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Implementing risk management in accordance with the IVDR

# Introduction

Annex I, Chapter I, Section 3 of the IVDR requires the implementation, documentation and continuous maintenance of a risk management system (see Table 1). Risk management is understood here to be a “continuous, iterative process throughout the entire lifecycle of a device” which requires “regular systematic updating”.

“Device” in the context of this document means an in-house IVD or, where applicable, a generic device group developed by a medical laboratory (laboratory) and used for diagnostic purposes.

Table 1 IVDR - Annex I, Chapter I, Section 3 of the IVDR

|  |  |
| --- | --- |
| **IVDR** | Points in this document  |
| Annex I Chapter I |
| Section 3 | *Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:*  |  |
| *a)* | *establish and document an RM-plan for each device* | *2.1* |
| *b)* | *identify and analyse the known and foreseeable hazards associated with each device*  | *2.2* |
| *c)* | *estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse*  | *2.3* |
| *d)* | *eliminate or control the risks referred to in point c in accordance with the requirements of Annex I, Chapter I, Section 4 of the IVDR*  | *2.4* |
| *e)* | *evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, the risk-benefit ratio and risk acceptability; and*  | *2.5* |
| *f)* | *based on the evaluation of the impact of the information referred to in point e, if necessary, amend control measures in line with the requirements of* *Annex I, Chapter I, Section 4 of the IVDR.*  | *2.6* |

The purpose of this document is to address the above points in relation to the IVDR-compliant use of in-house IVDs by laboratories.

The following sections of the IVDR must therefore also be considered:

Table 2 IVDR - Annex I, Chapter I, Sections 1 and 8 of the IVDR

|  |
| --- |
| **IVDR** |
| Annex I Chapter I |
| *Section 1* | *Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.* *They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.*  |
| *Section 8* | *All known and foreseeable risks, and any undesirable effects shall be minimised and be acceptable when weighed against the evaluated potential benefits to the patients and/or the user arising from the intended performance of the device during normal conditions of use.*  |

Although it is not explicitly required, the criteria of EN ISO 22367:2020, which apply to the examination procedures developed by medical laboratories for their own use, i.e., in-house IVDs, are used here as a possible basis for the implementation of risk management as required by the IVDR. **Annex 1** of this document contains an overview of how the sections of the IVDR covered here can be placed within the context of a risk management process as defined by EN ISO 22367:2020.

# Addressing Annex I, Chapter I, Section 3 of the IVDR

The risk management required by the IVDR (see Table 1 and Annex I, Chapter I, Section 3 of the IVDR) is addressed below and, where possible and appropriate, the procedure for implementing them in medical laboratories is described within the context of EN ISO 22367:2020 (see also **Annex 1** of this document). Section 4 of EN ISO 22367:2020 provides guidance on the overarching application of a risk management system. In addition, **Annex 2** of this document illustrates how risk management can be integrated into an (existing) risk management system.

## Annex I, Chapter I, Section 3a: Risk management plan

According to this section, the laboratory must define and document a risk management plan as part of an overall risk management process for each in-house IVD or for generic device groups (see Article 2, point 8 of the IVDR). However, the IVDR does not provide any further information on the content and format of such a risk management plan. Therefore, medical laboratories can again refer to the EN ISO standard ISO 22367:2020 as it outlines in Section 4.4 the structure of a risk management plan within an (existing) risk management system.

Risk analysis and risk assessment

The risk management plan also contains documentation for a risk analysis and risk assessment, which is to be carried out in accordance with the IVDR and is described below (see Section 4.4.5 of EN ISO 22367:2020). The IVDR itself does not specify which risk analysis method should be used but does list the types of risks that need to be considered (see **Annex 3** of this document).

In terms of a general implementation of a risk analysis, reference can be made at this point to Section 5 of EN ISO 22367:2020. Section 5.1 deals with the design of the scope, extent and applicable and pre-existing information of a risk analysis. Tools and procedures for a risk analysis can also be found in Annexes G and H. Information on the process and documentation of a risk analysis is also provided in Section 5.2 ff of EN ISO 22367:2020.

The risk assessment process is described in Section 6 of EN ISO 22367:2020. Section 6.1 deals with the acceptability criteria for individual risks and the overall residual risk, which must be defined, approved and documented by the laboratory as part of its risk management plan. The acceptability criteria for individual risks can be documented in a matrix, for example in a failure mode and effects analysis (FMEA), to indicate the combinations of probability of occurrence, probability of detection and severity of damage. Corresponding guidelines and examples can be found in Annex B.5 and Annex C as well as Annex I of EN ISO 22367:2020. As part of the risk assessment process, the collected data shall determine whether risk reduction measures are necessary (see Section 6.2 of EN ISO 22367:2020).

The IVDR stipulates that as many risks as possible should be eliminated before a risk assessment is conducted (see Chapter 2.4 of this document -> Annex I, Chapter I, Section 3d or Section 4 of the IVDR). Risks should, on the whole, be minimised as far as possible without this process negatively impacting the risk-benefit ratio (see Tab. 3 or Annex I, Chapter I, Section 2 of the IVDR).

Table 3 IVDR - Annex I, Chapter I, Section 2

|  |
| --- |
| ***IVDR*** |
| *Annex I* *Chapter I* |  |
| *Section 2* | *The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the risk-benefit ratio.*  |

Even though both aspects overlap in day-to-day practice, within the framework of a risk analysis and a risk assessment, a distinction can be principally made between the design and manufacture of an in-house IVD (device) on the one hand, and its actual use in the laboratory on the other. Sections 3b (device) and 3c (use) of Annex I, Chapter I of the IVDR are described below and interpreted accordingly in this document. It is assumed here that, prior to its use, the performance and safety aspects of the in-house IVD (device or a generic device group) have already been optimised as much as possible in accordance with the overriding quality objectives and strategies of the laboratory that uses it, as well as in accordance with the aspects under Point 2.2 of this document, which is reflected, for example, in the corresponding “Technical Documentation”. Thus, in terms of risk management, the points on risk analysis and risk assessment listed above would primarily relate to the use of an optimised device in the laboratory.

## Annex I, Chapter I, **Section 3b**: Identifying and analysing the known and foreseeable hazards associated with each device

As this section of the IVDR refers specifically to the “device”, i.e., the in-house IVD or a generic device group, the known and foreseeable hazards, as defined by the IVDR, should already have been taken into account during the design and manufacturing process and minimised as far as possible. Other sections of the IVDR are also relevant and/or can be covered in this point: Annex I, Chapter I, Sections 1 and 8 (see Table 2 above), as well as Section 4 (see Point 2.4 in this document). In addition to considering the applicable points of Annex I of the IVDR (see “Checklist Annex I” issued by the AWMF’s Ad Hoc Commission IVD), potential misuse is to be anticipated and eliminated as far as possible in advance. This can include measures such as the clear labelling of reagents, the use of qualified personnel, the establishment of adequate SOPs, etc. (see Annex I, Chapter I, Section 4). There should also be a description of the safety characteristics, including the identified performance characteristics, and confirmation that these are sufficient and safe for the patient group being tested (Annex I, Chapter I, Section 1). In terms of the risk analysis described in Section 5 of EN ISO 22367:2020, Sections 5.3 and 5.4 (incl. Annex D) appear to be of particular importance.

## Annex I, Chapter I, **Section 3c**: Estimating and evaluating the risks associated with, and occurring during the intended use and during reasonably foreseeable misuse

As described above, this section of the IVDR refers to an assessment of the risks involved in using the optimised device in medical laboratories in accordance with Section 3b of the IVDR, whereby, in addition to its intended use, its potential misuse should also be anticipated.

In general, risk is defined as the combination of the probability of occurrence and the severity of an associated harm. Harm is understood to mean physical injury or damage to the health of people, or damage to goods or the environment (source: EN ISO 14971).

Possible harm to patients (which this document will limit itself to) caused by the analyses offered in diagnostic laboratories, includes, but is not limited to the following:

* delayed treatment
* false treatment
* renewed sample taking
* unnecessary follow-up testing
* …

Depending on the in-house IVD or a corresponding generic device group, there are different causal chains for each of these harms which can lead to different hazardous situations and ultimately to one of the harms listed above. In the context of a risk analysis and risk assessment, it is important to bear in mind that the severity of the potential harm, and thus ultimately the risk assessment, primarily depends on the clinical significance of the analyte under investigation and less on the causal chain triggering the hazardous situation. This will be illustrated in **Annex 4** by way of a risk analysis of a generic device group of in-house IVDs.

## Annex I, Chapter I, **Section 3d**: Eliminating or controlling the risks referred to in point c (see Section 3c above) in accordance with the requirements of Annex I, Chapter I, Section 4 of the IVDR

Annex I, Chapter I, Section 4 of the IVDR gives clear guidance on how possible risks should be eliminated and controlled as much as possible in advance (see Table 4). It should be noted that points a) to d) listed here were already addressed as part of the development of the in-house IVD (see Point 2.2) or in the course of the preventive measures listed under Point 3.3. Reference shall also be made here to Section 7 and Annex G of EN ISO 22367:2020

Table 4 IVDR - Annex I, Chapter I, Section 4

|  |
| --- |
| ***IVDR*** |
| *Annex I* *Chapter I* |  |
| *Section 4* | *Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To minimise risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is deemed acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:*  |
| *a)* | *eliminate or reduce risks as far as possible through safe design and manufacture;* |
| *b)* | *where appropriate, take adequate protection measures, including alarms, if necessary, in relation to risks that cannot be eliminated; and*  |
| *c)* | *provide safety information (warnings/precautions/contra-indications) and, where appropriate, provide training for users.* |
| *d)* | *Manufacturers shall inform users of any residual risks.*  |

## Annex I, Chapter I, **Section 3e**: Evaluating the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, the risk-benefit ratio and risk acceptability

The IVDR does not specify how a system for monitoring an in-house IVD should be designed. This requirement is partly covered by the requirement outlined in Article 5.5.i of the IVDR:

Table 5 IVDR - Article 5, Section 5i

|  |
| --- |
| ***IVDR*** |
| *Article 5.5.i* | *The health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions* |

The IVDR stipulates that the laboratory must collect and verify information about the in-house IVD from the development phase (the actual manufacturing) and post-development phase. Guidance on this can be found in Chapter 10.1 of EN ISO 22367:2020, which also describes the need to evaluate the information collected in this way to determine whether the risk control measures are effective and the risks (still) acceptable. As already stated above, special attention must be paid to whether a positive risk-benefit ratio can be ensured with respect to the intended purpose (as also required by Annex I, Chapter I, Sections 1, 2 and 8 of the IVDR).

There are both internal and external sources of risk information and data that can be included in the monitoring system. EN ISO 22367:2020 provides examples of such sources in Chapters 10.2 and 10.3.

## Annex I, Chapter I, **Section 3f:** Adjusting the control measures in line with the requirements of Annex I, Chapter I, Section 4 of the IVDR and, if necessary, based on an impact evaluation of the information listed under point e (see Section 3e above)

This section states that if an assessment, conducted in accordance with Section 3e, shows that the risk control measures are not/no longer effective and the risks are not/no longer acceptable, the control measures pursuant to Annex I, Section 4 of the IVDR must be adjusted (see also Table 4). In combination with Section 3e above (Point 2.5), EN ISO 22367:2020 Sections 8 (Risk-Benefit Analysis), 9 (Risk Management Review) and 10 (Risk Monitoring, Analysis and Control Activities) can provide further guidance on implementation.

**Annex 1**

# Reference to EN ISO 22367:2020

EN ISO22367:2020 *Medical laboratories - Application of risk management to medical laboratories* can serve as a good starting point and standard for the implementation of IVDR-compliant risk management. It is important to note that it is not necessary to comply with the standard in full - the differences have been outlined in previous chapters - but the standard does contain many helpful examples.

As the figure below (based on Figure 1 of EN ISO 22367:2020) shows, the IVDR’s requirements regarding risk management are reflected in the process described in EN ISO 22367.

Comparable Sections in Annex I, Chapter I of the IVDR:

 3a 3b 3c 3d 3e 3f

Risk management process as outlined in EN ISO 22367:2020



Risk analysis

● Specification if intended users

● Determination of search criteria

● Recognition of potential hazards, hazardous situations and harm

● Identification of current control procedures

● Estimation of risks

Risk assessment

Monitoring of risk

● Establishment of a monitoring system

● Monitoring of internal indicators

● Monitoring of external indicators

● Determination of changes to risk profile

Review of risk management

● Review of the thoroughness of controlling risks

● Assessment of acceptability of residual risks

● Approval of risk management report

Controlling risk

● Decision whether risk reduction is needed

● Establishment of options for controlling risk

● Verification of the effectiveness of risk control measures

● Assessment of residual risks

● Examination of whether risk control measures lead to new risks

Risk assessment

● Assessment of risk acceptability

● Risk-benefit analysis

Risk management plan

● Determination of scope of risk analysis

● Allocation of responsibilities and authorisations

● Specification of risk management reviews

● Determination of acceptability criteria for risks

● Specification of verification, risk monitoring and documentation requirements

Figure 1 Comparison of Annex I, Chapter I, Section 3 of the IVDR to EN ISO 22367:2020

**Annex 2**

# Documentation, integration in an existing risk management system

The IVDR does not specify the type of documentation required for the risk management process. EN ISO 22367:2020 indicates that there is a large degree of leeway here, as described in Chapter 4.2 (Management Responsibilities). Guidelines on integrating risk management into an existing quality management system (for example in accordance with ISO 15189) can be found in Annex A of EN ISO 22367:2020.

Chapter 4.4.5 of EN ISO 22367:2020 covers the risk management documentation. According to this, the risk management documentation must, among other things, enable all identified hazards to be traced to the process steps listed in the table below.

It also states that “the risk management documentation [may] take on any form and be stored on any type of medium”. This chapter also goes into detail about the possibility of a superordinate structure for risk management documentation.

Thus, all documents relating to the risk management process - from planning to the final report - would be brought together in one risk management file. If the subject matter listed in Chapter 4.4.5 of EN ISO 22367:2020 is taken into account alongside the subject matter of the risk management plan and the risk management report described in Chapter 9.3 of EN ISO 22367:2020, this would result in a documentation structure for the main activities of the risk management process as shown in the Figure 2 below.

|  |
| --- |
| **Risk management file**Documentation of the main activities of the risk management process along with the results |
| * Risk management plan
* Scope and the individual phases
* Responsibilities and authorisations
* Requirements for reviewing the activities
* Criteria for the acceptance of risks
* Process for assessing the overall residual risk
* Verification activities
* Post-market surveillance activities
 | * Risk analysis
* Risk assessment
* Implementation and verification of the measures
* Risk-benefit analysis
 | * Risk management report
* Documentation of the results of the risk management process
* Must enable every hazard to be traced back to the analysis and assessment of the risk
* Must contain an explanation that the residual risk (the sum of the individual residual risks) is acceptable
* The risk management report is part of the risk management file
 |

Figure 2 Documentation of the RM process. The RM file forms the framework for the documentation of the planning, implementation, and the final risk management report (see Chapter 9.3 of EN ISO 22367:2020).

**Annex 3**

# Risks which, according to the IVDR, must be considered

The potential risks should be kept as low as possible or reduced as far as reasonably practicable. The following tables show all of the types of risks described in Annex I of the IVDR that must be taken into account in the risk analysis.

## Risks due to use error:

Risks due to use error must be eliminated or reduced in accordance with Annex I, Section 5.

Table 6 IVDR, Annex I, Chapter I, Section 5

|  |
| --- |
| ***IVDR*** |
| *Annex I Chapter I* |  |
| *Section 5* | *In eliminating or reducing risks related to use error, the manufacturer shall:*  |
| *a)* | *reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and* |
| *b)* | *give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).*  |

## Risks when designing and manufacturing devices

Risks from contaminants and residues are to be minimised as far as possible in accordance with Annex I, Sections 10.2, 10.3 and 10.4, taking into account the intended purpose of the product.

*Table 7 IVDR - Annex I, Chapter 2, Sections 10.2, 10.3 and 10.4*

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 10.2* | *Devices shall be designed, manufactured and packaged in such a way as to minimise the risk posed by contaminants and residues to patients - taking account of the intended purpose of the device - and to the persons involved in the transport, storage and use of the devices.* *Particular attention shall be paid to tissues exposed to those contaminants and residues and to the duration and frequency of exposure.*  |
| *Section 10.3* | *Devices shall be designed and manufactured in such a way as to reduce to a level as low as reasonably practicable the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device.* *Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction (‘CMR’), in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council*[*(1)*](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746&from=DE#ntr1-L_2017117EN.01026001-E0001)*, and to substances having endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council*[*(2)*](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746&from=DE#ntr2-L_2017117EN.01026001-E0002)*.*  |
| *Section 10.4* | *Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by the unintentional ingress of substances into the device, taking into account the device and the nature of the environment in which it is intended to be used.*  |

## Risks related to infection and microbial contamination

Table 8 IVDR - Annex I, Chapter 2, Sections 11.1 and 11.5

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 11.1* | *Devices and their manufacturing processes shall be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the user or, where applicable, other persons. The design shall*  |
| *a)* | *allow easy and safe handling;* |
| *b)* | *reduce as far as possible any microbial leakage from the device and/or microbial exposure during use; and, where necessary*  |
| *c)* | *prevent microbial contamination of the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen.* |
| *Section 11.5* | *Packaging systems for non-sterile devices shall maintain the integrity and cleanliness of the device and, where the devices are to be sterilised prior to use, minimise the risk of microbial contamination; the packaging system shall be suitable for the method of sterilisation indicated by the manufacturer.*  |

## Risks related to the interaction of devices with their environment

Risks related to the interaction of devices with their environment are to be analysed, evaluated and controlled in accordance with Annex I, Sections 13.2 and 13.3.

Table 9 IVDR - Annex I, Chapter 2, Sections 13.2 and 13.3

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 13.2* | *Devices shall be designed and manufactured in such a way as to remove or reduce the following risks as far as possible:*  |
| *a)* | *the risk of injury in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features of a device;*  |
| *b)* | *risks connected with reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with diagnostic or therapeutic procedures, pressure, humidity, temperature, variations in pressure and acceleration, or radio signal interferences;*  |
| *c)* | *risks associated with the use of the device when it comes into contact with materials, liquids, and substances, including gases, to which it is exposed during normal conditions of use;*  |
| *d)* |

|  |
| --- |
| *risks associated with the possible negative interaction between software and the IT environment within which it operates and interacts;* |

 |
| *e)* | *risks of accidental ingress of substances into the device;*  |
| *f)* | *the risk of incorrect identification of specimens and the risk of erroneous results due to, for example, confusing colour and/or numeric and/or character codings on specimen receptacles, removable parts and/or accessories used with devices in order to perform the test as intended;* |
| *g)* | *risks of any foreseeable interference with other devices.* |
| *Section 13.3* | *Devices shall be designed and manufactured in such a way as to minimise the risk of fire or explosion during normal use and in a single fault condition. Particular attention shall be paid to devices whose intended use includes exposure to or use in association with flammable or explosive substances or substances which could cause combustion.*  |

## Risks related to radiation

Table 10 IVDR - Annex I, Chapter 2, Section 15.3

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 15.3* | *The operating instructions for devices emitting hazardous or potentially hazardous radiation shall contain detailed information as to the nature of the emitted radiation, the means of protecting the user, and on ways of avoiding misuse and of reducing the risks inherent to installation as far as possible and appropriate. Information regarding the acceptance and performance testing, the acceptance criteria, and the maintenance procedure shall also be specified.*  |

## Risks related to software

Table 11 IVDR - Annex I, Chapter 2, Sections 16.1 and 16.2

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 16.1* | *Devices that incorporate electronic programmable systems, including software, or devices that are software in and of themselves, shall be designed to ensure repeatability, reliability and performance in line with their intended use. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance.*  |
| *Section 16.2* | *For devices that incorporate software or for devices that are software in and of themselves, the software shall be developed and manufactured in accordance with the state of the art taking into account the principles of development life cycle, risk management (including information security), verification and validation.*  |

## Risks related to devices connected to an energy source

Table 12 IVDR - Annex I, Chapter 2, Sections 17.1, 17.3 and 17.5

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 17.1* | *For devices connected to or equipped with an energy source, in the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks.*  |
| *Section 17.3* | *Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks of creating electromagnetic interference which could impair the operation of the device in question or other devices or equipment in the intended environment.*  |
| *Section 17.5* | *Devices shall be designed and manufactured in such a way as to avoid as far as possible the risk of accidental electric shocks to the user or other person both during normal use of the device and in the event of a single fault condition in the device, provided the device is installed and maintained as indicated by the manufacturer.*  |

## Mechanical and thermal risks

Table 13 IVDR - Annex I, Chapter 2, Sections 18.1, 18.3-7

|  |
| --- |
| ***IVDR*** |
| *Annex 1 Chapter 2* |  |
| *Section 18.1* | *Devices shall be designed and manufactured in such a way as to protect users and other persons against mechanical risks.* |
| *Section 18.3* | *Appropriate means of protection shall be incorporated where there are risks due to the presence of moving parts, risks due to break-up or detachment, or the risk of a leakage of substances.*  |
| *Section 18.4* | *Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.*  |
| *Section 18.5* | *Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.*  |
| *Section 18.6* | *Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user or other person has to handle shall be designed and constructed in such a way as to minimise all possible risks.*  |
| *Section 18.7* | *Errors likely to be made when fitting or refitting certain parts, which could be a source of risk, shall be made impossible by the design and construction of such parts or, failing this, by information given on the parts themselves and/or their housings.* *The same information shall be given on moving parts and/or their housings where the direction of movement needs to be known in order to avoid a risk.* |

**Annex 4**

# Example of performing a risk analysis and risk assessment in medical laboratories

The risk analysis presented below utilises a failure mode and effects analysis (FMEA). It is based on the following factors, which are classified as follows:

Probability of occurrence [P]

|  |  |
| --- | --- |
| **Score** | **Classification** |
| 1 | Unlikely |
| 2 | Occasional |
| 3 | Frequent |

Probability of detection [D]

|  |  |
| --- | --- |
| **Score** | **Classification** |
| 1 | High, certain to be detected  |
| 2 | Moderate, will probably be detected  |
| 3 | Low, will probably not be detected  |

Severity of the damage [S]

|  |  |
| --- | --- |
| **Score** | **Classification** |
| 1 | Low, no risk to patients  |
| 2 | Minor, possible risk to patients  |
| 3 | High, risk to patients |

The risk priority number (RPN) is determined by multiplying these scores: RPN = [A] \* [E] \* [S]. The higher the RPN (max. value = 27), the higher the underlying risk. After implementing further measures to minimise risk, these factors are re-evaluated. The following classification of risk acceptance is made based on the calculated RPN values:

|  |  |
| --- | --- |
| **RPN**  | **Classification** |
| 1 – 4 | Non-critical  |
| 6 – 9 | Borderline, risk reduction when patients at risk  |
| 12 - 27 | Critical, risk reduction necessary  |

Risk Analysis Part 1: Laboratory

A sample generic device group is considered in Part 1 of the risk analysis. This includes the collection and documentation of the probability of occurrence [P] and detection [D] of a chain of causes leading to potential damage. The sample generic device group considered here: **ELISA, manual processing in a batch**.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trigger** | **Hazard** | **Hazardous situation** | **Potential harm** | **Preventative measures taken** | **Doc.** | **[P]** | **[D]** |
| Kit components: temperature outside acceptable range | False result | Erroneous result | False diagnosis/therapy | Bring necessary kit components to room temperature early on (possibly overnight) | AA-GH-0133 | 1 | 3 |
| Test run invalid | Delayed result | Delayed diagnosis/therapy | 2 | 1 |
| Kit components: false/ incomplete composition or storage | False result | Erroneous result | False diagnosis/therapy | Only use kits within one batch | Generally only rely on reagents from one kit (no “stealing” | systematically run whole, half or a third of a plate | aliquot opened reagents/controls to store as one-shots. | AA-GH-013 | 1 | 3 |
| Test run invalid | Delayed result | Delayed diagnosis/therapy | 2 | 1 |
| Error in cleaning process | False result | Erroneous result | False diagnosis/therapy | Prepare new washing solution or bring to RT before use | Prime washer before every washing process | Service washer daily | Regularly check/service washer | AA-GH-013 | AG-GH-214 | 1 | 3 |
| Test run invalid | Delayed result | Delayed diagnosis/therapy | 2 | 1 |
| Error in reading OD values | False result | Erroneous result | False diagnosis/therapy | Turn on reader in a timely manner (prewarm lamp) | Make sure correct protocol is used (read-only!) | Check reader regularly (calibration plate). | AA-GH-013 | AG-GH-101 | 1 | 3 |
| Test run invalid | Delayed result | Delayed diagnosis/therapy | 1 | 1 |
| Error in manually transferring the quantitative values to the LIS | False result | Erroneous result | False diagnosis/therapy | Proofread (four eyes principle) | VA-IT-037 | AA-GH-013 | 2 | 2 |

Risk Analysis Part 2: Patient and Risk Assessment

In Part 2 of the risk analysis, the potential harms to the patient, which were identified and listed in the first part (Risk Analysis, Laboratory), are listed together with the most unfavourable combination of probability of occurrence [P] and probability of detection [D] in each case.

It should be noted that the severity of the potential harm primarily depends on the clinical significance of the analyte under investigation and less on the chain of causes triggering the hazardous situation (see also Chapter 2.3). The assessment of the severity of the damage [S] and thus a final risk assessment based on the risk acceptance table (RPN classification) is therefore carried out based on the analyte under investigation.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Test method** | **Potential harm** | **[P]** | **[D]** | **[S]** | **RPN** | **Risk assessment** | **Risk/benefit analysis** |
| vWF:CBA\* | False diagnosis/therapy | 2 | 2 | 2 | 8 | Borderline |  |
| Delayed diagnosis/therapy | 2 | 1 | 1 | 2 | Non-critical |  |
| ADAMTS-13-Activity | False diagnosis/therapy | 2 | 2 | 3 | 12 | Critical | Unacceptable risk, particularly of a false diagnosis. Reduction of risk through automated procedures in connection with an LIS |
| Delayed diagnosis/therapy | 2 | 1 | 3 | 6 | Borderline |

\* Von Willebrand factor (vWF): Collagen-binding activity

The sample approach implemented above reflects the dependence of the severity of potential harm to the patient on the clinical significance of the analyte under investigation, as described under Point 2.3 of this document. This approach allows a summary analysis to be made of a defined, generic device group of in-house IVDs. In a more conventional approach, the factors [P], [D] and [S], as well as the resulting RPN, would be presented on a test-specific basis in only one table (see, for example, Table G.1 in EN ISO 22367:2020).