Risk Management for Combination Products

New Requirements posed by the EU MDR

Combination products consisting of a drug and/ or a biological substance and a medical device must cover and fulfill the risk management requirements of two industries in their processes imposed by the EU Medical Device Regulation (MDR) Article 117. One is according to ICH Q9 from the pharmaceutical industry and the other is according to ISO 14971 from the medical device industry. The AAMI TIR105:2020 guideline can be helpful in terms of practical implementation.

The basic procedure is very similar in both risk management processes and consists of the same main components

- Risk Assessment
- Risk Control
- Production and Post-Production Risk Review

The target of both risk management processes is that the Market Authorization Holder knows and controls the current risk-benefit ratio at all times, so that the benefit of the product outweighs the existing residual risks.

The different requirements of the two standards only become apparent when you dive deeper into the risk management process.

Risikomanagement Plan

ISO 14971 requires a number of predefinitions that are not explicitly required by ICH Q9. In ISO 14971, the risk management plan is a substantial part of the risk management process, in which, among other things, product-specific determinations are made that concern the entire life cycle of the product.

Risk Assessment

In case of combination products, the risk of each component of the combination product must be evaluated separately (e.g. drug/biological preparation/ medical device). The product is therefore not "only" considered as a unit; rather, the interactions between the combination product components are evaluated. They can create new risks, but also reduce risks by working as mutual risk control measures. The documentation of the risk assessment can be simplified if the assessment level is defined during the risk analysis: Single component or final product.

Risk Control

Risk Control Measures

In order to meet the control measures of both industries, special attention must be paid to ISO 14971, as it additionally requires compliance with a clear hierarchy of control measures which have to be applied.

Effectiveness of the Control Measures

Again, ISO 14971 requires "more" by holding verification and validation documents for each risk control measure and making them part of the risk file.

Residual Risks – Risk Acceptance

According to ICH Q9, it is not mandatory to specify the individual residual risks. ISO 14971, on the other hand, requires that all individual residual risks have to be identified and reduced as far as possible.

Risk-Benefit Analysis

Here, too, ISO 14971 sets specific requirements. For all unacceptable individual residual risks, the risk-benefit ratio must be determined and the predominant benefit must be substantiated by data and literature.

Final Risk Review before Product Release

Prior to product release to the market, ISO 14971 requires a risk review, the results of which are recorded in the risk management report.

The following are reviewed:

- The correct implementation of the risk management plan,
- the stronger weighting of benefits compared to the totality of residual risks, and
- The introduction of all necessary processes that continuously monitor the risk in the market phase.

Conclusion

It is useful to set up a project for the introduction of the new requirements. Changes can then be prioritized and implemented in a timely manner. Prior training of the project team on ISO 14971 supports the correct risk management process and, above all, the identification of the combination products for which the risk management file needs to be updated.