical device. It is important to understand that there are generally two types of fault that can lead to a hazardous situation: random and systematic faults.

D.2.2.2 Hazardous situations resulting from random faults

For many events, a numerical value can be given for the probability that the fault will occur. Some examples of random faults are given below.

— The failure of a part such as an integrated circuit in an electronic assembly.

— The contamination of an IVD reagent leading to incorrect results due to deterioration over time.

— The presence of an infectious or toxic substance in or on a medical device. A quantitative estimate can only be applied to biological risks if sufficient information is known about the hazard and the circumstances affecting the probability of the hazardous situation occurring, for example in the use of sterility assurance levels. This situation would be treated in the same way as a random fault for hardware. In many other instances the presence of an infectious or toxic substance would have to be treated as a systematic fault (see D.2.2.3). The risk arising from the presence of a toxic substance in a device material should be estimated in line with ISO 10993-17[7]. This can provide assurance that the degree of exposure anticipated from the use of the device is lower than that likely to cause harm to health.

D.2.2.3 Hazardous situations resulting from systematic faults

A systematic fault can be caused by an error in any activity. It will systematically give rise to a failure when some particular combination of inputs or environmental conditions arises, but will otherwise remain latent.

Errors leading to systematic faults can occur in both hardware and software and can be introduced at any time during a medical device's development, manufacture or maintenance. Some examples of systematic faults are:

— an incorrectly rated fuse fails to prevent a hazardous situation: the fuse rating might have been incorrectly specified, or the fuse is incorrectly fitted during manufacture or incorrectly replaced during repair;

— a software database does not provide for the condition of full database: if the database is full, it is not clear what the software will do; a possible consequence is that the system will simply replace existing records with new ones;

— a fluid, used during the production of a medical device, has a boiling point lower than body temperature: residues of the fluid can, in certain circumstances, be introduced into the blood, possibly leading to an embolism;

— the antibody in a hepatitis assay does not detect some (new) variants of the virus;

— inadequate environmental control, or a breakdown in environmental control systems, leads to contamination with a toxic substance or an infectious agent.

The accurate estimation of systematic fault rates is difficult. This occurs primarily for the following reasons.

— Systematic fault rates are laborious and expensive to measure. Achieving a reasonable level of confidence in the result will not be possible without extensive data on fault rates or parameters relevant to risk control.

— Consensus does not exist for a method of estimating systematic fault rates quantitatively.

Because risk estimation is difficult in these circumstances, the emphasis should be on the implementation of robust systems to prevent hazardous situations from arising.

D.3 Risk estimation

D.3.1 General

Various methods can be used to estimate risk. While this International Standard does not require that a particular method be used, it does require that risk estimation be carried out (see 4.4). Quantitative risk estimation is preferable when suitable data are available; however, without suitable data, qualitative methods of risk estimation can suffice.

The concept of risk is the combination of the following two components:

— the probability of occurrence of harm;

— the consequences of that harm, i.e., how severe it might be.

Risk estimation should examine, for example:

— the initiating event or circumstance (see E.3);

— the sequence of events that could lead to a hazardous situation occurring;

— the likelihood of such a situation arising;

— the likelihood that the hazardous situation leads to harm;

— the nature of the harm that could result.

Depending on the area of application, only certain elements of the risk estimation process need be considered. For example, in some instances, when the harm is minimal or when the probability cannot be estimated, it will not be necessary to go beyond an initial hazard and consequence analysis.

Risk should be expressed in terms that facilitate risk control decision making, for example, using harms and probability scales and units that will mirror actual use. In order to analyse risks, their components, i.e. probability and severity, should be analysed separately.

A risk chart such as that shown in Figure D.1 can provide a depiction of the estimated risks, which is useful for later decision making. The risks would be plotted on the chart as they are estimated. Risk matrices developed from Figure D.1 will be used in examples throughout this annex. This does not imply that this method has general applicability to medical devices; however, it can be useful in many instances. If a risk chart or risk matrix is used for ranking risks, the particular risk chart or risk matrix and the interpretation used should be justified for that application.

D.3.2 Probability

D.3.2.1 General

In situations where sufficient data are available, a quantitative categorization of probability levels is preferred. If this is not possible, the manufacturer should give a qualitative description. A good qualitative description is preferable to an inaccurate quantitative description. For a qualitative categorization of probability levels, the manufacturer can use descriptors appropriate for the medical device.

D.3.2.2 Probability estimation

Although probability is in reality a continuum, in practice a discrete number of levels can be used. In this case, the manufacturer decides how many probability levels are needed, based upon the expected confidence in the estimates. With greater confidence, a greater number of probability levels can be used. At least three levels should be used to facilitate decision making. The levels can be descriptive (e.g. not expected to occur during

the lifetime of the medical device, likely to occur a few times, likely to occur frequently, etc.) or symbolic (P_1, P_2, etc.). Manufacturers should define the categories explicitly so that there will be no confusion over what is meant. A particularly effective way is to assign a range of numerical values to the discrete levels.

Probability estimation will encompass the circumstances and entire sequence of events from the occurrence of the initiating cause through to the occurrence of harm. Implicit in the consideration of the probability of harm is the concept of exposure. For example, if there is no exposure to a hazard, there can be no harm. Therefore the probability of harm should take into consideration the level or extent of exposure. This includes answering the following types of question.

— Does the hazardous situation occur in the absence of a failure?

— Does the hazardous situation occur in a fault condition?

— Does the hazardous situation occur only in a multiple-fault condition?

— How likely is it that a hazardous situation will lead to harm?

The likelihood that a hazardous situation will lead to harm is influenced by the life-cycle of the medical device and estimated number of devices in the market.

Seven approaches are commonly employed to estimate probabilities:

— use of relevant historical data;

— prediction of probabilities using analytical or simulation techniques;

— use of experimental data;

— reliability estimates;

— production data;

— post-production information;

— use of expert judgment.

All these approaches can be used individually or jointly. The first three approaches are complementary; each has strength where the other has weaknesses. Wherever possible, multiple approaches should be used. In this way, they work as independent checks on each other, and this might serve to increase confidence in the results. When these approaches cannot be used or are not sufficient, it might be necessary to rely only on expert judgment.

D.3.2.3 Risks whose probability cannot be estimated

Confidence in a risk estimate is enhanced when a quantitative estimate of the probability of occurrence can be made on the basis of accurate and reliable data or when a reasonable qualitative estimate is possible. However, this is not always achievable. For example, the probabilities of systematic faults, such as those discussed in D.2.2.3, are extremely difficult to estimate. When the accuracy of the probability estimate is in doubt, it is often necessary to establish a broad range for the probability, or determine that it is no worse than some particular value. Examples where probabilities are very difficult to estimate include:

— software failure;

— situations, such as sabotage or tampering with a medical device;

— novel hazards that are poorly understood: e.g. imprecise knowledge of the infectivity of the causative agent of Bovine Spongiform Encephalopathy (BSE) prevents quantification of the risk of transmission;

— certain toxicological hazards, such as genotoxic carcinogens and sensitizing agents, where it might not be possible to determine a threshold of exposure below which toxic effects do not occur.

In the absence of any data on the probability of occurrence of harm, it is not possible to reach any risk estimate, and it is usually necessary to evaluate the risk on the basis of the nature of the harm alone. If it can be concluded that the hazard is of little practical consequence, the risk can be judged to be acceptable and no risk control measures are necessary. However, for significant hazards, that is, hazards which could inflict harm of high severity such as those noted above, no level of exposure can be identified that corresponds to a risk so low that there is no need to bother about it. In such cases, the risk estimate should be made on the basis of a reasonable worst-case estimate of probability. In some instances, it is convenient to set this default value of the probability to one and to base risk control measures on preventing the hazard entirely, reducing the probability of harm to an acceptable level or in reducing the severity of the harm (see D.4).

It is usually assumed that there is an inverse relationship between the rigors of the processes used in the design and development of complex systems and the probability of systematic faults being introduced or remaining undetected. It is often appropriate to determine the required rigor of the development process by taking account of the severity of the consequence of the systematic faults and the effect of risk control measures external to the medical device. The worse the consequence and the less the effect of external risk control measures, the higher the required rigor of the development process.

D.3.3 Severity

To categorize the severity of the potential harm, the manufacturer should use descriptors appropriate for the medical device. Severity is, in reality, a continuum; however, in practice, the use of a discrete number of severity levels simplifies the analysis. In such cases, the manufacturer decides how many categories are needed and how they are to be defined. The levels can be descriptive (e.g., does not require medical intervention, requires medical intervention, requires hospitalization, causes death, etc.). They can also be symbolic (S_1, S_2, etc.), but, in this case, each symbol should be explicitly defined. In either case, they should not include any element of probability. See the examples in D.3.4.

Severity levels will need to be chosen and justified by the manufacturer for a particular medical device under clearly defined conditions of use.

D.3.4 Examples

D.3.4.1 Qualitative analyses

Several approaches can be used for qualitative analysis. A typical approach is to use an N-by-M matrix to describe the probabilities and severities of the risk associated with each hazardous situation. One carefully defines N levels of probability and M levels of severity. Each cell of the matrix represents a subset of the full set of possible risks. Cells are created by partitioning the range of possible probabilities and the range of possible consequences. A simple example is a 3×3 matrix based upon the definitions in Tables D.1 and D.2. Manufacturers should make these definitions as device-specific and explicit as needed to ensure their reproducible use.

Table D.1 — Examples of qualitative severity level

Common terms	Possible description
Significant	Death or loss of function or structure
Moderate	Reversible or minor injury
Negligible	Will not cause injury or will injure slightly

Table D.2 — Simplified examples of qualitative probability levels

Common terms	Possible description
High	Likely to happen, often, frequent
Medium	Can happen, but not frequently
Low	Unlikely to happen, rare, remote

Using the probability as rows and the severity of the harm as columns, a 3 × 3 risk matrix is produced. The estimated risks (R_1, R_2, R_3,...) are entered into the appropriate cells. The result is shown in Figure D.2.

		Qualitative severity levels		
		Negligible	**Moderate**	**Significant**
Qualitative probability levels	**High**	R_1	R_2	
	Medium		R_4	R_5, R_6
	Low		R_3	

Figure D.2 — Example of a qualitative 3 × 3 risk matrix

D.3.4.2 Semi-quantitative analysis

Here is an example of a semi-quantitative analysis. The scale is semi-quantitative because the value for probability has not been precisely determined but is known to be within an estimated range (such as an order of magnitude). Judgments are made on the relative values for the severity levels, but no attempt is made to provide a numeric scale. In practice, severity is seldom quantified because of the difficulty in comparing the value of a death to the value of a permanent disability or the value of an injury that requires a surgical intervention.

In this example, a 5 × 5 risk matrix is used. The levels of probability and severity are defined in Tables D.3 and D.4 respectively.

Table D.3 — Example of five qualitative severity levels

Common terms	Possible description
Catastrophic	Results in patient death
Critical	Results in permanent impairment or life-threatening injury
Serious	Results in injury or impairment requiring professional medical intervention
Minor	Results in temporary injury or impairment not requiring professional medical intervention
Negligible	Inconvenience or temporary discomfort

Table D.4 — Example of semi-quantitative probability levels

Common terms	Examples of probability range
Frequent	$\geqslant 10^{-3}$
Probable	$< 10^{-3}$ and $\geqslant 10^{-4}$
Occasional	$< 10^{-4}$ and $\geqslant 10^{-5}$
Remote	$< 10^{-5}$ and $\geqslant 10^{-6}$
Improbable	$< 10^{-6}$

The definitions for probability can be different for different product families. For example, a manufacturer can choose to use one set of definitions for X-ray machines, but can have a different set of definitions for sterile disposable dressings. Different measures of probability will be appropriate, depending upon the application. Scales for probability can include “probability of harm per use,” “probability of harm per device,” “probability of harm per hour of use,” etc.

There are several significant factors and statistics that are important for analysing the probability of occurrence. These statistics include, but are not limited to, the following.

— How often is a particular medical device used?

— What is the lifetime of the medical device?

— Who makes up the user and patient populations?

— What is the number of users/patients?

— How long and under what circumstances is the user/patient exposed?

The estimated risks (R_1, R_2, R_3….) are entered into the appropriate cells.

An example of a completed 5 × 5 matrix is shown in Figure D.3.

		Qualitative severity levels				
		Negligible	**Minor**	**Serious**	**Critical**	**Catastrophic**
Semi-quantitative probability levels	**Frequent**					
	Probable	R_1	R_2			
	Occasional		R_4		R_5	R_6
	Remote					
	Improbable			R_3		

Figure D.3 — Example of a semi-quantitative risk matrix

Other matrices besides 3 × 3 or 5 × 5 can be utilized; however, matrices with more than five levels can require significantly more data to be able to meaningfully distinguish between the various levels. Rationales for the selection of matrices and their outcome scores should be documented. Note that matrices with three levels might not always be sufficiently accurate for adequate decision making. While the above examples were 3 × 3 and 5 × 5, there is no need that these matrices be balanced. For example, a 4 × 5 matrix could be appropriate for a given application.

D.4 Risk evaluation and risk acceptability

This International Standard does not specify acceptable risk. That decision is left to the manufacturer. Methods of determining acceptable risk include, but are not limited to, the following:

— using applicable standards that specify requirements which, if implemented, will indicate achievement of acceptability concerning particular kinds of medical devices or particular risks;

— comparing levels of risk evident from medical devices already in use;

— evaluating clinical study data, especially for new technology or new intended uses;

taking into account the state of the art and available information such as technology and practice existing at the time of design.

“State of the art” is used here to mean what is currently and generally accepted as good practice. Various methods can be used to determine "state of the art" for a particular medical device. Examples are:

— standards used for the same or similar devices;

— best practices as used in other devices of the same or similar type;

— results of accepted scientific research.

State of the art does not necessarily mean the most technologically advanced solution.

It is well established that the perception of risk often differs from empirically determined risk estimates. Therefore, the perception of risk from a wide cross section of stakeholders should be taken into account when deciding what risk is acceptable. To meet the expectations of public opinion, it might be necessary to give additional weighting to some risks. In some cases, the only option could be to consider that identified stakeholder concerns reflect the values of society and that these concerns have been taken into account when the manufacturer has used the methods listed above.

One way of applying acceptability criteria is by indicating in a matrix such as Figure D.4 and Figure D.5 which combinations of probability of harm and severity of harm are acceptable or unacceptable. Such charts are usually, but not always, specific to a product and its particular intended use.

Qualitative probability levels	Qualitative severity levels: Negligible	Moderate	Significant
High	R_1	R_2	
Medium		R_4	R_5, R_6
Low		R_3	

Key

unacceptable risk

acceptable risk

Figure D.4 — Example of a qualitative 3 × 3 risk evaluation matrix

Semi-quantitative probability levels	Qualitative severity levels: Negligible	Minor	Serious	Critical	Catastrophic
Frequent					
Probable	R_1	R_2			
Occasional		R_4		R_5	R_6
Remote					
Improbable			R_3		

Key

unacceptable risk

acceptable risk

Figure D.5 — Example of a semi-quantitative risk evaluation matrix

It is also noted that the manufacturer's policy can further subdivide the acceptable region of the matrix (e.g. insignificant, investigate further risk reduction). See D.8.5.

D.5 Risk control

D.5.1 Risk control option analysis

There are several approaches to reducing risk, which can be used alone or in combination with each other. The designer/engineer has accordingly to explore different options how, in a reasonably practical way, to reduce risk(s) to acceptable levels. The following is a non-exhaustive list of risk control approaches that are commonly used.

a) Designing for inherent safety by:

— eliminating a particular hazard,

— reducing the probability of occurrence of the harm

or

— reducing the severity of the harm.

b) Adding protective measures by:

— using automatic cut-off or safety valves

or

— using visual or acoustic alarms to alert the operator to hazardous conditions.

c) Providing information for safety by:

— placing warnings in the labelling of the medical device,

— restricting the use or circumstances of use of the medical device,

— communicating about improper use, hazards that can occur, or other information that can help reduce risk,

— promoting use of personal protective equipment, such as gloves and eye-glasses, when handling toxic or hazardous materials,

— including information about measures to reduce harm,

— providing training for the operators to improve their performance or their capability in detecting errors,

or

— specifying necessary maintenance and maintenance intervals, maximum expected product service life, or how to dispose of the medical device properly.

Approaches a) to c) are listed in descending order with regard to their generally recognised effectiveness in reducing risk. The designer/engineer should take this and other factors into account before decisions are made on which combination of measures will be used.

D.5.2 Components and devices not designed using ISO 14971

It is recognised that the manufacturer might not be able to follow all the processes identified in this International Standard for each constituent component of the medical device, such as proprietary components, subsystems of non-medical origin, and medical devices designed prior to the publication this International Standard. In this case, the manufacturer should take special account of the need for additional risk control measures.

D.5.3 Risk control examples

Figure D.6 lists some examples of risk control measures that are commonly used. The decision to use any of these measures is product- and process-specific.

Product/ process	Example devices	Hazard	Inherent safe design	Protective measure	Information for safety
Single use medical device	Catheter	Bio-(cross)-contamination	Self-destruction after use	Obvious indication after first use	Warning against re-use and of the adverse consequence(s) that could arise from any such re-use
Active implant	Pacemaker	Electric fields	Use of non-electric drives and controls	Use of differential amplifiers and additional filter algorithms	Warning for commonly encountered hazardous situations
IVD medical device	Blood analyser	Incorrect result due to method bias	Implement traceable calibrators	Provide traceable trueness controls	Inform users of unacceptable deviation from assigned values
Software	Patient data management	Erroneous data	High integrity software	Use of checksums	Warnings on screen for user
Steam sterilization	Biopsy device, operation forceps	High temperature (material degradation)	Use of material that is compatible with high temperatures	Pressure and temperature monitoring and recording	Packaging and loading instructions

Figure D.6 — Some examples of risk control measures

D.5.4 Manufacturing processes and risk control

The lack of control of the manufacturing process can compromise safety requirements of the medical device, for example, by:

— introducing residues or unwanted particulates;

— affecting critical physical and chemical material properties like surface coating, tensile strength, resistance to ageing, homogeneity, etc.;

— exceeding critical tolerances

or

— impairing the integrity of welding, gluing, or bonding of components.

It is important to identify elements of the manufacturing process to control such risk(s).

Some of these risks are controlled most effectively by careful attention to the manufacturing process. In these instances, techniques such as Hazard Analysis of Critical Control Points (HACCP) can be useful (see G.6).

D.5.5 Standards and risk control

By applying a standard, the manufacturer can simplify the task of analysing the remaining residual risk, but it needs to be emphasised that standards might not address all the risks associated with a device.

Many standards address inherent safety, protective measures, and information for safety for medical devices. When relevant safety standards exist, they can address some or all of the risks that need to be dealt with for a particular medical device. It is presumed that, in the absence of objective evidence to the contrary, meeting the requirements of the relevant standards results in particular risks being reduced to an acceptable level, but the responsibility for verifying that this is the case for a particular device rests with the manufacturer.

D.6 Risk/benefit analysis

D.6.1 General

A risk/benefit analysis is not required by this International Standard, for every risk. A risk/benefit analysis is used to justify a risk once all practicable measures to reduce the risk have been applied. If, after applying these measures, the risk is still not judged acceptable, a risk/benefit analysis is needed to establish whether the medical device is likely to provide more benefit than harm.

Generally, if all practicable risk control measures are insufficient to satisfy the risk acceptability criteria in the risk management plan, the design shall be abandoned. In some instances, however, greater risks can be justified, if they are outweighed by the expected benefits of using the device. This International Standard allows manufacturers an opportunity to do a risk/benefit analysis to determine whether the residual risk is acceptable based on benefit.

The decision as to whether risks are outweighed by benefits is essentially a matter of judgment by experienced and knowledgeable individuals. An important consideration in the acceptability of a residual risk is whether an anticipated clinical benefit can be achieved through the use of alternative design solutions or therapeutic options that avoid exposure to that risk or reduce the overall risk. The practicability of further risk reduction should be taken into account before considering benefit (see D.8.4). This International Standard explains how risks can be characterized so that a risk estimate can be determined with confidence. Unfortunately, there is no standardized approach to estimate benefit.

D.6.2 Benefit estimation

The benefit arising from a medical device is related to the likelihood and extent of improvement of health expected from its use. Benefit can be estimated from knowledge of such things as:

— the performance expected during clinical use;

— the clinical outcome expected from that performance;

— factors relevant to the risks and benefits of other treatment options.

Confidence in the benefit estimate is strongly dependent on the reliability of evidence addressing these factors. This includes recognition that there is likely to be a range of possible outcomes and factors such as the following that need to be taken into account.

— It will be difficult to compare different outcomes, e.g. which is worse, pain or loss of mobility? Different outcomes can result from the side effects being very different from the initial problem.

— It is difficult to take account of non-stable outcomes. These can arise both from the recovery time and long-term effects.

Because of the difficulties in a rigorous approach, it is generally necessary to make simplifying assumptions. Therefore, it will usually prove expedient to focus on the most likely outcomes for each option and those that are the most favourable or unfavourable.

An estimate of clinical benefit can vary markedly between different stages of the design cycle. If reliable clinical data demonstrating the consistent performance and effectiveness of the product are available, the clinical benefit can be estimated confidently. In cases where clinical data are limited in quantity or quality, benefit is estimated with greater uncertainty from whatever relevant information is available. For example, it is sometimes necessary early in the process to estimate the expected degree of improvement to health from the design intention; however, in the absence of relevant clinical data, the likelihood of achieving the intended performance and the desired clinical effect will have to be predicted by reference to quality assurance measures and *in vitro* or *in vivo* performance characteristics.

Where significant risks are present, and there is a high degree of uncertainty in the benefit estimate, it will be necessary to verify the anticipated performance or efficacy as soon as possible through a surrogate study or a clinical investigation. This is essential to confirm that the risk/benefit balance is as expected and to prevent unwarranted exposure of patients to a large residual risk. ISO 14155-1[10] and ISO 14155-2[11] specify procedures for the conduct and performance of clinical investigations of medical devices.

D.6.3 Criteria for risk/benefit judgments

Those involved in making risk/benefit judgments have a responsibility to understand and take into account the technical, clinical, regulatory, economic, sociological and political context of their risk management decisions. This can involve an interpretation of fundamental requirements set out in applicable regulations or standards, as they apply to the product in question under the anticipated conditions of use. Since this type of analysis is highly product-specific, further guidance of a general nature is not possible. Instead, the safety requirements specified by standards addressing specific products or risks can be presumed to be consistent with an acceptable level of risk, especially where the use of those standards is sanctioned by the prevailing regulatory system. Note that a clinical investigation, in accordance with a legally recognised procedure, might be required to verify that the balance between medical benefit and residual risk is acceptable.

D.6.4 Risk/benefit comparison

A direct comparison of risks and benefits is only valid if a common scale is used. When a common scale is used, the risk to benefit comparison can be evaluated quantitatively. Indirect risk/benefit comparisons do not use a common scale and are evaluated qualitatively. Whether quantitative or qualitative, risk/benefit comparisons should take the following into account.

— Initially, a literature search for the hazard(s) and product class in question can provide significant insight into the ratio of benefit to risk.

— High-benefit/high-risk devices usually represent the best available technology that provides a medical benefit but does not completely eliminate risk of injury or illness. Therefore, an understanding of current technology as it relates to medical practice is required for accurate risk/benefit analysis. The risk/benefit comparison can be expressed in terms of a comparison to other marketed products.

— To validate that a device meets acceptable risk/benefit criteria, clinical testing is often required. Clinical testing can quantify benefits and risks. Also, acceptability to society could be addressed in a clinical study, i.e., patients, users, medical practitioners.

— For high-risk/high-benefit devices, labelling should convey adequate information to appropriate users, patients, and medical practitioners to ensure appropriate risk/benefit decisions are made by individuals prior to use.

— High-risk/high-benefit devices typically have additional regulatory requirements that have to be achieved prior to marketing.

Prior to launching a new or revised product requiring a risk/benefit analysis, the manufacturer should summarise the available information related to the risk/benefit determination and document the risk/benefit conclusions with rationales as applicable. Guidance on conducting a literature search of clinical data can be found in Annex A of ISO 14155-1:2003[10].

D.6.5 Examples of risk/benefit decisions

Example 1: Burns can occur where the return electrode of a high-frequency surgery device is improperly attached to the patient. Although conformance to the relevant product standard minimizes the probability of such burns, they still occur. Nevertheless, the benefit of using a high-frequency surgery device as compared to other surgical techniques outweighs the residual risk of burns.

Example 2: Although applying X-rays to patients is known to cause harm, the clinical effectiveness of conventional diagnostic imaging almost always justifies its use. However, the unwanted effects of radiation on the patient are not ignored. Standards exist to minimize unnecessary radiation exposure to patients, embodying the risk/benefit decision. When a new application of ionizing radiation to diagnostic imaging is contemplated and existing standards are not applicable, the manufacturer should verify that the results of the risk/benefit analysis are at least as favourable as that of alternative products and treatments.

Example 3: Once implanted, some cochlear implant components, such as the implant receiver stimulator with electrode array, cannot easily be replaced. They are intended to remain implanted for life and are required to perform reliably for years and even decades. (This is an especially important consideration in the case of a young adult or child.) Accelerated reliability testing of these components can be conducted for specific failure mechanisms. However, validating the reliability of components that are to last for decades is not practical. Therefore, the overall residual risk including the risk of device failure is weighed against the benefit afforded by the potential for hearing improvement. The overall residual risk will depend on the estimated reliability of the components and the confidence that can be given to the reliability estimates for those components that cannot be validated. In some cases the residual risk will outweigh the benefit; in other cases the benefit will outweigh the risk.

D.7 Overall residual risk evaluation

D.7.1 General

Overall residual risk evaluation is the point where residual risk is viewed from a broad perspective. The manufacturer shall consider how to evaluate the remaining residual risk with respect to the acceptability criteria.

Overall residual risk evaluation needs to be performed by persons with the knowledge, experience, and authority to perform such tasks. It is often desirable to involve application specialists with knowledge of and experience with the medical device (see 3.3).

There is no preferred method for evaluating overall residual risk and the manufacturer is responsible for determining an appropriate method. Some possible techniques are listed together with considerations affecting their selection.

D.7.2 Event tree analysis

A specific sequence of events can lead to several different individual risks, each of which contributes to the overall residual risk. For example, the re-use of a single-use device can be associated with re-infection, leaching of toxic substances, mechanical failure due to ageing and bio-incompatible disinfectant residues. An event tree can be a suitable method for analysing these risks. The individual residual risks need to be considered together to determine if the overall residual risk is acceptable.

D.7.3 Review for conflicting requirements

Risk control measures that are appropriate for individual risks can result in conflicting requirements, e.g. a warning to address the risk of an unconscious patient falling off a patient table could be “never leave an unconscious patient unattended”; this could conflict with a warning “make X-ray exposure away from the patient” intended to protect an operator from being exposed to X-rays.

D.7.4 Fault tree analysis

Harm to a patient or user can originate from different hazardous situations (see Annex E). In such cases, the probability of the harm used to determine the overall residual risk is based on a combination of the individual probabilities. A fault tree analysis can be a suitable method for deriving the combined probability of harm.

D.7.5 Review of warnings

A warning considered on its own could provide adequate risk reduction, however too many warnings can reduce the effect of individual warnings. Analysis might be needed to assess if there is an over-reliance on warnings and the impact that such over-reliance could have on the risk reduction and on the overall residual risk.

D.7.6 Review of the operating instructions

A consideration of all the operating instructions for the device might discover that information is inconsistent or too difficult to follow.

D.7.7 Compare risks

Another method would be to compare the collated individual residual risks posed by the device against that for similar existing devices, e.g. risk by risk taking account of different contexts of use. Care should be taken in such comparisons to use up-to-date information on adverse events for the existing devices.

D.7.8 Review by application experts

An assessment of the benefits to the patient associated with the use of the device can be required in order to demonstrate acceptability of the device. One approach could be to get a fresh view of the overall residual risk by using application specialists that were not directly involved in the development of the device. The application specialists would evaluate the acceptability of the overall residual risks considering aspects such as usability by using the device in a representative clinical environment. Then, evaluation of the device in the clinical environment could confirm the acceptability.

D.8 As-low-as-reasonably-practicable approach

D.8.1 General

When establishing the risk acceptability policy, the manufacturer might find it convenient to use an as-low-as-reasonably-practicable approach.

After a particular risk control option has been applied, there are three possible results:

a) the residual risk exceeds the manufacturer's criterion for risk acceptability;

b) the residual risk is acceptable because it is so small as to be negligible

or

c) the residual risk is between the two states specified in a) and b); for these risks the residual risk is acceptable for the option that reduces the risk to the lowest practicable level, bearing in mind the benefits resulting from its acceptance and taking into account the costs of any further reduction.

The as-low-as-reasonably-practicable approach can be used as part of risk control options analysis (6.2). Risks for which the probability cannot be estimated would normally use the as-low-as-reasonably-practicable approach.

D.8.2 Risk levels

Below a certain level the residual risk will be regarded as so insignificant that it is comparable with the everyday risks we all experience and tolerate. Such risks can be called negligible.

There is an important distinction to be made between residual risks that are so low that there is no need to consider them and residual risks which are greater than that but which are accepted because of the associated benefits and the impracticability of reducing the risks.

When a risk is estimated, the first question to be asked is whether the risk is already negligible and therefore there is no need to investigate risk reduction options. This decision is made once for each risk.

D.8.3 Risk control option analysis

Risk reduction options are investigated for each risk that is not negligible. Risk reduction might or might not be practicable, but it should be considered. The possible outcomes are:

— one or more risk control measures brings the risk down to an insignificant level and it is not necessary to consider it further

or

— whether or not some risk reduction is possible, reducing the risk to an insignificant level is not practicable.

Any specific residual risk that remains after the risk control measures are applied should be evaluated using the criteria defined in the risk management plan. If the residual risk does not exceed the manufacturer's criterion for risk acceptability and the as-low-as-reasonably-practicable approach has been applied, then no further risk reduction is necessary.

D.8.4 Practicability considerations

It might be thought that any risk associated with a medical device would be acceptable if the patient's prognosis were improved. This cannot be used as a rationale for the acceptance of unnecessary risk. All risks should be reduced to the lowest level practicable, bearing in mind the state of the art and the benefits of accepting the risk and the practicability of further reduction.

Practicability refers to the ability of a manufacturer to reduce the risk. Practicability has two components:

— technical practicability;

— economic practicability.

Technical practicability refers to the ability to reduce the risk regardless of cost. The following are a few examples where technical practicability is questionable:

— including so many warning/caution labels that the user is hampered in operating the medical device;

— multiple alarms that create confusion;

— communicating too many residual risks so that the operator has difficulty understanding which ones are really important;

— overly complex procedures for using the medical device so that the intended use is compromised;

— using risk control measures that compromise the intended use (e.g. reducing the power of an electrosurgical unit below its effective level).

Economic practicability refers to the ability to reduce the risk without making the medical device an unsound economic proposition. These decisions necessarily involve making trade-offs between accepting risks and availability of treatments or diagnosis. Cost and availability implications are considered in deciding what is practicable to the extent that these impact upon the preservation, promotion or improvement of human health. However, economic practicability should not be used as a rationale for the acceptance of unnecessary risk. The following is an example in which economic practicability is questionable:

— duplication of every critical component in a defibrillator.

Risks that nearly exceed the manufacturer's criterion for risk acceptability should normally be reduced, even at considerable cost. Near the insignificant region, further risk reduction might not be needed unless it can be easily accomplished.

In some cases, an as-low-as-reasonably-achievable approach is used (e.g. radiation protection). In this case the achievability instead of the practicability is taken into account. In effect this means only taking into account the technical achievability and ignoring the economic practicability.

D.8.5 Example

Figure D.7 is an example of a risk chart where the acceptable region of the matrix has been further subdivided. The estimated risks (R_1, R_2, R_3,...) have been entered into the appropriate cells.

Semi-quantitative probability levels	Qualitative severity levels: Negligible	Minor	Serious	Critical	Catastrophic
Frequent					
Probable	R_1	R_2			
Occasional		R_4		R_5	R_6
Remote					
Improbable			R_3		

Key

unacceptable risk

investigate further risk reduction

insignificant risk

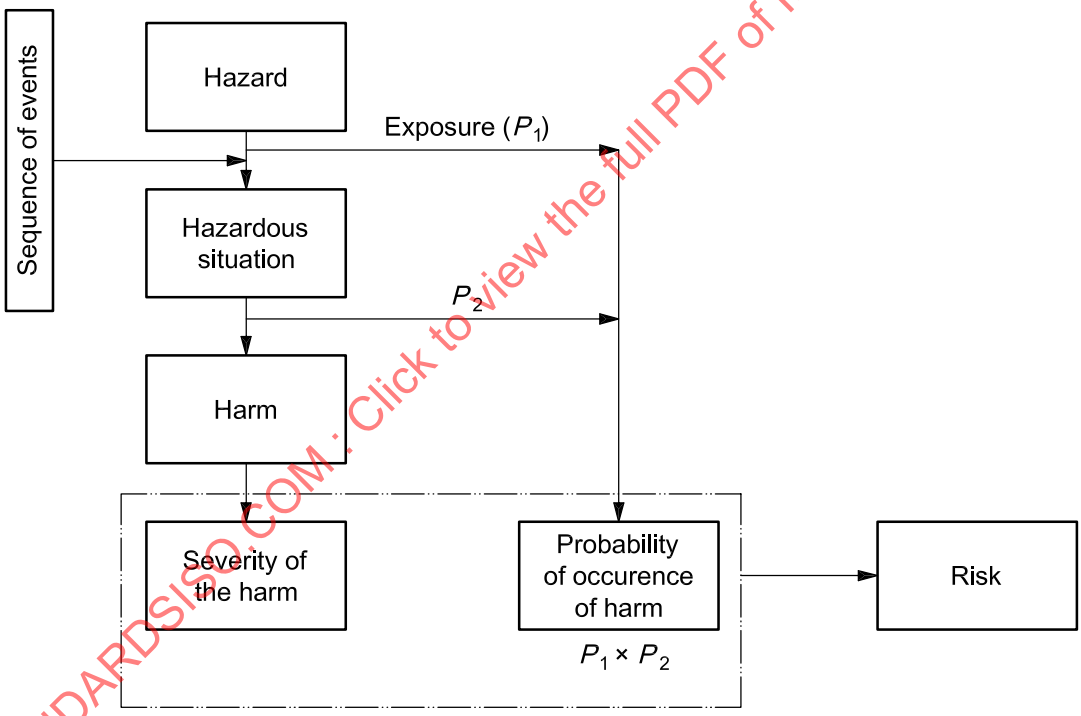
Figure D.7 — Example of a three-region evaluation matrix

Annex E
(informative)

Examples of hazards, foreseeable sequences of events and hazardous situations

E.1 General

Subclause 4.3 requires that the manufacturer compile a list of known and foreseeable hazards associated with the medical device in both normal and fault conditions. Subclause 4.4 requires the manufacturer to consider the foreseeable sequences of events that can produce hazardous situations and harm. According to the definitions, a hazard cannot result in harm until such time as a sequence of events or other circumstances (including normal use) lead to a hazardous situation. At this stage the risk can be assessed by estimating both severity and probability of occurrence of harm that could result (see Figure E.1).



NOTE P_1 is the probability of a hazardous situation occurring.

P_2 is the probability of a hazardous situation leading to harm.

Figure E.1 — Pictorial representation of the relationship of hazard, sequence of events, hazardous situation and harm

A good starting point for this compilation is a review of experience with the same and similar types of device. The review should take into account a manufacturer's own experience as well as the experience of other manufacturers as reported in adverse event databases, publications and other available sources. This type of review is particularly useful for the identification and listing of typical hazardous situations for a device and the associated harm that can occur. Next, this listing and aids such as the list of examples in Table E.1 can be used to compile an initial list of hazards.

It is then possible to begin identification of some of the sequences of events that together with hazards could result in hazardous situations and harm. Since many hazards might never result in harm and can be eliminated from further consideration, it could be useful to perform this analysis by starting with the harm the device might cause and work backwards from there. However, although this approach is useful for the reason described, it should be recognised that it is not a thorough analysis. Many sequences of events will only be identified by the systematic use of risk analysis techniques such as those described in Annex G. Analysis and identification are further complicated by the many initiating events and circumstances that have to be taken into consideration such as those listed in Table E.2. Thus, more than one risk analysis technique, and sometimes the use of complementary techniques, are needed to complete a comprehensive analysis. Table E.3 provides examples of the relationship between hazards, sequences of events, hazardous situations, and harm.

Although compilation of the lists of hazards, hazardous situations, and sequences should be completed as early as possible in the design and development process to facilitate risk control, in practice identification and compilation is an ongoing activity that continues throughout post-production.

This annex provides a non-exhaustive list of possible hazards that can be associated with different medical devices (Table E.1) and a list of initiating events and circumstances (Table E.2) that can result in hazardous situations, which can result in harm. Table E.3 provides examples in a logical progression of how a hazard can be transformed into a hazardous situation and produce harm by a sequence of events or circumstances.

Recognising how hazards progress to hazardous situations is critical for estimating the probability of occurrence and severity of harm that could result. An objective of the process is to compile a comprehensive set of hazardous situations. The identification of hazards and sequences of events are stepping stones to achieve this. The lists in the tables in this annex can be used to aid in the identification of hazardous situations. What is called a hazard needs to be determined by the manufacturer to suit the particular analysis.

E.2 Examples of hazards

The list in Table E.1 can be used to aid in the identification of hazards associated with a particular medical device, which could ultimately result in harm to the patient or others.

Table E.1 — Examples of hazards

Examples of energy hazards	Examples of biological and chemical hazards	Examples of operational hazards	Examples of information hazards
Electromagnetic energy Line voltage Leakage current — enclosure leakage current — earth leakage current — patient leakage current Electric fields Magnetic fields **Radiation energy** Ionizing radiation Non-ionizing radiation **Thermal energy** High temperature Low temperature **Mechanical energy** Gravity — falling — suspended masses Vibration Stored energy Moving parts Torsion, shear and tensile force Moving and positioning of patient Acoustic energy — ultrasonic energy — infrasound energy — sound High pressure fluid injection	**Biological** Bacteria Viruses Other agents (e.g. prions) Re- or cross-infection **Chemical** Exposure of airway, tissues, environment or property, e.g. to foreign materials: — acids or alkalis — residues — contaminates — additives or processing aids — cleaning, disinfecting or testing agents — degradation products — medical gasses — anaesthetic products **Biocompatibility** Toxicity of chemical constituents, e.g.: — allergenicity/ irritancy — pyrogenicity	**Function** Incorrect or inappropriate output or functionality Incorrect measurement Erroneous data transfer Loss or deterioration of function **Use error** Attentional failure Memory failure Rule-based failure Knowledge-based failure Routine violation	**Labelling** Incomplete instructions for use Inadequate description of performance characteristics Inadequate specification of intended use Inadequate disclosure of limitations **Operating instructions** Inadequate specification of accessories to be used with the medical device Inadequate specification of pre-use checks Over-complicated operating instructions **Warnings** Of side effects Of hazards likely with re-use of single-use medical devices **Specification of service and maintenance**

E.3 Examples of initiating events and circumstances

In order to identify foreseeable sequences of events, it is often useful to consider initiating events and circumstances that can cause them. Table E.2 provides examples of initiating events and circumstances, organized into general categories. Although the list is certainly not exhaustive, it is intended to demonstrate the many different types of initiating events and circumstances that need to be taken into account to identify the foreseeable sequences of events for a device.

Table E.2 — Examples of initiating events and circumstances

General Category	Examples of initiating events and circumstances
Incomplete requirements	Inadequate specification of: — design parameters — operating parameters — performance requirements — in-service requirements (e.g. maintenance, reprocessing) — end of life
Manufacturing processes	Insufficient control of changes to manufacturing processes Insufficient control of materials/materials compatibility information Insufficient control of manufacturing processes Insufficient control of subcontractors
Transport and storage	Inadequate packaging Contamination or deterioration Inappropriate environmental conditions
Environmental factors	Physical (e.g. heat, pressure, time) Chemical (e.g. corrosions, degradation, contamination) Electromagnetic fields (e.g. susceptibility to electromagnetic disturbance) Inadequate supply of power Inadequate supply of coolant
Cleaning, disinfection and sterilization	Lack of, or inadequate specification for, validated procedures for cleaning, disinfection and sterilization Inadequate conduct of cleaning, disinfection and sterilization
Disposal and scrapping	No or inadequate information provided Use error
Formulation	Biodegration Biocompatibility No information or inadequate specification provided Inadequate warning of hazards associated with incorrect formulations Use error
Human factors	Potential for use errors triggered by design flaws, such as — confusing or missing instructions for use — complex or confusing control system — ambiguous or unclear device state — ambiguous or unclear presentation of settings, measurements or other information — misrepresentation of results — insufficient visibility, audibility or tactility — poor mapping of controls to actions, or of displayed information to actual state — controversial modes or mapping as compared to existing equipment — use by unskilled/untrained personnel — insufficient warning of side effects — inadequate warning of hazards associated with re-use of single-use medical devices — incorrect measurement and other metrological aspects — incompatibility with consumables/accessories/other medical devices — slips, laps and mistakes

Table E.2 (*continued*)

General Category	Examples of initiating events and circumstances
Failure modes	Unexpected loss of electrical/mechanical integrity Deterioration in function (e.g. gradual occlusion of fluid/gas path, or change in resistance to flow, electrical conductivity) as a result of ageing, wear and repeated use Fatigue failure

E.4 Examples of relationships between hazards, foreseeable sequences of events, hazardous situations and the harm that can occur

Table E.3 illustrates the relationship between hazards, foreseeable sequences of events, hazardous situations and harm for some simplified examples. Another general example of a sequence of events involving indirect risk is shown in Figure H.1 for IVD medical devices.

Remember that one hazard can result in more than one harm and that more than one sequence of events can give rise to a hazardous situation.

The decision on what constitutes a hazardous situation needs to be made to suit the particular analysis being carried out. In some circumstances it can be useful to describe a cover being left off a high voltage terminal as a hazardous situation, in other circumstances the hazardous situation can be more usefully described as when a person is in contact with the high voltage terminal.

Table E.3 — Relationship between hazards, foreseeable sequences of events, hazardous situations and the harm that can occur

Hazard	Foreseeable sequence of events	Hazardous situation	Harm
Electromagnetic energy (Line voltage)	(1) Electrode cable unintentionally plugged into power line receptacle	Line voltage appears on electrodes	Serious burns Heart fibrillation Death
Chemical (Volatile solvent)	(1) Incomplete cleaning of volatile solvent used in manufacturing (2) Solvent residue converts to gas at body temperature	Development of gas bubbles in the blood stream during dialysis	Gas embolisms Brain damage Death
Biological (Microbial contamination)	(1) Inadequate instructions provided for decontaminating re-used anaesthesia tubing (2) Contaminated tubing used during anaesthesia	Bacteria released into airway of patient during anaesthesia	Bacterial infection Death
Electromagnetic energy (ESD)	(1) Electrostatically charged patient touches infusion pump (2) ESD causes pump and pump alarms to fail (3) Insulin not delivered to patient	Failure to deliver insulin unknown to patient with elevated blood glucose level	Minor organ damage Decreased consciousness Coma, death
Function (No output)	(1) Implantable defibrillator battery reaches the end of its useful life (2) Inappropriately long interval between clinical follow-up visits	Device cannot deliver defibrillation shock when an arrhythmia occurs	Death

Annex F
(informative)

Risk management plan

F.1 General

The risk management plan can be a separate document or it can be integrated within other documentation, e.g. quality management system documentation. It can be self-contained or it can reference other documents to fulfil the requirements described in 3.4.

The makeup and level of detail for the plan should be commensurate with the level of risk associated with the medical device. The requirements identified in 3.4 are the minimum requirements for a risk management plan. Manufacturers can include other items such as time-schedule, risk analysis tools, or a rationale for the choice of specific risk acceptability criteria.

F.2 Scope of the plan

The scope identifies and describes the medical device and the life-cycle phases for which each element of the plan is applicable.

All elements of the risk management process should be mapped to the manufacturer's defined product life-cycle. Some of the elements of the risk management process will occur during the phases of the manufacturer's established product realization process (see for example ISO 13485:2003[8]), such as the design and development control. The remaining elements will occur during the other life-cycle phases through to product decommissioning. The risk management plan provides this mapping for a specific product either explicitly or by reference to other documents.

Although all the risk management activities need to be planned, a manufacturer can have several plans covering different parts of the life-cycle. By making it clear what scope each plan has, it is possible to confirm that the whole life-cycle is covered.

F.3 Assignment of responsibilities and authorities

The risk management plan should identify the personnel with responsibility for the execution of specific risk management activities, for example reviewer(s), expert(s), independent verification specialist(s), individual(s) with approval authority (see 3.2). This assignment can be included in a resource allocation matrix defined for the design project.

F.4 Requirements for review of risk management activities

The risk management plan should detail how and when these management reviews will occur for a specific medical device. The requirements for the review of risk management activities could be part of other quality system review requirements (see for example ISO 13485:2003[8], 7.3.4).

F.5 Criteria for risk acceptability including criteria for accepting risks when the probability of occurrence of harm cannot be estimated

Criteria for risk acceptability are derived from the manufacturer's policy for determining acceptable risk (see D.4). The criteria can be common for similar categories of medical device. Criteria for risk acceptability can be part of the manufacturer's established quality management system, which can be referenced in the risk management plan (see for example ISO 13485:2003[8], 7.1).

F.6 Verification activities

The risk management plan will specify how the two distinct verification activities required by this International Standard will be carried out (see also A.2.6.3). Verifying the effectiveness of risk control measures can require the collection of clinical data, usability studies, etc. (see also 2.28) The risk management plan can detail the verification activities explicitly or by reference to the plan for other verification activities.

F.7 Method or methods of obtaining relevant post-production information

The method or methods of obtaining post-production information can be part of established quality management system procedures (see for example ISO 13485:2003[8], 8.2). Manufacturers should establish generic procedures to collect information from various sources such as users, service personnel, training personnel, incident reports and customer feedback. While a reference to the quality management system procedures can suffice in most cases, any product-specific requirements should be directly added to the risk management plan.

The risk management plan should include documentation of decisions, based on a risk analysis, about what sort of post-market surveillance is appropriate for the device, for example, whether reactive surveillance is adequate or whether proactive studies are needed. Details of clinical studies envisaged should be specified.

Annex G
(informative)

Information on risk management techniques

G.1 General

This annex provides guidance on some available techniques for risk analysis, which can be used under 4.3. These techniques can be complementary and it might be necessary to use more than one of them. The basic principle is that the chain of events is analysed step by step.

Preliminary Hazard Analysis (PHA) is a technique that can be used early in the development process to identify the hazards, hazardous situations, and events that can cause harm when few of the details of the medial device design are known.

Fault Tree Analysis (FTA) is especially useful in safety engineering, early in the development stages, for the identification and prioritization of hazards and hazardous situations as well as for analysing adverse events.

Failure Mode and Effects Analysis (FMEA) and Failure Mode, Effects and Criticality Analysis (FMECA) are techniques by which an effect or consequences of individual components are systematically identified and is more appropriate as the design matures.

Hazard and Operability Study (HAZOP) and Hazard Analysis and Critical Control Point (HACCP) are typically used in the latter stages of the development phase to verify and then optimize design concepts or changes.

G.2 Preliminary Hazard Analysis (PHA)

PHA is an inductive method of analysis with the objective of identifying the hazards, hazardous situations and events that can cause harm for a given activity, facility or system. It is most commonly carried out early in the development of a project when there is little information on design details or operating procedures and can often be a precursor to further studies. It can be useful when analysing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used.

In a PHA, one formulates a list of hazards and generic hazardous situations by considering characteristics such as:

a) materials used or produced and their reactivity;

b) equipment used;

c) operating environment;

d) layout;

e) interfaces among system components.

The method is completed with the identification of the probabilities that the accident happens, the qualitative evaluation of the extent of possible injury or damage to health that could result, and the identification of possible remedial measures. The results obtained can be presented in different ways such as tables and trees.

See IEC 60300-3-9:1995[21], A.5, for more information on the procedures for PHA.

G.3 Fault Tree Analysis (FTA)

FTA is primarily a means of analysing hazards identified by other techniques and starts from a postulated undesired consequence, also called a “top event.” In a deductive manner, starting with the top event, the possible causes or fault modes of the next lower functional system level causing the undesired consequence are identified. Following stepwise identification of undesirable system operation to successively lower system levels will lead to the desired system level, which is usually either the component fault mode or the lowest level at which risk control measures can be applied. This will reveal the combinations most likely to lead to the postulated consequence. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). The fault modes identified in the tree can be events that are associated with hardware faults, human errors, or any other pertinent event, which leads to the undesired event. They are not limited to the single-fault condition.

FTA allows a systematic approach, which, at the same time, is sufficiently flexible to allow analysis of a variety of factors, including human interactions. FTA is used in risk analysis as a tool to provide an estimate of fault probabilities and to identify single fault and common mode faults that result in hazardous situations. The pictorial representation leads to an easy understanding of the system behaviour and the factors included, but, as the trees become large, processing of fault trees can require computer systems, which are readily available.

See IEC 61025[28] for more information on the procedures for FTA.

G.4 Failure Mode and Effects Analysis (FMEA)

FMEA is a technique by which the consequences of an individual fault mode are systematically identified and evaluated. It is an inductive technique using the question “What happens if ... ?”. Components are analysed one at a time, thus generally looking at a single-fault condition. This is done in a “bottom-up” mode, i.e., following the procedure to the next higher functional system level.

The FMEA is not restricted to a failure of a component's design but can also include failures in the manufacturing and assembling of components (Process FMEA) and the use or misuse of the product by the end user (Application FMEA). FMEA can be extended to incorporate an investigation of the individual component fault modes, their probability of occurrence and detectability (only to the degree that detection will enable preventive measures in the context of this International Standard) and also the degree of severity of the consequences. The FMEA can become a Failure Mode, Effects and Criticality Analysis (FMECA). In order to perform such an analysis, the construction of the medical device should be known in some detail.

FMEA can also be a useful technique to deal with use error. Disadvantages of this technique can arise from difficulties in dealing with redundancies and the incorporation of repair or preventive maintenance actions, as well as its restriction on single-fault conditions.

See IEC 60812[27] for more information on the procedures for FMEA.

G.5 Hazard and Operability Study (HAZOP)

HAZOP is similar to an FMEA. HAZOP is based on a theory that assumes accidents are caused by deviations from the design or operating intentions. It is a systematic technique for identifying hazards and operability problems. It was originally developed for use in the chemical process industry. While the use of HAZOP studies in the chemical industry focuses on deviations from design intent, there are alternative applications for a medical device developer. A HAZOP can be applied to the operation/function of the medical device (e.g., to the existing methods/processes used for the diagnosis, treatment or alleviation of disease as the “design intent”), or to a process used in the manufacture or maintenance/service of the medical device (e.g., sterilization) that can have significant impact on the function of the medical device. Two particular features of a HAZOP are as follows:

— it uses a team of people with expertise covering the design of the medical device and its application;

— guide words (NONE, PART OF, etc.) are used to help identify deviations from normal use.

The objectives of the technique are:

— to produce a full description of the medical device and how it is intended to be used;

— to review systematically every part of the intended use in order to discover how deviations from the normal operating conditions and the intended design can occur;

— to identify the consequences of such deviations and to decide whether these consequences can lead to hazards or operability problems.

When applied to the processes used to manufacture a medical device, the last objective is particularly useful in those cases where the medical device characteristics depend upon the manufacturing process.

See IEC 61882[29] for more information on the procedures for HAZOP.

G.6 Hazard Analysis and Critical Control Point (HACCP)

This is a systematic approach to the identification, evaluation and control of hazards. It was originally developed by NASA to prevent food poisoning of astronauts. It is based on a set of principles and defined terms. Applied to medical devices, HACCP is used for the control and monitoring of initiating causes of product hazards originating in processes, particularly manufacturing processes.

The core curriculum of HACCP consists of the following seven principles:

1	Conduct hazard analysis (4.3) and identify preventive measures (6.2)	2	Determine the critical control points (CCPs) (6.2)
3	Establish critical limits (4.2 and Clause 5)	4	Monitor each CCP (6.3 and Clause 9)
5	Establish corrective actions (Clause 9)	6	Establish verification procedures (6.3 and Clause 9)
7	Establish record-keeping and documentation procedures (3.5 and Clause 8)		

Each product has its own hazards that are related to its intended use. Hazardous situations could be initiated by events (causes or contributing factors) during different life-cycle stages, such as design, manufacturing, service, use, disposal, etc. For examples of some types of hazard, see Annex E.

The heart of an effective HACCP system focuses on the continuing control and monitoring **(HACCP principles 2, 3 and 4)**, of the identified hazards. A manufacturer demonstrates the effectiveness of established control measure(s), **(HACCP principles 5 and 6)**, by establishing methodically documented process mapping, process hazard analysis and critical control plan, **(HACCP principle 7)**.

The HACCP system uses the following tools as documented evidence for record keeping:

a) Process flow diagram

The purpose of the diagram is to provide a clear and simple description of the steps involved in the process. The diagram is necessary to the HACCP team in its subsequent work. The diagram can also serve as a future guide for others who need to understand the process for their verification activities. The scope of the flow diagram should cover all the processing steps that are directly under the control of the manufacturer.

b) Hazard analysis worksheet

Hazard analysis is the identification of hazards and of their initiating causes. The analysis records contain:

1) the identification and listing of steps in the process where hazards of significance occur;

2) the listing of all identified hazards and their significance associated with each step;

3) the listing of all preventive measures to control each hazard;

4) the identification of all the CCPs and their monitoring and controls.

c) HACCP plan

The written document is based upon the seven principles of HACCP and delineates the procedures to be followed to assure the control of a specific design, product, process or procedure. The plan includes:

1) identifying critical control points and critical limits identification;

2) monitoring and continuing control activities;

3) identifying and monitoring corrective action, verification and record-keeping activities.

Annex H
(informative)

Guidance on risk management for *in vitro* diagnostic medical devices

H.1 General

This annex provides additional guidance on the application of risk management to *in vitro* diagnostic (IVD) medical devices. It focuses on the management of risk to patients from the use of IVD examination results. Examples used are intended to illustrate concepts and serve as a starting point for risk management of IVD medical devices. They are not meant to be exhaustive. For definitions of terms used in this annex, see ISO 18113-1 [42].

IVD medical devices are intended for use in the collection, preparation and examination of samples taken from the human body. These devices include reagents, instruments, software, sample collection devices and receptacles, calibrators, control materials and related accessories. These devices can be used alone or in combination as a system.

Results provided by IVD medical devices can be used in the diagnosis of disease or other conditions, including determination of the state of health, in order to cure, mitigate, treat or prevent disease, as well as monitoring of therapeutic drugs and determining the safety of donated blood or organs. These devices can be used by persons with various levels of education, training and experience and in different settings with various degrees of environmental control. For example, some IVD medical devices are intended for use by professional analysts in medical laboratories, others by healthcare providers at the point-of-care, and still others by lay users at home.

At one end of the spectrum, IVD examinations performed in a laboratory are reported to a physician, who interprets the data and diagnoses, treats or monitors a patient; at the other end, IVD examinations are performed by the patient, who uses the results to monitor and medicate his/her condition.

Because of the diversity of IVD medical devices and their intended uses, these guidelines might not be applicable in all cases. For IVD medical devices for self-testing, the terms “patient” and “lay user” will be used interchangeably, even though these can be different individuals (e.g. a parent can perform glucose measurements on a diabetic child). Where the term “physician” is used, it should be recognised that other healthcare providers can also order, receive, interpret and act on IVD examination results.

IVD medical devices have the potential to contribute to patient harm. Incorrect or delayed results can lead to inappropriate or delayed medical decisions and actions that result in harm to patients. Incorrect results from IVD medical devices intended for transfusion or transplantation screening have the potential to cause harm to blood or organ recipients, and incorrect results from IVD medical devices intended for detecting infectious diseases have the potential to be a hazard to public health.

One risk model for IVD medical devices used in a laboratory is illustrated in Figure H.1. In this example, a failure of the manufacturer’s quality system (e.g. during design, development, manufacturing, packaging, labelling, distribution or servicing) initiates a sequence of events, beginning with a defective or malfunctioning IVD medical device. When the device fails in the medical laboratory, an incorrect examination result is produced. If the result is not identified as incorrect by the laboratory, it will be reported to the healthcare provider. If the healthcare provider does not recognise the result as incorrect, it could adversely influence the diagnosis and create a hazardous situation for the patient.

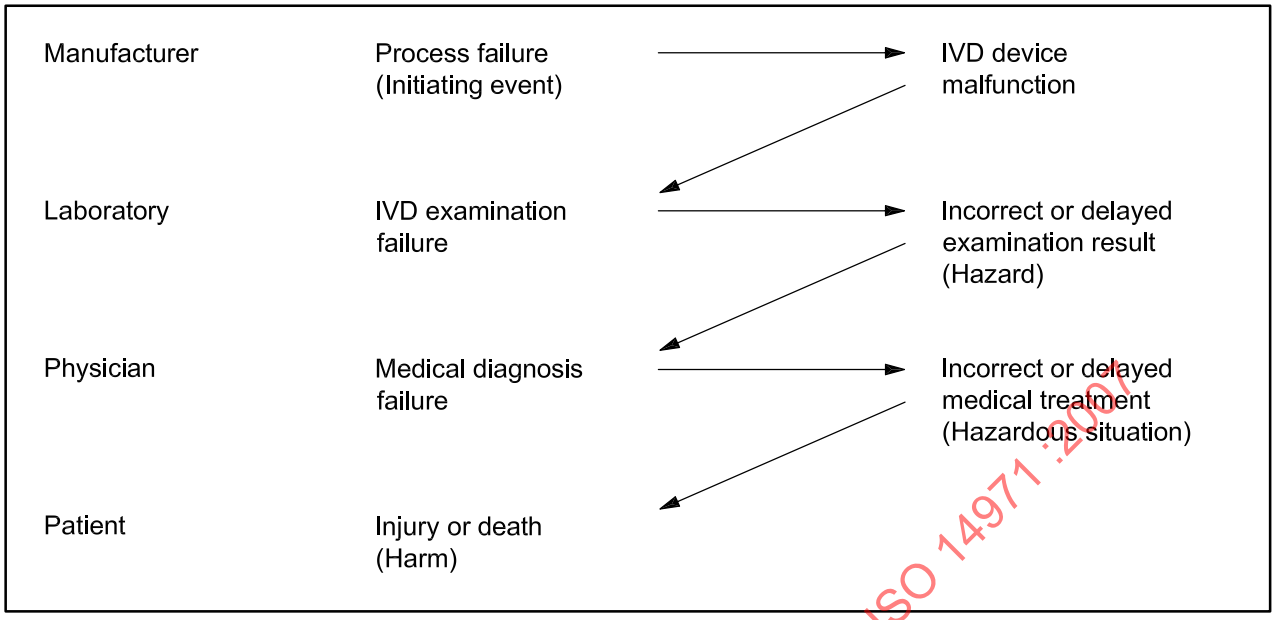


Figure H.1 — A risk model for laboratory use of IVD medical devices

Physicians use IVD examination results together with other available medical information to evaluate a patient and reach a diagnosis or guide therapy. In some cases, the IVD result can be the primary or even the only basis for a medical decision. The probability of a patient being harmed is a combination of the probabilities that each event illustrated in Figure H.1 would occur. Each individual probability of occurrence is partially offset by a probability that the hazard or hazardous situation will be detected by the manufacturer, the laboratory or the physician, thus allowing intervention and avoiding harm. The actual sequence of events will depend on the particular IVD medical device and its application.

Figure H.1 also shows that the laboratory can contribute to incorrect or delayed examination results, for example as a consequence of failing to follow procedures, adhere to maintenance or calibration schedules, or heed warnings or precautions. In addition, events leading to patient harm can also be initiated in the laboratory. The need for reduction of errors through risk management in the medical laboratory has been recognised, and information for safety as an output of the manufacturer's risk management process could serve as an input to the laboratory's risk management process.

H.2 Risk analysis

H.2.1 Identification of intended uses

H.2.1.1 General

IVD medical devices for laboratory or point of care examinations have two users: (1) an operator who performs the examination, and (2) a healthcare provider who receives, interprets and acts on the results. In the case of IVD medical devices for self-testing, the patient could be the only user.

Identification of intended uses should consider the objective intent of the manufacturer with respect to both elements of use: (1) use of the IVD medical device to produce an examination result, and (2) use of the examination result to reach a decision on the diagnosis, treatment or monitoring of a patient.

In this annex, the following terms should be interpreted broadly:

— “Operator” means the individual performing the IVD examination; this individual can be a laboratory worker, a healthcare provider or a lay person with minimal or no training;

— “Healthcare provider” means the individual ordering, receiving or acting upon the examination results on behalf of a patient; this individual can be a physician, nurse, ambulance attendant or any other person making a medical decision based upon IVD examination results.

H.2.1.2 Intended use

The intended use of an IVD medical device can include the measurement system, analyte, kind-of-property, sample matrix, examination procedure (qualitative, semi-quantitative or quantitative), type of operator and site of use.

For example, quantitative examinations for beta-human chorionic gonadotropin (β-hCG) concentration can be ordered for serum, plasma or urine samples. Not every β-hCG examination procedure has performance characteristics suitable for all three types of sample matrix.

H.2.1.3 Indications for use

The indications for use include the medical applications and patient populations for which the IVD medical device is intended.

For example, β-hCG results can be used for detecting pregnancy, for screening pregnant women for foetal Down's syndrome, and for monitoring certain cancers. Each medical application may have different requirements for measurement sensitivity, specificity, precision and trueness.

H.2.2 Identification of possible use errors

H.2.2.1 Use errors

Use errors include actions not intended by the manufacturer, such as procedure shortcuts, optimization attempts and improvization, as well as omissions of actions intended by the manufacturer, such as those prescribed in the instructions for use.

H.2.2.2 Examples of possible use errors by laboratory personnel

The following are examples of possible use errors in the laboratory. These examples are intended to illustrate the principles and are not an exhaustive checklist:

— use of an IVD medical device with an inappropriate calibrator, reagent, instrument or sample matrix;

— attempt to optimize an examination procedure in order to improve its performance characteristics;

— abbreviation of an examination procedure (taking “shortcuts”);

— neglect of instrument maintenance;

— disabling or failing to enable safety features;

— operation in adverse environmental conditions.

H.2.2.3 Examples of possible use errors by healthcare providers

The following are examples of possible use errors by a healthcare provider. These examples are intended to illustrate the principles and are not an exhaustive checklist:

— use of IVD examination results in order to screen a population for a disease when the examination procedure is intended for diagnosing the disease (the performance characteristics might not be appropriate for population screening);

— use of IVD examination results in order to diagnose a disease when the examination procedure is intended for monitoring a condition (the performance characteristics might not be appropriate for diagnosis);

— use of IVD examination results for a new clinical application that is not claimed by the manufacturer (the performance characteristics might not be appropriate for the new application).

H.2.2.4 Examples of possible use errors by patients in self-testing

The following are examples of possible use errors by a patient during self-testing. These examples are intended to illustrate the principles and are not an exhaustive checklist:

— using insufficient volume of sample;

— failure to insert a reagent module properly;

— dividing reagent strips (e.g. to reduce cost);

— disabling or failing to enable safety features;

— storing reagent in inappropriate conditions.

H.2.3 Identification of characteristics related to safety

H.2.3.1 General

In addition to chemical, mechanical, electrical and biological characteristics in common with other medical devices, IVD medical devices have performance characteristics that determine the accuracy of the examination results. Failure to meet the performance characteristics required for a specific medical use could result in a hazardous situation that should be evaluated for risk to patients.

H.2.3.2 Performance characteristics of quantitative examination procedures

Quantitative examination procedures are intended to determine the amount or concentration of an analyte. Results are reported on an interval scale. The main analytical performance characteristics of quantitative examination procedures are precision (imprecision), trueness (bias), analytical specificity and quantitation limit. Performance requirements depend on the medical application. A falsely high or falsely low result can lead to an incorrect diagnosis or delayed treatment, and the consequent harm to the patient could depend on the concentration of analyte and magnitude of bias.

H.2.3.3 Performance characteristics of qualitative examination procedures

Qualitative examination procedures are only intended to detect the presence or absence of an analyte. Results are reported as positive, negative or inconclusive. Performance of qualitative examination procedures is generally expressed in terms of diagnostic sensitivity and specificity. A positive result when the analyte is absent or a negative result when the analyte is present can lead to incorrect diagnosis or delayed treatment and to harm to the patient.

H.2.3.4 Dependability characteristics

When physicians depend on IVD examination results to help make urgent medical decisions, such as in an intensive critical care setting, timely results can be as important as accurate results. Failure to produce a result when it is needed could result in a hazardous situation.

H.2.3.5 Ancillary patient information

In some cases, examination results can require demographic information about the patient, as well as pertinent information about the sample or its examination for proper interpretation. Patient identification, sample identification, sample type, sample description, measurement units, reference intervals, age, gender, and genetic factors are examples of such information, which might be entered manually by a laboratory analyst or automatically by a laboratory computer system. If an IVD medical device is designed to report ancillary information with the examination result, failure to associate the correct information with the examination result could affect the proper interpretation of the result and lead to a hazardous situation.

H.2.4 Identification of known and foreseeable hazards

H.2.4.1 Hazards to the patient

From the standpoint of a patient, an IVD examination result is a hazard if it might lead to (1) inappropriate medical action that could result in injury or death, or (2) failure to take appropriate medical action that could prevent injury or death. An incorrect or delayed IVD examination result can be caused by an IVD medical device malfunction, which is the initiating hazard in a foreseeable sequence of events leading to a hazardous situation. The identification of hazards and sequences of events are intended to help the manufacturer compile a comprehensive list of hazardous situations. The manufacturer determines what is considered a hazard during the risk analysis.

As illustrated in Figure H.1, a hazardous situation can occur if a healthcare provider receives an incorrect result and acts upon it. A hazardous situation can also occur if a result is not available when it is needed. In the case of devices for self-testing, a hazardous situation can occur when an incorrect result is obtained by a patient, or a result is not available when it is needed.

For quantitative examination procedures, a result can be considered incorrect if the difference from a correct value exceeds a limit based on clinical utility. The clinical significance of an incorrect result can depend on the magnitude of the difference between the measured value and a correct value, as well as the physiological status of the patient (e.g., hypoglycaemic or hyperglycaemic).

For qualitative examination procedures, in which only a positive or negative result is provided, (e.g., HIV and pregnancy examinations), results are either correct or incorrect.

The following hazards could cause or contribute to misdiagnosis with the potential for harmful medical intervention or delays:

— incorrect results (see H.2.3.2 and H.2.3.3);

— delayed results (see H.2.3.4);

— incorrect information accompanying the result (see H.2.3.5).

H.2.4.2 Relationship to performance characteristics

Failure to meet specifications for any of the performance characteristics related to safety (see H.2.3) should be evaluated in order to determine if a hazardous situation could result.

Tools for analysing such hazards, such as Preliminary Hazard Analysis (PHA), Fault Tree Analysis (FTA), Failure Mode and Effects Analysis (FMEA), and Hazard Analysis and Critical Control Points (HACCP), are described in Annex G.

H.2.4.3 Identifying hazards in fault conditions

Failure modes that can result in not meeting the performance characteristics required for medical use (e.g., trueness, precision, specificity, etc.) should be considered when identifying IVD hazards in fault conditions; e.g.,

— within-batch inhomogeneity;

— batch-to-batch inconsistency;

— non-traceable calibrator value;

— non-commutable calibrator;

— non-specificity (e.g., interfering factors);

— sample or reagent carryover;

— measurement imprecision (instrument-related);

— stability failures (storage, transportation, in-use).

Failure modes that can result in delayed results in urgent care situations should be considered when identifying IVD hazards in fault conditions; e.g.,

— unstable reagent;

— hardware/software failure;

— packaging failure.

Failure modes that can result in incorrect patient information should be considered when identifying IVD hazards in fault conditions; e.g.,

— incorrect patient name or identification number;

— incorrect birth date or age;

— incorrect gender.

H.2.4.4 Identifying hazards in normal use

Incorrect results can also occur in normal use, even when the IVD medical device meets the performance characteristics claimed by the manufacturer. This could be due to the uncertainty of examination results, the biological variability of patient samples, choice of a cut-off value or other factors. An incorrect result in normal use could lead to a hazardous situation for an individual patient; e.g.,

— imperfect discrimination between positive and negative samples: qualitative examination procedures typically exhibit inherent false negative and false positive rates, caused in part by uncertainties associated with determination of a suitable cut-off value;

— uncertainty of measurement: state-of-the-art technology can limit the precision of quantitative IVD medical devices, such as glucose monitoring systems described in ISO 15197[13]; if performance criteria only require 95 % of the results to meet a specified limit based on medical utility, then up to 5 % of the individual results are allowed to fall outside the limit;

— unexpected influence of other constituents (interfering factors) in the sample matrix: new drugs, biochemical metabolites, heterophilic antibodies and sample preparation materials can affect the performance characteristics of an IVD examination procedure;

— natural heterogeneity of the analyte: antibodies and other proteins in blood samples are mixtures of different isoforms; published performance characteristics of an IVD examination procedure might not apply to all components of the mixture.

H.2.4.5 Identifying hazardous situations

Examples of hazardous situations created by IVD medical devices include:

— a blood bank receives false negative HIV or HBsAg results when screening transfusion blood;

— a physician makes a diagnosis of liver disease based on liver function examination results that were affected by bilirubin interference;

— a hypoglycaemic diabetic patient obtains falsely elevated blood glucose concentration measurements from a self-monitoring device.

H.2.5 Estimation of risks to patients

H.2.5.1 General

Risk estimation is based on the severity and probability of harm from each identified hazardous situation associated with the IVD medical device, in both normal and fault conditions.

In the case of an incorrect IVD examination result, key determinants are (a) the probability that the result will be recognised as incorrect and (b) the probability that the result will lead to an adverse medical action.

For results that falsely indicate that medical intervention should not be taken (e.g., false negative results or false “normal” results), assessment of risk should include (1) the prognosis of the condition left untreated, (2) the possibility of diagnosing the condition by other means and (3) the implications for individuals other than the patient (such as transmissibility of an infectious agent or a heritable condition, or exposure of a foetus to hazardous substances).

For results that falsely indicate that medical intervention should be taken (e.g., false positive results or false “abnormal” results), assessment of risk should consider (1) the potential harm of inappropriate treatment, (2) the possibility of excluding the condition by other means and (3) the implications for others (such as examination or treatment for exposure to an infectious agent, and counselling or treatment for a heritable condition).

H.2.5.2 Estimating severity of harm

The medical use of an IVD examination result determines the potential harm that an incorrect result can cause to a patient. The intended uses and possible misuses discussed in H.2.1 and H.2.2 should be considered.

Estimating the severity of harm requires an understanding of the medical use of the IVD examination results, the analytical performance requirements for each application and the extent to which medical decisions are based on IVD examination results. For this reason, qualified medical input to the risk estimation process is essential.

H.2.5.3 Estimating probability of occurrence

As illustrated in Annex E, the probability that use of an IVD medical device will result in harm depends on the cumulative probabilities associated with a series of events.