ISO 14971:2012

Ensuring Compliance to Annex Z Requirements

David Amor, MS, CQA

Managing Partner

MEDgineering

www.medgineering.com

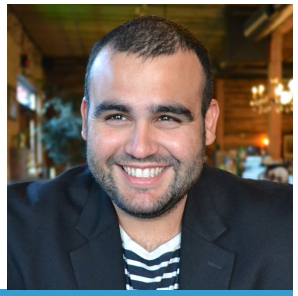
david@medgineering.com

Agenda

- Risk Management Best Practices Overview
- ISO 14971:2012 overview
- Annex Z changes
- How to address content deviations

Logistics and Notes

- ISO 14971:2012 is very controversial: please note that solutions presented herein attempt to balance business needs with patient safety / product effectiveness
- Case studies may not be representative or guaranteed to work 100% of the time
- Most Annex Z presentations tell you what not to do – we take a stab at giving you solutions and what to do to navigate these new obstacles



David Amor, MSBE, CQA is partner at MEDgineering, a medical device compliance consulting firm specializing in remote consulting solutions, remediation projects and quality systems. A graduate of the Senior Innovation Fellows program at the University of Minnesota's Medical Device Center, David was named a Top 40 Under 40 Medical Device Innovator in 2012. David has helped set up med-tech start-ups with quality systems, risk management infrastructures and product development programs that were cited as 'best practices' by the FDA and European notified bodies likes DEKRA and TUV. Most recently, David co-founded and helped launch Remind Technologies, a Texas based mobile health company developing the world's first smartphone based pill dispenser.

More importantly: *I have worked directly in managing teams performing risk management remediation (483s, warning letters, NB audits, etc.) for several of the top medical device companies.*

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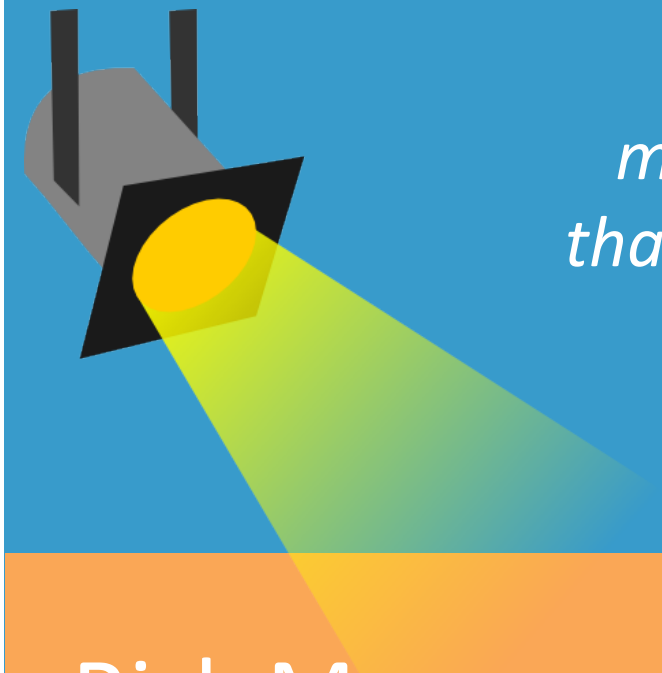

Maintaining an appropriate risk management file per ISO 14971 ensures that you comply with most of FDA and EU Essential Requirements for risk management.

Risk Management Best Practices

Risk Management

Best Practices in Risk Assessment

- **Risk:** combination of the probability of occurrence of harm and the severity of that harm
- **Risk Assessment:** overall process comprising a risk analysis and a risk evaluation
- **Risk Analysis:** systematic use of available information to identify hazards and to estimate the risk
- **Risk Control:** process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels
- **Risk Evaluation:** process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

REMEMBER: ISO 14971 defines risk in terms of HARM only

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Risk Management

Best Practices in Risk Assessment

- **Predicate device information**
  - On-market product performance
  - Known device failures
  - CAPAs, design changes
  - Complaint data / MDRs
- **Functional analysis**
- **Product characterization studies**
  - Bench-top testing, animal or clinical studies
- **Product labeling**
- **Intended Use**
  - Known off-label use
  - Normal state hazards
- **Clinical and scientific literature**
- **Task Analysis**
  - Forseeable mis-use
  - Interaction with accessories or other products
  - Clinical use environment
- **Regulatory Standards**
  - Product specific standards
  - Safety standards

Table E.1 — Examples of hazards

Examples of energy hazards	Examples of biological and chemical hazards	Examples of operational hazards	Examples of information hazards
Electromagnetic energy	**Biological**	**Function**	**Labelling**
Line voltage	Bacteria	Incorrect or inappropriate output or functionality	Incomplete instructions for use
Leakage current	Viruses	Incorrect measurement	Inadequate description of performance characteristics
— enclosure leakage current	Other agents (e.g. prions)	Erroneous data transfer	Inadequate specification of intended use
— earth leakage current	Re- or cross-infection	Loss or deterioration of function	Inadequate disclosure of limitations
— patient leakage current	**Chemical**	**Use error**	**Operating instructions**
Electric fields	Exposure of airway, tissues, environment or property, e.g. to foreign materials:	Attentional failure	Inadequate specification of accessories to be used with the medical device
Magnetic fields	— acids or alkalis	Memory failure	Inadequate specification of pre-use checks
Radiation energy	— residues	Rule-based failure	Over-complicated operating instructions
Ionizing radiation	— contaminates	Knowledge-based failure	**Warnings**
Non-ionizing radiation	— additives or processing aids	Routine violation	Of side effects
Thermal energy	— cleaning, disinfecting or testing agents		Of hazards likely with re-use of single-use medical devices
High temperature	— degradation products		**Specification of service and maintenance**
Low temperature	— medical gasses		
Mechanical energy	— anaesthetic products		
Gravity	**Biocompatibility**		
— falling	Toxicity of chemical constituents, e.g.:		
— suspended masses	— allergenicity/ irritancy		
Vibration	— pyrogenicity		
Stored energy			
Moving parts			
Torsion, shear and tensile force			
Moving and positioning of patient			
Acoustic energy			
— ultrasonic energy			
— infrasound energy			
— sound			
High pressure fluid injection			

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Risk Management

Best Practices in Risk Assessment

Hazard Analysis

- Top down analysis
- Hazard → Hazardous Situation → Harm
- Sequence of events analysis
- Normal state hazards
- Interface hazards
- Correlates to post-market surveillance
- Does not provide root cause failure information

FMEA / FMECA

- Bottom up analysis
- Single fault failures
- Allows for discrete failure perspectives (use, design, process)
- Allows for multiple levels of analysis
- Single failure / single level focus is limiting

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Risk Management

Best Practices in Risk Assessment

- Manufacturer should utilize a consistent approach to determining probability of occurrence and severity of harm
  - Qualitative or quantitative
  - Clearly define how probability and severity values are determined
  - Master library of harms and associated severities to ensure consistency
  - FTA to provide supportive evidence of probability values (sequence of events)
- Risk level is defined by the manufacturer
  - Matrix format
- Risk level drives risk reduction activities based on manufacturer definitions
- Refer to 14971 Annex D.3 Risk Estimation for additional guidance

KEY TAKE AWAY: Proceduralize how to determine all values utilized in risk analysis, and implement the approach in all product files!

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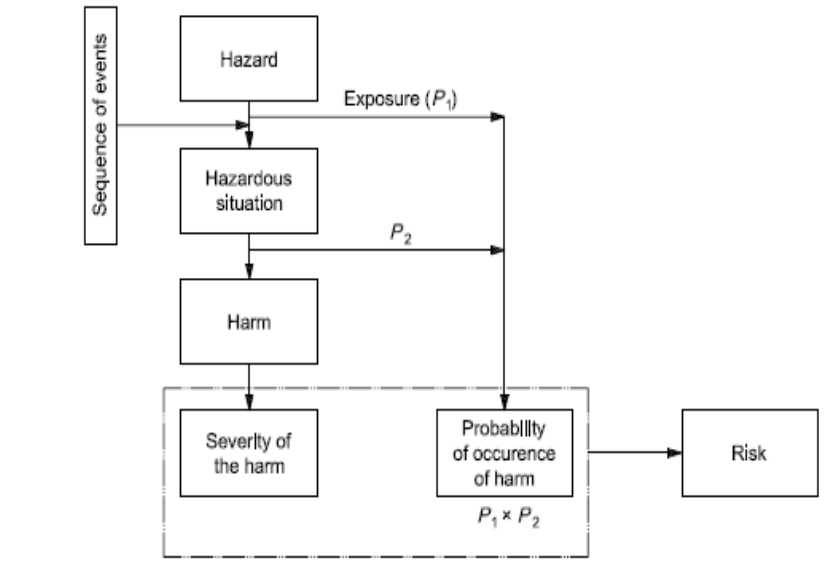
Risk Management

Best Practices in Risk Assessment

Probability of occurrence of harm should take into account the probability of the **hazard** *(i.e. product failure, use error)* and the occurrence of the **hazardous situation** *(i.e. failure detected prior to use vs during clinical use)*

The resulting **risk** should also account for the likelihood of this **harm** occurring at a specified level of **severity** *(i.e. patient exposure to product with compromised sterility has a higher likelihood of resulting in a treatable infection than sepsis)*



NOTE P_1 is the probability of a hazardous situation occurring.
P_2 is the probability of a hazardous situation leading to harm.

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

KEY TAKE AWAY: Don't overestimate your occurrence values! An accurate risk profile is important for post-market risk monitoring.

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Risk Management

Best Practices in Risk Assessment

- **Inherent safety by design**
  - Needless design
  - Proprietary connectors
  - Use of appropriate materials
  - Back check valves
- **Protective measures in the medical device itself or in the manufacturing process**
  - Fuse
  - Back up internal battery
  - Design for assembly
  - Alarms
- **Information for safety**
  - Safety symbols
  - Warnings
  - Preventative maintenance
- Refer to 14971 Annex D.5.1 for additional guidance

Remember: all risk controls must be evaluated to determine whether or not they introduce additional risk

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Risk Management

Best Practices in Risk Assessment

- **Final assembly inspections / 100% in process inspection**
  - Quality inspections may reduce out of box failures, but will not reduce failures due to inadequate reliability
  - 100% in process inspection will not catch all non-conformances
- **Compliance to standards as risk controls**
  - Standard requirements for product performance may not be rigorous enough for the defined use environment
  - Risk controls should be based on product design requirements; compliance to relevant standards can be referenced as evidence of risk control effectiveness
  - Exception for standards that provide direct verification (i.e. EMC, biocompatibility, sterilization)
- **Labeling**
  - Manufacturers shall not attribute any additional risk reduction to the information for safety given to the users
  - Can be referenced in conjunction with other risk control options
  - Do not reduce risk to an acceptable level based on information for safety alone

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Risk Management

Best Practices in Risk Assessment

- **Manufacturer defines criteria for risk acceptability**
  - documented in RMP
- **Manufacturer should define (on a procedural level) risk reduction activity required as a result of risk evaluation**
  - Clearly identify when risk reduction is not required
  - Required risk reduction dependent on identified risk level
- **Residual risk evaluation**
  - Shall be performed on an individual risk basis as well as overall, considering all residual risks combined
  - If residual risk is unacceptable, further risk reduction must be applied
  - Residual risk disclosed to user

KEY TAKE AWAY: Clearly defined risk acceptability criteria is critical for a compliant Risk Management process!

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Risk Management

Best Practices in Risk Assessment

- Evaluate risk controls early and often
- Be aware of all applicable product specific standards
- Utilize clinical input
  - Thorough understanding of the use environment is critical
  - Identifying actual likelihood of exposure of hazard to the patient / user
- Do not artificially over-inflate occurrence levels
  - Risk levels should be baselined such that expected values are evaluated for acceptability in order to serve as a post-market threshold
  - Ensure that you are taking into account the hazardous situation when determining occurrence values (i.e. occurrence of out of box failure that is not exposed to the user vs. failure during clinical use)
- Utilize tools to determine SOE where necessary
  - High severity harms
  - Fault tree analysis to show more actual likelihood of occurrence of HARM
  - Consider detectability

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Best Practices in Risk Assessment

- Residual risk acceptability should take into account state of the art
  - does not necessarily mean the most technologically advanced solution
  - Implement all feasible risk controls consistent with the accepted state of the art to achieve as low as possible risk
- Risk Benefit Analysis
  - Utilized when individual residual risk is unacceptable
  - Further risk reduction should be implemented prior to considering benefit
- Can consider restricting intended use or use environment
  - i.e. indicate not for pediatric populations, or provide information on allowable operating conditions (temperature and humidity ranges)

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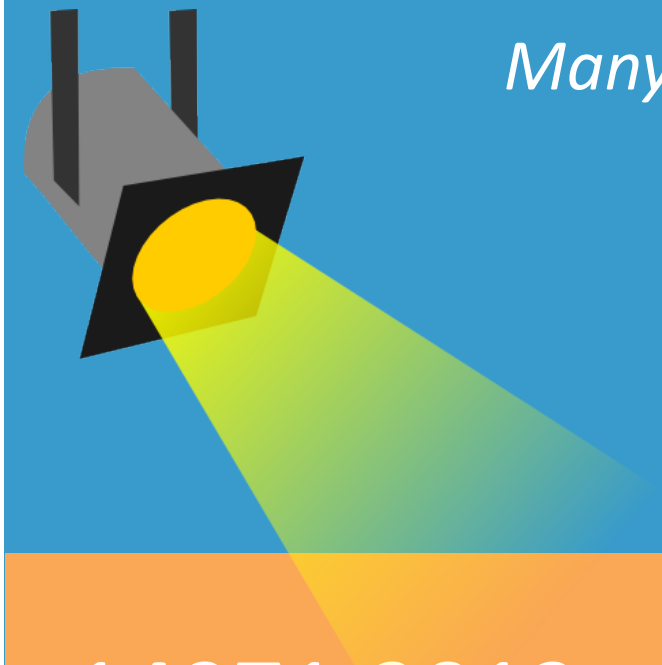

Many of the content deviations described in Annex Z overlap and are similar.

14971:2012 – Annex Z Overview

Risk Management

FDA Perspective

"**RISK MANAGEMENT** begins with the development of design input requirements. As the design evolves, new risks may become evident. To systematically identify and, when necessary, reduce these risks, the risk management process is integrated into the design process. In this way, UNACCEPTABLE RISKS can be identified and managed earlier in the design process when changes are easier to make and less costly."

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Risk Management

ISO 14971

- ISO 14971 – *Medical Devices – Application of Risk Management to Medical devices*
  - As ISO 13485 is more specific to QMS than ISO 9001, ISO 14971 ~ ISO 31000
  - Normative text update in 2007
  - European harmonized standard released in 2009 and recently updated in 2012
  - ISO 14971:2012 resolves remaining discrepancies between the Essential Requirements of 93/42/EEC MDD and 90/385/EEC AIMD

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Risk Management

EU Essential Reqs

	MDD 93/42/EEC	AIMDD 90/385/EEC	IVDD 98/79/EC
"Risk"	ERs: 1 2 6 7.2, 7.4, 7.5, 7.6 8.1, 8.6 9.2, 9.3 11.2, 11.4 12.1, 12.5, 12.6, 12.7 13.5, 13.6	ERs: 1 5 8 9 10 11 15	ERs: A – 1 2 B – 1.2 2.1, 2.2, 2.5, 2.7 3.2, 3.3, 3.4 5.3 6.2, 6.3, 6.4 7.1 8.6, 8.7
Total	**41**	**18**	**24**

**Source: BSI Group*

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ISO 14971:2012 Recap

- **Good news:** none of the normative text changed from ISO 14971:2007
- **Bad news:** harmonized standard to comply with EU directives includes Informative Annex Z which clarifies gaps between global standard and Essential Requirements

Bottom Line: Annex Z has many "minor" clarifications that have significant impact on **how risk is analyzed, assessed, mitigated and evaluated and which together = new "requirements"**

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ISO 14971:2012

Summary of Deviations

1. **All risks** need to be to mitigated.
2. **Risk / benefit analysis** must be performed for all risks.
3. All risks must be reduced **as low as possible**.
4. **All risk mitigations should be taken** regardless of the risk level.
5. Risks must be reduced by **inherent design.**
6. **Labeling and use information** does not constitute risk reduction.

NOTE! *Many of the above are interrelated.*

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Summary of Deviations

	Essential Requirements (ERs) Impacted		
Deviation	**MDD**	**AIMDD**	**IVDD**
1 – Treatment of negligible risks	1, 2, 6, 7.1	1, 5, 9	A.1, A.2, B.1.1
2 – Discretionary power of mfr as to acceptability of risks	1, 2, 6, 7.1	1, 5, 9	A.1, A.2, B.1.1
3 – Risk reduction "as far as possible" vs "as low as reasonably practicable"	1, 2, 6, 7.1	1, 5, 6, 9	A.1, A.2, B.1.1
4 – Discretion as to whether a risk-benefit analysis needs to take place	1, 6, 7.1	5 & 9	A.1 & B.1.1
5 – Discretion as to the risk control options / measures	2 & 7.1	-	A.2 & B.1.1
6 – Deviation as to the first risk control option	2 & 7.1	-	A.2 & B.1.1
7 – Information of the users influencing the residual risk	2 & 7.1	-	A.2 & B.1.1

**Source: BSI Group*

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Deep dive review

1. "All risks need to be mitigated"

Whereas previously you were able to determine risk acceptability and only mitigate risks above a certain threshold, all risks must now have mitigations in place.

Directives (MDD/ AIMD/ IVD)

*"Ensure **that all risks, regardless of their dimension, need to be reduced as much as possible** (and need to be balanced, together with all other risks, against the benefit of the device)."*

Where's the deviation?

ISO 14971:2009

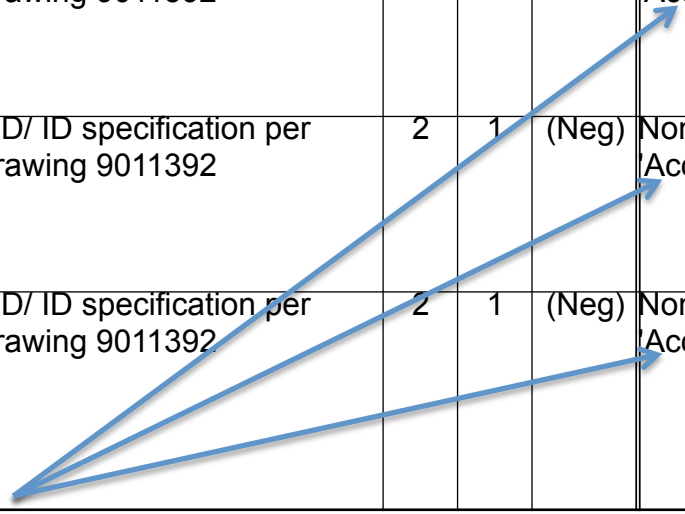
*"…the manufacturer **may discard negligible risks."***

Deep dive review

1. "All risks need to be mitigated"

The Current Dilemma

Potential Failure Mode	Potential Root Cause(s) of Failure Mode	Prod Spec Ref	Preventive Measures / Current Controls	S	O	RI	Recommended Actions (Further Risk Mitigation Needed?)
Core fracture	Diameter too small Material fault/fatigue/ defect	6.0 8.1	OD/ ID specification per drawing 9011392	3	1	(Acc)	None - Risk is 'Acceptable' (RI = 2)
Kinking of core	Diameter too small Material fault/fatigue Improper use Damaged during removal	6.0 8.1 14.2	OD/ ID specification per drawing 9011392	2	1	(Neg)	None - Risk is 'Acceptable' (RI = 1)
Inner Core Penetration	Diameter Too Small Material Fault/Fatigue Improper Use	6.0 8.1 11.0	OD/ ID specification per drawing 9011392	2	1	(Neg)	None - Risk is 'Acceptable' (RI = 0)



Negligible or *Acceptable* risks require mitigation!!

Deep dive review

1. "All risks need to be mitigated"

Possible Solutions

- Blanket Mitigation: in the FMEA conclusions or risk management report, include list of clinical or design mitigations that cover multiple risks (if possible- all).
- 1:1:1 Rule: is there a mitigation in place for use, process and design that can act as a mitigation for a certain *set* of risks?
- If all else fails, do a line item analysis of why the risk is mitigated as low as possible, without referring to financial / cost considerations

Deep dive review

2. Risk / benefit analysis must be performed for all risks.

Risk benefit analysis was traditionally only required if an unacceptable risk was determined. A risk benefit analysis would be performed to demonstrate that the medical benefit outweighed the risk to allow for continued development/ manufacturing.

Directives (MDD/ AIMD/ IVD)

*'....an overall risk-benefit analysis **must take place in any case**, regardless of the criteria established in the risk management plan and requires undesirable side effects to "constitute an acceptable risk when weighed against the performance intended").'*

Where's the deviation?

ISO 14971:2009

*'...an overall risk- benefit analysis **does not need to take place** if the overall residual risk is judged acceptable when using the criteria established in the risk management plan..'*

Deep dive review

2. Risk / benefit analysis must be performed for all risks.

The Current Dilemma

Verification / Validation References	S	O	RI		Clinical Risk Benefit Analysis (CRBA)?
90331637; 90340453 per section 8.2 EN ISO 11070	5	1	2		no
90331637; 90340453 per section 8.2 EN ISO 11070	5	1	2		no
90331637; 90340453 per section 8.2 EN ISO 11070; 90033662	5	3	4		yes

*RBA must be available for **all** risks, not just above a threshold!*

Deep dive review

2. Risk / benefit analysis must be performed for all risks.

Possible Solutions

- Line item risk benefit analysis
- Overall risk benefit analysis (in risk analysis documents)
    - Clinical Evidence Report (CER) / Clinical Risk Benefit Analysis (CRBA) / Clinical Experience Summary (CES)

1. **CER:** leverage predicate or similar devices and demonstrate low risk profile. Involves literature searching, product comparisons, etc. Reference GHTF SG5/N2R8: 2007
2. **CRBA:** analysis all risks and assigns medical opinion, literature and validation work as basis.
3. **CES:** demonstrates safety through small trial data or predicate data (if for example submitting a special 510(k). Best for “me-too” products.

Deep dive review

2. Risk / benefit analysis must be performed for all risks.

Example solution

Verification / Validation References	S	O	RI		Risk Benefit Analysis
90331637; 90340453 per section 8.2 EN ISO 11070	5	1	2		The benefits described in Clinical Evidence Report 12345 outweigh the risk associated with **[hazard, harm].**
90331637; 90340453 per section 8.2 EN ISO 11070	5	1	2		[HARM] likelihood is low per X, Y, Z.
90331637; 90340453 per section 8.2 EN ISO 11070; 90033662	5	3	4		Per input from Medical (approver of this document), clinical benefit of this product outweighs the risks herein.

An overall risk benefit analysis that is referenced in a line item fashion.

Instead of by line item, RBA by Harm category with a reference to literature, market data, etc.

KOL or Medical Input as RBA is valid.

Deep dive review

3. All risks must be reduced as low as possible.

ALARP – “as low as reasonably practicable” is replaced by ALAP – “as low as possible”. Risks must now be reduced as low as possible independent of any business / cost considerations.

Directives (MDD/ AIMD/ IVD)

'....risks to be reduced "as far as possible" without there being room for economic considerations.'

Where's the deviation?

ISO 14971:2009

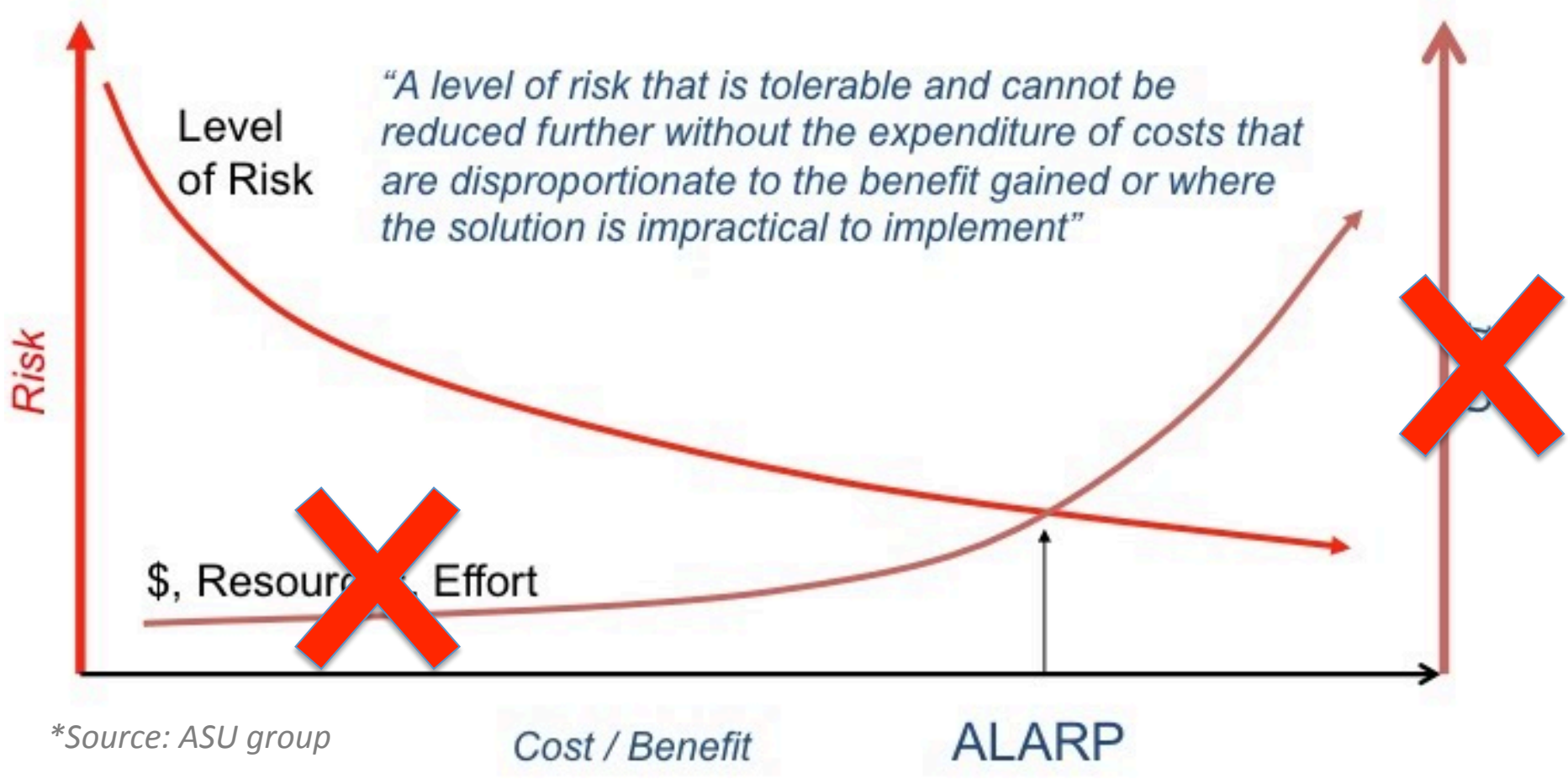
'...contains the concept of reducing risks "as low as reasonably practicable."

The ALARP concept contains an element of economic consideration.'

Deep dive review

3. All risks must be reduced as low as possible.

The Current Dilemma



*Source: ASU group

Deep dive review

3. All risks must be reduced as low as possible.

The Current Dilemma

Rating ↓→		Severity: Catastrophic 5	Critical 4	Serious 3	Minor 2	Negligible 1
Frequent	5	Unacceptable	Unacceptable	Unacceptable	Unacceptable	ALARP
Probable	4	Unacceptable	Unacceptable	Unacceptable	ALARP	ALARP
Occasional	3	Unacceptable	Unacceptable	ALARP	ALARP	ALARP
Remote	2	Unacceptable	ALARP	ALARP	ALARP	Acceptable
Improbable	1	ALARP	ALARP	ALARP	Acceptable	Acceptable

ALARP — As Low as Reasonably Practicable

ALARP must be eliminated as a risk level.

**Source: MasterControl*

Deep dive review

3. All risks must be reduced as low as possible.

Possible Solutions

- Remove ALARP from documentation
- Reducing risk without regard to cost is impractical and several organizations are fighting this resolution
    1. Current effective strategy has included implementation of overall risk benefit analysis
    2. If a design input can be tied to risk, it may be used as evidence of mitigation consideration
- Overall, the risk management documentation and process should indicate that risks are reduced as low as possible.

Deep dive review

4. All risk mitigations should be taken regardless of the risk level / 5. "… by design"

Traditionally, if a risk was acceptable, you would stop there. New interpretation is that all possible mitigations (design, information, mfg) should be in place. **This is very similar to all risks should be mitigated** and **ALAP."**

Directives (MDD/ AIMD/ IVD)

'...by applying cumulatively what has been called "control options" or "control mechanisms" in the standard.'

Where's the deviation?

ISO 14971:2009

'...indicates that further risk control measures do not need to be taken if, after applying one of the options, the risk is judged acceptable according to the criteria of the risk mgmt plan.'

Deep dive review

6. Labeling and use information does not constitute risk reduction.

Labeling (IFU/ Warning Labels/ etc.) was used as a risk mitigation to reduce risk indices. Now, labeling may be used as a risk control but not as a control that reduces risk levels.

Directives (MDD/ AIMD/ IVD)

'…users shall be informed about the residual risks. This indicates that....the information given to the users does not reduce the (residual) risk any further.'

Where's the deviation?

ISO 14971:2009

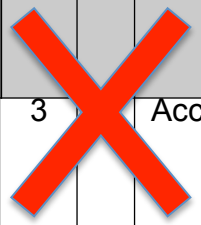
'…regards "information for safety" to be a control option.'

Deep dive review

6. Labeling and use information does not constitute risk reduction.

The Current Dilemma

S	O	RI	Recommended Actions (Further Risk Mitigation Needed?)	Responsibility	Actions Implemented and Supporting Documents	S	O	RI
3	3	ALARP	Yes	Quality	IFU - Warn against bending / flexing	3		Acc



IFU/ Labeling cannot be used to reduce residual risk.

**Source: MasterControl*

Deep dive review

6. Labeling and use information does not constitute risk reduction.

Possible Solutions

- Reference labeling (including IFU) but do not use it as a residual risk reduction.
- As with other deviations, consider design mitigations.
- “Assume the doctors toss the IFU when they open the package.”

Thanks!

www.medgineering.com
david@medgineering.com
Medgineering
786.546.1806