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NSF Whitepaper

Warnings, Cautions, and Clarity: Getting Medical Device Labeling Right

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Risk management has always been a crucial component of a medical device's technical documentation. With the transition from the Medical Device Directive 93/42/EEC to Regulation (EU) 2017/745, also known as the Medical Device Regulation (MDR), its importance has increased to ensure the safety of medical devices.

One step is the elimination or reduction of risks within the risk analysis, evaluation, and control. Therefore, various options should be considered, including the provision of safety information as part of the labeling. Manufacturers are faced with extensive interfaces between various processes within their quality management systems. Each warning and symbol provided in a device's labeling must be derived from the risk management file, and each risk control measure related to the device's labeling identified in the risk management file must be documented in the labeling documentation. But how is the kind of information to be provided determined? When is a safety note sufficient, and when should a (pre-)caution or warning be provided? How can it be ensured that the provided information is well understood? Therefore, other processes, such as design and development or usability engineering, should also reflect the identified risk control measures. The key element that notified bodies pay attention to is consistency.

This whitepaper describes one way to consistently transfer safety information identified through the risk management to the product labeling, and which other interfaces should be considered. Having a well working quality management system in place including a functioning risk management process that considers the relevant interfaces is essential to ensure that information documented as part of one process is consistent throughout all relevant processes and documentation and to ensure that the information provided, and its level of importance is clear and comprehensible to the user, patient, and if applicable, third party.

Why Does Risk Communication Matter in Medical Device Labeling?

Regulatory Background

Risk management is a key element within the development of medical devices. Used correctly, it contributes to the production of safe medical devices and enhances product quality. Besides the general benefits that risk management activities provide, they are also a regulatory requirement.

Today, the MDR provides the regulatory framework for risk management in Article 10, which outlines the general obligations of manufacturers. Section 2 requires manufacturers to *"establish, document, implement and maintain a system for risk management as described in section 3 of Annex I"*.

Looking into Annex I - *General Safety and Performance* requirements of the Regulation, it provides further information on the elements required to fulfill the described obligation of a manufacturer. Annex I is divided into three chapters. Chapter I describes general requirements, of which section 3 refers to the elements that shall be part of the risk management system:

- A risk management plan,
- the identification and analysis of known and foreseeable hazards,
- the estimation and evaluation of risks,
- **the elimination or reduction of risks in accordance with section 4 and**
- the evaluation of the impact of information from the production and post-production phases, and, if necessary, based on that, amended risk control measures

With regards to risk control measures, section 4 provides the following order of priority that shall be applied:

- Eliminating or reducing risks by safe design and manufacture
- Implementing adequate protection measures
- Providing information for safety and, where appropriate, training to users.

Further, manufacturers shall inform users of any residual risk.

Chapter II of that Annex outlines specific requirements for the design and manufacture of a medical device. The chapter primarily addresses risks associated with specific device characteristics (e.g., mechanical hazards, risks related to active devices or devices emitting radiation), whereas Chapter III focuses on the requirements for the information provided with the devices.

EN ISO 14971

Besides the regulatory framework, the harmonized standard EN ISO 14971 *Medical Devices - Application of Risk Management to Medical Devices* provides more detailed requirements for the application of risk management to medical devices.

The standard includes requirements on the contents of elements required as part of the risk management systems, including the following:

- A risk management plan,
- the risk analysis, risk evaluation, and risk control,
- the evaluation of the individual and overall residual risk and
- the risk management report.

When it comes to risk control measures, ISO 14971 and the MDR share the priority order in which risk control measures shall be implemented. In addition, the standard requires these risk control measures to be verified regarding their implementation and effectiveness.

Implementation

What might this look like for a medical device?

The risk analysis and evaluation (risk assessment) for a syringe incorporating the mechanical hazard of a sharp tip and the biological hazard of microbiological contamination could indicate that risk control measures need to be implemented due to a too high risk:

Hazard	Sequence of events & Hazardous situation	Harm	Severity*	Probability of occurrence*	Risk evaluation
Contaminated device (biological hazard)	1. A syringe is used on a patient. 2. The syringe is not disposed of and instead is reused on another patient. 3. The patient comes into contact with bacteria.	Bacterial infection	3	3	
Sharp needle tip (mechanical hazard)	1. The syringe is removed from the packaging. 2. The user accidentally touches the needle tip.	Finger prick	2	2	

**The severity of harm and the probability of occurrence of harm depend on the criteria defined in the risk management plan of a medical device.*

Therefore, a risk control option analysis is conducted for the previously identified risks, which might lead to the identification of the following measures:

For the mechanical hazard:

1. Designing the syringe without a needle tip
2. A protective cover for the needle tip
3. Providing a caution regarding the needle tip

The analysis shows that there are possibilities to eliminate the hazard by a safe design. However, the risk control measure is not practicable since the lack of a needle tip would not only eliminate the risk on the one hand but would also eliminate the benefit on the other hand. The MDR considers such cases and therefore limits the requirement to reduce risks as far as possible to that point where it can be done without adversely affecting the benefit-risk ratio. An adverse effect on the benefit-risk ratio can be either an increased risk or a reduced benefit.

For the biological hazard:

1. A self-destructing device after use
2. A clear indication of a first use (e.g., change of color)
3. Warning against reuse

A safe design for a self-destructing device is currently not practicable, while a clear indication of first use depends on the device design, but it might be possible. At least a warning against reuse is feasible.

Safety information is displayed on the label itself (in the form of a symbol) and/or provided in the instructions for use. The requirement of providing such information needs to be documented either in the design documentation or within the user interface specification (if a usability engineering procedure according to IEC 62366-1 is in place). Furthermore, additional requirements must be considered when it comes to risk reduction, including providing safety information in the labeling.

When is a Warning, Caution or Note Truly Needed?

Labeling

Labeling refers to the "*label, instructions for use, and any other information that is related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents*" [ISO 13485,3.8]. The manufacturer's main labeling requirements can be found in Annex I, Chapter III - *Requirements regarding the information supplied with the device* of MDR. It is divided into four sections (23.1 to 23.4):

- General requirements regarding the information supplied by the manufacturer,
- Information on the label,
- Information on the packaging that maintains the sterile condition of a device ('sterile packaging'), and
- Information in the instructions for use.

The first section, which outlines the general requirements, stipulates that the information provided by the manufacturer must include an identification of the device and its manufacturer, as well as any safety and performance information relevant to the user or other persons, as applicable. However, the term 'appropriate' lacks a clear definition. What must be included within the labeling?

Label requirements outlined in the second and third sections apply to any written, printed, or graphic information that appears on the device or its packaging, whether it is a single unit or multiple devices [MDR, Article 2 (13)]. The last section addresses the requirements for the instructions for use, which inform the user of the device's intended purpose and proper use, as well as any necessary precautions [MDR, Article 2 (14)].

Whether it is a label or instructions for use, both require general information about the product, such as the trade name, specific materials, and the sterile state, if applicable. These kinds of elements can be approached as a checklist. For more detailed information on how to establish them, the state-of-the-art standard ISO 20417 *Medical devices - Information to be supplied by the manufacturer* is available. This standard was developed in accordance with MDR and includes a cross-reference to it in Annex D. Where appropriate, the information must be provided in the form of symbols, especially on labels. The harmonized standard EN ISO 15223-1: *Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements* exists for this purpose and thus reduces translation efforts.

Having a well working quality management system in place including a functioning risk management process is essential to ensure that information documented as part of one process is consistent.

What Risk Information Belongs on the Labeling and Where?

In addition to the necessary product information, a significant amount of risk-related information must also be considered. The label itself must provide any warnings or precautions that need to be brought to the immediate attention of the device's user and others. EN ISO 15223-1 contains several useful symbols for these cases, but additional safety symbols can be found in ISO 7010 *Graphical symbols - Safety colors and safety signs - Registered safety signs*. The color assignment of these symbols is based on the ISO 3864 series.

If more detailed information beyond what is provided on the label is required, it should be included in the instructions for use, taking into account the intended users. There are five different requirements in section 23.4 identifying risks:

- Residual risks,
- Risks from re-used single-use devices,
- General warnings and precautions, as well as contraindications,
- Risks from substances, and
- Risks during disposal.

Providing safety information through labeling is the last option for risk control measures. This information can be conveyed through instructions on how to use the medical device or accessory, explanations of safety features, as well as warnings, precautions, and contraindications.

Neither the MDR nor any MDCG Guidance defines the term *"contraindication"*. Only the FDA provides a definition in the *"Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers"*:

"Contraindications are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit."

Unless contraindicated, safety information will be listed as a Warning, Precaution, or other category. But how can these be categorized? According to ISO 3864-2, the following signal words are specified and defined as:

Danger	*Signal word used to indicate an imminently hazardous situation which, if not avoided, will result in death or serious injury*
Warning	*Signal word used to indicate a potentially hazardous situation which, if not avoided, could result in death or serious injury*
Caution	*Signal word used to indicate a potentially hazardous situation which, if not avoided, could result in minor or moderate injury*

If the hazardous situation does not result in personal injury but does result in damage to the product or other property, a *Notice* may be given. This may also be in addition to any *Danger, Warning*, or *Caution*.

Implementation

How can a risk be translated into labeling of the medical device?

One approach would be to incorporate the above-mentioned definitions of *Danger, Warning* and *Caution* into the Risk Management. Typically, manufacturers use an N-by-M matrix to describe the probabilities and severities of the risk associated with each hazardous situation and select the levels of both elements that are appropriate for their products. Each cell of the matrix represents a subset of the full set of possible risks [ISO/TR 24971].

But what about the probability of the harm occurring?

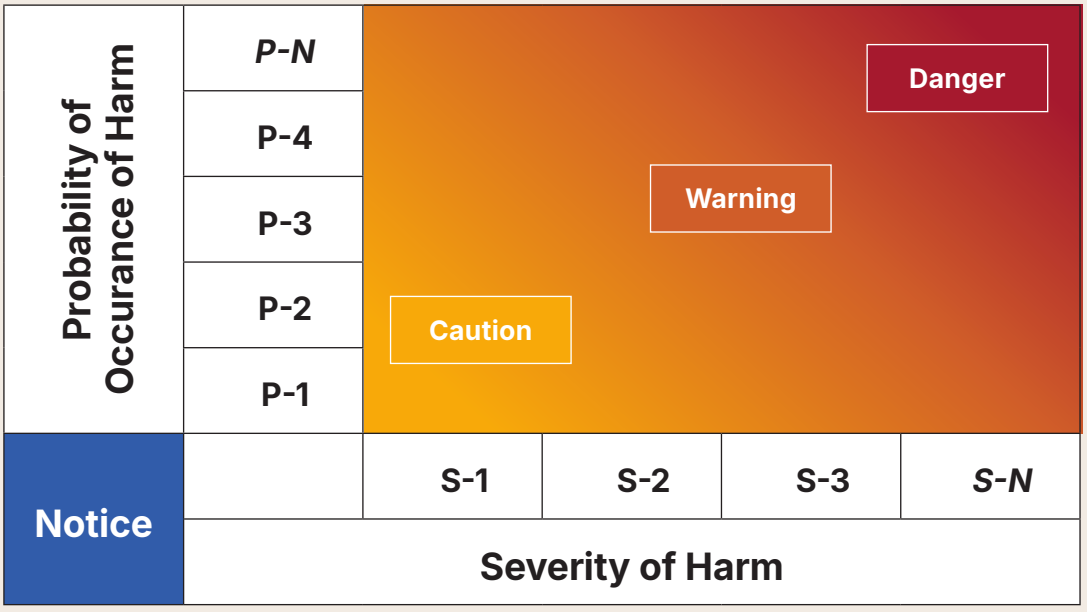
The probability of occurrence (p) is made up of two values (p1*p2):

- the probability of a hazardous situation occurring (p1) and
- the probability of a hazardous situation leading to harm (p2).

In particular, the latter should be considered for translation into labeling. If a hazardous situation is certain to result in death or serious injury *(Harm)*, the safety information in the IFU should be labeled as "*Danger*" if this is listed as a risk control measure for risk mitigation. Otherwise, it will most likely be a "*Warning*" that could lead to death or serious injury. For all minor or moderate injuries, the safety information would be categorized as "*Caution*" or "*Precaution*".

The following figure illustrates an example of a 4×5 matrix that maps the signal words.

Potential Risk Management Output Based On The Severity of Risk



In any case, "*Notices*" may be given if the device or other property would also be damaged.

Verification of Risk Control Measures

Once the determined risk control measures have been implemented, the ISO 14971 requires them to be verified regarding their implementation and effectiveness. In terms of safety information, the evidence for verification of implementation is most likely to be found in the instructions for use or the label.

When it comes to verifying effectiveness, a test report is expected. To verify the effectiveness of risk control measures in the form of information for safety, the usability process outlined in IEC 62366-1 *Medical Devices - Application of Usability Engineering to Medical Devices* may be applied. The IEC 62366-1 requires defining the use specification for a medical device and establishing the user interface specification, which is either a separate document or part of the design documentation. The user interface specification includes requirements related to the user interface of a medical device, which the device's labeling is a part of. In the further course of the process, formative evaluation/s and at least one summative evaluation are conducted, which may include the evaluation of the labeling. Formative evaluations do not represent objective evidence for verifying effectiveness, as they do not require acceptance criteria. In contrast, summative evaluations require the definition of acceptance criteria and can therefore be used to verify the effectiveness of risk control measures implemented on the user interface, such as device labeling.

Hazard	Risk evaluation	Risk control measure	Verification of implementation	Verification of effectiveness	Residual risk evaluation
Contaminated device (biological hazard)		Caution regarding the needle tip in the IFU	*IFU*	*Summative evaluation*	
Sharp needle tip (mechanical hazard)		Single use symbol on the label Warning against reuse in the IFU	*Label* *IFU*	*Summative evaluation*	

**The illustration focuses on the risk control. Therefore, other relevant elements that are part of the risk analysis, evaluation, and control are not displayed.*

If the risk control measures can be verified regarding their implementation and effectiveness, the risks are re-evaluated. If it is determined that the risks have been reduced as far as possible without adversely affecting the benefit-risk ratio, the risk control process can be considered complete for the time being.

Risk management and labeling work very closely together. Both processes are not only highly dependent on each other but also require input from other processes, such as usability engineering, which underscores the importance of a clear and accurate description of the interfaces within the quality management system. Having a team in place that handles the appropriate exchange is essential to maintaining the consistency of information and the value of the processes. The scope of that exchange depends, for example, on the medical device, risk classification, and level of innovation.

There is no prescribed way for the processes to interact with each other; however, it is the manufacturer's responsibility to ensure that this interaction occurs.

Risk management is a key element within the development of medical devices. Used correctly, it contributes to the production of safe medical devices and enhances product quality.

How NSF Can Help

We bring together global regulatory knowledge with industry experience to support manufacturers in navigating the complex intersection of risk management and labeling. With a focus on clarity, compliance and traceability, we help teams strengthen their processes and meet evolving global expectations.

Our services include:

- Preparation and implementation or update of risk management systems,
- Preparation and implementation or update of usability engineering procedures,
- Preparation and implementation or update of labeling procedures,
- Support in conducting formative and/or summative evaluations,
- Preparation, review, and update of the risk management file and documentation,
- Preparation, review, and update of the usability engineering file,
- Consistency check between risk management, labeling and usability documentation,
- Preparation, review, and update of labeling master documentation, and
- Consultancy services across all global regulatory compliance matters.

Get in touch or visit our website to learn more about how we can help you and your business thrive.

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