



Manufacturers Webinar Risk Management

**9 May 2018
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Introduction



- Risk management was required in ISO 13485:2003 (clause 7.2)
- The 2003 edition mentioned risk 4 times, while the 2016 edition mentions it about 20 times
- ISO 14971 is a standard for risk analysis of medical devices, and is widely used
- Note that ISO 14971 is still not a normative reference in ISO 13485.
- EN/ISO 14971 uses the same main text as ISO 14971 but is different

Introduction – cont..



- ISO 13485, clause 7.1 requires the manufacturer to establish **documented** requirements for risk management throughout product realization, and to maintain records for arising from it.
- The new edition draws its risk-based definitions from ISO 14971.
- Most factories have done some form of risk analysis and evaluation – which is only part of what is now required

The definition of Risk



- It depends who you ask!!!
- According to ISO 9000 & the ISO Directives, risk is the effect of uncertainty. This could be good or bad.
- In ISO 13485 & ISO 14971, risk is the combination of the probability of occurrence of **harm** & its severity. It applies to the users of the device.
- We will use only the 2nd definition, dealing only with possible negative effects. It pertains to safety or performance of a medical device, or meeting applicable regulatory requirements (cl 0.2 in ISO 13485)



Relevance

- WHO/UNFPA ask for a copy of the risk management plan as part of pre-qualification
- It's a requirement of ISO 13485
- EN ISO 14971:2012 is a harmonized standard in the EU. Thus if you comply with it, it is presumed that you comply with this aspect of the Medical Device Regulations
- Many other countries accept ISO 14971 as the way to manage risk.

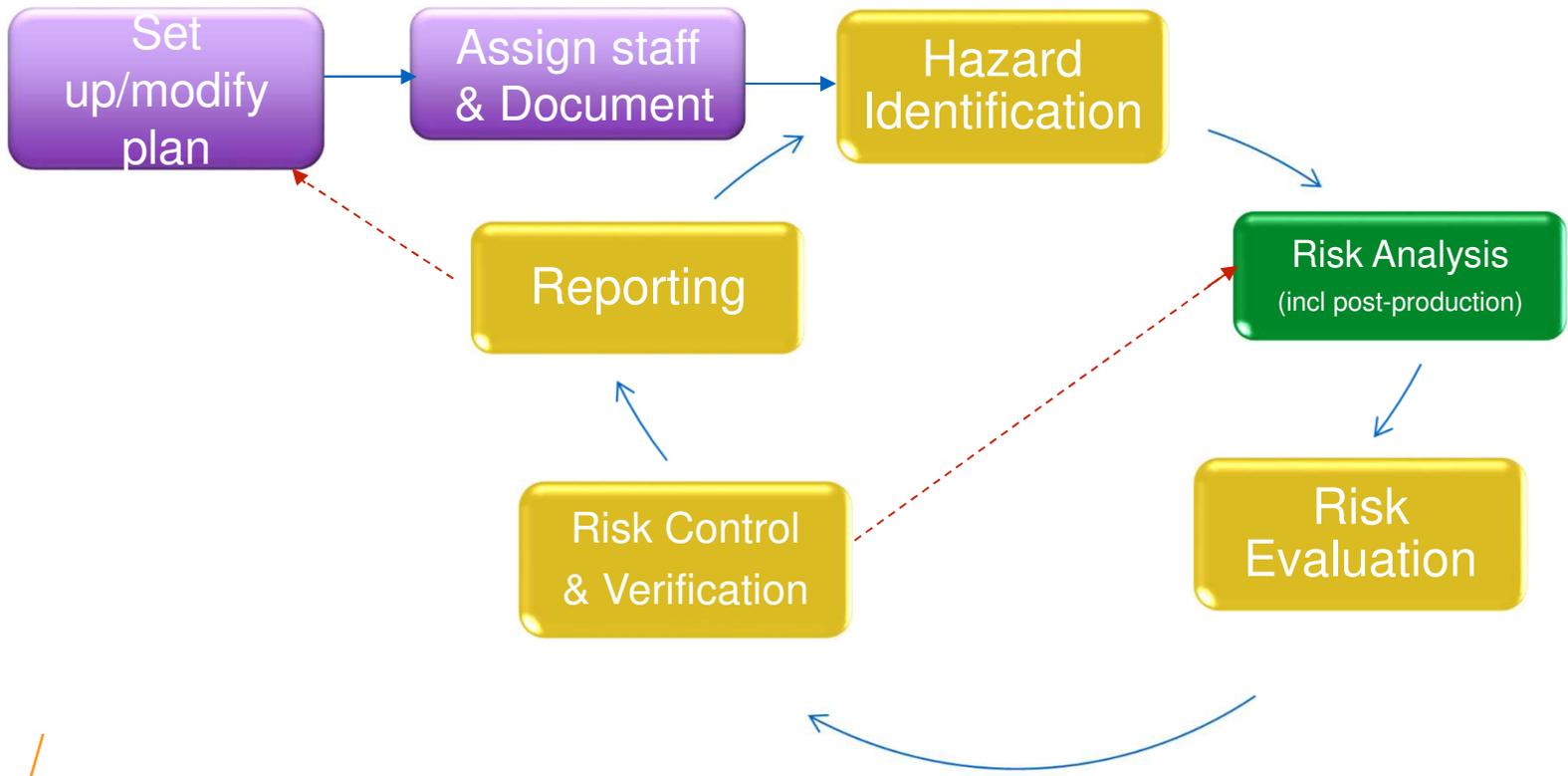
ISO 14971 – Medical devices – Application of risk management to medical devices

- 1. Scope
- 2. Terms and Definitions
- 3. General Requirements
- 4. Risk Analysis
- 5. Risk Evaluation
- 6. Risk Control & Verification
- 7. Evaluation of Overall Residual Risk Acceptability
- 8. Risk Control Option Analysis
- 9. Production and Post-Production Information
- Annexes A to J

The previous common approach – Failure Mode Effects Analysis

- Determine all the possible hazards that the product presents, and the potential harms
- Pretend that the process involves no precautions at all against any of the harms that may arise to the users
- Associate a severity with each harm
- Estimate a probability for the occurrence of each harm
- Multiply the two together to get a risk for each harm
- Take steps to reduce the risk for those harms falling above a predetermined threshold, until they fall below it.
- File the outcome.

Risk Management Process (ISO 14971)



Before we start – Key definitions from ISO 14971



- Harm – physical injury, damage to health (*or damage to property or the environment*)
- Hazard – potential source of harm
- Residual risk – risk remaining after risk control measures have been taken
- Risk – combination of the probability of occurrence of harm and its severity
- Risk analysis – systematic use of available information to identify hazards and estimate risk

Key definitions cont...

- Risk assessment – risk analysis followed by risk evaluation
- Risk control – process of choosing and implementing risk reduction measures
- Risk estimation – assessing the probability of harm occurrence and its severity
- Risk evaluation – comparing estimated risk with given criteria to determine acceptability

Key definitions cont....



- Risk Management – Systematic application of management policies, procedures and practices to the task of analysing, evaluating, controlling and monitoring risk
- Risk Management File – set of records and other documents that are produced by risk management.
- Risk for this purpose is risk of harm to the user(s) of the device

Essentials of Risk Management

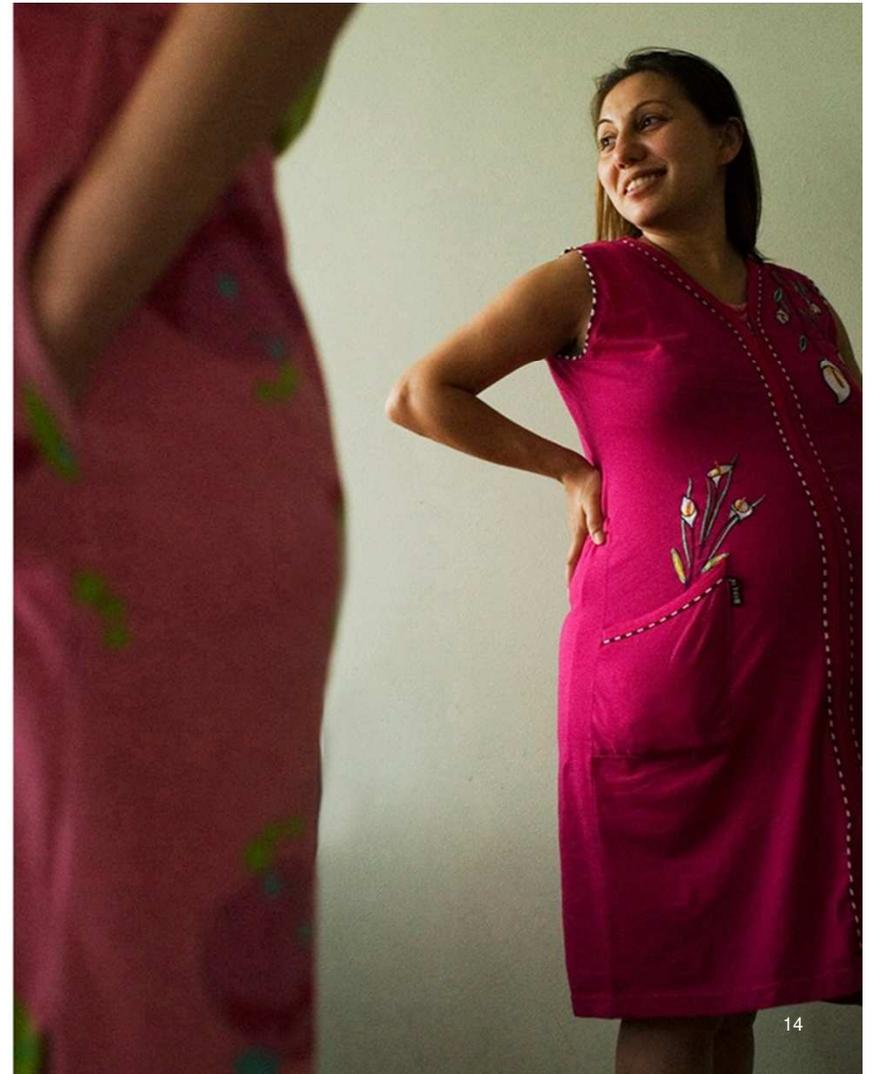
- Management policy to support the activity
- Procedures & people to identify possible causes of harm, & continue to monitor for new ones
- *Risk analysis (like FMEA) procedures*
- *Risk evaluation procedures & reduction (control) as required*
- Verification that the control measures have been implemented and are working
- Continued monitoring of post production information and changes in the production method and related information to keep the analysis and evaluation current
- Appropriate documentation of above

The essential difference between FMEA and ISO 14971:2007

- ISO 14971 has built a structure round the risk analysis, that incorporates on-going revision in the light of new information as it comes to hand.
- This includes your own post-market data (eg complaints, adverse events), published scientific information, information about other manufacturers' products
- An overall appraisal is called for, not just reducing individual risks
- It requires setting criteria for the analysis and evaluation, and verification of any control measures
- Implicitly, it starts at the product design stage.
- It is an on-going process.

The Structure

- Top Management must be committed to Risk Management
- There must be an overall risk management plan
- They must define **and document** the policy for determining risk acceptability
- They must review the process at planned intervals
- There must be procedures for doing the work
- People doing risk management tasks must have suitable skills and experience
- Information about use effectiveness and safety must be included
- For each device, there must be a risk management file, to contain the plan & records.



The Risk management Plan



- This may be a stand-alone document, or may be more deeply integrated with the quality management system.
- The plan should:
 - Have a scope
 - Assign responsibilities
 - Detail how & when risk management reviews occur
 - Give criteria for risk acceptability
 - Detail how reduction and verification activities will work
 - Indicate what post-market information will be used

Risk management plan scope



- The plan should include identification assessment and continued monitoring of risks of harm to the user of device X, and documentation of the process and outcomes
- The scope should include a commitment to comply with ISO 14971 (or EN ISO 14971)
- In simple cases, the responsibilities can be added to the scope

Assign Responsibilities



For Example

- The Quality Manager is responsible for coordinating risk management, and for maintaining documentation
- The Chief Engineer is responsible for conducting the risk analysis
- The Risk Management committee is responsible for identifying hazards and evaluating the analysis, with external assistance from Dr X, a public health expert

Review



- For an established device, the risk management review can be done as part of the general management review, or just before
- BUT there must be a way of considering new information as it comes to hand
- The review should consider whether any changes are needed to the current risk management assessment – i.e have any new hazards been identified, has the process changed, has there been a new type of complaint, has the rate of complaints changed significantly, has another manufacturer had a problem.....?

Criteria for acceptability



- The method of analysis needs to be defined.
- For condoms, most of the hazards and associated risks, and the severity are not precisely quantified
- For IUDs, some hazards may be better quantified, but not all
- Thus you will opt for a qualitative or “semi-quantitative” approach
- Indicate the interpretations (acceptability limits) of the scores you generate in the analysis (in advance)



The Risk Management Process (ISO 14971 Clause 3.1)



1. Get management commitment to resources
2. Set up the structure and nominate personnel
3. Risk Analysis
4. Risk Evaluation
5. Risk Control and Verification
6. Evaluation of Overall Residual Risk (OK?) PLUS Risk re-evaluation if needed
7. Risk Management Report
8. Production and Post-Production information
9. Re-evaluate items 2 to 6 and 8 and do new report

Risk Analysis (Clause 4 & Annex D)

- Define uses and reasonably foreseeable misuses of the device
- Identify the issues that could affect safety
- Identify known and foreseeable hazards and the associated harms
- Estimate the probability of occurrence of harm
- Estimate the severity of the harm
- Estimate risk for each hazard using available information
- If this is not possible, list the adverse consequences
- Note the method of categorization in the risk management file

Reasonably Foreseeable?



Misuse?



Risk Evaluation (clause 5)

- Use the criteria defined in the Risk Management Plan to decide if risk reduction is required for each risk
- Record the results in the RMF
- If no risk reduction is needed, then the risk control section (clause 6) is not relevant
- There should be procedures for doing the analysis and evaluation

Risk Control (reduction) (Clause 6)

- There is an order of priorities for risk reduction:
 - i. Inherent safety by design
 - ii. Protective measures in the device or in the manufacturing process
 - iii. Information for safety (but check MDR requirements)
- The measures selected must be recorded in the RMF
- The effectiveness of the measures must be verified and recorded in the RMF.
- Additional risks arising from risk control measures shall be evaluated, managed and recorded in the RMF.

Overall Risk Acceptability (Clause 7)

- When all risk control measures have been implemented and verified, the manufacturer must decide whether the overall risk is acceptable using the criteria in the risk management plan
- If the residual risk is judged unacceptable by the pre-determined criteria, then the product could still be released based on a benefit/risk analysis.
- The results of this evaluation must be recorded in the RMF. The rationale should also be recorded.

Risk Management Report (Clause 8)

- The risk management report is the report of the risk management review.
- The initial review, carried out prior to the device being marketed, will ensure that:
 1. The risk management plan has been properly implemented
 2. The overall residual risk is acceptable
 3. Appropriate methods are in place to obtain relevant production and post-production information

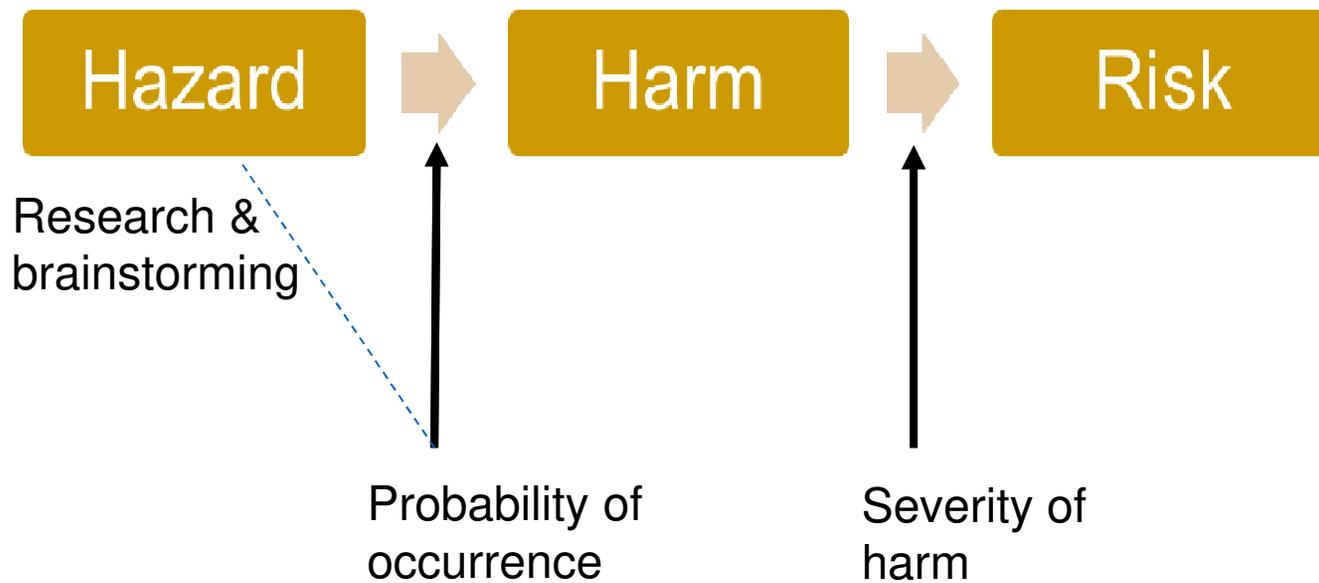
Annual update reports should be issued, even if they say there is no new information.

Production and Post-Production Information (Clause 9)



- There must be a system to collect and review information about the device and similar devices in the production and post-production phases.
- This information could include new standards, complaint analysis, adverse event reports, scientific literature, information on related products.....
- Ordinarily, this can be periodic (eg annual), but an immediate response is important for major new hazards
- If any previously unrecognised hazards emerge, or the estimated risks from a hazardous situation change, the risk assessment process (plus control if needed) must be repeated
- The results must be recorded in the RMF.

Risk Assessment



Hazard and Harm

- Although a hazard may arise relatively frequently (e.g. about 1 in 100 condoms break in use), it may not always lead to harm
- To work out the risk, you need to assess the probability of harm occurring from the hazard
- The significant harms for condoms are unintended pregnancy or and STIs.
- One hazard could lead to multiple harms (e.g. condom breakage could lead to pregnancy, HIV, Syphilis.....) with different probabilities

Meeting the standard – Identify the possible Hazards



- There is no universal recipe for finding the hazards
- It will most likely involve brainstorming
- Ensure the product meets all relevant product standards
- Do literature searches for articles about your type of product, your material, & related products & materials
- Check adverse incident reports
- Document the outcomes, eg as a table of hazards and the harms they may cause (to be completed later with severity of harm)
- In-house hazards need revision if anything changes, post-production hazards need monitoring

Meeting the standard – Estimate the probability & severity of harms

- For this part, and the estimation of probability of occurrence, the standard is implicitly asking users to quantify (to some degree) the frequency of events.
- In many cases, this is impossible, and one needs to work with qualitative, or at best, semi-quantitative, approaches.
- This approach is very similar to that used for FMEA evaluations.

Meeting the Standard – Estimate probability of harm



- The standard says “a good qualitative description is preferable to an inaccurate quantitative description”
- Simplest method – totally qualitative - Use 3 levels:
 - High (likely to happen, frequent)
 - Medium (can happen, but not frequently)
 - Low (unlikely to happen, rare)



Meeting the Standard – Estimate probability of harm



- Next simplest “semi-quantitative” –
- Can use 5 levels:
 - Frequent ($>1/1000$)
 - Probable ($<1/1\ 000$ and $>1/10\ 000$)
 - Occasional ($<1/10\ 000$ and $>1/100\ 000$)
 - Remote ($<1/100\ 000$) and $> 1/1\ 000\ 000$)
 - Improbable ($<1/1\ 000\ 000$)
- The probability ranges are given as examples in ISO 14971. You can vary them (but don't)

Severity of Harms



- The standard says it “prefers” quantitative approaches, but recognises that these may not be possible.
- It calls a qualitative assessment of severity one where there are 3 levels defined:
 - Significant (e.g. death or permanent disability)
 - Moderate (e.g. reversible or minor injury)
 - Negligible (e.g. minor irritation)

Severity of Harms cont...

- Alternatively, 5 levels of severity may be defined, & a semi-quantitative approach used:
 - Catastrophic (e.g. death) 5
 - Critical (permanent impairment) 4
 - Serious (requires significant medical treatment) 3
 - Minor (temporary injury requiring minor treatment) 2
 - Inconsequential (inconvenience or temporary discomfort) 1
- You can use more levels if you want to, or even vary the definitions
- You can have different numbers of levels for probability and severity (but don't)

Severity of Harms cont...



- The people involved in the risk assessment need to agree on the probability & severity by consensus, and include that in the RMF
- Although the standard expresses a preference for quantified data, it only gives examples of qualitative or semi-quantitative data

Meeting the Standard – Documentation

- You need to record the estimates of the probabilities you have assigned to each hazard in the RMF, together with the reason for what was chosen.
- You need to record the estimates of severity you have assigned to each hazard in the RMF
- You need to record all the risk control (reduction) activities and their outcomes
- You need to record the risk analyses and evaluations
- Update the analysis and evaluation if anything changes in the process or any post-market information becomes available

Meeting the Standard – “Calculate” the risk for each hazard

- For each combination of severity and probability of occurrence, there can be a cell in a matrix, e.g. for the qualitative case:

Severity→ Probability↓	Negligible	Moderate	Significant
High	??	Unacceptable?	Unacceptable
Medium	Acceptable?	??	Unacceptable?
Low	Acceptable	Acceptable?	??

- Acceptability must be defined in the plan

Meeting the Standard – “Calculate” the risk for each hazard



- For the semi-quantitative approach

Severity→ Probability↓	Negligible (1)	2	3	4	Significant (5)
High (5)	5	10	15	20	25
4	4	8	12	16	20
3	3	6	9	12	15
2	2	4	6	8	10
Negligible (1)	1	2	3	4	5

- Acceptability must be defined in the plan

Meeting the Standard – Deciding which items to control

- The company needs to use its own risk management policy to decide **in advance** the levels at which it will take action, and what it will do (NB excluding EN).
- In the 3x3 table, risk policy will determine the action in the ?? cells. In the 5x5 matrix, limit values set in the policy will determine actions.
- This involves initial risk reduction efforts, followed by re-analysis, and decisions as to whether or not the product continues to be developed.

Priorities for risk control



- If a risk needs to be reduced, the order of action is:
 1. Redesign to eliminate the risk (safety in design)
 2. Use protective measures in device or process
 3. Information for safety (i.e. instructions)
- Once the controls have been implemented, the risk analysis must be re-done, until the product is either deemed acceptable, or abandoned
- A benefit/risk analysis can be used if the product does not meet the predetermined criteria



Applicability of the Standard



- Required by many regulators
- It builds a structure round the actual risk assessment, and makes it on-going
- It makes good sense to use during design of a new product followed by monitoring once they are marketed, and in that respect is like the Clinical Evaluation
- For existing products, a less onerous approach would be more appropriate

Useful Annexes to ISO 14971

- Annex A: Rationale
- Annex D: Risk concepts
- Annex E: Examples of hazards, etc
- Annex F: Risk management plan
- Annex G: Risk management techniques
- Annex I: Biological hazards
- Annex J: Information for Safety
- Note Annex C is mainly about features that do not apply to non-hormonal contraceptives

There is also an ISO TR – 24971 - guidance

Concluding remarks



- The essential elements of risk analysis remain:
 - Identify the hazards and resulting harm
 - Assess the probability of harm occurring
 - Assess the severity should they occur
 - Combine these
 - Make a judgement as to what is acceptable and what is not

These have been surrounded by a system of planning, documentation and continuing implementation. The standard is intended for use from the design stage onwards.

THE END

THANK YOU



Delivering a world where
every pregnancy is wanted
every childbirth is safe and
every young person's
potential is fulfilled

UNFPA



EN ISO vs ISO 14971



- The texts are the same, but the Z annexes explain the differences between the MDD and the standard, specially:
 - Reduce risks “as far as possible” (versus “as low as reasonably practicable”) for all risks
 - Establish risk control measures for all risks (not just the unacceptable ones)
 - Need for a risk/benefit analysis for all risks
 - Risk reduction has to be more than information provided to the user (e.g. labeling and instructions for use)

EN ISO vs ISO 14971



- Ironically, the EN ISO annexes virtually negate the concepts of the body of the standard
- The implicit concept in the body is that risks which do not exceed an acceptable level can be tolerated, that there are practical limits to the reductions that can be achieved, and that one focusses on the most serious risks.