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Medical Device & IVD Risk/Benefit Analysis

Risk management to meet ISO 14971 requirements



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Risk Management Challenges for Smaller Manufacturers

While all medical device and in vitro diagnostic (IVD) manufacturers that claim conformity to ISO 14971:2007 should be familiar with the risk management documentation requirements established in this standard, small and medium-sized manufacturers frequently encounter challenges in preparing their risk management files, especially those wishing to market CE-marked devices in accordance with the requirements of EN ISO 14971:2012.

One of these challenges specifically relates to the risk/benefit analysis requirements of this harmonized standard and how they can be met by organizations wishing to obtain CE Marking for their devices. As the standard does not specify acceptable risk due to the lack of standardized approaches in benefit estimation and the conflicting requirements of the European Medical Device Directive (MDD) and In Vitro Diagnostic Device Directive (IVDD) in regards to risk management, this can be a difficult endeavor for manufacturers in order to demonstrate the clinical benefits of their devices when weighed against the risks inherent in their use.

This provides a brief introduction to risk/benefit analysis concepts for medical devices and IVDs, including a general overview of the differences between these two versions of ISO 14971 and the European Directives in relation to risk/benefit analysis, and descriptions and summaries of the tools and resources available for use in these types of analyses.

ISO 14971 and Risk/Benefit Analysis

The ISO 14971:2007 is quite clear in regards to what constitutes risk/benefit analysis and when such analyses should be performed.

In accordance with this standard, a risk/benefit analysis is the gathering and reviewing of data and literature to determine whether the medical benefits of the intended use outweigh the residual risk. Furthermore, the standard establishes that if residual risk is not judged acceptable in accordance with pre-established criteria in the risk management plan and further risk control is not practicable, the manufacturer may perform such a risk/benefit analysis.

Within ISO 14971:2007 there are two clauses that describe risk/benefit analyses and establish when such analyses should be performed in accordance with the above descriptions, with additional guidance on risk/benefit analysis in Annex D:

- Clause 6.5 covers risk/benefit analysis for individual residual risks;
- Clause 7 covers risk/benefit analysis for overall residual risk;
- Annex D.6 covers risk/benefit analysis general guidance.

When the risk/benefit analysis for individual risks demonstrates that the risk is outweighed by the benefits, the manufacturer shall determine which information is necessary to include in the accompanying documentation, such as the instructions for use, in order to disclose the residual risk (e.g. warning, precautions, contraindications). Manufacturers are also required to make the same determination when the overall residual risk is found to be acceptable.

While ISO 14971:2007 requirements for risk/benefit analysis are straightforward, they and other risk management processes do conflict with the requirements for risk management established in both the MDD and IVDD; hence, the European Commission published a harmonized version of this standard. The EN ISO 14971:2012 harmonized standard was published in order to clarify the expectations for risk management for CE-marking purposes so that manufacturers could continue to declare conformity with the Essential Requirements.

Risk/Benefit Analysis Requirements of EN ISO 14971:2012

While the clauses of ISO 14971:2007 are identical to those of EN ISO 14971:2012, annexes ZA and ZC of the latter clarify the correspondence and deviations of the standard in relation to the Essential Requirements for MDs and IVDs, respectively.

Specifically, in regards to deviations in the standard related to risk/benefit analysis, these include:

- **Treatment of negligible risks**
  As stated in the annex to EN ISO 14971:2012, the manufacturer must take all risks into account when assessing compliance with the Essential Requirements. However there is a critical difference between the Essential Requirements of Section 1 of the MDD (Annex I) and Section A.1 of the IVDD (Annex I).

  Section 1, Annex I of the MDD states that "*…any risks that may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient…" while Section A.1, Annex I of the IVDD states that "Any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient…*".

  Considering this difference, the requirement to consider all risks, established in annexes ZA and ZC, is applicable only to risks associated with medical device intended use however in the case of IVDs it is associated with all uses, inclusive of off-label or unintended uses.

- **Discretionary power of manufacturers as to the acceptability of risks**
  According to the annexes to EN ISO 14971:2012, the standard implies that only unacceptable risks must be integrated into the overall risk-benefit analysis; however, as is the case for the treatment of negligible risks, Section 1, Annex I of the MDD establishes that any risks associated with the intended use must be assessed as part of the risk/benefit analysis and Section 1.A, Annex I of the IVDD establishes that any risks associated with any use must be assessed.

- **Discretion as to whether a risk-benefit analysis needs to take place**
  Annexes ZA and ZC of EN ISO 14971:2012 describe that Sections 1 and A.1 of the MDD and IVDD, respectively, require an overall risk-benefit analysis be performed, regardless of the application of risk acceptability criteria established in the risk management plan. Both annexes therefore establish that manufacturers must undertake risk/benefit analyses for both individual risks and the totality of overall risks associated with the device in all cases.

In summary, the differences between the requirements for risk/benefit analysis of ISO 14971:2007 and EN ISO 14971:2012 for MDs and IVDs can be described as follows:

Table 1 – Risk/Benefit Analysis Differences between ISO 14971:2007 and EN ISO 14971:2012

Standard (Device Type)	Risks to be considered in risk/ benefit analysis	Risk acceptability determination	Risk/benefit analysis required to be performed
ISO 14971:2007 (MDs & IVDs)	Unacceptable residual risks	Performed before risk/ benefit analysis	1. For each individual unacceptable residual risk; 2. For overall residual risk if it is determined to be unacceptable
EN ISO 14971:2012 (MDs)	All risks associated with intended use	Performed after risk/ benefit analysis	1. For each individual risk associated with intended use; 2. For overall residual risk acceptability
EN ISO 14971:2012 (IVDs)	All risks associated with use		1. For each individual risk associated with use; 2. For overall residual risk acceptability

Understanding the differences and similarities highlighted in the table above is critical for identifying the data and literature information that is necessary to perform risk/benefit analyses for CE-marking purposes.

The type and extent of data and literature available for risk/benefit analyses depends greatly upon whether the MD or IVD is a novel device or is based upon, or can be compared with, existing technology. For individual manufacturers the question of which data to use is also determined by the life cycle stage of the device in question, i.e. whether the device is under development or has been on the market for some time with accumulated post-market surveillance (PMS) data available.

In the case of novel devices, the normal expectation is that clinical investigations are executed by the manufacturer in order to demonstrate the clinical or medical utility of the device. Such clinical investigations allow for the quantification of benefits and risks in addition to establishing evidence on user/patient tolerance levels or thresholds for inherent risks when compared with the benefits of the device, such as in the case of terminal or currently untreatable/incurable conditions. Some of the methodologies used to quantify benefits and risks under such circumstances, which are also used widely in the pharmaceutical industry, include:

- Number needed to treat (NNT) & Number needed to harm (NNH)
- Incremental net health benefit (NHB)
- Quality-adjusted Time Without Symptoms and Toxicity (Q-TWIST)
- Risk-benefit Contour (RBC)
- Quantitative Framework for Risk and Benefit Assessment (QFRBA)

For CE-marking purposes, such studies on MDs should be performed in accordance with EN ISO 14155:2011. There is no equivalent standard for IVD clinical investigations.

Following the launch of a novel device, notified bodies can also establish the need for post-market clinical follow-up (PMCF) as part of the post-market surveillance effort undertaken by a manufacturer in order to verify the benefits and risks associated with routine device use. As such information is collected in an essentially uncontrolled environment, it has the potential to identify risks and benefits not observed during tightly-controlled clinical investigations.

For devices that are comparable with, or based upon, existing MD or IVD technology, a literature search and review of clinical experience data, in the form of a clinical evaluation report (CER) would be the minimum expectation for a Notified Body in order to demonstrate the risks and benefits of the inherent design of the device prior to commercialization. For data in such reports to be relevant, equivalency with the comparative device must be demonstrated. This is true for even Class I devices.

Regardless of the scope of clinical data being assessed, whether it be from literature searches, clinical experience or clinical investigation, the CER is the documentation that a Notified Body will need to review during the their determination of CE-marking suitability. In order to be compliant with EN ISO 14971:2012, these reports must contemplate the risks listed in Table 1, or be complemented with additional risk/benefit reporting that includes those risks not covered by the CER.

European guidance on clinical evaluation, as established in MEDDEV 2.7.1 Rev.3[1], clearly states that clinical experience data may include:

- Manufacturer-generated PMS reports, registries or cohort studies;
- Adverse events databases (held by either manufacturers or Regulatory Authorities);
- Compassionate use data for the device obtained prior to marketing;
- Details of clinically relevant field corrective actions such as recalls, notifications and hazard alerts

Neither version of ISO 14971 establishes requirements that risk/benefit analyses be qualitative or quantitative in nature. However, Notified Bodies generally expect that as the risk profile of the MD or IVD in question increases, clinical investigations, and hence quantitative risk/benefit analyses, become more important in order to understand the risk-benefit profile of a device.

As mentioned previously, there are a number of quantitative methodologies available to perform quantitative risk analyses. However, there are limitations and observations that should be considered for each of these and other methodologies, as follows:

Table 2 – Summary Table of Example Quantitative Risk/Benefit Methodologies[2,3]

Methodology	Theoretical model and key features	Explicit Preferences*	Easily-interpreted*	Threshold*	Economic Evaluation Measures Integration	Incorporates Uncertainty*	Inclusive*	Comprehensive*
Quantitative Framework for Risk and Benefit Assessment (QFRBA)	· Theoretically sound quantitative method; · Probability driven assessment for risk of adverse events (AEs) and benefits of improved outcomes; · Relatively simple calculation; · Often used for safety surveillance.	✓	✓	✓	✓	✓	✓	✓
Benefit-less-risk analysis (BLRA)	· Simple empirical method with sound theoretical basis; · Differences between treatments can be statistically analyzed (t-test or ANOVA); · Requires subjective rankings of AE intensity scores; · Patient preferences are incorporated using a discounting process; · Subjective ranking for AEs and proportionality a potential threat to internal validity; · Useful for comparing one treatment to a placebo or alternative treatment using clinical investigation data.	✓	✗	✓	✓	✗	✗	✗
Quality-adjusted Time Without Symptoms and Toxicity (Q-TWIST)	· Statistical method can be conducted to compare alternative treatments; · Quality-adjusted life-years (QALYs) incorporate patients preference measurement changes over time; · Validity of QALY measurements and differences between techniques are potential concerns; · Widely used risk-benefit assessment technique in clinical oncology.	✓	✓	✓	✓	✗	✗	✓
Number needed to treat (NNT) and number needed to harm (NNH)	· Well-defined quantitative framework; · Simple calculation used for comparing treatment and control groups; · Lack of strong statistical properties; · Risk-benefit relation can be compared directly by NNT to NNH ratio; · NNT should be lower than NNH for the device; · Widely used in different therapy areas; · Difficult to incorporate more than one outcome (AE or benefit reduction) simultaneously.	**	**	**	**	**	✗	✗

Table 2 – Summary Table of Example Quantitative Risk/Benefit Methodologies[2,3]

Methodology	Theoretical model and key features	Explicit Preferences*	Easily-interpreted*	Threshold*	Economic Evaluation Measures Integration	Incorporates Uncertainty*	Inclusive*	Comprehensive*
Relative value adjusted number needed to treat (RV-NNT)	· Well-defined quantitative framework; · RV measures involve patient's preference for specific AEs or avoidance of negative clinical outcomes; · RV-NNT must be higher than the RV-NNH.	✓	✗	✗	✗	✗	✗	✗
Minimum clinical efficacy (MCE)	· Quantitative framework for integrating risk-benefit data into a single decision rule; · New treatment is warranted over conventional; treatment if efficacy exceeds probability of AE; · More than one type of AE can be considered; · Lack of strong statistical properties; · Does not incorporate uncertainty in the benefit or risk measurements; · Applied primarily for cardiovascular treatments.	✓	✓	✓	✗	✗	✗	✗
Incremental net health benefit (NHB)	· Theoretically sound modeling method; · Risk-benefit relation presented as an incremental difference; · QALY data from clinical trials are required; · Statistical variance in the estimates of both risks and benefits can be calculated; · Potential application in clinical and regulatory decision-making.	✓	✓	✓	✓	✓	✓	✓
Risk-benefit Contour (RBC)	· Graphical depiction of both benefit and risk; · Risk-benefit contours for comparative treatments are plotted as a set of nonlinear curves; · For each individual patient, RBC scores can be identified with confidence intervals; · Useful tool for clinical decision making.	✓	✓	✗	✗	✗	✗	✗

**Explicit Preferences = Weighs individual harms and benefits according to an explicit set of preferences from a relevant group; Easily-interpreted = Produces a graphical harm-benefit profile to facilitate comparison against no therapy or an appropriate comparator; Threshold = Has an intrinsic harm-benefit acceptability threshold; Incorporates Uncertainty = Accounts for the quality and source of the benefit/harm information entered into the model. Provides a measure of precision (uncertainty) around the harm-benefit metric; Inclusive = Can incorporate multiple harms AND multiple benefits; Comprehensive = Can quantity both objective harms (e.g. mortality) and subjective benefits. Can quantify the duration, intensity and reversibility of harms and benefits.*

***Depending upon the type of NNT methodology employed (there are a number of variations for the NNT methodology), these criteria may or may not be applicable.*

While these tools are useful for quantitative risk/benefit analysis there is also additional guidance available that may be used for qualitative analyses. In 2012 the FDA published guidance on factors to consider when making benefit-risk determinations in medical device premarket approvals[4]. This very guidance includes worksheets, including examples of completed worksheets for hypothetical situations that illustrate risk-benefit concepts in a practical manner and indicate the agency's current thinking on this topic.

Regardless of whether quantitative, qualitative or a combination of both methods are used in risk/benefit analysis this documentation should be reviewed during the defined life cycle of the device, as additional PMS data is accrued, at planned intervals in accordance with the risk management plan and ISO 14971 requirements.

Conclusion

While many manufacturers struggle with risk management in general, risk-benefit analysis can be a particularly daunting activity. This paper has provided a brief overview of risk/benefit analysis concepts for MDs and IVDs, including the differences in such analyses for CE-marking purposes. It also provides the reader with a number of useful links and references to tools and resources that can be used in this endeavor.

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References:

1 http://ec.europa.eu/growth/sectors/medical-devices/guidance/index_en.htm

2 Guo, Jeff J. et al, A Review of Quantitative Risk-Benefit Methodologies for Assessing Drug Safety and Efficacy-Report of the ISPOR Risk-Benefit Management Working Group. VALUE IN HEALTH, Vol. 13, Number 5 (2010), pp. 657 – 666.

3 Lynd, Larry et al, First steps in developing a risk-benefit analysis framework: a systemic review and critical evaluation of risk-benefit analysis methods. Centre for Health Economics, University of York, UK (https://www.york.ac.uk/media/che/documents/papers/presentations/04.pdf)

4 Guidance for Industry and Food and Drug Administration Staff – Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications. March 28, 2012 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm267829.htm)