
**Medical laboratories — Application
of risk management to medical
laboratories**

*Laboratoires de biologie médicale — Application de la gestion des
risques aux laboratoires de biologie médicale*





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Foreword

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

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

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

This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

This first edition cancels and replaces (ISO/TS 22367:2008) which has been technically revised. [It also incorporates the Technical corrigendum ISO/TS 22367:2008/Cor.1:2009.]. The main changes compared to the previous edition are as follows:

- Change in title to indicate this document focusses on the complete risk management cycle for all processes in the medical laboratory. The part on continual improvement is left out;
- The numbering of the clauses is in accordance with the formal risk management process as indicated in [Figure 1](#);
- The content is as far as possible in agreement with the approach used in ISO 14971 Medical devices -Application of risk management to medical devices;
- The relation with ISO 15189:2012 is indicated in Annex A in which [Figure A.1](#) provides a flow chart which indicates how to apply risk management in the laboratory;
- Addition of 10 new annexes, all informative, providing valuable information about the different processes in the risk management cycle without demanding more than justified for the specific purpose;
- [Annex F](#) provides an extensive list of aspects which could be considered as source for risks in the different types of medical laboratories.

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

Introduction

This document provides medical laboratories with a framework within which experience, insight and judgment are applied to manage the risks associated with laboratory examinations. The risk management process spans the complete range of medical laboratory services: pre-examination, examination and post-examination processes, including the design and development of laboratory examinations.

ISO 15189 requires that medical laboratories review their work processes, evaluate the impact of potential failures on examination results, modify the processes to reduce or eliminate the identified risks, and document the decisions and actions taken. This document describes a process for managing these safety risks, primarily to the patient, but also to the operator, other persons, equipment and other property, and the environment. It does not address business enterprise risks, which are the subject of ISO 31000.

Medical laboratories often rely on the use of in vitro medical devices to achieve their quality objectives. Thus, risk management has to be a shared responsibility between the IVD manufacturer and the medical laboratory. Since most IVD manufacturers have already implemented ISO 14971:2007, "Medical devices - Application of risk management to medical devices," this standard has adopted the same concepts, principles and framework to manage the risks associated with the medical laboratory.

Activities in a medical laboratory can expose patients, workers or other stakeholders to a variety of hazards, which can lead directly or indirectly to varying degrees of harm. The concept of risk has two components:

- a) the probability of occurrence of harm;
- b) the consequence of that harm, that is, how severe the harm might be.

Risk management is complex because each stakeholder may place a different value on the risk of harm. Alignment of this standard with ISO 14971 and the guidance of the Global Harmonization Task Force (GHTF) is intended to improve risk communication and cooperation among laboratories, IVD manufacturers, regulatory authorities, accreditation bodies and other stakeholders for the benefit of patients, laboratories and the public health.

Medical laboratories have traditionally focused on detecting errors, which are often the consequence of use errors during routine activities. Use errors can result from a poorly designed instrument interface, or reliance on inadequate information provided by the manufacturer. They can also result from reasonably foreseeable misuse, such as intentional disregard of an IVD manufacturer's instructions for use, or failure to follow generally accepted medical laboratory practices. These errors can cause or contribute to hazards, which may manifest themselves immediately as a single event, or may be expressed multiple times throughout a system, or may remain latent until other contributory events occur. The emerging field of usability engineering addresses all of these 'human factors' as preventable 'use errors.' In addition, laboratories also have to contend with occasional failures of their IVD medical devices to perform as intended. Regardless of their cause, risks created by device malfunctions and use errors can be actively managed.

Risk management interfaces with quality management at many points in ISO 15189, in particular complaint management, internal audit, corrective action, preventive action, safety checklist, quality control, management review and external assessment, both accreditation and proficiency testing. Management of risk also coincides with the management of safety in the medical laboratories, as exemplified by the safety audit checklists in ISO 15190.

Risk management is a planned, systematic process that is best implemented through a structured framework. This standard is intended to assist medical laboratories with the integration of risk management into their routine organization, operation and management.

Medical laboratories — Application of risk management to medical laboratories

1 Scope

This document specifies a process for a medical laboratory to identify and manage the risks to patients, laboratory workers and service providers that are associated with medical laboratory examinations. The process includes identifying, estimating, evaluating, controlling and monitoring the risks.

The requirements of this document are applicable to all aspects of the examinations and services of a medical laboratory, including the pre-examination and post-examination aspects, examinations, accurate transmission of test results into the electronic medical record and other technical and management processes described in ISO 15189.

This document does not specify acceptable levels of risk.

This document does not apply to risks from post-examination clinical decisions made by healthcare providers.

This document does not apply to the management of risks affecting medical laboratory enterprises that are addressed by ISO 31000, such as business, economic, legal, and regulatory risks.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

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

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <http://www.electropedia.org/>

3.1

benefit

impact or desirable outcome of a *process* (3.19), *procedure* (3.17) or the use of a medical device on the health of an individual or a positive impact on patient management or public health

Note 1 to entry: Benefits include prolongation of life, reduction of pain, (relief of symptoms), improvement in function, or an increased sense of well-being.

3.2

event

occurrence or change of a particular set of circumstances

Note 1 to entry: An event can be one or more occurrences, and can have several causes.

Note 2 to entry: An event can consist of something not happening.

Note 3 to entry: An event can sometimes be referred to as an “incident” or “accident”.

Note 4 to entry: An event without consequences can also be referred to as a “near miss”, “incident”, “near hit” or “close call”.

[SOURCE: ISO Guide 73:2009, 3.5.1.3]

3.3

examination

set of operations having the object of determining the value or characteristics of a property

Note 1 to entry: In some disciplines (e.g., microbiology) an examination is the total activity of a number of tests, observations or measurements.

Note 2 to entry: Laboratory examinations that determine a value of a property are called quantitative examinations; those that determine the characteristics of a property are called qualitative examinations.

Note 3 to entry: Laboratory examinations are also often called assays or tests.

[SOURCE: ISO 15189:2012, 3.7]

3.4

frequency

number of *events* (3.2) or outcomes per defined unit of time

Note 1 to entry: Frequency can be applied to past *events* (3.2) or to potential future *events* (3.2), where it can be used as a measure of likelihood or *probability* (3.18)

[SOURCE: ISO Guide 73:2009, 3.6.1.5]

3.5

harm

injury or damage to the health of people, or damage to property or the environment

[SOURCE: ISO/IEC Guide 51:2014, 3.1]

3.6

hazard

source of potential *harm* (3.5)

[SOURCE: ISO Guide 73:2009, 3.5.1.4, modified – Note 1 to entry has been deleted.]

3.7

hazardous situation

circumstance in which people, property, or the environment are exposed to one or more *hazard(s)* (3.6)

[SOURCE: ISO/IEC Guide 51:2014, 3.4]

3.8

healthcare provider

individual authorized to deliver health services to a patient

EXAMPLE Physician, nurse, ambulance attendant, dentist, diabetes educator, laboratory technician, laboratory technologist, biomedical laboratory scientist medical assistant, medical specialist, respiratory care practitioner.

[SOURCE: ISO 18113-1:2009, 3.23]

3.9

in vitro diagnostic manufacturer

IVD manufacturer

natural or legal person with responsibility for the design, manufacture, packaging, or *labelling* (3.12) of an *IVD medical device* (3.10), assembling a system, or adapting an *IVD medical device* (3.10) 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 to entry: Provisions of national or regional regulations can apply to the definition of manufacturer.

[SOURCE: ISO 14971:2007, 2.8, modified – “manufacturer” has been changed to “in vitro diagnostic manufacturer”. “A medical device” has been changed to “an *IVD medical device*” (3.10). “Attention is drawn to the fact that” has been deleted in Note 1 to entry. In addition, Note 2 to entry has been deleted.]

3.10

in vitro diagnostic medical device

IVD medical device

device, whether used alone or in combination, intended by the manufacturer for the in vitro *examination* (3.3) of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes and including reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles

[SOURCE: ISO 18113-1:2009, 3.27]

3.11

in vitro diagnostic instrument

IVD instrument

equipment or apparatus intended by a manufacturer to be used as an *IVD medical device* (3.10)

[SOURCE: ISO 18113-1:2009, 3.26]

3.12

information supplied by the manufacturer

labelling

written, printed or graphic matter

- affixed to an *IVD medical device* (3.10) or any of its containers or wrappers or
- provided for use with an *IVD medical device* (3.10),

related to identification and use, and giving a technical description, of the *IVD medical device* (3.10), but excluding shipping documents

EXAMPLE Labels, *instructions for use* (3.13).

Note 1 to entry: In IEC standards, documents provided with a medical device and containing important information for the responsible organization or operator, particularly regarding safety, are called “accompanying documents”.

Note 2 to entry: Catalogues and material safety data sheets are not considered labelling of *IVD medical devices* (3.10).

[SOURCE: ISO 18113-1:2009, 3.29]

3.13

instructions for use

information supplied by the manufacturer (3.12) to enable the safe and proper use of an *IVD medical device* (3.10)

Note 1 to entry: Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an *IVD medical device* (3.10), as well as warnings and precautions.

[SOURCE: ISO 18113-1:2009, 3.30]

3.14

intended use

intended purpose

objective intent of an *IVD manufacturer* (3.9) regarding the use of a product, *process* (3.19) or *service* (3.37) as reflected in the specifications, instructions and information supplied by the *IVD manufacturer* (3.9)

Note 1 to entry: Intended use statements for *IVD labelling* (3.12) can include two components: a description of the functionality of the *IVD medical device* (3.10) (e.g., an immunochemical measurement *procedure* (3.17) for the detection of analyte “x” in serum or plasma), and a statement of the intended medical use of the *examination* (3.3) results.

[SOURCE: ISO 18113-1:2009, 3.31, modified — Note 2 has been deleted.]

3.15

laboratory management

person(s) who direct and manage the activities of a laboratory

Note 1 to entry: The term 'laboratory management' is synonymous with the term 'top management' in ISO 9000:2015, 3.1.1.

[SOURCE: ISO 15189:2012, 3.10]

3.16

likelihood

chance of something happening

Note 1 to entry: In risk management terminology, the word "likelihood" is used to refer to the chance of something happening, whether defined, measured or determined objectively or subjectively, qualitatively or quantitatively, and described using general terms or mathematically (such as a *probability* (3.18) or a *frequency* (3.4) over a given time period).

Note 2 to entry: The English language term "likelihood" does not have a direct equivalent in some languages; instead, the equivalent of the term "*probability*" (3.18) is often used. However, in English, "*probability*" (3.18) is often narrowly interpreted as a mathematical term. Therefore, in risk management terminology, "likelihood" is used with the intent that it should have the same broad interpretation as the term "*probability*" (3.18) has in many languages other than English.

[SOURCE: ISO Guide 73:2009, 3.6.1.1]

3.17

procedure

specified way to carry out an activity or a *process* (3.19)

Note 1 to entry: Procedures can be documented or not.

[SOURCE: ISO 9000:2015, 3.4.5]

3.18

probability

measure of the chance of occurrence expressed as a number between 0 and 1, where 0 is impossibility and 1 is absolute certainty

Note 1 to entry: See definition of *likelihood* (3.16), Note 2 to entry.

[SOURCE: ISO Guide 73:2009, 3.6.1.4]

3.19

process

set of interrelated or interacting activities that use inputs to deliver an intended result

Note 1 to entry: Whether the "intended result" of a process is called output, product or *service* (3.37) depends on the context of the reference.

[SOURCE: ISO 9000:2015, 3.4.1, modified — Note 2 to entry to Note 6 to entry have been deleted.]

3.20

reasonably foreseeable misuse

use of a product, *process* (3.19) or *service* (3.37) in a way not intended by the supplier, but which may result from readily predictable human behaviour

Note 1 to entry: Readily predictable human behaviour includes the behaviour of all types of intended *users* (3.42).

Note 2 to entry: In the context of consumer safety, the term "reasonably foreseeable use" is increasingly used as a synonym for both "*intended use*" (3.14) and "reasonably foreseeable misuse."

Note 3 to entry: Applies to use of *examination* (3.3) results by a *healthcare provider* (3.8) contrary to the *intended use* (3.14), as well as use of *IVD medical devices* (3.10) by the laboratory contrary to the *instructions for use* (3.13).

Note 4 to entry: Misuse includes abnormal use, i.e. intentional use of the device in a way not intended by the manufacturer.

Note 5 to entry: Adapted from ISO Guide 63:2012, 2.8, to apply to medical laboratories.

Note 6 to entry: Misuse is intended to mean incorrect or improper performance of an *examination* (3.3) *procedure* (3.17) or any *procedure* (3.17) critical for patient safety.

[SOURCE: ISO/IEC Guide 51:2014, 3.7, modified — “a product or system” has been changed to “a product, process (3.19) or service” (3.37), and “can” has been changed to “may”. In addition, “Note 3 to entry to Note 6 to entry” have been added.]

3.21 record

document stating results achieved or providing evidence of activities performed

Note 1 to entry: Records can be used, for example, to formalize traceability and to provide evidence of *verification* (3.44), preventive action and corrective action.

Note 2 to entry: Generally records need not be under revision control.

[SOURCE: ISO 9000:2015, 3.8.10]

3.22 residual risk

risk (3.23) remaining after *risk* (3.23) control measures have been taken

[SOURCE: ISO/IEC Guide 63:2012, 2.9]

3.23 risk

combination of the *probability* (3.18) of occurrence of *harm* (3.5) and the *severity* (3.38) of that *harm* (3.5)

Note 1 to entry: In standards that focus on management of risks to a business enterprise, such as ISO 31000, risk is defined as “the effect of uncertainty on objectives.” ISO 14971 and this document have retained the definition from ISO/IEC Guide 51:1999 because they are externally focused on risks to the safety of patients and other persons.

[SOURCE: ISO/IEC Guide 51:2014, 3.9]

3.24 risk analysis

systematic use of available information to identify *hazards* (3.6) and to estimate the *risk* (3.23)

Note 1 to entry: Risk analysis includes *examination* (3.3) of different sequences of *events* (3.2) that can produce *hazardous situations* (3.7) and *harm* (3.5).

[SOURCE: ISO/IEC Guide 51:2014, 3.10, modified — Note 1 to entry has been added.]

3.25 risk assessment

overall *process* (3.19) comprising a *risk analysis* (3.24) and a *risk evaluation* (3.28)

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.26 risk control

process (3.19) in which decisions are made and measures implemented by which *risks* (3.23) are reduced to, or maintained within, specified levels

[SOURCE: ISO/IEC Guide 63:2012, 2.12]

3.27

risk estimation

process (3.19) used to assign values to the *probability* (3.18) of occurrence of *harm* (3.5) and the *severity* (3.38) of that *harm* (3.5)

[SOURCE: ISO/IEC Guide 63:2012, 2.13]

3.28

risk evaluation

process (3.19) of comparing the estimated *risk* (3.23) against given risk criteria to determine the acceptability of the *risk* (3.23)

[SOURCE: ISO/IEC Guide 63:2012, 2.14]

3.29

risk management

systematic application of management policies, *procedures* (3.17) and practices to the tasks of analysing, evaluating, controlling and monitoring *risk* (3.23)

[SOURCE: ISO/IEC Guide 63:2012, 2.15]

3.30

risk management documentation

set of *records* (3.21) and other documents that are produced by *risk management* (3.29)

[SOURCE: ISO 14971:2007, 2.23]

3.31

risk management plan

scheme specifying the approach, the management components and resources to be applied to the management of *risk* (3.23)

[SOURCE: ISO 31000:2009, 2.6]

3.32

risk management policy

statement of the overall intentions and direction of an organization related to *risk management* (3.29)

[SOURCE: ISO Guide 73:2009, 2.1.2]

3.33

risk matrix

tool for ranking and displaying *risks* (3.23) by defining ranges for consequence and *likelihood* (3.16)

[SOURCE: ISO Guide 73:2009, 3.6.1.7]

3.34

risk monitoring

surveillance

continual checking, critically observing or determining the status in order to identify change from the *risk* (3.23) level required or expected

[SOURCE: ISO Guide 73:2009, 3.8.2.1, modified — “Monitoring” has been changed to “risk monitoring”. “Supervising” has been deleted, and “performance” has been changed to “*risk*” (3.23) In addition, Note 1 to entry has been deleted.]

3.35

risk reduction

actions taken to lessen the *probability* (3.18) or negative consequences or both, associated with a *risk* (3.23)

[SOURCE: ISO 22300:2018, 3.210]

3.36**safety**

freedom from unacceptable *risk* (3.22)

[SOURCE: ISO/IEC Guide 63:2012, 2.16]

3.37**service**

<laboratory medicine> activity performed by a medical laboratory for the *benefit* (3.1) of patients and the *healthcare providers* (3.8) responsible for the care of those patients

Note 1 to entry: Medical laboratory services include arrangements for *examination* (3.3) requests, patient preparation, patient identification, collection of samples, transportation, storage, processing and *examination* (3.3) of clinical samples, together with subsequent interpretation, reporting and advice, in addition to the considerations of *safety* (3.36) and ethics in medical laboratory work.

Note 2 to entry: Adapted from ISO 15189:2012, Introduction.

3.38**severity**

measure of the possible consequences of a *hazard* (3.6)

[SOURCE: ISO/IEC Guide 63:2012, 2.17]

3.39**stakeholder**

person or organization that can affect, be affected by, or perceive themselves to be affected by a decision or activity

Note 1 to entry: A decision maker can be a stakeholder.

[SOURCE: ISO Guide 73:2009, 3.2.1.1]

3.40**state of the art**

developed stage of technical capability at a given time as regards products, *processes* (3.19) and *services* (3.37), based on the relevant consolidated findings of science, technology and experience

Note 1 to entry: The state of the art embodies what is currently and generally accepted as good practice. The state of the art does not necessarily imply the most technologically advanced solution. The state of the art described here is sometimes referred to as the “generally acknowledged state of the art”.

[SOURCE: ISO/IEC Guide 63:2012, 2.19]

3.41**use error**

<laboratory medicine> *user* (3.42) action or lack of *user* (3.42) action while performing a laboratory *examination* (3.3) or using an *IVD medical device* (3.10) or performing any task in any *procedure* (3.17) that leads to a different result than that intended by the laboratory or manufacturer or expected by the *user* (3.42)

Note 1 to entry: Use error includes the inability of the *user* (3.42) to complete a task.

Note 2 to entry: Use errors can result from a mismatch between the characteristics of the *user* (3.42), user interface, task, or use environment.

Note 3 to entry: *Users* (3.42) might be aware or unaware that the use error has occurred.

Note 4 to entry: An unexpected physiological response of the patient is not by itself considered use error.

Note 5 to entry: A malfunction of an IVD medical device that causes an unexpected result is not considered a use error.

Note 6 to entry: Use error includes the use of an *examination* (3.3) result for an unintended target group or for an unintended diagnostic or patient management purpose.

Note 7 to entry: The term was chosen over “user error”, “human error” or “laboratory error” because not all causes of error are partially or solely due to the *user* (3.42). Use errors are often the result of poorly designed *user* (3.42) interface or *processes* (3.19), or, inadequate *instructions for use* (3.13).

[SOURCE: ISO/IEC 62366-1:2015, 3.21 modified — “(laboratory medicine)” has been added. “Performing a laboratory *examination* (3.3) or”, “an IVD” and “laboratory or” have also been added. Note 6 to entry was deleted. A new Note 6 to entry and a Note 7 to entry were added.]

3.42

user

individual responsible for an action that is intended to lead to a desired outcome

Note 1 to entry: Although such individuals are often laboratory personnel that are expected to be trained and competent to perform the action, this term is not limited to such personnel

Note 2 to entry: The use of this term is not intended to imply that a device is utilized for the action; it is used as a general term to include any individual that has a role in producing the desired outcome.

3.43

validation

confirmation, through the provision of objective evidence, that the requirements for a specific *intended use* (3.14) or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word “validated” is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13]

3.44

verification

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

Note 1 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The activities carried out for verification are sometimes called a qualification *process* (3.19).

Note 3 to entry: The word “verified” is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.12]

4 Risk management

4.1 Risk management process

The medical laboratory shall establish, document, implement and maintain a process for identifying hazards associated with its examinations and services, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process shall include the following elements:

- risk management plan;
- risk analysis;

- risk evaluation;
- risk control;
- risk management review and;
- risk monitoring.

Where a documented quality management system exists, such as that described in ISO 15189, it shall incorporate risk management into the appropriate parts.

NOTE 1 Annex A provides additional guidance for using a documented quality management system, such as is required in ISO 15189, to address patient safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in order to implement appropriate risk control measures.

NOTE 2 Annex H of ISO/TR 24971:2019^[2]^[1] provides guidance on risk management for in vitro diagnostic medical devices.

NOTE 3 A schematic representation of the risk management process is shown in [Figure 1](#).

4.2 Management responsibilities

The medical laboratory management shall show evidence of its commitment to the risk management process by providing adequate resources and qualified personnel for risk management to ensure conformance to this document (see [4.3](#)).

The laboratory management shall:

- define and document the laboratory's risk management policy, including the policy for determining risk acceptability (see [6.1](#));
- approve all risk assessments and risk management reports;
- review the suitability of the risk management process at planned intervals to ensure its continuing effectiveness, and document any decisions and actions taken during the review. This review may be part of the quality management system review.

The laboratory shall retain records for each activity required in this standard. The records shall be retrievable and available for review as needed.

NOTE The required documentation and records can be incorporated within the documentation produced by the laboratory's quality management system.

1) Under preparation. Stage at the time of publication: ISO/DTR 24971:2019.

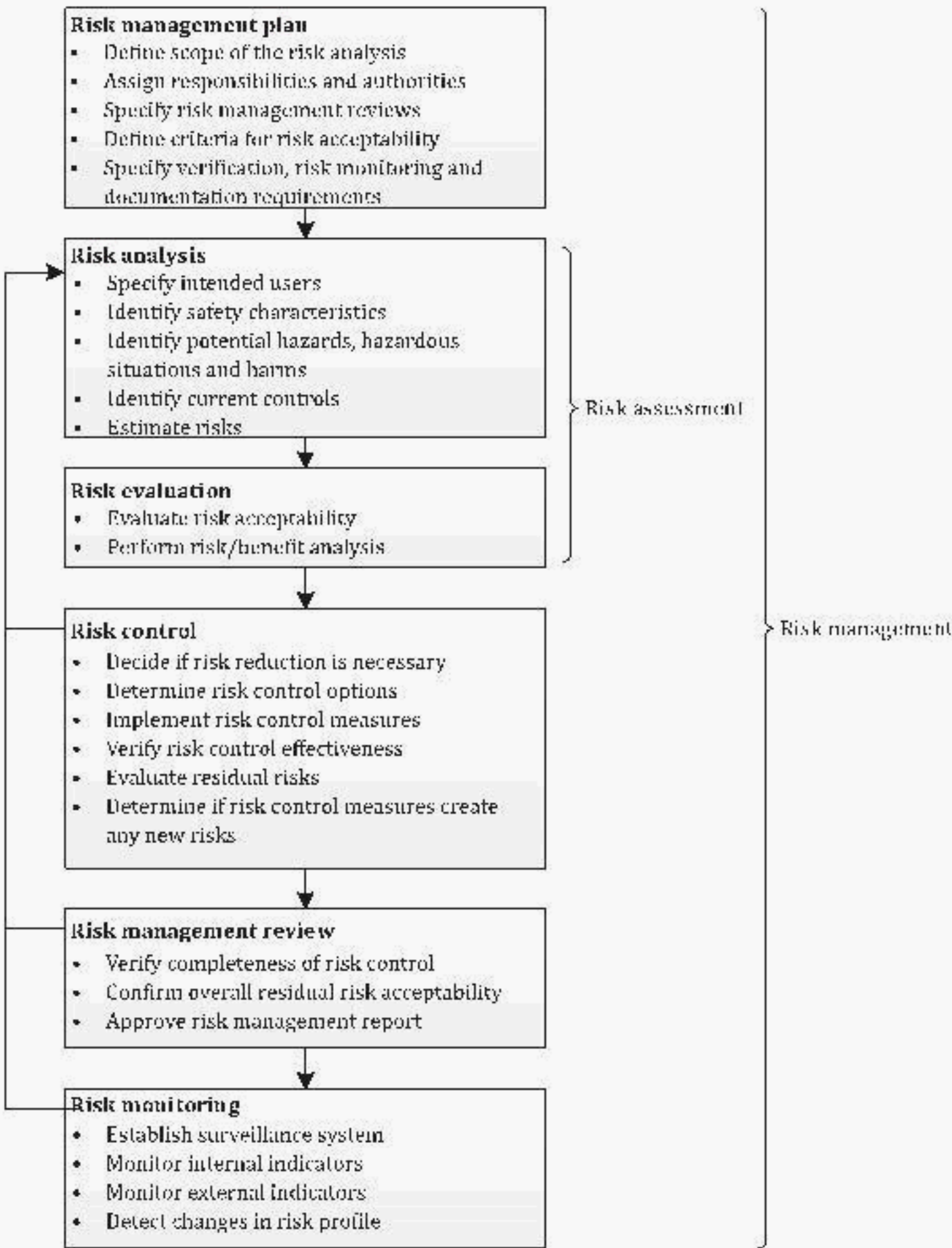


Figure 1 — Schematic representation of the risk management process

4.3 Qualification of personnel

Persons performing risk management tasks shall have the knowledge and experience for the tasks assigned to them. This knowledge and experience shall include, where appropriate, the process and procedures to be assessed including particular medical laboratory examinations; the medical uses of the examination results; and the techniques used to assess the risks.

Risk management tasks may be performed by a team of representatives of several functions of the laboratory, each contributing their specific knowledge and expertise.

Records shall be maintained to document personnel qualifications.

4.4 Risk management plan

4.4.1 General

Risk management activities shall be planned. The risk management plan(s) shall be in accordance with the risk management process described in this document. Therefore, the medical laboratory shall establish, document, and implement one or more risk management plans for the services or examinations performed by the laboratory.

4.4.2 Scope of the plan

The scope of the plan or plans shall be determined by laboratory management. A risk management plan may be created, for example, for technical and management processes, for specific pre- and post-examination aspects, for one or more examinations performed by a particular IVD system, for a particular examination developed by the laboratory, or for all of the examinations performed by the laboratory in which risks could be identified and assessed.

The scope of the plan and the extent of the risk management activities required shall be proportional to the risks associated with the examinations. Factors that should be considered include but are not limited to:

- a) relevant quality specifications;
- b) medical decision levels and critical values;
- c) patient populations;
- d) reliability of the measurement system and measurement uncertainty;
- e) performance characteristics (precision, bias, specificity, etc.);
- f) pre-examination contact with the patient (e.g., phlebotomy); and
- g) clinical use of the examination results (e.g., screening, diagnostic, confirmatory tests).

Unless specified otherwise and justified, the risk management plans for medical laboratory examinations shall include pre- and post-examination aspects and the processes that are identified as presenting a risk to patients or other persons.

4.4.3 Contents of the plan

Each risk management plan shall include at least the following:

- a) description of the examinations and services, any IVD medical devices involved, and all relevant pre- and post-examination aspects within the scope of the plan;
- b) assignment of responsibilities and authorities;
- c) requirements for review of risk management activities;
- d) criteria for individual and overall risk acceptability, based on the laboratory's policy for determining acceptable risk;
- e) risk control verification and monitoring activities.

NOTE Refer to [Annex C](#) for guidance on risk acceptability considerations, and [Annex B](#) for guidance on establishing risk acceptability criteria.

4.4.4 Revisions to the plan

The plan shall be updated if significant changes occur that could affect the risk assessment. A record of changes to the plan shall be maintained.

NOTE Examples of significant changes that could affect the risk assessment include:

- a) modification of laboratory facilities or utilities;
- b) introduction of new policies, procedures or work instructions;
- c) acquisition, purchase or introduction of new equipment, including laboratory information systems;
- d) introduction of new examinations or services, or change in service delivery level;

- e) change to a different vendor;
- f) development of in-house examinations;
- g) modification of existing examination procedures;
- h) any other changes that could affect characteristics related to user or patient safety.

4.4.5 Risk management documentation

For each examination procedure or service, or group of related examinations or services within scope of the plan, the laboratory shall establish and maintain risk management documentation. In addition to the requirements of other clauses of this document, the risk management documentation shall provide traceability for each identified hazard to:

- the risk analysis;
- the risk evaluation;
- the implementation and verification of the risk control measures; and
- the assessment of the acceptability of any residual risk(s).

The risk management documentation may be in any form or type of medium.

To enhance the laboratory's ability to gather all risk management documentation, a virtual risk management file may be designated. While this risk management file may not physically contain all the records and other documents, it needs to contain at least references or pointers to all required documentation (e.g., in a controlled index).

Compliance with the requirements of this document is assessed by inspection of the risk management documentation. All components of this document should be addressed and recorded in this documentation.

5 Risk analysis

5.1 General

The scope of the risk analysis may be broad (e.g., for the development of a new examination with which a laboratory has little or no experience), or the scope may be limited (e.g., for analysing the impact of a change to an existing examination procedure for which much information already exists in the laboratory, for analysing the risk associated with a specific examination procedural failure or IVD medical device malfunction, or for analysing specific aspects of a laboratory examination, such as sample collection and transportation, or reporting examination results).

If an examination procedure involves an IVD medical device, and if the IVD manufacturer followed a risk management process in conformance with ISO 14971, the laboratory's risk analysis may start, but should not be limited to, the residual risks disclosed by the IVD manufacturer.

If a risk analysis, or other relevant information, is available for a similar examination procedure or service, that analysis or information may be used as a starting point for the new analysis. The degree of relevance depends on the differences between the examinations or services. The extent that an existing risk analysis can be used should be based on a systematic evaluation of whether these differences could:

- significantly affect the outputs, characteristics, performance or results;
- cause the introduction of new hazards;
- lead to the development of new hazardous situations.

NOTE 1 Some risks which can occur in medical laboratory examinations are described in [Annexes D, E and F](#).

NOTE 2 Some risk analysis techniques are described in [Annex G](#) and [H](#).

5.2 Risk analysis process and documentation

A risk analysis shall be performed for each examination procedure or service within the scope as described in [5.3](#) to [5.8](#). The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded. (see [4.4.5](#))

In addition to the records required in [5.3](#) to [5.8](#), the documentation of the conduct and results of the risk analysis shall include at least the following:

- a) a description and identification of the subject(s) of the risk analysis (e.g., the examinations and IVD medical devices, including the processes of delivering samples, performing quality control and reporting the results);
- b) identification of the persons who carried out the risk analysis, their expertise and the dates of the analysis;
- c) scope of the risk analysis (see [4.4.2](#));
- d) approval.

5.3 Intended medical laboratory use and reasonably foreseeable misuses

For the particular examination or service being considered, the laboratory shall document the intended medical laboratory uses and any reasonably foreseeable misuses.

NOTE Misuse is intended to mean incorrect or improper performance of an examination, procedure or any procedure critical for patient safety.

5.4 Identification of characteristics related to safety

For the particular examination being considered, the laboratory shall identify and document those qualitative and quantitative characteristics that could affect the safety of the patient, and where appropriate, their defined limits.

EXAMPLES diagnostic specificity, diagnostic sensitivity, measurement specificity, measurement precision, measurement bias, analytical interference, reagent stability, analyte stability, sterility (for phlebotomy services), biological reference intervals.

NOTE [Annex D](#), contains a series of questions that can serve as a guide in identifying the characteristics of the examination and any IVD medical devices involved that could have an impact on safety.

5.5 Identification of hazards

The laboratory shall identify and document known and foreseeable hazards associated with the examination and other critical processes and their causes (e.g., potential failure modes and use errors). Hazards in both normal use (i.e., correct use and use errors), reasonably foreseeable misuse and fault conditions shall be addressed.

For examinations involving the use of an IVD medical device, the laboratory may obtain information from the IVD manufacturer about potential hazards that were identified but not fully eliminated during the manufacturer's risk management process.

NOTE 1 The most common hazards to patients from medical laboratory examinations are incorrect results, misidentified results and delayed results. The examples of possible hazards in [Annex E](#) can be used as guidance when identifying hazards to laboratory workers, service personnel and other persons.

NOTE 2 [Annex F](#) can be used to obtain information on the different steps where nonconformities can lead to errors in different steps (pre-examination, examination and post-examination) and for different medical laboratory disciplines.

NOTE 3 Sources that can help identify the potential causes of hazards include laboratory investigations of complaints, nonconformities, use errors and incidents, as well as the IVD manufacturer involved. IVD manufacturers that follow ISO 14971 are required to disclose significant residual risks to laboratory users.

5.6 Identification of potentially hazardous situations

Reasonably foreseeable sequences or combinations of events that can lead to a hazardous situation shall be considered and the resulting hazardous situation(s) shall be recorded. The decision regarding which event in the sequence of events exposes a patient to the possibility of harm (i.e., a hazardous situation) should be made by the laboratory to suit the risk analysis.

NOTE 1 Sources of information about potential hazardous situations associated with medical laboratory examinations or services include the manufacturer(s) of any medical device used, the medical and scientific literature, experience with similar examinations, expert medical or scientific opinion, and consensus positions of medical laboratory associations. Refer to [Annexes E](#) and [F](#) for guidance for developing the list of hazardous situations.

NOTE 2 An incorrect result received by a healthcare provider can be considered the event that creates a hazardous situation for a patient, since subsequent medical decisions and actions that could harm the patient are beyond any reasonable means of risk control by the laboratory. Examples of other hazardous situations are provided in [Annex E](#).

NOTE 3 Hazardous situations can arise from use errors in the performance of laboratory examinations, either from a laboratory worker choosing to do something or failing to do something. Refer to [Annex H](#) for guidance on identifying and classifying use errors for risk analysis.

5.7 Identification of foreseeable patient harms

Reasonably foreseeable harms that could result from each hazardous situation shall be identified and classified along with the severity of each harm. This process and the identified harms, shall be documented.

NOTE Sources of information about foreseeable patient harms that could be caused by incorrect or delayed examination results include medical literature, experience with similar examinations, expert medical opinion and consensus positions of professional medical societies. Refer to [Annex E](#) for guidance for developing the list of foreseeable patient harms.

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

For each identified hazardous situation, the associated risk(s) shall be estimated using available information or data. Risk estimation may be quantitative or qualitative and will need to focus on the whole process rather than individual components of the situation.

NOTE 1 Methods of risk estimation, including those resulting from systematic faults, are described in [Annex I](#), which gives examples of probability and severity scales based on quantitative, semi-quantitative or qualitative levels.

If the likelihood of the occurrence of harm cannot be estimated, for example in the case of software defects or other systemic faults, the possible consequences should be listed for use in risk evaluation and risk control.

NOTE 2 Information or data for estimating risks can be obtained, for example, from:

- a) external quality assessment results;
- b) relevant failure investigations;
- c) use error and nonconformity reports;
- d) complaints received from laboratory customers;
- e) usability evaluations involving typical users;

- f) experience with similar examinations, including publicly available incident data;
- g) performance and reliability specifications for IVD medical devices;
- h) product technical literature and disclosure of residual risks from IVD manufacturers;
- i) medical literature and published clinical evidence;
- j) published standards and medical practice guidelines;
- k) expert scientific, engineering or medical opinion;
- l) scientific, technical or clinical performance evaluations.

6 Risk evaluation

6.1 Risk acceptability criteria

The laboratory shall define, approve and document risk acceptability criteria for individual risks and the overall residual risk in the appropriate risk management plan.

NOTE 1 Established criteria for risk acceptability are essential for the effectiveness of the risk management process.

The risk acceptability criteria shall:

- be determined according to the laboratory's policy for determining risk acceptability criteria;
- be based on applicable national or regional regulations, applicable safety standards, and relevant medical practice standards;
- take into account the generally accepted state of the art and known stakeholder concerns;
- be approved by the laboratory director.

NOTE 2 It is not necessary to apply the same risk acceptability criteria for all examinations or services performed by the laboratory. The criteria can differ based on the intended use or other factors.

For individual risks, the acceptability criteria may be documented in a matrix to indicate the combinations of probability of occurrence and severity of harm that are acceptable or unacceptable.

NOTE 3 See guidance on risk acceptability considerations and examples in [Annex C](#).

Such a matrix may be further subdivided into zones that indicate which risks are considered negligible and which risks are acceptable if the risks are minimized (i.e., the risks are first reduced as far as reasonably possible).

NOTE 4 See guidance and examples in Annexes B.5 and C for determining endpoints for risk reduction.

Considerations in establishing overall residual risk acceptability criteria may include:

- compliance with required regulations such as National Quality Regulations;
- laboratory accreditation to standards of quality and competence;
- participation in recognized proficiency testing schemes;
- whether informed consent is required.

The laboratory shall determine and document acceptability criteria for evaluating the overall residual risk.

NOTE 5 [Annex I](#) describes three criteria that can be the basis for evaluating acceptability of the overall residual risk: a) The risk associated with an examination procedure or laboratory service compares favourably to similar examination procedures or laboratory processes already in use. b) The medical benefits of the examination procedure or laboratory service outweigh the overall residual risk. c) The overall residual risk has been reduced as far as reasonably feasible and verification of the risk control measures demonstrates that they are effective.

6.2 Risk evaluation process

For each identified hazardous situation, the laboratory shall apply the approved risk acceptability criteria (see [6.1](#)) to decide if risk reduction is required. Generally, if the risk is considered negligible, then the risk is acceptable and no further risk reduction is necessary.

If risk reduction is required, then risk control activities, such as described in [7.1](#) to [7.4](#), shall be performed.

If the level of risk is considered unacceptable, and cannot be reduced to an acceptable level, laboratory management shall decide whether the examination or service in question may be commenced or continued based on a documented risk – benefit analysis as described in [Clause 8](#).

If risk reduction is not required, then the risk control requirements in [7.1](#) to [7.4](#) do not apply for the particular hazardous situation being evaluated, and the laboratory may proceed to [Clause 9](#).

7 Risk control

7.1 Risk control options

The laboratory shall identify, implement and verify risk control measure(s) that reduce the risk(s) to an acceptable level.

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

In selecting risk control measures, priority shall be given to risk control options in the following preferred order:

- a) inherent safety by process design (e.g., potential for failure is reduced or eliminated);
- b) protective measures in the IVD medical device (e.g., alarms, failure detection, fail-safe mechanism) or in the examination, pre-examination, post-examination and quality assurance procedures (e.g., calibration, quality control activities, including new control activities added by the laboratory to reduce residual risk);
- c) information for staff on safety;
- d) training.

When implementing option b) or c), the laboratory should select risk control measures that will reduce the risk as far as reasonably possible before determining whether the residual risk is acceptable.

The laboratory may also consider whether use of an examination for a specific patient population should be contraindicated based on risk evaluation ([Clause 6](#)) or risk-benefit analysis ([Clause 8](#)).

If the laboratory determines during risk control option analysis that risk reduction is not feasible, the laboratory may conduct a risk/benefit analysis of the residual risk to determine whether to continue to develop or implement the examination or service (see [Clause 8](#)).

7.2 Risk control verification

The correct implementation of each risk control measure shall be verified.

The effectiveness of the risk control measure(s) shall be verified. Verification of effectiveness may be performed as part of validation activities.

7.3 Role of standards in risk control

Conformance to relevant standards should be considered as part of the risk control option analysis.

Application of relevant standards during the design and development of an examination or another procedure might constitute a risk control activity, and may meet the requirements given in [7.1](#) to [7.5](#). It is up to the laboratory to determine whether application of the standard meets all of the requirements.

7.4 Role of IVD medical devices in risk control

If the examination involves an IVD medical device that was designed, developed, validated and manufactured in conformance to a recognized risk management standard such as ISO 14971, the laboratory should follow the manufacturer's instructions regarding any risk control measures incorporated in or provided with the device. Exceptions shall be justified.

NOTE This recommendation is intended to enable laboratories to rely on risk management activities performed by the IVD manufacturer, thus avoiding unnecessary duplication of efforts. This promotes effective risk communication between stakeholders.

Risk control measures incorporated in or provided with an IVD medical device may not require further verification if:

- the IVD manufacturer certifies that the device was designed, developed, validated and manufactured in conformance to ISO 14971, and;
- the information provided by the manufacturer in the device labelling shows that the risk control measures are effective.

The laboratory shall review the risk control measures incorporated in or provided with the IVD medical device and decide whether the effectiveness of the risk control measures requires additional verification by the laboratory.

Modifications to the IVD medical device that could affect the risk control measures may require revalidation by the laboratory.

7.5 Risks arising from risk control measures

Each risk control measure shall be reviewed with regard to whether:

- any new hazards or hazardous situations have been introduced; or
- the estimated risks for previously identified hazardous situations will be affected by introduction of the risk control measure.

Any new or increased risks shall be analyzed, evaluated and controlled in accordance with [4.4](#) to [7.4](#).

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

7.6 Residual risk evaluation

After the risk control measures are applied, each residual risk shall be evaluated using the approved risk acceptability criteria (see [6.1](#)). The results of this evaluation shall be recorded.

If the residual risk is judged not acceptable using these criteria, further options for risk control shall be considered (see [7.1](#)).

If further risk reduction is not feasible, the laboratory may conduct a risk/benefit analysis of the residual risk to determine whether to continue to develop or implement an examination or service (see [8](#)).

For residual risks that are judged acceptable, the laboratory shall determine what information is necessary to communicate to the intended recipients in order to disclose the residual risks. Copies of any communications that disclosed the residual risks shall be maintained in the risk management documentation.

NOTE Guidance on how residual risk(s) can be disclosed is provided in [Annex L](#).

8 Benefit-risk analysis

The medical laboratory may perform an analysis of relevant clinical evidence to determine if the medical benefits of the intended use outweigh the residual risk. This analysis may be performed at the level of an individual residual risk or for the overall residual risk.

NOTE Clinical evidence is obtained from sources such as the medical literature, clinical studies, performance evaluations, adverse event experience, and expert medical opinion. Refer to [Annex K](#) for further guidance for performing a benefit-risk analysis.

If the residual risk is demonstrated to be outweighed by the benefits, then the risk may be considered acceptable. The laboratory shall determine which information is necessary to disclose the residual risk.

If the evidence does not support the conclusion that the medical benefits outweigh the residual risk, then the risk is not acceptable.

The results of the benefit-risk analysis and the information to be disclosed to intended recipients shall be recorded.

9 Risk management review

9.1 Completeness of risk control

Prior to reporting results from the examinations addressed in the risk management plan, the laboratory shall carry out a comprehensive review of the entire risk management process. The responsibility for review should be assigned in the risk management plan (see [4.4.3 b](#)).

This review shall at least ensure that:

- the risk management plan (see [4.4](#)) has been appropriately implemented;
- the risk(s) from all identified potential hazardous situations have been considered (see [5.6](#));
- the overall residual risk is acceptable (see [9.2](#)); and
- appropriate methods are in place to obtain the information necessary to monitor the risks (see [10](#)).

9.2 Evaluation of overall residual risk

After the individual assessment of every identified hazardous situation associated with an examination or service, and after the identified risk control measures have been implemented and verified, the laboratory shall consider the combined impact of the individual residual risks and decide whether the overall residual risk for each examination or service is acceptable using the criteria defined in the risk management plan.

NOTE For guidance on overall residual risk evaluation, refer to [Annex J](#).

If the overall residual risk is judged not acceptable using the criteria established in the risk management plan, the laboratory may conduct a risk-benefit analysis (see [Clause 8](#)) to determine if the medical benefits of the intended use outweigh the overall residual risk. If the clinical evidence supports the conclusion that the medical benefits outweigh the overall residual risk, then the overall residual risk may be judged acceptable. Otherwise, the overall residual risk remains not acceptable.

For an overall residual risk that is judged acceptable, the laboratory shall determine what information is necessary to give healthcare providers to disclose the overall residual risk. Copies of the communications that disclosed the overall residual risk shall be maintained in the risk management file.

NOTE Guidance on how residual risk(s) can be disclosed is provided in [Annex L](#).

9.3 Risk management report

The results of this comprehensive risk management review shall be recorded in a risk management report, which shall summarize the evidence that:

- the risk management plan has been satisfactorily fulfilled;
- the results confirm that the residual risks are acceptable; and,
- the risk management report shall be approved by laboratory management.

10 Risk monitoring, analysis and control activities

10.1 Surveillance procedure

The laboratory shall establish, document and maintain a suitable procedure to collect, review and analyze information about risks associated with the pre-examination, examination, and post-examination processes.

When establishing a surveillance system, the laboratory should consider among other things:

- a) the mechanisms by which information generated by the laboratory, the healthcare providers, the IVD medical device manufacturer, or those accountable for the installation and servicing of the equipment is collected and processed; and
- b) new or revised healthcare regulations and standards.

Risk-based alert and action triggers should be established to ensure timely response to any identified adverse event or trend.

The information collected as part of risk monitoring shall be evaluated to ensure the risk controls remain effective and the risks remain acceptable. In particular, the laboratory shall determine if:

- an unanticipated failure mode, use error, hazard, hazardous situation or harm may have occurred;
- the previously unrecognized potential for any of these events to occur may be present; or
- the estimated risk(s) arising from a hazardous situation is (are) no longer acceptable.

If any of the above conditions occur:

- a) the need for immediate action to reduce imminent risks to patients or users shall be evaluated, and if so, the appropriate actions to be taken by the laboratory to address the risks shall be initiated (see [10.4](#));
- b) the impact on previously implemented risk management activities shall be evaluated and shall be fed back as an input to the risk management process;

- c) a review of the risk management documentation for the examination or service shall be conducted, and if there is a potential that the residual risk(s) or its acceptability may have changed, the impact on previously implemented risk control measures shall be evaluated.

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

NOTE Aspects of monitoring for unanticipated risks are often the subject of national regulations.

10.2 Internal sources of risk information

Sources of risk information and data within the laboratory may include:

- a) performance evaluation studies;
- b) statistical quality control data;
- c) incident reports;
- d) complaints, nonconformities or corrective actions;
- e) internal audits and other evaluations.

10.3 External sources of risk information

Sources of risk information and data outside the laboratory may include:

- a) EQAS (External Quality Assurance Services) reports;
- b) physician complaints;
- c) manufacturer advisory notices;
- d) regulatory authorities;
- e) adverse event databases;
- f) literature reports;
- g) accreditation bodies (e.g., audits).

NOTE A product recall, field correction or safety notice from an IVD manufacturer can indicate a change in risk that requires immediate action by the laboratory.

10.4 Immediate actions to reduce risk

If examination results reported by the laboratory are found to present unacceptable risks to patients, immediate actions shall be taken in proportion to the risks. Actions to reduce the risks may include, but are not limited to the following:

- a) alert the affected healthcare providers to the erroneous results;
- b) if possible, repeat the examinations and revise reports to correct the erroneous results;
- c) notify healthcare providers of changes in diagnostic performance;
- d) update and issue revised reference ranges;
- e) suspend further examinations until the cause is corrected;
- f) notify the IVD manufacturer of any clinically significant malfunction, use error or deficiency in IVD device design or labelling;
- g) report adverse events or serious incidents to authorities, where appropriate.

The immediate actions may also include an investigation to determine the root causes and reassessments of the risks.

Annex A **(informative)**

Implementation of risk management within the quality management system

A.1 General guidance

Where a documented quality management system exists, such as that described in 4.2 of ISO 15189:2012, 4.1 of ISO 22367 requires that it should incorporate risk management into the appropriate parts.

Risk is inherent in all aspects of a quality management system. There are risks in all systems, processes and functions. Risk-based thinking ensures these risks are identified, considered and controlled throughout the design and use of the quality management system.

By using risk-based thinking the consideration of risk is integral. It becomes proactive rather than reactive in preventing or reducing undesired effects through early identification and action. Preventive action is built-in when a management system is risk-based. Risk-based thinking is something laboratories do automatically in everyday life.

Not all the processes of a quality management system represent the same level of risk in terms of their potential for harm to users or patients. Some need more careful and formal planning and controls than others. By considering risk throughout the system and all processes the user and patient safety is improved, output is more consistent and healthcare providers can be confident that they will receive the expected product or service (see [Figure A.1](#)).

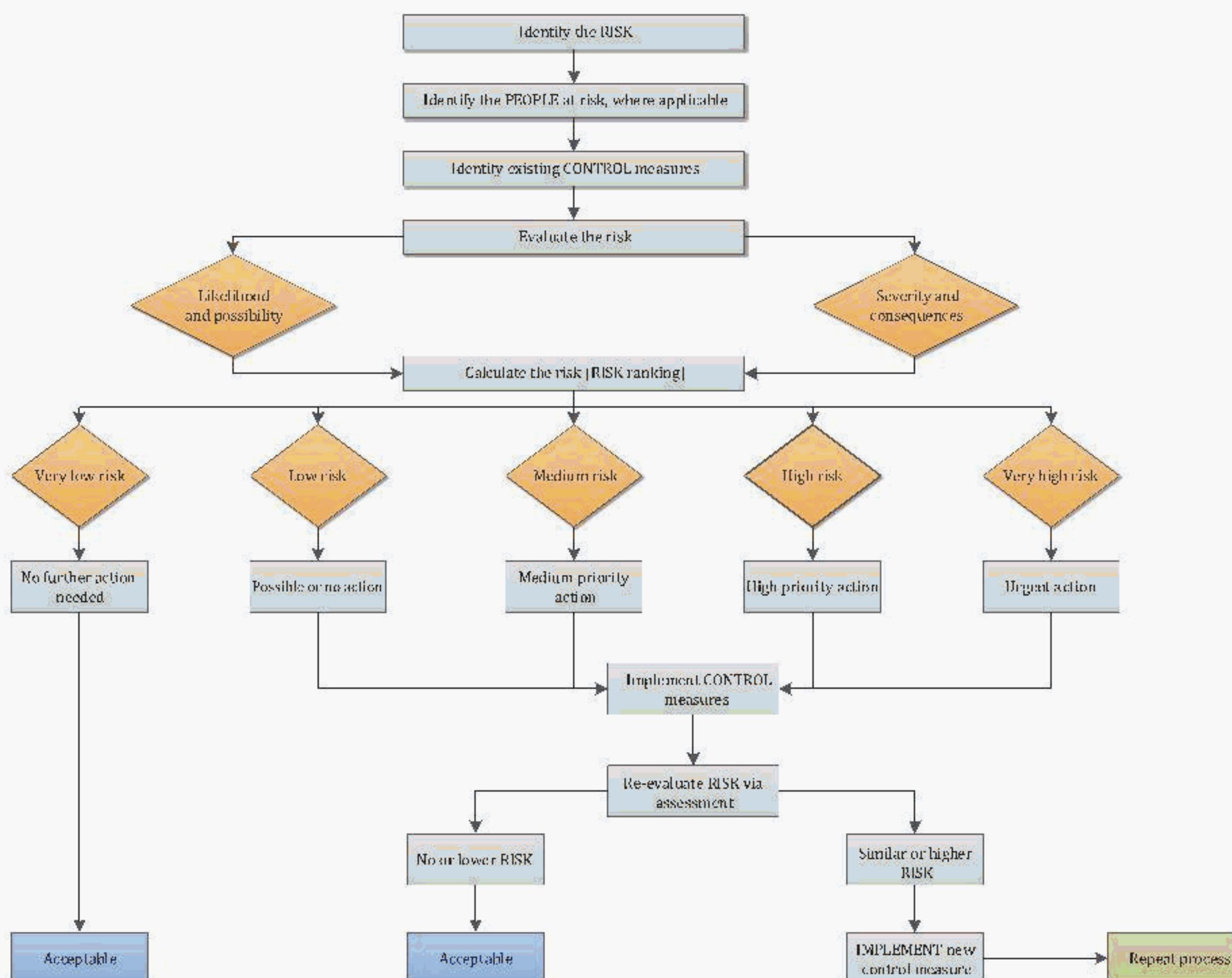


Figure A.1 — Risk assessment flow chart

This Annex provides guidance for medical laboratories that have implemented ISO 15189, which requires that risk management be incorporated into their quality management system. All reference to clauses in ISO 15189 will be so stated (e.g., ISO 15189:2012, 4.6); if a clause is listed by itself (e.g., [4.4.5](#)), it refers to the clause in this document.

A.2 Documents and records control

See ISO 15189:2012, 4.3 and 4.13.

The document and records control requirements of ISO 15189:2012, 4.3 apply to all laboratory policies, procedures, work instructions and other documents created for the risk management process and maintained as part of the risk management documentation (see [4.4.5](#)).

A.3 Supplier management

See ISO 15189:2012, 4.6.

A.3.1 General

The degree of supplier control required varies with the examination or service and the associated risks to patients or laboratory workers. The extent of specification detail necessary to ensure that the purchased product or service, including referral laboratory services, meets requirements depends on the nature of the product or service purchased and the identified risks (see [Clause 5](#)).

Assessment of risks introduced by vendors should result in clarification of the roles and responsibilities of the laboratory and supplier. For examples, contractual considerations may include:

- ownership of the specifications and the change control process;
- ensuring that new information is communicated when it becomes available;
- specifying the extent of risk management to be conducted by the laboratory and by their supplier.

Supplier management and acceptance activities generate information and data that should be part of the risk monitoring that continues throughout the examination cycle. The output of risk management activities may result in risk control measures to be carried out such as purchasing controls and acceptance activities.

A.3.2 Purchasing

The procedures for the selection and purchasing of external services, equipment, reagents and consumable supplies should require identification of hazards and evaluation of risks potentially introduced by suppliers, and should require risk-based decisions regarding the selection and approval of suppliers.

Where appropriate, prescribed risk control measures derived from the laboratory's risk management process ([Clause 7](#)) should be included in the purchasing requirements as part of the purchasing information.

Criteria for selection, evaluation and re-evaluation of suppliers of purchased products, including IVD medical devices, and services, such as referral and reference laboratories and external quality assessment programs, should be established based upon the risk associated with identified hazards related to the purchased products and services.

A.3.3 Acceptance activities

In developing the acceptance criteria for purchased product and services, results of risk management activities should be considered. Specifically, the identified hazards and their related risk control measures should be taken into account when developing criteria for verification and acceptance activities.

A.3.4 Servicing

Laboratory equipment and IVD medical devices may require installation, maintenance and repair activities provided by internal or external suppliers.

When servicing is a specified requirement, information from risk management activities should be considered. Periodic servicing and maintenance as a means to ensure proper functioning of a device can be an effective method of risk control.

If a certain risk control measure is necessary for an examination process, it may also be necessary to apply the same (or similar) risk control measure to the servicing process.

When there is a hazard to service personnel, clear instructions should be included in servicing manuals or documentation and appropriate training shall be provided.

A.4 Design and development activities

A.4.1 General

This subclause applies only to medical laboratories that develop examination procedures for their own use, or modify previously validated examination procedures or IVD medical devices.

Risk management activities (e.g., risk assessment and risk control) should be an integral part of the design and development process for laboratory examinations.

NOTE An examination procedure developed for a laboratory's own use is often referred to as a "laboratory developed test", "LDT", or "in-house test".

The following guidance is based on the iterative design and development process described in 7.3 of ISO 13485:2016 (8), in which design and development is conducted in the stages listed below. This approach is followed by most IVD manufacturers, and should be considered by laboratories when developing examinations for their own use.

- design and development planning;
- design and development inputs;
- design and development outputs;
- design and development review;
- design and development verification;
- design and development validation;
- design and development transfer;
- control of design and development changes.

Risk management activities should begin as early as possible in the design and development process, when it is feasible to incorporate safety features in the design. For each identified hazard, the risk in both normal and fault conditions is estimated (Clause 5). The laboratory decides whether risk reduction is needed (Clause 6). The results from this risk evaluation, such as the need for risk control measures, then become part of the design and development input.

Risk control measures (Clause 7) are part of the design and development output and their effectiveness is verified during design and development verification. This design and development input/output/verification cycle iterates and continues throughout the overall design control process until the residual risks have been reduced to an acceptable level and can be maintained at an acceptable level. The overall effectiveness of the risk control measures is confirmed during design and development validation.

A.4.2 Design and development planning

Design and development planning ensures that risk management activities are coordinated during design and development and continue throughout the life time. Design and development planning should identify:

- the inter-relationship(s) between appropriate risk management activities and design and development activities;
- the design and development resources required, including the expertise to address potential safety concerns.

A.4.3 Design and development input

Design and development inputs are documented as the foundation for subsequent design and development activities. Design and development inputs include adequate consideration of intended use and functional, performance, safety and regulatory requirements.

Risk control measures are an output from risk management activities, which become inputs into the design and development process.

Hazard identification starts with consideration of the intended use, the characteristics related to safety and the use environment and results in a preliminary list of known and foreseeable hazards. Each

identified hazard could lead to several different harms, and several different hazards could lead the same harm. The probability of occurrence of each harm and its severity are determined to estimate the risks (see [Clause 5](#)). Each risk is evaluated against previously established acceptability criteria to determine whether risk controls are needed.

During development, any proposed changes to the identified design characteristics, specifications, and/or risk control measures and their associated hazards from the current risk analysis should be carefully evaluated with respect to continued safety and specified performance of the examination procedure before approval.

If the examination procedure is intended to be used in combination with any equipment or IVD medical device, then hazards and risk control measures should be evaluated for each component individually as well as for the system or combination.

When establishing design and development inputs, the need for risk control measures should be considered. When risk control measures are determined to be necessary and are initially defined, these become an output as part of the iterative cycle.

A.4.4 Design and development outputs

The risk control measures identified during the input phase are evaluated during design and development, and if feasible, will be incorporated into the design in the order of priority given in [7.1](#). If inherent safety or design for protective measures are not reasonably feasible, less effective risk control measures such as labelling or training may be necessary. The design and development output includes the design specifications for the risk control measures.

Design and development outputs are generally of three types:

- specification of the characteristics of the examination procedure, in particular those essential for its safe and proper use;
- requirements for purchasing, production, handling, distribution and servicing;
- acceptance criteria.

All types may include information essential for safe and proper use. Risk control measures may fall into any of these categories.

A.4.5 Design and development review

Design and development reviews should be conducted at appropriate points to ensure the examination procedure meets the identified medical needs. The reviews should confirm that any individual residual risks as well as any overall residual risk are acceptable and adequately disclosed. These reviews should confirm the validity of risk/benefit decisions related to the acceptance of the residual risks. Reviewers should have the necessary competence to assess design decisions concerning risk acceptability.

Design review procedures should define risk review tasks that should be performed at appropriate stages of design and development. Design and development reviews should assess, for example:

- whether all hazards have been identified, risk has been properly assessed and potential risk control measures have been identified;
- the effectiveness of risk control measures for individual risks;
- if design validation activities effectively assessed the overall residual risk associated with the performance of the examination procedure by the intended user;
- whether any new risk-related issues identified during the design transfer process were controlled and verified.

A.4.6 Design and development verification

Verification generates objective evidence that the design requirements were met, including requirements that identified risks were addressed, risk control measures were implemented as necessary, and risk control measures were effective so that the end result meets the defined acceptability criteria.

Procedures should define appropriate verification methods and should ensure traceability between identified hazards, risk control measures, design and development requirements, test plans, and test results. [Annex F](#) contains an example of a risk management summary in a table format, which also demonstrates traceability.

A.4.7 Design and development validation

Validation confirms that the examination or service meets client needs, intended uses, and that the overall residual risk meets the approved acceptability criteria. To ensure risk control measures are adequately addressed, the validation plan should include all intended uses to give confidence that the overall residual risk determination is consistent with expectations. Any simulated use testing should be designed to provide similar levels of confidence. Any unforeseen hazards that emerge from validation should be assessed ([Clauses 5](#) and [6](#)) and, if necessary, controlled ([Clause 7](#)).

A.4.8 Design and development transfer

During transfer of the examination procedure from research and development to laboratory operations, the laboratory should ensure that the required risk control measures were implemented and will be effective in the actual use environment. The laboratory should also ensure that any newly identified risk-related issues are resolved prior to the release of the examination procedure to laboratory operations.

A.5 Identification and control of nonconformities

See ISO 15189:2012, 4.9.

Each nonconformity related to a laboratory examination, including pre- and post-examination aspects, should be investigated and handled in a controlled manner (i.e., using a documented nonconformity handling process). The level of control should be commensurate with the risk associated with the nonconformity.

Identified nonconformities, including use errors and incidents, should be classified for analysis, review and reporting. Risk assessments ([Clauses 5](#) and [6](#)) should enable the laboratory to classify and prioritize the nonconformity according to its significance, primarily in terms of patient and user safety. Classification may also include, but is not limited to:

- cycle phase of event;
- event location;
- event characterization;
- event predictability and prevention.

A.6 Complaint evaluation and investigation

See ISO 15189:2012, 4.8.

The procedures for the management of complaints or other feedback received from clinicians, patients, laboratory staff or other parties should require that each complaint be evaluated to determine if it involves an adverse event, a known hazard, a previously unknown risk, or a change in risk level.

The prioritization and extent of complaint investigations should be commensurate with the level of risk represented by the event, based on the risk assessments ([Clause 5](#) and [6](#)). If so, review of the existing risk analysis may be necessary to determine whether it requires an update.

Complaint evaluation and investigation activities generate information and data that should be part of the risk monitoring that continues throughout the lifetime of an examination.

A.7 Corrective action

See ISO 15189:2012, 4.10.

The root cause investigation should include determination of whether the level of risk estimated in [Clause 5.8](#) is still acceptable, and if the original risk assessment remains valid.

The comprehensiveness and depth of failure investigations should be commensurate with the magnitude of the nonconformity, event or incident being investigated, and the risk it presents to the patient or user.

Procedures should include or reference the method to be used to determine the level of risk associated with the failure ([Clause 5](#)) and the decision process used to determine the depth of investigation based upon that level of risk.

The results of corrective action activities should be reviewed to identify any previously unrecognized risks and to monitor the effectiveness of risk control measures. This information should also be utilized to determine the effectiveness of the risk management activities and determine required actions to be taken to correct the identified issues and prevent recurrence.

A.8 Preventive action

See ISO 15189:2012, 4.11.

Relevant information from the laboratory's examination processes should be continually monitored, analyzed and used in reviewing revising current risk assessments and where appropriate, performing new risk assessments.

Additional sources of information to be considered include:

- information on laboratory examinations or IVD medical devices from interlaboratory quality assessment schemes;
- information on similar laboratory examinations or IVD medical devices;
- public information on recalls, vigilance reports, etc.;
- scientific literature, consensus guidelines and expert medical opinion;
- new or amended standards and regulations.

The analysis of data should demonstrate that the decisions and risk control measures determined within the risk management process are appropriate.

If a situation or condition is identified that could contribute to a nonconformity and increase the level of risk, laboratory management should take action to prevent occurrence of the nonconformity. The preventive action plan should include:

- the scope of the plan;
- a description of the specific failure mode effect, nonconformity, error, or incident;
- the identification of potential hazards associated with the potential error or nonconformity;

- allocation of responsibilities to address the changes required;
- requirement for review;
- criteria for acceptable resolution.

A.9 Continual improvement

See ISO 15189:2012, 4.12.

Laboratory management should review information gained about the laboratory nonconformities, errors and incidents. This information should be evaluated for possible relevance to patient and laboratory safety, especially with regard to the following:

- whether previously unrecognized hazards are present;
- whether original assessments of laboratory nonconformities, errors and incidents are invalidated as a result.

If either of the above applies, the results of the evaluation should be used to assess the adequacy of the corrective action process and the corrective action plan should be modified if appropriate.

In addition, an in-depth investigation into the root cause of any high-risk laboratory nonconformities, errors and incidents should be carried out immediately, in order to prevent their recurrence.

NOTE In this context, immediately means without a delay that cannot be justified.

A.10 Evaluation and audits

See ISO 15189:2012, 4.14.

Quality management system audits should include the risk management process described in this document.

Audit observations of quality management system deficiencies should be prioritized according to the risks associated with the nonconformities, and special follow-up audits should be conducted to ensure higher risk issues are addressed in a timely manner. Lower risk audit observations may be followed-up during the next routine audit. The laboratory should consider the result of risk management activities to assign priorities to high risk processes when performing audit program.

The frequency of internal audit of specific items can be based on the risk management approach to warrant that the time spent is focused.

A.11 Accommodation and environmental controls

See ISO 15189:2012, 5.2.

Where the work environment, including facilities, could have an adverse impact on the examination process or the examination results, and has been determined to result in or contribute to risk for the patients, then risk control measures should be defined, documented and implemented. The effectiveness of these risk control measures should be periodically assessed.

A.12 Control of laboratory equipment, reagents and consumables

See ISO 15189:2012, 5.3.

The suitability of equipment and the frequency of cleaning, maintenance and calibration should be verified and/or validated with reference to the risks associated with the examination processes.

Work instructions should be reviewed and updated to reflect any risk control measures identified according to [Clause 7](#).

Information may be communicated to distribution, handling, and storage personnel from the risk management activity, if distribution, handling, or storage practices or conditions could cause or contribute to a hazard from the use of any reagent or other product (e.g., storage temperature and humidity, temperature and humidity control during shipping, need for protective packaging).

Laboratory equipment, reagents, and consumables should be controlled in a manner that is commensurate with their risk.

When considering the frequency of the quality control, which include internal and external controls, a risk based principle should be applied with consideration of the method validation/verification outcome, the stability of the equipment, method and environment and the clinical outcome of the results.

A.13 Control of laboratory information systems

See ISO 15189:2012, 5.10.

Laboratory information systems should be validated for use to a degree commensurate with the risks associated with the examinations being performed and the examination results being reported and the integrity of the system and its data. Typically, such systems are integral to the workflow of the laboratory and can present potential risks predominantly in the pre-examination and post-examination phases of patient care.

Issues to potential risks can include:

- ability to properly identify and trace a patient and all relevant personnel throughout the examination process;
- ability to properly and correctly transmit and display information that is readable and comprehensible, including:
 - ordering instructions from the healthcare giver to the specimen collector or laboratory
 - results of examinations
 - issues with the sample or the examination that may impact interpretation
- ability to tolerate and/or recover from disruptions of the laboratory information system;
- middleware integrity and dependability;
- potential for hacking into systems connected to internet (directly or indirectly) and changing or stealing patient data;
- attention for cybersecurity in general.

A.14 Quality control of examination processes

See ISO 15189:2012, 5.6.

The development of an internal quality control plan can be conducted based on risk management principles and should include at least the next steps:

1. Collection of information of quality specifications and requirements from manufacturers, users, laboratory, accreditation agencies, literature;
2. Performing of risk assessment;

3. Identifying control measurement to reduce risk;
4. Development of a quality control plan;
5. Monitoring performance.

To identify potential hazards and their causes the laboratory could implement some of the tools mentioned in [Annex G](#): process mapping, fishbone diagram, FMEA. It could be useful for the laboratory to map the entire testing process with a high-level process map, identified the potential causes of harm in each process step with a fishbone diagram and conduct a FMEA to evaluate if risks are acceptable and if existing controls are effective. In this case the laboratory should implement a quality control plan which can include statistical techniques, types, levels, frequency and number of quality control samples.

A.15 Change management

Changes to laboratory personnel, processes and/or services can introduce new hazards, eliminate existing hazards, or change the level of risk associated with a hazard. All changes to laboratory processes and services should be controlled according to the degree of risk associated with the process or service. All changes to an examination or service require a review of the applicable risk assessment.

If a change is planned or has occurred inadvertently (i.e., unplanned change), the current risk assessment should be reviewed and updated as necessary. If any single characteristic of a system changes, the entire system may need to be evaluated. The decision should be based on the risk associated with the system.

Examples of changes include:

- departure of bench or supervisory personnel;
- a change of reagents (even nominally identical material from a different supplier);
- replacement of laboratory equipment by another;
- the cumulative effect of seemingly minor changes to a process;
- change from one supplier to another;
- change made by suppliers;
- change of intended use, the intended user or the intended use environment.

Prior to implementing a proposed change, it is important to ensure that any individual residual risk(s), as well as the overall residual risk, are defined and remain acceptable.

Proposed changes to validated examination procedures or IVD medical devices should be assessed for risk ([Clause 5](#) and [6](#)) early in the change management process in order to determine whether known risks are controlled satisfactorily or whether they could introduce new risks. Unacceptable risks should be addressed ([Clause 7](#) and [8](#)) prior to the decision to approve the change.

Annex B **(informative)**

Developing a risk management plan

The following guidance is adapted from ISO/TR 24971:2019.

B.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 [4.4](#).

The level of detail for the plan should be commensurate with the complexity of the risk associated with the process, laboratory service or examination and its associated risks. The requirements identified in [4.4](#) are the minimum requirements for a risk management plan. Laboratories can include other items such as time-schedule, risk analysis tools, or a rationale for the choice of specific risk acceptability criteria.

B.2 Scope of the plan

The scope identifies and describes the process, examination procedure or laboratory service for which each element of the plan is applicable.

The elements of the risk management process should cover all aspects of the medical laboratory examinations or service. The plan should include all risks associated with the laboratory's services, examinations and operations, including risks identified during the design and development of an examination procedure, during selection and acquisition of equipment and devices, until discontinuation of the examination or service and decommissioning of any equipment involved. A laboratory's risk management plan may consist of a number of individual plans, which together cover all of the laboratory's services, processes and examinations. A high-level master plan should identify all of the individual plans and the areas they cover, and each individual plan should have a clear statement of its scope.

B.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 reviewers, experts, independent verification specialists, individuals with approval authority (see [4.2](#)). This assignment can be included in a resource allocation matrix defined for the project.

B.4 Requirements for review of risk management activities

The risk management plan is part of the quality management system and should therefore be subject to internal audits at planned intervals and be included in the management review. (e.g., ISO 15189:2012, 4.15).

B.5 Criteria for risk acceptability

Criteria for risk acceptability are derived from the laboratory's policy for determining acceptable risk (see [4.2](#) and [Annex C](#)). The criteria can be common for similar categories of examination procedures or laboratory services. Criteria for risk acceptability can be part of the laboratory's established quality

management system, which can be referenced in the risk management plan (e.g., ISO 15189:2012, 4.1.2.4).

B.6 Verification activities

The risk management plan should specify how the two distinct verification activities required by this document will be carried out. Verifying the effectiveness of risk control measures can require the collection of laboratory data, usability studies, etc. The risk management plan can detail the verification activities explicitly or by reference to the plan for other verification activities.

B.7 Method or methods of obtaining relevant information for risk monitoring

The method or methods of obtaining information for risk monitoring can be part of established quality management system procedures (e.g., ISO 15189:2012, 4.8 to 4.12). The laboratory can establish generic procedures to collect information from various sources, such as healthcare providers, instrument operators, service personnel, training personnel, incident reports and customer feedback. While a reference to the quality management system procedures is sufficient in most cases, any examination-specific requirements (e.g., proactive surveillance, follow-up clinical studies) 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 surveillance is appropriate for the examination procedure or laboratory service, for example, whether reactive surveillance is adequate or whether proactive studies are needed. Details of such studies should be specified.

Annex C **(informative)**

Risk acceptability considerations

The following guidance is adapted from ISO/TR 24971:2019

C.1 General

According to [4.2](#) of this document, laboratory management is required to define and document the policy for determining the criteria for risk acceptability (see [6.1](#)). This policy is intended to ensure that criteria:

- are based upon applicable national or regional regulations;
- are based upon relevant International Standards;
- take into account available information such as the generally accepted state of the art and known stakeholder concerns.

NOTE Other relevant information can also be included.

The policy could cover the entire range of a laboratory's examinations or services, or it can take different forms depending on whether the examination procedures or laboratory services are similar to each other, or whether the differences between groups of examination procedures or laboratory services are significant.

C.2 Methods of determining acceptable risk

This document does not specify acceptable risk. That decision is left for the laboratory to determine. Methods of determining acceptable risk include, but are not limited to:

- using applicable standards that specify requirements which, if implemented, will indicate achievement of acceptability concerning particular kinds of examination procedures or particular risks;
- comparing levels of risk evident from other examination procedures already in use;
- evaluating clinical study data, especially for new technology or new intended uses;
- taking into account the state of the art regarding existing technology and current medical laboratory practice.

"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 examination procedure. Examples are:

- recognized standards for the same or similar examination procedures;
- best practices for other examination procedures of the same or similar type;
- results of peer-reviewed scientific research.

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

C.3 Recommendations

The laboratory should establish guidelines for developing the risk acceptability criteria for the particular examination procedures or laboratory services being considered, which will be included or referenced in the risk management plan as required by 4.4.

When developing or maintaining the policy, the following should be taken into consideration (see 6.1):

- applicable regulatory requirements in the regions where the medical laboratory operates and provides services;
- relevant recognized standards (preferably International Standards) for the particular examination or service, or for its intended use, that can help identify principles for setting the criteria for risk acceptability;
- information on the state of the art can be obtained from review of the literature and other information on similar examination procedures or laboratory services the laboratory has provided, as well as those from competing laboratories;
- validated and comprehensive concerns from the main stakeholders. Some potential sources of information on the patient and clinician perspective can include news media, social media, patient forums, as well as internal input from departments with expert knowledge of stakeholder concerns.

When determining the criteria for risk acceptability, the laboratory should consider whether death or serious deterioration of health is likely to occur, either due to a device malfunction, deterioration of characteristics or performance, any inadequacy in the labeling or instructions for use, or in normal operation. If serious adverse events are likely to occur, the laboratory should decide if the risk is acceptable. In any case, the risk should be reduced. In doing so, the laboratory may choose an end-point for risk reduction, using a reasonable decision process such as the following:

Risk acceptability should preferably be based on recognized standards specifying state of the art risk control measures for particular categories of examination procedures or laboratory services. Basing the risk reduction end-point on harmonized standards ensures that the risk is reduced to an acceptable level.

If no recognized standards are available, other published guidelines or scientific literature should be considered. Basing the risk reduction end-point on published guidelines or scientific literature helps to ensure that the risk is reduced to an acceptable level.

Where no independent publications are available, the laboratory should determine and document the best risk reduction means, and should include in the documentation the rationale for their selection. The criteria for risk acceptability should be based on historical data, best medical laboratory practices and the generally acknowledged state of the art, among other criteria.

If a reduction to the approved acceptable level cannot be achieved, a risk-benefit analysis can be conducted to demonstrate that the residual risk is outweighed by the medical benefit.

Compliance may be demonstrated by reflecting such end-points in the criteria for risk acceptability and documenting the decisions in the risk management file. Where safety cannot be demonstrated as such, clinical evidence may be used to demonstrate that the medical benefit outweighs the risk.

The review of the suitability of the risk management process at planned intervals, as required by 4.15 of ISO 15189:2012, can demonstrate the appropriateness of previously used criteria for risk acceptability or lead to changes in the policy. Such changes can also lead to reviewing the appropriateness of previous risk acceptability decisions.

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 over others. 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 laboratory has used the methods listed above.

C.4 Risk matrix

A common way of applying acceptability criteria is by indicating the combinations of probability of harm and severity of harm that are acceptable or unacceptable using a matrix, such as [Table I.4](#) or [Table I.5](#). Such charts may be specific to an examination procedure and its particular intended use, or may apply to a family of examination procedures that share similar characteristics and intended uses. Their visual nature makes risk charts an effective means of risk communication.

Annex D (informative)

Identification of characteristics related to safety

This following guidance is adapted from ISO 14971:2019 and ISO/TR 24971:2019, and has been expanded to address aspects of medical laboratory examinations and services.

D.1 General

[5.4](#) requires that the laboratory identifies those characteristics of the laboratory examination or service that could affect safety. Consideration of these characteristics is an essential step in identifying the hazards associated with the examination procedure or laboratory service as required in [5.5](#).

A useful way to develop the list of potential hazards is to ask a series of questions concerning the intended uses, users, use environment and any reasonably foreseeable misuses, as well as the development of the examination, preparation and use of patient specimens, reagents, equipment and accessories, and their ultimate disposal. If these questions are asked from the point of view of all the individuals involved (e.g., users, maintainers, healthcare providers, patients, etc.), a more complete picture can emerge of where the hazards can be found.

Questions starting in [D.3](#) are intended to aid the laboratory in identifying all the characteristics of the examination or laboratory service that could affect safety. The list is not exhaustive, nor representative of all examinations or laboratory services. The medical laboratory is advised to add questions and points-to-consider that can have applicability to the particular examination or laboratory service, and to skip questions that are not relevant. The laboratory is also advised to consider each question not only on its own, but also in relation to others.

D.2 Characteristics related to safety for examination procedures, including IVD medical devices

D.2.1 General

In addition to the chemical, mechanical, electrical and biological characteristics that create risk for medical laboratory personnel, IVD medical devices and medical laboratory examinations have performance characteristics that determine the accuracy and clinical utility of the examination results. Failure to meet the performance characteristics required for the intended medical use could result in a hazardous situation that should be evaluated for risk to particular patient populations.

Therefore, failure to meet the specifications established by the medical laboratory or the IVD manufacturer for any of the performance characteristics related to safety 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) and Failure Mode and Effects Analysis (FMEA) are described in [Annex G](#).

D.2.2 Performance characteristics of quantitative examination procedures

Quantitative examination procedures are intended to determine the amount or concentration of an analyte in a patient's specimen. Results are typically reported on an interval scale. Some of the analytical performance characteristics of quantitative examination procedures are precision (imprecision), trueness (bias), analytical specificity and quantitation limit. Performance requirements depend on the intended medical applications. A falsely high or falsely low result, for example, can lead to an incorrect diagnosis or delayed treatment, and the consequent harm to the patient could depend

on the concentration of the analyte and magnitude of the bias. For this reason, it is also important to include the correct biological reference intervals definition or verification.

D.2.3 Performance characteristics of qualitative examination procedures

Qualitative examination procedures are 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, diagnostic specificity and detection limit. 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.

D.2.4 Reliability or dependability characteristics

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

D.2.5 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 examination procedure 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.

D.3 Generic questions pertaining to IVD medical devices and medical laboratory examinations

D.3.1 What is the intended use and how are the examination results used?

Factors that should be considered include:

- What is the examination's role relative to diagnosis, prevention, monitoring, treatment or alleviation of disease?
- What are the indications for use (e.g., intended patient populations)?
- Are the examination results intended for critical medical decisions?
- Are the quality specifications appropriate for the intended use and decision levels?

D.3.2 Is the IVD medical device or examination procedure intended for use at the point of care?

Factors that should be considered include training of POCT operators, compliance and monitoring of POCT operators, comparison of results to those obtained in the central laboratory.

D.3.3 What materials or components are utilized to verify, validate or control the equipment used to perform the examination?

Factors that should be considered include quality assurance of materials, verification, quality control and quality assurance.

D.3.4 Are the reagents stored under special conditions to ensure stability?

Factors that should be considered include temperature, humidity, and time frame for storage.

D.3.5 Is the equipment or IVD medical device intended to be routinely cleaned and disinfected by the laboratory?

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. Consideration should be given to the effect of cleaning and disinfecting agents on the performance or reliability of the equipment or IVD medical device.

D.3.6 Are measurements correctly performed?

Factors that should be considered include the variables measured and the accuracy, traceability and uncertainty of the measurement results.

D.3.7 Do the examination results require interpretation by the laboratory or the healthcare provider?

Factors that should be considered include whether conclusions are presented by the IVD 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.

D.3.8 Is the examination procedure intended for use in conjunction with other examinations or IVD medical devices?

Factors that should be considered include identifying any other equipment, IVD medical devices, or accessories that can be involved and the potential problems associated with such interactions.

D.3.9 Are the examination results intended for use by the healthcare provider in conjunction with other examination results?

Factors that should be considered include identifying any other examination results that can be involved and the potential problems associated with their combined interpretation.

D.3.10 Are there unwanted outputs of energy or substances generated by the measurement system or the examination procedure?

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 installation, cleaning or testing having unwanted physiological effects if they remain in the system.

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

D.3.11 Is the instrumentation or IVD 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.

D.3.12 Are there essential consumables or accessories associated with the examination procedure or IVD 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.

D.3.13 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?

D.3.14 Does the examination procedure or IVD medical device contain or use 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.

D.3.15 Do the components of the examination procedure or IVD medical device have a restricted shelf-life?

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

D.3.16 Are there any delayed or long-term use effects?

Factors that should be considered include ergonomic and cumulative effects. Examples could include repetitive actions, mechanical fatigue, loosening of straps and attachments, vibration effects, labels that wear or fall off, long term material degradation.

D.3.17 What determines the lifetime of the examination components or IVD medical device?

Factors that should be considered include ageing, battery depletion, etc.

D.3.18 What is the intended use and how are the examination results used?

Factors that should be considered include: is the result used in confirmation with its intended use. For instance, is it used for population study, diagnosis in a patient or follow up.

D.3.19 Is the medical device intended for single use or multiple use

Factors that should be considered are: does the medical device self-destruct after use? Is it obvious that the device has been used? What are the possible consequences associated with re-use?

D.3.20 Is safe disposal of the consumables or any waste materials necessary?

Factors that should be considered include whether the waste products that are generated by the examination process, maintenance and servicing contain toxic or hazardous material or could contain biological agents.

D.3.21 Is safe decommissioning of the equipment or IVD medical device necessary?

Factors that should be considered include whether it contains toxic or hazardous material or could be contaminated with biohazardous waste? Is the material recyclable?

D.3.22 Does installation or use of the equipment or IVD medical device require special training or special skills?

Factors that should be considered include:

- the novelty of the examination procedure or IVD medical device;
- the likely skill and training of the person installing, using or servicing the equipment;
- commissioning and handing over to the laboratory and whether it is likely/possible that installation can be carried out by people without the necessary skills.

D.3.23 How will information for safe use be provided?

Factors that should be considered include:

- whether adequate information has been provided to the laboratory by the IVD manufacturer?
- whether provision of the information involves the participation of third parties such as installers, care providers, or health care professionals, and whether this will have implications for training;
- based on the expected life of the device, whether re-training or re-certification of operators or service personnel would be required.

D.3.24 Will new examination processes need to be established, introduced or modified?

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

D.3.25 Is successful use of the instrumentation or IVD medical device critically dependent on human factors, such as the user interface?

Factors that should be considered include staff training and competence assessment.

D.3.26 Can the user interface design 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. [Annex F](#) and IEC 62366-1 contain additional guidance on usability evaluation.

D.3.27 Is the IVD 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.

D.3.28 Does the IVD 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.

D.3.29 Does the IVD 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.

D.3.30 Does the examination equipment or IVD 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.

D.3.31 Has the IVD medical device been tested in relation with cybersecurity?

Factors that should be considered are mentioned in [F.9](#)

D.3.32 Is the instrument or IVD 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.

D.3.33 Can the user interface be used to initiate user actions?

Factors that should be considered include the possibility of initiating 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.

D.3.34 Does the IVD 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.

D.3.35 In what ways might the IVD 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.

D.3.36 Does the IVD medical device or the LIS hold data critical to patient care?

Factors that should be considered include the potential for intrusion by malevolent actors and consequence of the data being modified, corrupted or deleted.

D.3.37 Is the IVD medical device intended to be mobile or portable (e.g., for point of care applications)?

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

D.3.38 Are specimens adequate for the examination procedure?

Factors that should be considered include type, volume, storage, transport, handling and disposal.

D.3.39 Are personnel trained and periodically monitored in the use of equipment?

Factors that should be considered include competence assessment, training and responsibility assignments.

D.3.40 Are turnaround times (TAT) adequate during operational processes?

Factors that should be considered include proper defining of the time intervals from phlebotomy to report release

D.3.41 Are quality control processes adequate to assure quality of examination results?

Factors that should be considered include proper planning, performing and monitoring of internal quality control and monitoring of external quality assessment.

Annex E

(informative)

Examples of hazards, foreseeable sequences of events and hazardous situations

E.1 General

[5.3](#) requires that the laboratory compile a list of known and foreseeable hazards associated with the examination in both normal and fault conditions. [5.4](#) requires the laboratory 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 exposure to the hazard occurs, creating a hazardous situation. Sequences of events or other circumstances can lead to the creation of a hazard from some initiating event, to the development of a hazardous situation, and/or to the occurrence of harm. Each event in the sequence can occur with a certain probability, and the overall probability of harm is the cumulative probability of all of the events occurring. The goal of risk management should be to prevent the hazardous situation from occurring, if possible; otherwise, to minimize the overall probability that the hazardous situation will occur.

[Figure E.1](#) represents the progression from initiating event to harm, and shows how the overall probability of harm can be estimated by combining estimates of the component probabilities, in this case P_1 representing the probability that a hazardous situation would occur (e.g., in the case of an instrument malfunction or use error), and P_2 representing the probability that the hazardous situation would lead to harm. This approach allows the component probabilities to be estimated by qualified experts, e.g., laboratory personnel for P_1 and medical experts for P_2 . The level of risk is determined as a function of both the probability of harm and the severity of harm.

In situations where either P_1 or P_2 can be estimated and the other probability cannot, a conservative approach can be followed by setting the unknown probability equal to 1. The risk can then be assessed based on the severity and the conservative estimate of the probability of occurrence of harm.

Although the quantitative probabilities P_1 and P_2 are difficult to formally establish by the medical laboratory, literature or in-laboratory historic data may be used as a source for these values. [Annex I](#) will discuss qualitative approaches to risk assessment. Nonetheless, the progression leading to harm as given in the figure is valid whether quantitative probabilities can be determined or not.

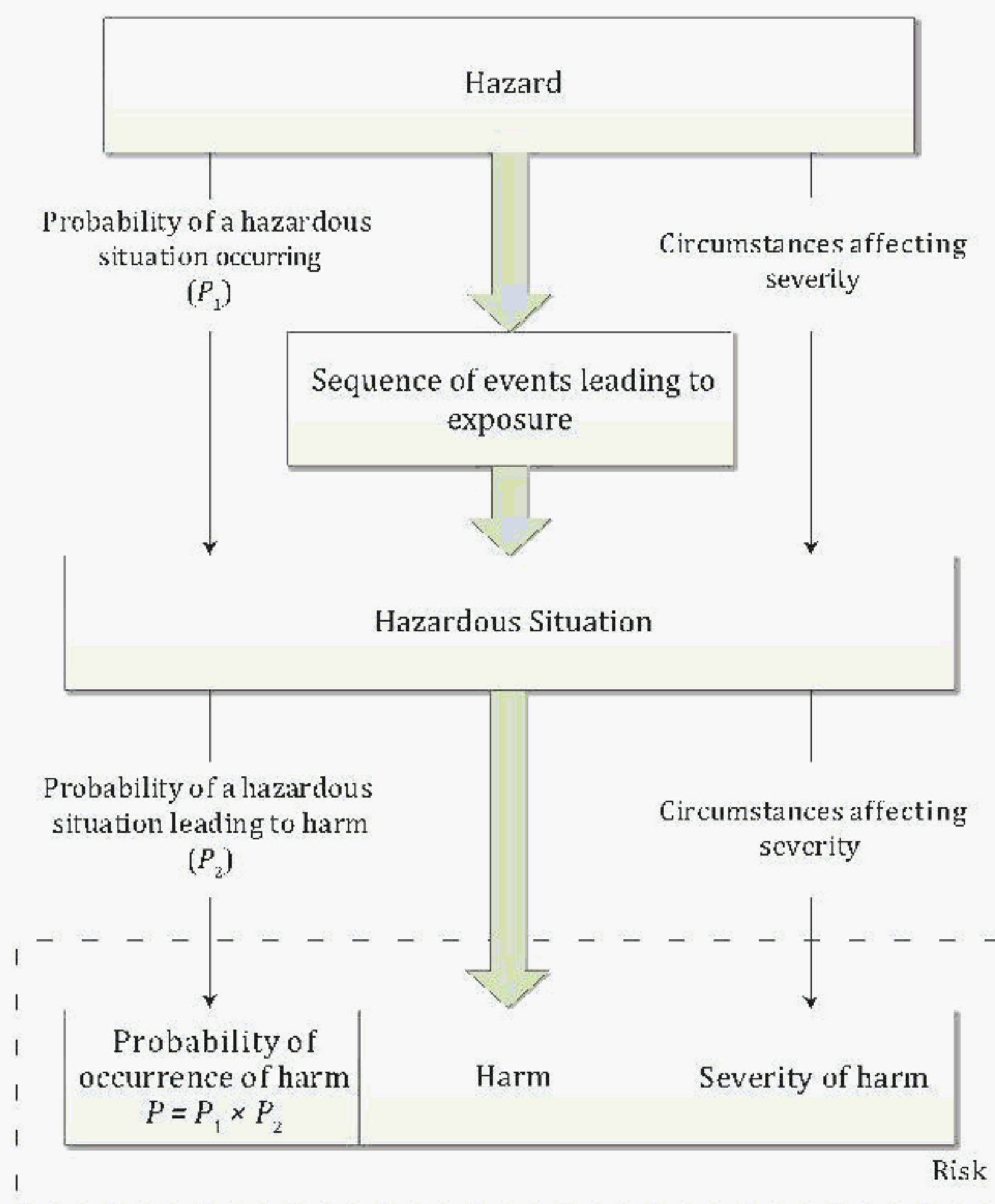


Figure E.1 — Pictorial representation of the relationship of hazard, sequence of events, hazardous situation and harm.

The thin arrows represent elements of risk analysis and the thick arrows depict how a hazard can lead to harm.

E.2 Identification of hazards

A starting point for the compilation of a list of potential hazards is a review of experience with the same or similar types of examinations and IVD medical devices to identify the likely causes of hazards. The review should take into account the laboratory's own experience as well as the experience of other laboratories 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 and the harms that can occur. This listing and aids such as the list of examples in [Table E.1](#) can be used to compile an initial list of hazards.

The laboratory can then begin to identify some of the sequences of events that can transform the hazards into hazardous situations and harm. Hazards that would not result in a hazardous situation and thus could never result in harm can be eliminated from further consideration.

Although useful, it should be recognized that this approach is not a thorough analysis. Many sequences of events will only be identified by the use of systematic risk analysis techniques aimed at the causes of potential hazards, such as FMEA, FTA and other methods 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, may be needed to complete a comprehensive analysis. [Table E.3](#) provides examples of the relationship between initiating events (causes), 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 identification of appropriate risk control measures, in practice identification and compilation is an ongoing activity that continues throughout the use of examination procedures and IVD medical devices. IVD manufacturers rely on feedback from medical laboratories (e.g., complaints) to help identify causes of IVD device malfunctions and adverse events (actual and potential).

This annex provides non-exhaustive lists of possible hazards that can be associated with different types of examination procedures and IVD medical devices ([Table E.1](#)), and of initiating events and circumstances ([Table E.2](#)) that can result in hazardous situations that can lead to harm. [Table E.3](#) gives examples of logical progressions of hazards transformed by sequences of events or circumstances into hazardous situations and ultimately harm.

Recognizing how a hazard can progress to a hazardous situation and how a hazardous situation can progress to harm, is critical for estimating the probability of occurrence and the severity of the harm that could result. The objective is to compile a comprehensive set of hazardous situations for use in risk analysis. The tables in this annex are intended to aid in the identification of hazardous situations.

It is important to emphasize that it is up to the laboratory to determine what events in the sequence are called a hazard and a hazardous situation (i.e., exposure to the hazard) to suit the risk analysis being performed, as illustrated in [Figure E.1](#).

E.3 Hazards to the patient

From the standpoint of a patient, an 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. Incorrect or delayed examination results, as well as incorrect information accompanying the result, are the most common hazards to patients from laboratory examinations. These hazards can be initiated by a use error, equipment malfunction, reagent deterioration or other malfunction, which can cause a sequence of events to occur leading to delayed or inappropriate medical care. These are hazardous situations for the patient, although for the purpose of risk analysis the laboratory may decide that a hazardous situation existed when the healthcare provider received the incorrect result from the laboratory, or did not receive the result when it was needed for a medical decision. The laboratory has no control over the subsequent actions of the healthcare provider.

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

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., hypoglycemic or hyperglycemic).

E.4 Hazards from 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 hazards in fault conditions; e.g.,

- incorrect patient name or identification number;
- incorrect birth date or age;
- incorrect gender.

E.5 Hazards due to use error

Incorrect results can occur in normal use, due to use error.

For examples of use errors see [Annex H](#).

E.6 Hazards in correct use

Incorrect results can even occur in correct use, when the examination procedure meets its established performance characteristics claims and no use errors have occurred. Although the results may be as expected for the intended patient population, an incorrect result can occur for an individual patient due to one of the following causes:

- Measurement uncertainty – The precision of quantitative examination procedures is limited by the state of art in measurement technology. Performance claims are often based a specified limit based on medical utility that 95 % of the results meet, which means that up to 5 % of the individual results are allowed to fall outside the limit.
- Influence of 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 with certain patient sample. The presence of these influences is usually unknown to the laboratory or the healthcare provider.
- Heterogeneity of the analyte – Antibodies and other proteins in blood samples are mixtures of different isoforms. Performance characteristics of the examination procedure might not apply to all patient samples.
- Imperfect discrimination between positive and negative samples – Qualitative examination procedures typically exhibit inherent false negative and false positive rates, caused by uncertainties associated with determination of a suitable cut-off value as well as factors discussed above (e.g., measurement uncertainty and sample-related influences).

E.7 Hazardous situations

For medical laboratory examinations, where incorrect and delayed results are considered hazards to patients (see [E.3](#)), a hazardous situation occurs when the incorrect result is reported to a clinician or when a critical result is delayed. The subsequent decisions and actions by the clinician, which can cause harm to the patient, are outside the control of the laboratory.

Examples of hazardous situations created by examination results include:

- a caregiver monitoring a diabetic patient obtains a falsely elevated blood glucose concentration measurement when the patient is actually hypoglycemic;
- the lab reported a false normal troponin result to the ER for a patient who presented with chest pains;
- a blood analyzer misidentified a sample from the ICU as a sample from a different patient;
- electrolyte results for a patient undergoing invasive heart surgery were not received when needed during the procedure.

E.8 Examples of known and foreseeable hazards

The list in [Table E.1](#) can be used to aid in the identification of hazards associated with the use of a particular equipment or IVD medical device, which could ultimately result in harm to the instrument operator or the patient. This list is not exhaustive.

Table E.1 — Examples of hazards

Hazard category	Examples
Operator	Use error <ul style="list-style-type: none"> — Attentional failure — Memory failure — Rule-based failure — Knowledge-based failure — Routine violation — Reagents added incorrectly — Sample omitted — Clotted sample not detected
Operational	<ul style="list-style-type: none"> — Incorrect or inappropriate specimen — Incorrect measurement — Erroneous data transfer — Incorrect sample presentation — Incorrect conditions of transport of samples — Sample volume insufficient for retest — Contaminated sample

Table E.1 (continued)

Hazard category	Examples	
Information	Data communication	Warnings and precautions
	— Inadequate network security	— Inadequate information about:
	— Inadequate malware protection	— electrical hazards
	— Insufficient data storage capacity	— toxic reagents
		— essential training
	Results	Service and maintenance
	— Delay	— Inadequate installation instructions
	— Incorrect report	— Inadequate preventive maintenance specifications
	— Critical values not reported	— Inadequate troubleshooting and repair instructions

E.9 Examples of initiating events and circumstances

In order to identify foreseeable sequences of events, it may be useful to consider the 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 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 an examination procedure or IVD medical device.

Table E.2 — Examples of initiating events and circumstances

General category	Examples
Incomplete requirements	Inadequate specification of: — Performance requirements — Regulatory requirements
Laboratory processes	— Inadequate sample: low volume, hemolyzed, inappropriate container — Internal control fails — Insufficient control of changes to laboratory processes — Insufficient control of materials
Sample Transport, storage and preparation	— Inadequate packaging — Contamination or deterioration — Inappropriate environmental conditions — Inadequate sample preparation
Reagent / instrument	— Reagent fail — Instrument alarm — Instrument stops — Instrument malfunction — Lack of reagents

Table E.2 (continued)

General category	Examples
Environmental factors	Adverse conditions <ul style="list-style-type: none"> — Physical (e.g., heat, pressure, time) — Chemical (e.g., corrosions, degradation, contamination) — Inadequate supply of power — Inadequate temperature control
Human factors	<ul style="list-style-type: none"> — Potential for use errors triggered by design flaws, such as confusing or missing instructions for use complex or confusing control system ambiguous or unclear instrument state. — Ambiguous or unclear presentation of settings, measurements or other information — Misrepresentation of results — Insufficient visibility, audibility or tactility — Insufficient or imprecise checks or process controls for actions or function. — Use by unskilled/untrained personnel — Insufficient warning of possible method/instrument malfunction — Failure to recognize inconsistent or incorrect results — Incompatibility with consumables/accessories.

E.10 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.

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. For example, 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	Possible harms
Inadequate sample	1) low volume 2) Insufficient sample to be read in the instrument 3) New sample required	<ul style="list-style-type: none"> — Patient receives Incorrect result or no result — delay in result 	<ul style="list-style-type: none"> — delay in diagnosis and treatment — Erroneous diagnosis

Table E.3 (continued)

Hazard	Foreseeable sequence of events	Hazardous situation	Possible harms
No action with unacceptable quality control results	1) No action to investigate cause of unacceptable control results and take actions 2) Patient samples Processed 3) Patient results reported	Patient receives Incorrect result	— Erroneous diagnosis — Death
Equipment improperly functioning	1) POCT glucose analyzer battery reaches the end of its useful life 2) Analyzer measure incorrect result	Hypoglycemic patient receives falsely elevated glucose result, leading to inappropriate insulin administration	Death
Sample misidentified	Patient sample is misidentified with another patient's ID number		

Annex F (informative)

Nonconformities potentially leading to significant risks

F.1 General

The investigation of nonconformities in the medical laboratory includes an evaluation of the potential for it to result in a hazard.

The examples of nonconformities can be used as starting points to help identify hazards associated with the main laboratory services. The nonconformities are roughly grouped by the laboratory specialty and phase (pre-examination, examination and post-examination) where they commonly occur. Added is as well a list related to information safety (see [F.9](#)). They are not intended to be complete lists.

F.2 Nonconformities associated with the core medical laboratory

F.2.1 Pre-examination phase

- incorrect patient identification;
- incorrect or missing diagnostic information;
- incorrect interpretation of medical request;
- incorrect patient preparation;
- incorrect collection container or preservative;
- incorrect collection container labelling;
- incorrect phlebotomy technique;
- incorrect mixing of sample;
- incorrect collection timing;
- incorrect transport conditions or timing.

F.2.2 Examination phase

- discrepant quality control result;
- procedural non-conformity;
- equipment or reagent error;
- delayed time to completion (turnaround time);

NOTE Time delays can occur throughout the total laboratory cycle.

- invalid quality control of equipment, reagents, materials;
- personnel (active, cognitive, non-cognitive) errors;
- latent (systemic) errors;

- the phase of verifying/validating the examination procedures:
 - insufficient or incorrect documentation of scientific evidence for analytic validity or clinical validity of any examination procedure;
 - not verifying or validating the examination procedure in appropriate patient population;
 - selecting inappropriate examination methods.
- using incorrect or inappropriate reference values;
- not using sufficient number and variety of samples in verification or validation;
- incorrectly determined accuracy, analytic sensitivity and specificity, reportable range/cut-off values, etc.;
- non-optimized examination procedures.

F.2.3 Post-examination phase

- incorrect result;
- incorrect transcription of result;
- ambiguous report;
- result ascribed to incorrect patient;
- report sent to incorrect person;
- missing information about restrictions on interpretations of result.

F.3 Nonconformities associated with the anatomical pathology laboratory

F.3.1 Pre-examination phase

- incomplete or incorrect patient identification;
- incorrect or incomplete specimen identification (e.g., absent or erroneous marking of margins or orientation identifiers);
- mismatching of specimen, specimen container and request form;
- incorrect sample collection (e.g., no preservative or unsatisfactory slides);
- incomplete or incorrect clinical information provided on request form;
- inadequate checking at accessioning to ensure that request form and specimen details match;
- specimens with the same or similar surnames not separated at accessioning;
- specimens of the same tissue type not separated at accessioning;
- single piece workflow accessioning not adhered to;
- incorrect transport of specimen to laboratory.

F.3.2 Examination phase

- no effective separation between specimens at dissection;
- no confirmation that the specimen and request form details match before performing dissection;

- more than one specimen pot opened at a time during dissection;
- inadequate checking at cut-up that the request form, specimen and cassette/s details match;
- designated area for cut-up does not provide a suitable environment to minimize distractions and interruptions;
- pre-labelling cassettes rather than single piece work flow at dissection;
- more than one cassette open at a time for transfer of tissue at embedding;
- cases that require isolation/interruption to workflow at microtomy, such as for cooling or decal, not being effectively separated from other cases;
- pre-labelling slides before the embedded tissue is microtomed;
- tissue sections not cleared from the water bath between each block at microtomy;
- designated area for microtomy does not provide a suitable environment to minimize distractions and interruptions;
- using slide labels that do not survive subsequent staining processes and require replacement at the issuing stage;
- no checks performed at the issuing stage to ensure that the macro appearance of the block correlates to the corresponding slide;
- specimens of the same tissue type are not effectively separated when cases are being assembled for microscopy;
- specimens of patients with the same or similar surnames are not separated when cases are being assembled for microscopy;
- no checks performed to ensure that patient's details on the slides and request form match prior to examination of the slides.

F.3.3 Post-examination phase

- details of any relevant discrepancies identified during the procedures, including pre-laboratory issues, not included on the final examination report;
- delayed reporting of examination results;
- no mechanism in place for feedback and follow-up of discrepant anatomical pathology findings.

F.4 Nonconformities associated with the transfusion medicine laboratory

F.4.1 Pre-examination phase

- failure to reject improperly labelled sample;
- failure to exclude from inventory fresh frozen plasma prepared from a unit collected from a donor with pregnancy history;
- failure to exclude from inventory apheresis platelet units not screened for HLA antibodies;
- failure to exclude from allogeneic inventory units testing positive for transfusion transmissible disease;
- failure to exclude from allogeneic inventory units collected from donors not screened for transfusion transmissible disease;

- failure to exclude from allogeneic inventory units collected from donors not screened for use of teratogenic drugs.

F.4.2 Examination phase

- incorrect typing of blood unit;
- incorrect typing of patient sample;
- failure to provide clinically indicated, antigen negative blood for a patient with known red blood cell antibodies;
- failure to perform coombs crossmatch for patient with known red blood cell antibody.

F.4.3 Post-examination phase

- failure to irradiate a cellular blood unit for an immunodeficient or immunocompromised patient;
- failure to wash blood unit for an IgA deficient patient;
- release of blood unit for the wrong patient;
- release of blood unit contaminated with a bacterial pathogen.

F.5 Nonconformities associated with the microbiology laboratory

F.5.1 Pre-examination phase

- failure to reject improperly labelled sample;
- failure to reject specimen of inadequate quantity, past stability, or transported/stored at inappropriate temperatures;
- failure to reject inappropriate specimen types or sources for testing;
- failure to provide instructions for sample collection and transport and ensure compliance;
- failure to ensure unidirectional workflow for molecular testing;
- lost sample.

F.5.2 Examination phase

- failure to ensure appropriate turn-around times;
- failure to minimize risk for cross-contamination of patient samples;
- failure to include controls to identify inhibition of pathogen detection reactions;
- failure to control for appropriate performance of microbial staining reactions;
- failure to ensure absence of microbial targets from culture media and microbial detection reagents and/or systems;
- failure to quality control new reagent lots and shipments;
- failure to detect loss of antibiotic disk potency for susceptibility testing.

F.5.3 Post-examination phase

- release of antimicrobial susceptibility test results that are not appropriate for a given organism or specimen type (e.g., CSF);

- failure to ensure prompt communication of critical test results ('critical call');
- failure to ensure transmission of correct results;
- failure to minimize risk of incorrect data entry or transcription errors;
- failure to minimize risk for misinterpretation of laboratory results;
- failure to promptly correct erroneous results and communicate corrected results.

F.6 Nonconformities associated with the molecular laboratory

As technologies advance and molecular pathogenesis of diseases clarified, IVD's based on emerging technologies such as nucleic acid-based assay have been recently developed and utilized. The more complex the methods and procedures are, the higher the probability of inherent risks. For an example, in testing based on (massive parallel) sequencing, an IVD is an integrated system which comprises of a combination of extracting reagent, sequencer and software (algorithm and database). Traceability of version of each component and mutual compatibility of the system should be ensured.

F.6.1 Pre-examination phase

When performing molecular testing, background sample information including history such as acquisition, handling and transport is important.

Patient sample mix-up

- insufficient communication between the laboratory and clinical users causing ordering of incorrect examination procedures;
- failure to reject the test request with incomplete information concerning informed consent, genetic counselling or confidentiality;
- failure to indicate not sufficient information was present concerning the sample related to pre-analytical steps;
- lack of quality assurance monitors to track appropriate handling and transport of specimens.

Sample-derived risk

- lack of information regarding material source (FFPE, fresh, blood, urine, stool, others);
- incomplete information of handling and/or transport (temperature and/or mechanical stress);
- possibility of misidentification of patient sample (DNA fingerprinting could be performed).

F.6.2 Examination phase

Lack of/or incomplete traceability

- traceability of version of each component (extraction reagent, reaction reagent, sequencer and software (algorithm and database) not secured
- lack of mutual compatibility of the system (extraction reagent, reaction reagent, sequencer and software (algorithm and database)
- insufficient validation of examination methods (e.g., not including samples representing mutations/ variations or organisms that may be encountered in patient samples, not fully optimized assays or assay components such as primers, oligo's, or nucleic acid sequences, insufficient homology search, etc.);
- carryover contamination by post-amplification PCR products;

- near-neighbor interferences on multiplex assays;
- insufficient quality control practices such as not including adequate and appropriate control samples.

F.6.3 Post-examination phase

- inappropriate result reporting, such as improper mutation nomenclature, inappropriate description of mutations or variants that were test for and identified;
- failure to use updated and optimized software with relevant database, or their traceability;
- reporting “incidental/secondary findings” without sufficient validation of test result;
- misinterpretation of test results;
- not including information on performance characteristics and limitations on test reports;
- misinterpretation of reports by clinicians due to poor report clarity;
- release of incorrect patient results;
- delayed reporting of examination results.

F.7 Nonconformities associated with chemistry, haematology or haemostaseology laboratory

F.7.1 Pre-examination phase

- inadequate flushing of intravenous lines before sample collection;
- dosing and/or collect times are not accurate in therapeutic drug monitoring;
- incorrectly filled coagulation tubes;
- failure to detect use of expired collection tubes.

F.7.2 Examination phase

- improper calibration;
- unexpected shift in patient results not identified by quality control material;
- unrecognized analytical variation for measurand determinations performed on more than one instrument;
- specimen carryover causing spurious changes in subsequent result;
- method linearity exceeding without evidence of analytic error (i.e., immunoassay high dose hook effect);
- ambient air contamination of blood gas samples (note: this may occur in sample collection or during analysis);
- unrecognized sample problems in coagulation (high hematocrit, clots, use of incorrect citrate anticoagulant concentration, platelet level too high in plasma);
- incorrect international sensitivity index for conversion of prothrombin time to international normalized ratio;
- heparin therapeutic range monitoring by activated partial thromboplastin not corrected for lot changes;

- incorrect geometric mean in coagulation testing;
- incorrect reference range for current prothrombin and activated partial thromboplastin time lots;
- surreptitious elevation of platelet count by red cell fragments.

F.7.3 Post-examination phase

- critical value not communicated to caregiver.

F.8 Nonconformities associated with the pre-analytical phase

F.8.1 Pre-laboratory receipt phase (generally the responsibility of the healthcare provider)

- incomplete or incorrect patient identification;
- incomplete or incorrect clinical information provided;
- incorrect sample collection e.g., preservative;
- poorly made cytological smears;
- incorrect or incomplete specimen identification;
- absent or erroneous marking of margins or orientation identifiers;
- mismatching of specimen, specimen container and request form, i.e. specimen in wrongly labeled containers, this could occur when containers are pre-labeled;
- incorrect transport of specimens to laboratory.

F.8.2 Post-laboratory receipt phase – specimen accessioning

Initial receipt and accessioning into the medical laboratory is a critical area of risk. Should there be a specimen mix-up or incorrect data entry at this stage any future processes compromised. To alleviate the risks some of the following could be considered.

- adequate checking of specimen and request to ensure no mismatch; two independent checks to ensure specimen and request form match, including reconciliation between registration and accession number;
- any labeling discrepancies are recorded and followed throughout the test cycle with full audit trail and the issues identified on final report, including specimen information such as wrong site as well as patient information;
- procedures for minimum labeling requirements are documented and all specimens are checked against these minimum requirements;
- specimens not meeting minimum labeling requirements are recorded in Laboratory information system (LIS) and reported in final report;
- inadequately/unlabeled specimens may be re-labeled in laboratory for traceability but original label is retained;
- specimens on same tissue types are not sequentially numbered wherever possible;
- one specimen at a time is processed to minimize risk of specimen mix up.

F.8.3 Post-laboratory receipt phase – data entry

- failure in scanning of request form linked to data entry profile;
- failure in data entry taken directly from request form;
- any discrepancies between request form and sample recorded in Laboratory information and management system (LIMS);
- failure in double stage data entry of critical information wherever possible;
- failure in regular audit of data entry processes;
- failure in linking specimens and request forms to ensure gross cut-up notes recorded correctly.

F.9 Nonconformities associated with information technology

- failure or corruption of data transfer;
- security compromise (i.e., failure to log off a terminal, password compromise, database security breach [malware], insecure data transfer outside a protected network such as by email);
- failure of data hardware or software (disk drive failure, software application failure [crash], ransomware);
- failures due to breaches in cybersecurity;
- failures of digital software application in “smart” point of care devices.

Annex G

(informative)

Risk analysis tools and techniques

G.1 General

This annex provides an introduction to some techniques for risk analysis. These techniques can be complementary and it might be necessary to use more than one of them. The basic principle is that the sequence of events is analyzed step by step. In depth sources should be used to guide the application of these tools to a specific instance.

Preliminary Hazard Analysis (PHA) is a technique that can be used early in the development process of a new examination procedure or laboratory service, implementation of a new IVD device, or evaluation of a significant change in a process to identify the hazards, hazardous situations, and events that can cause harm when few of the details of the design of the examination procedure are known.

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

Failure Mode and Effects Analysis (FMEA) is a technique by which effects or consequences of individual failure modes (e.g., hazards) are systematically identified and addressed. It is more appropriate for a mature system, process or application, when the failure modes are known.

Process mapping is a technique by which a process is broken down into the individual steps for analysis. It is used together with FMEA to perform a process FMEA, which can be especially useful for laboratory examination processes including the pre-examination and post-examination aspects.

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 evaluating 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:

- materials used or produced and their reactivity;
- equipment used;
- operating environment;
- layout;
- 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/ISO 31010:2009^[14] for more information on performing a 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 a top event (e.g., hazardous situation), the possible causes or fault modes of the next lower functional system level causing the undesired consequence are identified. In itself, FTA is a failure reduction tool, which can help reduce the likelihood that a hazardous situation (the top event) will occur. This tool is useful for risk control (5.1).

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.

FTA 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 assessment 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 specialized computer programs, which are readily available.

See IEC 61025:2006 for more information on performing FTA.

G.4 Failure Mode and Effects Analysis (FMEA)

Failure modes and effects analysis (FMEA) is a technique used to identify the ways in which components, systems or processes can fail to fulfil their design intent, and to systematically evaluate the consequences of each failure mode. FMEA is a technique that answers the question, “What happens if ... fails?”.

The main applications of FMEA for medical laboratories are: Design FMEA, which can be used during the development of new assays (examinations); System FMEA, which is used for analytical systems comprising multiple components; Process FMEA, which is used for examination processes; and Application FMEA, which is used to prevent use errors with examination procedures and IVD medical devices.

The design of an examination procedure, the steps of a laboratory process, or the actions of an operator can be evaluated in a formal manner, 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. Failure Mode, Effects and Criticality Analysis (FMECA) extends an FMEA so that each fault mode identified is ranked according to its importance or criticality.

FMEA identifies:

- potential failure modes of the various parts of a system (a failure mode is what is observed to fail or to perform incorrectly);
- the effects these failures may have on the system;
- the mechanisms of failure;
- how to avoid the failures, and/or mitigate the effects of the failures on the system.

In order to use FMEA to support risk management, the examination, system or process should be known in some detail.

Note that in conventional FMEA, the probability estimate represents the probability that the cause of the failure will occur, not the probability of the failure mode. It is assumed that the immediate and long-term consequences of the failure will occur.

Detectability may be considered only if three conditions are met. The operator or user needs to:

- know what to do and how;
- have enough time to react; and
- be expected to take the correct action.

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 60812:2006 for more information on the procedures for performing FMEA.

G.5 Process FMEA

FMEA is particularly useful when deciding whether to introduce a new process within the laboratory. While it is not possible to anticipate every failure mode, a team of laboratory participants can formulate as extensive a list of potential failure modes.

The approach begins by creating a diagram or flowchart of the process, indicating the major process steps. This diagram shows the logical relationships of components and establishes a structure around which the FMEA can be developed.

Then, possible failure modes are evaluated (often by brainstorming in a team format). These failure modes are identified as the manner in which the process could fail, and described in a way that allows the team to determine what the effects of the failure will be.

The potential effects of each failure mode are then identified and listed. The effects can be 'local effects' (the immediate consequence of the failure, such as the impact on the process), the 'end effects' (the ultimate consequence of the failure, such as the impact on the patient or laboratory worker), as well as 'next effects' (consequences in between local and end effects).

A severity value is assigned to each failure mode based on an evaluation of the identified potential effect(s). A severity scale, such as with 1 = minor and 10 = major may be used. In addition, an occurrence value, rating the likelihood that this failure mode will actually happen, is also assigned.

The potential causes of each failure mode are then listed, together with the likelihood that this may happen.

It is important to note that the occurrence rate refers to the likelihood that the **cause** of the failure will occur, not the likelihood of the consequences or even the likelihood of the failure. In conventional FMEA methodology, unlike in risk analysis, if the failure cause occurs it is presumed that all downstream events will occur.

Any action or step that is in place to decrease the likelihood of a given failure is identified as a current control. A scale can be used to rate the likelihood that these controls would detect the identified failure cause in time to prevent the failure from occurring. For example, using a scale of 1 to 10, a rating of 1 means the control would be almost certain to prevent the failure, and a rating of 10 means it is not likely to detect the cause in time.

The Severity, Occurrence and Detection scores are summarized in column 9 from [Table G.1](#) as a “Risk Priority Number” (RPN), which is calculated by multiplying the three individual values. The FMEA methodology uses the RPN as a numerical index to prioritize the significance of the failures, based on

- the frequency of occurrence of the failure (actually the failure cause),
- the severity of the potential consequences, and
- the ability to detect the failures in time to prevent those consequences.

The use of RPN illustrates two other differences between FMEA and risk analysis. In FMEA, detection of the failure is identified a separate factor, whereas in risk analysis detectability of the hazard is included in the probability estimate. FMEA also multiplies the rankings from the severity, occurrence and detection scales, which is not mathematically valid because the ranks are ordinal numbers.

Nevertheless, FMEA methodology can be a useful reliability tool to drive reduction of failure rates.

As a general rule, preventive action should be considered for any RPN >100 when severity, frequency of occurrence and controls are evaluated using a 1-10 scale for each.

After implementation of the proposed new process, unanticipated failure modes might appear. The FMEA should be updated to include these new failure modes and using the RPN as a guide, the team may need to identify new actions to reduce the severity, occurrence and/or detection to an acceptable level.

An example is shown in [Table G.1](#) for specimen mislabeling, as stated in Column 1, Two potential failure modes are identified in Column 2: Failure to check armband and missing armband. The potential effects for both failure modes are the same, that being incorrect patient identification on the specimen. Therefore, the severity of both modes is the same, and is felt to be severe.

However, the likelihood of occurrence of each mode is different: Investigation shows that forgetting to check the armband as a cause of this failure mode rarely if ever occurs, so its occurrence is rated as 1 (unlikely). On the other hand, computer issues result in the admission of some patients without armbands, with an assessed occurrence of 3.

There is no control for not checking the armband, so it cannot be detected if it occurs (rating of 10), whereas a patient without an armband could still be asked for a name. As a control for a missing armband, this is felt to be relatively inadequate, since 80% of patients without armbands are trauma patients who cannot give their names, giving a detection rating of 8.

The risk priority number for not checking the armband is 100 ($10 \times 1 \times 10$), which is under the threshold for action. The situation with a missing armband has a risk priority number of 240 ($10 \times 3 \times 8$), so three recommended actions are listed. Each action is also rated for severity, occurrence and control, with resultant risk priority numbers; all three actions now are evaluated as having risk priority numbers below the threshold for action and the analysis stops at this point.

Table G.1 — FMEA Table

Action results													
Process function (1)	Potential failure mode (2)	Potential effects of failure (3)	Severity (4)	Potential causes of failure (5)	Occurrence (6)	Current controls (7)	Detection (8)	Risk priority number (9)	Recommended action (10)	Severity (11)	Occurrence (12)	Detection (13)	Risk priority number (14)
Specimen labelling	Phlebotomist does not check armband	Sample labelled with incorrect name	10	Forgets	1	None	10	100	None				
	Patient armband missing	Sample labelled with incorrect name	10	Computer issues in admitting	3	Ask patient their name	8	240	Resolve admitting issue	10	1	8	80
									New policy: no armband, no phlebotomy	10	3	1	30
									Resolve admitting issue AND new armband policy	10	1	1	10

Annex H

(informative)

Risk analysis of foreseeable user actions

H.1 Categories of user action

Adapted from IEC 62366-1:2015

For the purposes of this standard, user actions or inactions can be broadly categorized into actions that are foreseeable and those that are not foreseeable. Clearly, those user actions or inactions that are not foreseeable cannot be dealt with by this or any other standard. This document describes a process that deals with those user actions or inactions that can be foreseen. These foreseeable events can be further subdivided between intended and unintended user actions or inactions (see [Figure H.1](#)).

In [Figure H.1](#), intended user actions or inactions that fall within normal use can be a response that is intended by established processes and expected by the user, i.e. "correct use." Alternately, the intended action or inaction could result in a mistake or could result from conduct that deviates from established processes, i.e., "abnormal use." This does not necessarily mean that abnormal use results in a poor outcome for the patient. Often the clinical judgement of the user indicates that such use is in the best interest of the patient.

For the purposes of this standard, unintended actions or inactions are always classified as slips or lapses, which are all considered forms of use error. In the usability/human factors engineering process, it is helpful to differentiate between these categories while determining the root-cause of a particular use error to help ascertain which errors can be mitigated by design.

Slips and lapses are errors that result from some failure in the execution and/or storage stage of an action sequence, regardless of whether or not the plan that guided them was adequate to achieve its objective. Whereas slips are potentially observable as externalized actions not as planned (slips of the tongue, slips of the pen, slips of action), the term lapse is generally reserved for more covert error forms, largely involving failures of memory, that do not necessarily manifest themselves in actual behaviour and can only be apparent to the person who experiences them.

Mistakes can be defined as deficiencies or failures in the judgmental and/or inferential processes involved in the selection of an objective, whether or not the actions directed by this decision-scheme are according to plan (adapted from Reference [\[28\]](#)).

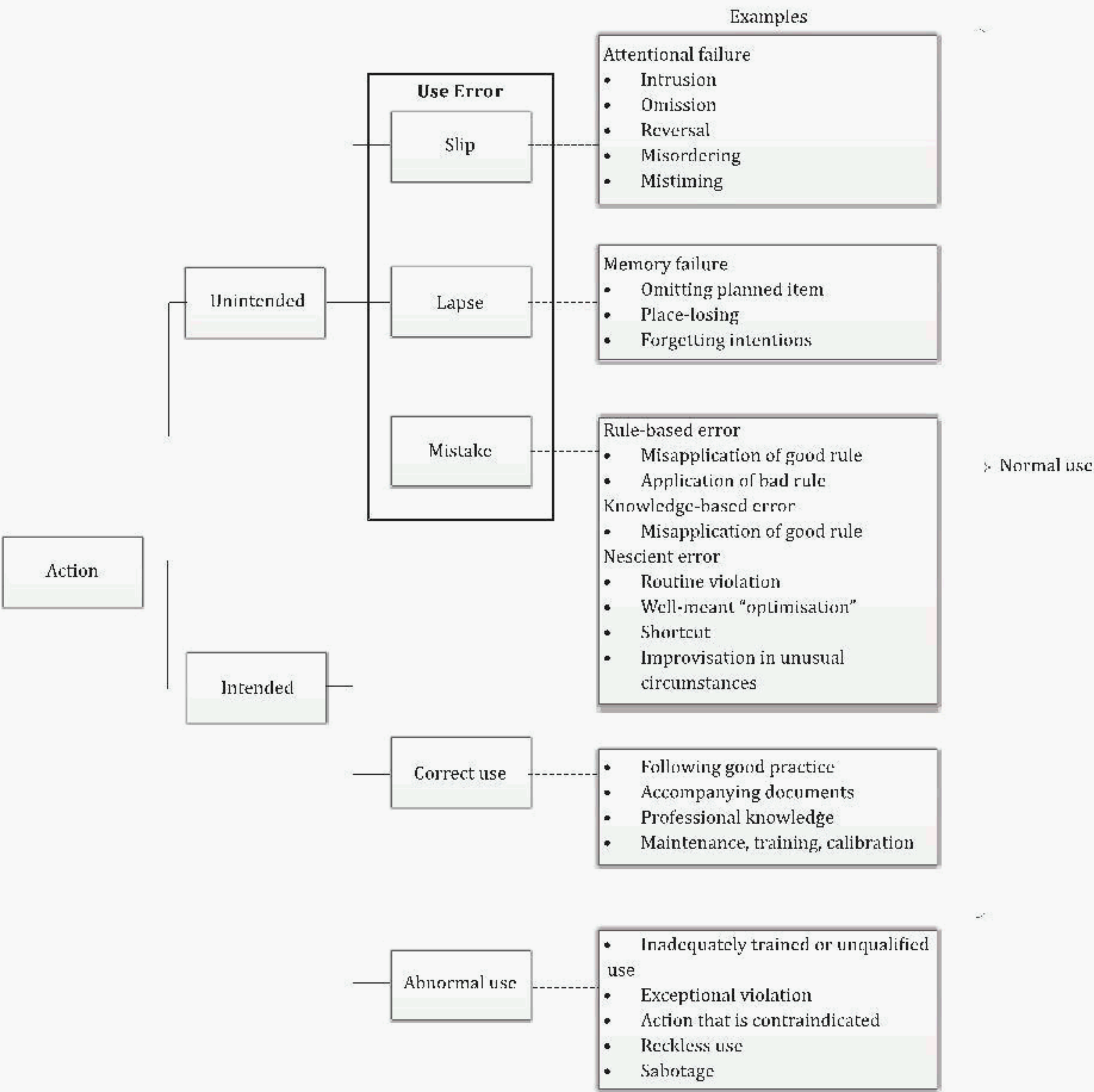


Figure H.1 — Categories of foreseeable user action

NOTE 1 In this figure, an action can result from a user:

- choosing to do something; or
- failing to do something.

NOTE 2 Nescient is used in the context of a lack of awareness of the adverse consequences of a skill-based action.

H.2 Examples of use errors, abnormal use and possible causes

The following use errors and abnormal use examples are based on adverse event reports collected by several regulatory authorities[24]. These examples are abbreviated descriptions of the actual events and have been modified to highlight the distinction between abnormal use and use error. The adverse events were classified as indicated following evaluation of the error against the intended action.

It is recognized that differentiating use error from abnormal use is not always an easy task and so often requires careful investigation, analysis, and documentation. A careful investigation might include trending and root cause analysis as techniques to classify events.

H.2.1 Examples of use errors

The following are brief descriptions based on actual events that were determined at the time to be examples of use errors.

- User confuses two buttons and presses the wrong button;
- User misinterprets the icon and selects the wrong function;
- User enters incorrect sequence and fails to initiate operation of a device;
- User fails to detect a dangerous increase in pressure because the alarm limit is mistakenly set too high and user is over-reliant on alarm system;
- User partially disconnects a plug when walking over an unprotected cable;
- User cleans a centrifugal pump with alcohol, although it is made from material that is incompatible with alcohol. It is reasonably foreseeable that alcohol might be used to clean the pump, since alcohol is readily available in the laboratory and no clear and prominent warning is provided;
- Unintentional use of pipette out of its calibration range;
- Analyzer placed in direct sunlight causing higher reaction temperature than specified;
- User uses a well-intentioned shortcut on procedure or pre-use checklist, etc., thereby omitting important steps. It is not obvious that the shortcut is hazardous;
- User unintentionally omits an important step in an excessively lengthy or complicated procedure or pre-use checklist.

H.2.2 Examples of abnormal use

The laboratory is responsible for applying all reasonable means of risk control. These can include information for safety, which is one element in a hierarchical approach to risk control. Following the process in ISO 14971, the laboratory uses one or more of the following in the priority listed:

- a) Inherent safety by design;
- b) Protective measures in the examination procedure or the IVD medical device;
- c) Information for safety, e.g., warnings in the instructions for use, display of a monitored variable, training and materials for training, maintenance details.

If, despite having been provided with validated information for safety, the user acts contrary to such information for safety, the incorrect use can be classified as abnormal use.

The following are brief descriptions of complaint reports taken from a Global Harmonization Task Force (GHTF) paper on reporting of use errors.^[24] These examples are based on actual events that were determined at the time to be examples of abnormal use. In each case, it was determined that the relevant risks had been addressed using reasonable means of risk control. These included proper design, proper training, information for safety, and descriptions of correct use as established by the laboratory. For IVD medical devices, information supplied by the manufacturer will typically specify intended correct use.

- Deliberate violation of a validated, simple pre-use safety checklist as specified in the accompanying information supplied by the manufacturer.
- Use of a method or an IVD medical device prior to completing installation, validation or verification.

- Continued use of an IVD medical device beyond the prescribed maintenance interval as clearly defined in the instructions for use because of the laboratory's failure to arrange for maintenance.
- The laboratory allowed an untrained user to use an IVD medical device leading to patient harm. The device is working in accordance with its specifications.
- The use of damaged equipment or supplies in spite of clear evidence of damage, causing an incorrect result that led to a patient injury.
- Use of an IVD instrument in violation of manufacturer's warnings; i.e.; defeating a safety interlock or ignoring a calibration expiration message.

NOTE There is a difference between well-intentioned and malevolent abnormal use. As the examples show, abnormal use is often well-intentioned (i.e., the user accepts a certain risk for the expected benefit of the patient). This is distinct from the situation where the user did not appreciate the risk involved in their action/inaction because the risk was not clearly indicated, where the event can be considered a use error.

Annex I (informative)

Methods of risk assessment, including estimation of probability and severity of harm

I.1 General guidance

Various methods can be used to estimate risk. While this document does not require that a particular method be used, it does require that risk estimation be carried out. 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.8](#));
- the sequence of events that could lead to a hazardous situation occurring;
- the likelihood of such a situation arising; the sequence of events that could lead to harm;
- the likelihood that the hazardous situation leads to harm;
- the nature of the harm that could result.

In some cases, only certain elements of the risk estimation process need be considered. For example, if the harm is minimal or if the probability cannot be estimated (see [I.3](#)), 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 analyze risks, their components, i.e. probability and severity, should be analyzed separately.

Risk matrices based on the probability and severity of harm will be used for ranking risks in examples throughout this annex. If a risk matrix is used, the particular risk matrix and the interpretation used should be justified for that application.

I.2 Estimating the probability of harm

In situations where sufficient data are available, a quantitative categorization of probability levels should be used. However, a good qualitative description is preferable to an inaccurate quantitative description. For a qualitative categorization of probability levels, the laboratory can use descriptors appropriate for the examination.

Although probability is in reality a continuum, in practice a discrete number of levels can be used. The laboratory decides how many probability levels are needed, based upon the expected confidence in the estimates. At least three levels should be used to facilitate decision making. As confidence in the estimated probabilities increases, a greater number of probability levels can be considered. The levels can be descriptive (e.g., not expected to occur, likely to occur a few times, likely to occur frequently,

etc.). Laboratories should define the categories explicitly so that there will be no confusion over what is meant. One approach is to assign a range of non- overlapping numerical values to each of the discrete levels (e.g., [Table I.2](#)). It is just an example because the indicated frequency will be strongly influenced by the number of examinations performed.

For prospective risk analysis, probability of harm estimates should 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. Therefore, the probability of harm should take into consideration the level and/or extent of exposure. For example, if there is no exposure to a hazard, there can be no hazardous situation and no harm can result. If there is greater exposure to a hazard, the probability of a hazardous situation will increase. Therefore, the number of examination performed by a laboratory will influence the likelihood that a hazard (e.g., incorrect or delayed result) will occur.

The likelihood that a hazardous situation will lead to harm is influenced by the estimated number of examinations that will be performed by the laboratory.

Common approaches to estimate probabilities include:

- projection from relevant historical data;
- prediction of probabilities using analytical or simulation techniques;
- generation of experimental data;
- reliability estimates;
- laboratory data;
- surveillance information;
- expert judgment.

These approaches can be used individually or jointly. Multiple approaches can be used to serve as independent checks on each other, and increase confidence in the results. Confidence is enhanced when a quantitative estimate of the probability of occurrence is based on accurate and reliable data. Otherwise a reasonable qualitative estimate should be made. In some cases, when sufficient data are not available, it might be necessary to rely solely on expert judgment.

Examples of qualitative and semi-quantitative definitions of probability levels are given in [Tables I.1](#) and [I.2](#). The descriptions are illustrative and the laboratory should make these definitions specific and explicit to ensure the levels are appropriate and reproducible for a given risk assessment.

Examples:

Table I.1 — Overall Probability of Harm Scale (Qualitative)

Level	Term	Description
5	Frequent	Likely to occur regularly with the examination procedure; expected to be experienced continuously in the laboratory
4	Reasonably Likely	Likely to occur multiple times with the examination procedure; expected to be experienced frequently in the laboratory
3	Occasional	Likely to occur sometimes with the examination procedure; expected to be experienced several times in the laboratory
2	Remote	Unlikely to occur but possible with the examination procedure; expected to be experienced only a few times in the laboratory
1	Unlikely	Extremely unlikely to occur with the examination procedure; expected to be experienced only once or twice in the laboratory

Table I.2 — Overall Probability of Harm Scale (Semi-Quantitative)

Level	Term	Description
5	Frequent	Each day
4	Reasonably Likely	Each week
3	Occasional	Each month
2	Remote	Each year
1	Unlikely	Less than once a year

I.3 Estimating risks when the probability cannot be estimated

The probabilities of systematic faults are 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 involving sabotage or tampering;
- novel, poorly understood hazards, such as the presence of an unexpected infectious agent in a specimen as the causative agent of Bovine Spongiform;
- 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 estimate the risk, and it may be necessary to evaluate the risk on the basis of the nature and severity 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. For significant hazards, however, which could inflict harm of high severity such as those noted above, no level of exposure can be identified that would correspond to a risk so low that it can be ignored. 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.

I.4 Estimating the severity of harm

To categorize the severity of the potential harm, the laboratory should use descriptors appropriate for the examination or laboratory service. 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 laboratory decides how many categories are needed and how they are to be defined. The levels can be descriptive, as in the examples in [Table I.3](#). In any case, severity levels should not include any element of probability.

Severity levels should be chosen and justified by the laboratory for a particular examination under clearly defined conditions of use. Laboratories should make these definitions as specific and explicit to ensure their use will be reproducible.

Example:

Table I.3 — Severity of Harm Scale (Qualitative)

Score	Category	Description
5	Critical	Life-threatening injury/death
4	Serious	Permanent (irreversible) bodily damage or impairment
3	Significant	Non-permanent bodily damage or impairment; reversible with medical intervention
2	Marginal	Temporary bodily damage or impairment; reversible with no medical intervention
1	Negligible	Temporary discomfort or inconsequential injury

1.5 Estimating the risk of harm

A typical approach to estimating risk is to create an N-by-M matrix to classify the probabilities and severities of the potential harm associated with each hazardous situation. The matrix represents a full set of the possible risks.

In this approach, the N levels of probability and M levels of severity are clearly defined, as in the preceding examples in [Tables I.1, I.2 and I.3](#). Thus, each cell of the matrix will represent a defined subset of the full set of possible risks.

A simple example is the following 5 × 5 matrix based upon the definitions in [Tables I.1 and I.2 and I.3](#). Laboratories should make these definitions as specific and explicit as needed to ensure their use will be reproducible. The actual zones will be established based on the risk acceptability criteria defined according to [6.1](#).

Table I.4 — Risk matrix with two zones

		Overall probability of harm				
		Unlikely (1)	Remote (2)	Occasional (3)	Likely (4)	Frequent (5)
Severity of harm	Critical (5)					
	Serious (4)					
	Significant (3)					
	Marginal (2)					
	Negligible (1)					
Key Green = broadly acceptable risk Red = unacceptable risk						

Table I.5 — Risk matrix with three zones

		Overall probability of harm				
		Unlikely (1)	Remote (2)	Occasional (3)	Likely (4)	Frequent (5)
Severity of harm	Critical (5)					
	Serious (4)					
	Significant (3)					
	Marginal (2)					
	Negligible (1)					
Key Green = broadly acceptable risk Yellow = acceptable risk if risk is reduced as far as reasonably possible Red = unacceptable risk						

I.6 Examples

I.6.1 Risk assessment example

The following table summarizes the results of a risk assessment of nonconformities associated with delayed or errant patient reporting. The decisions are based on the risk acceptability criteria shown in the Risk Chart in [Table I.5](#).

Table I.6 — Risk assessment of nonconformities associated with delayed or errant patient reporting

Nonconformity	Probability	Severity	Risk
Wrong patient identification	Occasional (3)	Critical (5)	Unacceptable
Wrong test result	Occasional (3)	Critical (5)	Unacceptable
Report delayed (stat)	Likely (4)	Marginal (2)	Acceptable with risk reduction
Report delayed (24 hours)	Likely (4)	Marginal (2)	Acceptable with risk reduction
Report lost	Occasional (3)	Marginal (2)	Acceptable with risk reduction
Sent to wrong primary clinician	Remote (2)	Marginal (2)	Acceptable
Sent to wrong clinician (copy)	Remote (2)	Negligible (1)	Acceptable

I.6.2 Corrective or preventive action decisions

The following table summarizes the corrective or preventive action decisions based on risk acceptability criteria shown in the Risk Chart in [Table I.5](#).

Table I.7 — Risk reduction decisions

Nonconformity	Sample collected from wrong patient	Sample collected with incorrect technique	Sample transport incorrect method	Sample transport delayed or late
Preventive or corrective action	Implement double identification check	Implement competency assessment check	Implement competency assessment check	Transport tracking
Severity	Critical	Critical	Marginal	Marginal
Occurrence				
Frequent	Prevent	Prevent	Prevent	Prevent
Likely	Prevent	Prevent	Prevent	Prevent

Table I.7 *(continued)*

Nonconformity	Sample collected from wrong patient	Sample collected with incorrect technique	Sample transport incorrect method	Sample transport delayed or late
Occasional	Prevent	Prevent	Medium	Prevent
Remote	Prevent	Medium	Medium	Monitor
Unlikely	Medium	Medium	Low	Low

Annex J (informative)

Overall residual risk evaluation and risk management review

The following guidance is adapted from ISO 14971:2019, and ISO/TR 24971:2019.

J.1 Overview

Overall residual risk evaluation is the point where residual risk is viewed from a broad perspective. After the assessment of every identified hazardous situation, the laboratory then considers the combined impact of the individual residual risks, and decides whether the overall residual risk meets or exceeds the criteria for residual risk acceptability.

This step is particularly important for complex examination procedures or laboratory services or those with a large number of individual risks. The evaluation can be used to determine whether the examination procedure or laboratory service is safe.

The determination of overall residual risk can be a difficult and challenging task that cannot be achieved simply by the numerical addition of all individual risks, because the risks are based on different probabilities and severities of harm. This difficulty also arises for the following reasons:

- Confidence in the probability estimates can vary considerably. Some probabilities are known precisely either from history with similar examinations or services, or from testing. Probabilities are generally imprecise estimates, and may not be known at all, such as the probability of harm resulting from a software failure. Further, it is usually not possible to combine the severities of individual harms within the broad categories typically encountered in risk analysis.
- The acceptability criteria for individual risks need to be the same as the criteria for overall risk acceptability. The criteria used to evaluate individual risks are usually based on the probability of occurrence of particular severities of harm.

The laboratory needs to decide how to evaluate the remaining residual risk with respect to the acceptability criteria. There is no preferred method for evaluating overall residual risk and the laboratory is responsible for determining an appropriate method. Some general approaches for evaluating overall residual risk, along with considerations affecting their selection, are given below. Both the criteria and the methods associated with applying them should be stated in the risk management plan. This guidance is intended to help in establishing such criteria and methods.

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 specialists with knowledge of and experience with the particular examination procedure or laboratory service (see [4.3](#)).

Ultimately, the evaluation of overall residual risk has to be based on clinical judgment. The results of the overall residual risk evaluation and the rationale for the acceptance of the overall residual risk should be documented in the risk management file.

J.2 Overall residual risk evaluation

The overall residual risk can only be assessed after all risk control measures have been implemented and verified. This means that all identified hazardous situations have been evaluated and that all risks have been reduced to an acceptable level or have been accepted based upon a risk/benefit analysis. Examples of inputs, acceptability criteria and methods for performing the overall residual risk evaluation are presented below.

The laboratory can compare the examination procedure or laboratory service under review to similar examination procedures or laboratory services already in use. The collated individual residual risks can be compared against the risks for similar examination procedures or laboratory services, 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 examination procedures or laboratory services. In order for the laboratory to make well considered conclusions about the overall residual risk in relation to the medical benefits, up-to-date information on intended use and associated adverse events of similar examination procedures or laboratory services should be reviewed, as well as information from scientific literature, including information about clinical experience. The key question is whether the examination procedure or laboratory service under review offers the same or better safety as an examination procedure or laboratory service that can be considered to have an acceptable overall residual risk.

- a) The laboratory can also use outside experts to provide input on overall residual risk in relation to the medical benefits of the examination procedure or laboratory service under review. These experts can come from a variety of disciplines, including those with clinical experience and those who have experience with similar examination procedures or laboratory services. They can help the laboratory to take into account stakeholder concerns. An assessment of the benefits to the patient associated with the use of the examination procedures or laboratory services can be performed in order to demonstrate acceptability of the overall residual risk. One approach could be to get a fresh view of the overall residual risk by using laboratory specialists that were not directly involved in the development of the examination procedure or laboratory service under review. The laboratory specialists would evaluate the acceptability of the overall residual risk, considering aspects such as usability in a representative medical laboratory environment. Then, the laboratory specialists would evaluate the examination procedure or laboratory service in the medical laboratory environment to confirm the acceptability.
- b) Even though all individual risks should have been identified and accepted prior to evaluation of the overall residual risk, some risks could need further analysis. For example, there could be many risks that are close to being not acceptable. Hence, the overall residual risk acceptability could be suspect and a further investigation can be appropriate for the examination procedure or laboratory service and the associated risk management file. Another example can be that there are risks that are interdependent with respect to either their causes or the risk control measures applied. Risk control measures should be verified for efficiency, not only individually but also in combination with other risk control measures. This can also be true for risk control measures that are designed to counter multiple risks simultaneously. A Fault Tree or Event Tree Analysis can be a useful tool to demonstrate such connections between the risks and risk control measures used.
- c) Other considerations for overall residual risk evaluation include the following:
 - The results of usability evaluation or clinical experience during design validation testing can provide useful information.
 - Visual representations of the residual risks can be useful. Each individual residual risk can be shown in a risk matrix, giving a graphic view of the distribution of the risks. If many of the risks are in the higher severity regions or in the higher probability regions of the risk matrix, or if clusters of risks are borderline, then the distribution of the risks can indicate that the overall residual risk may not be acceptable, even if each individual risk has been judged acceptable.
 - During overall residual risk evaluation, all individual risk/benefit analyzes should be taken into account.
 - When there have been trade-offs between risks in the risk analysis, this might be indicative that the overall residual risk should be analyzed more carefully. These are instances where one risk might have been allowed to increase somewhat in order that another risk could be reduced. For example, the risk to one person (the user) is allowed to increase so that the risk to another (the patient) can be reduced. This is called risk parallax. The evaluation can take the form of reviewing related major risks, describing why the trade-off balance is practical, and explaining why the combined risk level of the risks in the trade-off decision is acceptable.

Annex K (informative)

Conducting a benefit-risk analysis

The following guidance is adapted from ISO 14971:2019, ISO/TR 24971:2019 and MEDDEV 2.7/1.

K.1 General

A benefit-risk analysis is used to justify a risk once all reasonably feasible measures to reduce the risk have been applied. If, after applying these measures, the risk is still not judged acceptable, a benefit-risk analysis is needed to establish whether the examination results or laboratory service is likely to provide more benefit than harm.

Generally, if the risk control measures are insufficient to satisfy the risk acceptability criteria, the service, IVD device or examination should be abandoned. In some instances, however, greater risks can be justified, if they are outweighed by the expected benefits of examination results or laboratory service. This document allows laboratories an opportunity to perform a risk/benefit analysis to determine whether the residual risk can be accepted because of the benefits.

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 options that avoid a particular risk or reduce the overall risk. The feasibility of further risk reduction should be taken into account before considering the benefits. This document explains how risks can be characterized so that a risk estimate can be determined with confidence. There is no standardized approach for estimating benefits.

K.2 Benefit estimation

The benefit arising from laboratory examination results or services is related to the likelihood and extent of improvement of health expected from their clinical use. Benefits can be estimated from knowledge of such things as:

- Use of the examination results (including point of care) by clinicians;
- The patient outcome expected from use of the examination results;
- Factors relevant to the risks and benefits of other diagnostic 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 favorable or unfavorable.

An estimate of patient benefit can vary markedly before and after development of a new examination, inauguration of a new laboratory service, or acquisition of a new IVD device. If reliable clinical data demonstrating the consistent performance and effectiveness of the examination 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. 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 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 clinical evaluation or a clinical performance study. 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 20916 specifies good study practices for the conduct of clinical performance studies of IVD medical devices.

K.3 Criteria for benefit-risk judgments

Those involved in making benefit-risk judgments have a responsibility to understand and take into account the clinical, technical and regulatory 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 specific, further guidance of a general nature is not possible. Instead, the safety requirements specified by standards addressing specific laboratory examinations, IVD medical devices 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 performance study, in accordance with a legally recognized standard or procedure, might be required to verify that the balance between medical benefit and residual risk is acceptable.

K.4 Benefit-Risk comparison

A direct comparison of risks and benefits is valid only 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 hazards and medical applications in question can provide significant insight into the ratio of benefit to risk.
- High-benefit/high-risk examinations or IVD medical 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 benefit-risk analysis. The benefit-risk comparison can be expressed in terms of a comparison to other available examination procedures or IVD medical devices.
- To validate that an examination or IVD medical device meets acceptable risk/benefit criteria, a clinical evaluation or clinical performance study may be required to estimate benefits and risks. Also, acceptability to society could be addressed in a clinical evaluation involving medical laboratory users, medical practitioners, and patients.
- For high-benefit/high-risk examinations or IVD medical devices, labelling should convey adequate information to the medical laboratory so that medical laboratory users, medical practitioners, and patients can be informed to ensure appropriate benefit-risk decisions are made by appropriate individuals prior to use.
- High-benefit/high-risk IVD medical devices typically have additional regulatory requirements that the manufacturer has to meet prior to commercial distribution. These should be taken into account

Prior to launching a new or modified examination procedures or using new or modified IVD medical device based on a benefit-risk analysis, the laboratory should summarize the available information

related to the risk/benefit determination and document the benefit-risk conclusions with rationales as applicable. Guidance on conducting a literature search of clinical data for IVD medical devices can be found in in GHTF SG5/N2R8 (22).

Annex L **(informative)**

Residual risk(s)

This guidance is adapted from ISO 14971:2019 and ISO/TR 24971:2019.

L.1 General

Residual risk is the risk remaining after all risk control measures (which can include information for safety) have been taken.

The decision of the laboratory regarding disclosure of residual risk should be recorded in the appropriate risk management documentation.

Disclosure of residual risk is generally descriptive and can provide background on the residual risks involved in using the examination procedure or IVD medical device. The aim is to disclose relevant information to enable the user, the healthcare provider, and even potentially the patient, to make an informed decision that weighs the residual risks against the benefits of using the examination procedure, the IVD medical device or the examination results.

L.2 Disclosure of residual risk

When deciding how to disclose the residual risk, it is important to identify what is to be communicated and to whom it is directed in order to inform, motivate and enable users to follow the examination procedure and use equipment safely and to inform clinicians of any limitations that could affect patient safety. The laboratory should examine the residual risks identified in [7.6](#) and [9.2](#) to determine what should be disclosed.

The laboratory should consider:

- the level or detail needed;
- the wording to be used to ensure clarity and understandability;
- the intended recipients (e.g., instrument operators, service personnel, clinicians, patients);
- the means/media to be used.

The laboratory should determine the appropriate means and media to disclose the residual risk.

This information can be significant in the process of clinical decision making. Within the framework of the intended use, the laboratory director in communication with the clinicians decide in which clinical settings the examination results or IVD medical device (e.g., point of care) can be used to achieve certain benefits for the patients.

For example, performing a point of care glucose measurement in the neonatal setting has the risk of results being less precise because of the influence of high hematocrit value. However, having an immediate but less accurate glucose result can be important to alert the clinician to potential hypoglycemia, but especially with low values the doctor should be aware.

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