LA GESTIONE DEI RISCHI DI UN DISPOSITIVO MEDICO: SAFE-BY-DESIGN E NON SOLO

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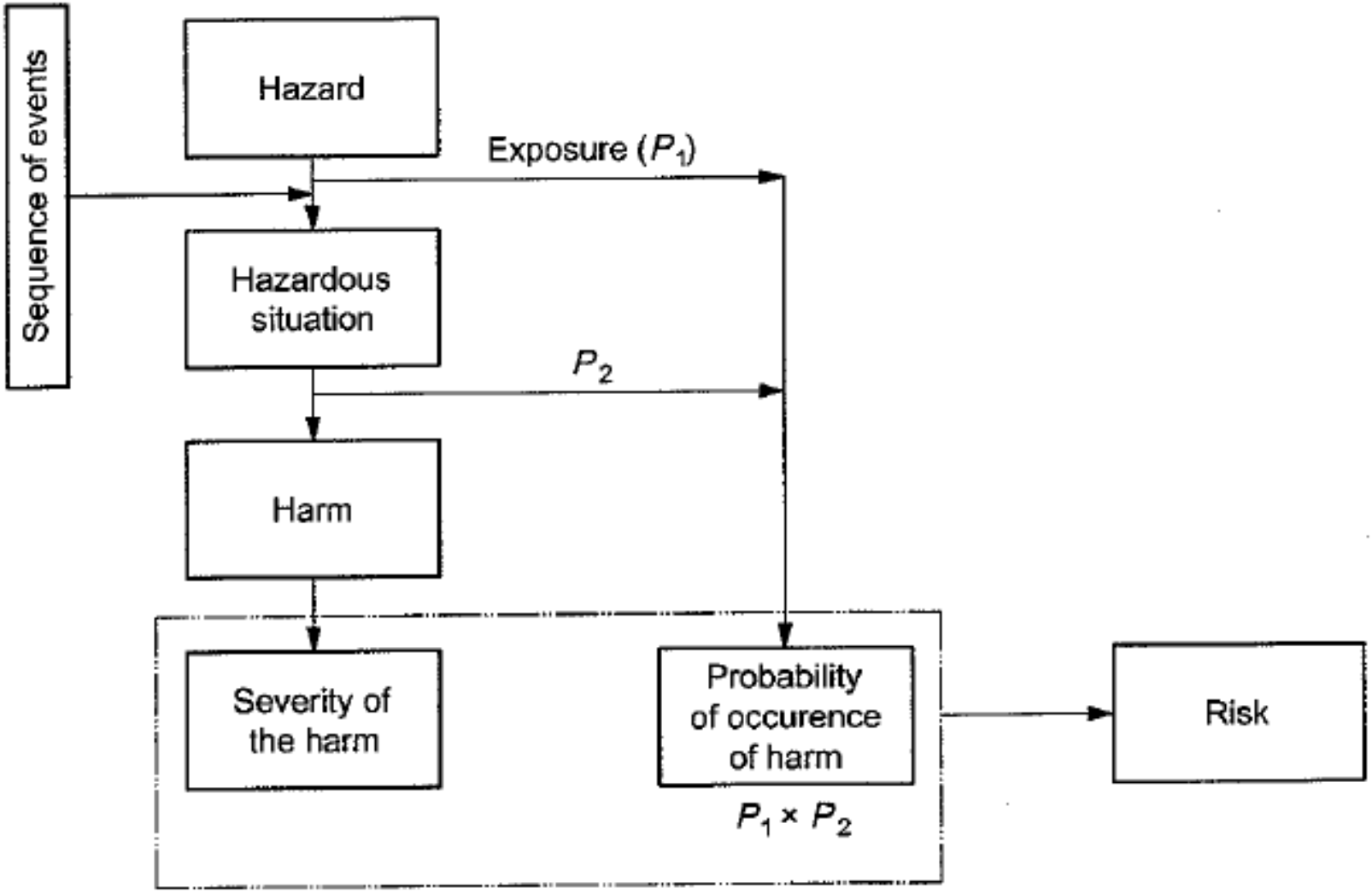
Venerdì 25 Maggio, ore 14:30-17.30
aula B32, Polo B

Some “heavy” definitions

- Harm: damage to the health of people, to property or to environment
  - All stakeholders: patient, operator, manufacturer, customer, general public, environment…
- Life cycle: all phases of the life of the medical device, from the initial conception to final decommissioning and disposal
  - Includes all manufacturing and control steps (as sources of hazard and as RCM)

Hazard as the initial source of risk

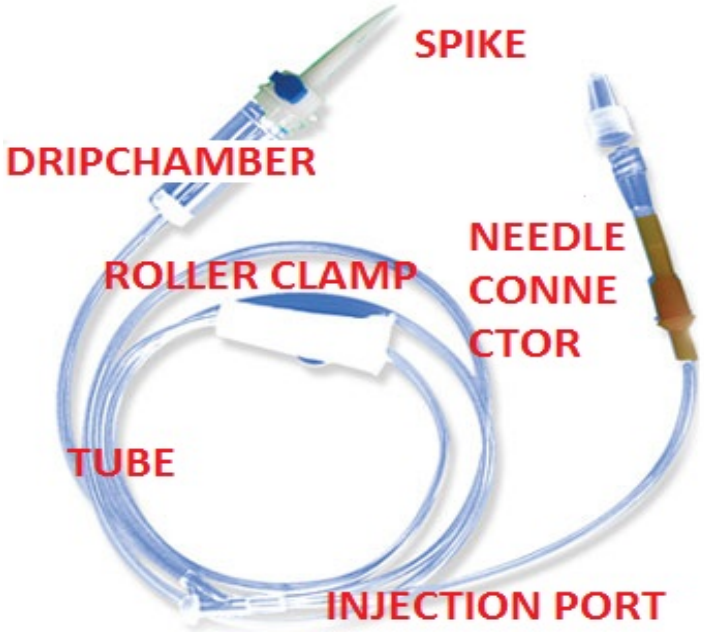


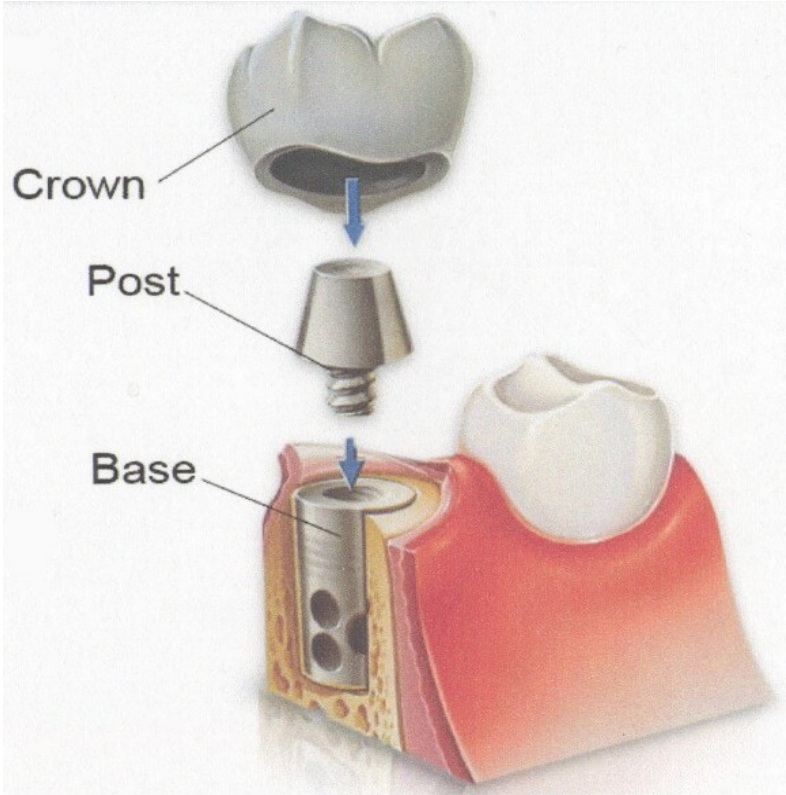
The risk analysis steps according to ISO 14971

- Identification of subject (product, process, decision)
- Identification of characteristics related to safety
- Identification of hazards
- Estimation of risk(s) for each hazardous situation
- Risk evaluation
- Risk control
- Implementation of risk control measure(s)
- Residual risk evaluation
- Risk/benefit analysis
- Risks arising from risk control measures
- Completeness of risk control
- Evaluation of overall residual risk acceptability

Product Identification

- Product:
  - description, part number, important subassemblies (functional groups)
  - Intended use





Characteristics related to safety

- Use of the checklist in the standard (Annex C)
- Review of history
- Opinion of experts
- State of the art
- Non harmonised design or testing

Checklist example

- C.2.1 What is the intended use and how is the medical device to be used?
  - 2.1.1 What is the medical device's role relative to:
    - 2.2.1.1 Diagnosis, prevention, monitoring, treatment or alleviation of disease;
    - 2.2.1.2 Compensation for injury or handicap;
    - 2.2.1.3 Replacement or modification of anatomy, or control of conception?
  - 2.1.2 What are the indications for use (e.g. patient population)?
  - 2.1.3 Does the medical device sustain or support life?
  - 2.1.4 Is special intervention necessary in the case of failure of
  - the medical device?
- C.2.2 Is the medical device intended to be implanted? Factors that should be considered include:
  - 2.2.1 The location of implantation;
  - 2.2.2 The characteristics of the patient population;
  - 2.2.3 Age;
  - 2.2.4 Weight;
  - 2.2.5 Physical activity;
  - 2.2.6 The effect of ageing on implant performance;
  - 2.2.7 The expected lifetime of the implant;
  - 2.2.8 The reversibility of the implantation

Hazard identification: what

- Known and foreseeable
- Normal use and first fault condition
- Technical and user related

Hazards identification: how

- Use of the checklist in the norm (Appendix E)
- Review of history
- Opinion of experts
- State of the art
- Test (challenging tests)
- Non compliance to (harmonised) standards

Risk Index

- Related to severity and occurrence
  - Example: Risk = severity x occurrence

- *Severity: measure of the possible consequences of a hazard (2.25*)

Assessment of S and O

Annex D

- Method:
  - Qualitative: description
  - Quantitative: actual numeric determination
  - Mixed: qualitative severity, quantitative probability
- Focus:
  - Systematic faults, first faults
  - Events

Probability of Occurrence

- From the probability of the initiating cause to the probability of the actual occurrence of harm
- Requires estimating the “chain of events” and the exposure of the final user to
  - the initiating cause,
  - to the following events
  - to the hazardous situation that may develop

Example of Occurrence estimation table - 1

Probability of occurrence O	Description of hazard/failure occurrence	Index
Very high	The event is almost sure	5
High	Many cases in the evaluated period	4
Moderate	Some cases in the evaluated period	3
Low	A few cases in the evaluated period	2
Remote	Potential hazard or failure, no known cases	1

Occurrence estimation table 1-comments

- Qualitative: gives a description of probability range
- Index associated to each range to simplify Risk Index evaluation
- Based on historical data, evaluated by field experts
  - Past production information
  - State of the art, literature

Example of Occurrence estimation table- 2

Probability of occurrence O	Range of occurrence	Index
Frequent	$\geq 10^{-3}$	5
Probable	$<10^{-3}$ and $\geq 10^{-4}$	4
Occasional	$<10^{-4}$ and $\geq 10^{-5}$	3
Remote	$<10^{-5}$ and $\geq 10^{-6}$	2
Improbable	$<10^{-6}$	1

Occurrence estimation table 2-comments

- Semi- quantitative: gives estimated ranges
- Index associated to each range to simplify Risk Index evaluation
- Based on data from:
  - Modellization
  - Production data
  - Evaluation of statistics on past defect data

Severity

- Measure of the possible outcome and consequences of a hazard
- Estimating the severity:
  - estimating consequences of a failure,
  - the nature of harm that may arise
  - the involvement of all stakeholders, in order of criticality

Criticality of stakeholders

- Severity score can be assigned more than one time, in order of criticality
- Helps define appropriate RCM is risk is un-acceptable
- Criticality order is
  - People
    - User
    - Operator
    - Third parts
  - Property
  - Environment

Example of Severity table

Severity S	Description of harm	Index
Catastrophe	Patient: death or permanant loss of major functions (senses, movement, intellectual…) Operator: death or permanant loss of major functions (senses, movement, intellectual…) Property:- Environment :-	4
Critical event	Patient: permanent lowering of major functions (senses, movement, intellectual…), surgery Operator: permanent lowering of major functions (senses, movement, intellectual…), surgery Property: loss of systems, innovative devices, major damage to structures and buildings Environment : major pollution of air, water, …	3
Major event	Patient: increase of required amount of care/ hospitalization time Operator: required medical care Property: loss of multiple use devices and/or other associated devices/ systems, damage to structures and buildings Environment : pollution of environment of given cares	2
Minor event	Patient: minor intervention of routine care Operator: required intervention to correct/ manage harm Property: loss of disposable devices, minor damages to other properties Environment: contamination of local appliances/ systems	1

Severity table- comments

- Usually qualitative, description of different levels of harm
- Should be detailed according to the device class and kind
  - Functions of the human body that may be affected
  - Possible kinds of pollution/contamination
  - Involved operators and other stakeholders (example: other patients in the same room)
  - Other systems and appliances involved

Sources for estimation

clause 4.4

- Review of history
- Opinion of experts
- State of the art
  - Standards
  - Predicate devices
  - Clinical evidence
- Simulation techniques, modellization

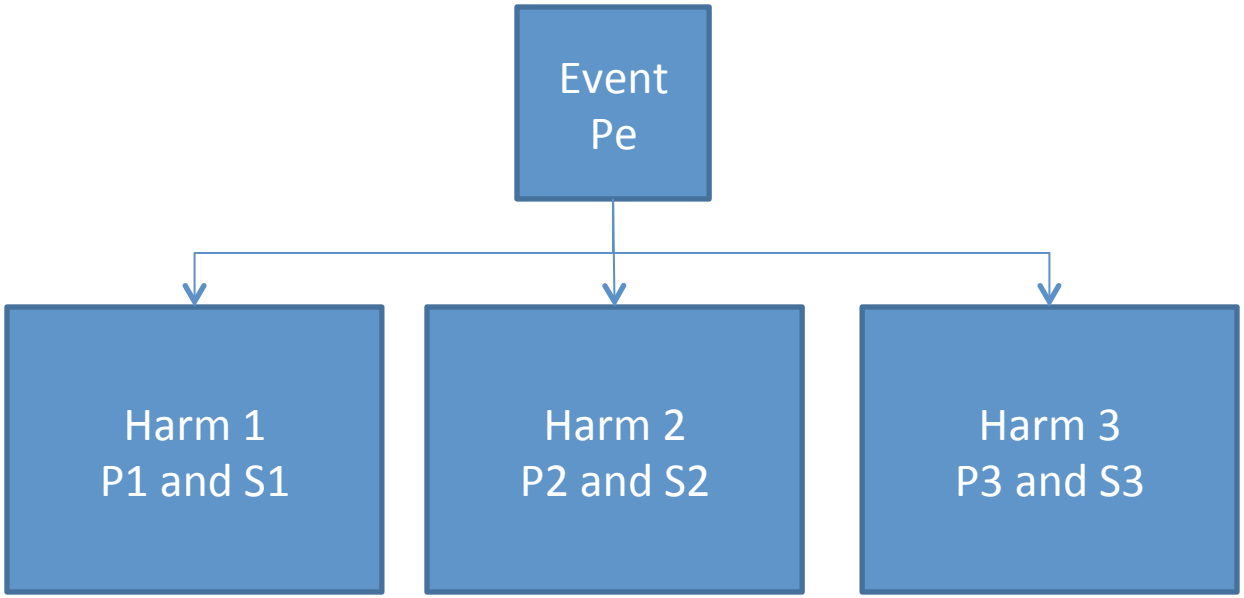
Main state of the art techniques

Annex G

- Preliminary Hazard Analysis
- Fault Tree Analysis (Event Tree Analysis)
- Failure Mode and Effect Analysis
- Hazard and Operability Study
- Hazard Analysis and Critical Control Point

Event Tree

- Estimation of the various consequences that arise from one single event
- Each consequence has its own probability of occurrence and severity

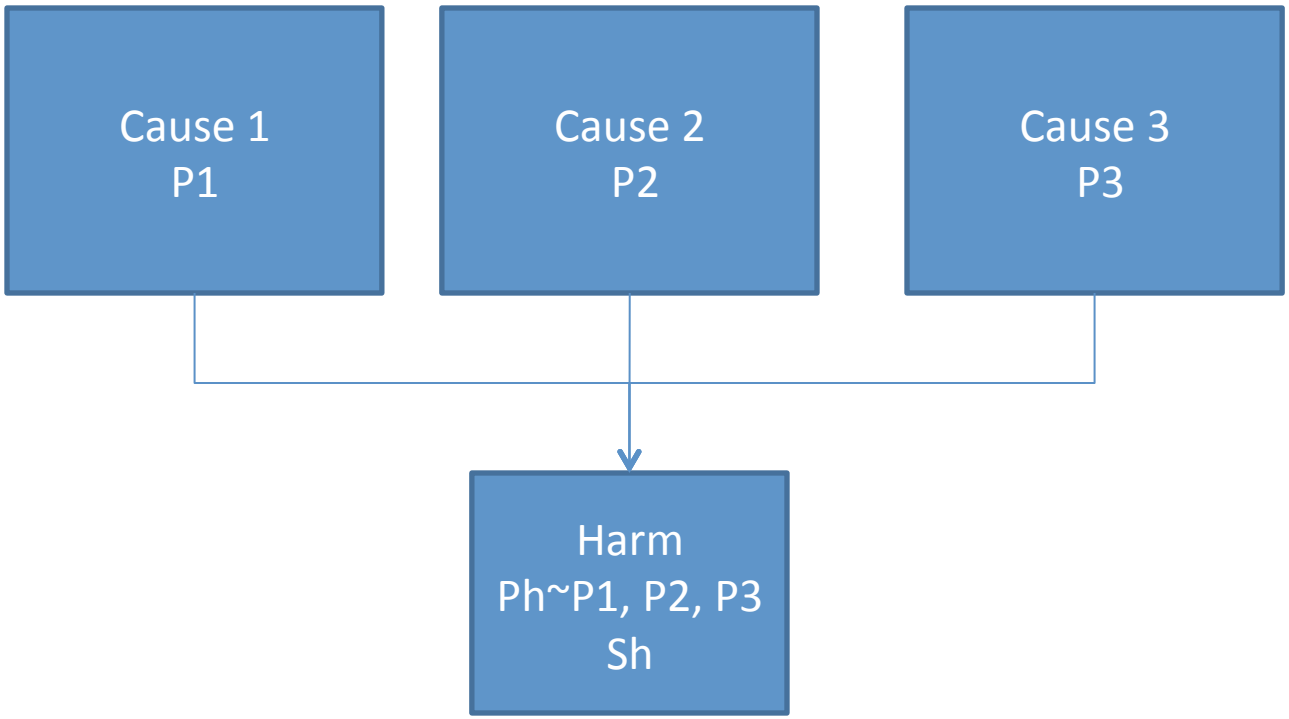


Event Tree- examples

- Reuse of a disposable
  - Infection
  - Degradation of mechanical functions
  - Lower bio- compatibility
- Insufficient screening of electro-magnetic fields
  - Interferences and wrong readings in other devices
  - Malfunction of involved device
- Un-proper closure of cardiac valve
  - Insufficient flow
  - Flow disturbance, backflow
  - Haemolysis and clotting

Fault Tree

- Estimation of the different causes of an harm
- Each cause has its own probability of occurrence, that are combined to obtain the overall probability of occurrence
- The harm has a defined severity



Fault Tree- examples

- Harm: infection at catheter connection
  - Unproper sterilization
  - Unproper handling, assembly
  - Entrance of bacteria during use
- Harm: sudden mechanical failure of artificial limb
  - Defective raw materials
  - Fault in design
  - Fault in assembly (manufacturing or at the site)

Fmea

- Estimation of consequences of each single fault
- Performed usually at “component” level (functional group) and at “system” level
- Can include Device, Process, Application analysis
- “what happens if….?”

Risk Control Measures

- the manufacturer must apply the following principles in the following order:
  - eliminate or reduce risks as far as possible (inherently safe design and construction),
  - where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated,
  - inform users of the residual risks due to any shortcomings of the protection measures adopted.

ISO 14971 annex D

Product/ process	Example devices	Hazard	Inherent safe design	Protective measure	Information for safety
Single use medical device	Catheter	Bio-(cross)-contamination	Self-destruction after use	Obvious indication after first use	Warning against re-use and of the adverse consequence(s) that could arise from any such re-use
Active implant	Pacemaker	Electric fields	Use of non-electric drives and controls	Use of differential amplifiers and additional filter algorithms	Warning for commonly encountered hazardous situations
IVD medical device	Blood analyser	Incorrect result due to method bias	Implement traceable calibrators	Provide traceable trueness controls	Inform users of unacceptable deviation from assigned values
Software	Patient data management	Erroneous data	High integrity software	Use of checksums	Warnings on screen for user
Steam sterilization	Biopsy device, operation forceps	High temperature (material degradation)	Use of material that is compatible with high temperatures	Pressure and temperature monitoring and recording	Packaging and loading instructions

Figure D.6 — Some examples of risk control measures

Risk index calculation

- Following the examples above

RI≤3 acceptable if no other RCMs

4≤ RI ≤10 requires further evaluation

RI≥11 not acceptable

		Severity			
		Minor	Major	Critical	Catastrophe
Occurrence		1	2	3	4
Very High	5	5	10	15	20
High	4	4	8	12	16
Moderate	3	3	6	9	12
Low	2	2	4	6	8
Remote	1	1	2	3	4

ALARP: an approach for all areas

- As low as reasonably practicable
- Requires evaluation of feasibility of RCM
  - Technical
  - Impact in lowering the risk
- If RCM is accepted, risk must be reviewed after RCM implementation
- If RCM is not accepted, this must be explained in a rationale

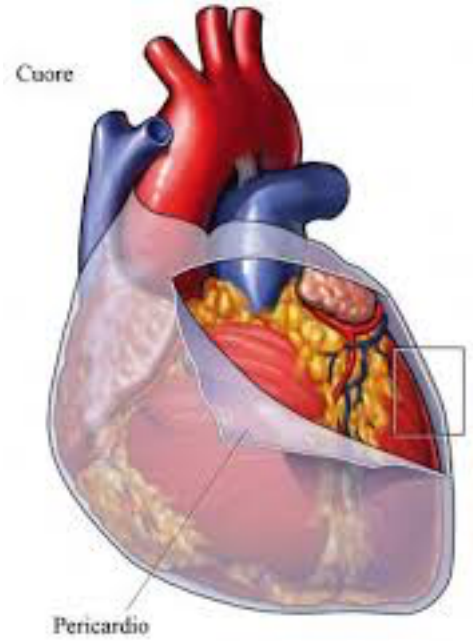
Identification of Risk control measures
clause 6.2 and ER 2

- Used to reduce risk (either occurrence or severity or both)
- Risk control methods, in the preferred order of
  - Safe design
  - Alarms and protections
  - Advertences and warnings

Some examples of RCM: Design

Single use device: self destruction after use (bandage comes to pieces at detaching from skin)

Devices incorporating animal derivatives: Raw materials sourced as BSE free (avoids need of inactivation of prion)



Some examples of RCM: Design

Device involving pressure: Standard connectors for inlet-outlet of each pipe (avoids connecting “weak” pipes to high pressure inlet);

Device ETO sterilized: raw materials sources as resistant to ETO

Some examples: Protections and alarms

- Single use device: coupled machine alarm if re-started prior of changing disposable set
- Device involving pressure: pressure sensors, alarms at ALERT limits of low/high pressure

Some examples: Warnings and advertences

- Single use device: no-reuse symbol; advertences in IFU regarding cross infection exc.
- Device involving pressure: assembly instructions, color code
- Device ETO sterilized: ETO symbol; request of flushing-priming prior of use in IFU

Implementation of RCM

- In the design
  - Inherent design for safety
  - Design of protection measures
- In the manufacturing or quality control
  - Process control
  - Additional/ dedicated testing
- In the final user training

RCM index R

- Measure of RCM impact on lowering the Occurrence and/or Severity of any harm
- Values according to impact on all steps of product life cycle:
  - Design
  - Manufacture
  - Use

Example of RCM Index table

RCM Index R	Description	Index
Negligible	Design: no control during design; harm not detected during manufacturing steps Alarms and protections: not activated; harm not detectable during a routine check Warning: no warnings foreseen in label/IFU	1
Very low	Design: no control during design; harm may be detected by a 100% control Alarms and protections: not activated; harm is detectable during a routine check Warning: no warnings foreseen in label/IFU	0.8
Low	Design: no control during design; harm easily detected by a 100% control Alarms and protections: not activated; harm is surely detected during a routine check Warning: general warning foreseen in label/IFU	0.6
Normal	Design: QC test designed for harm detection at manufacturing steps; OR characteristic is rendered less risky during design; harm may be detected by a sampling plan control Alarms and protections: activated after a certain amount of time Warning: normed warnings and symbols foreseen in label/IFU	0.4
High	Design: characteristic is rendered safe at design step (design solution or process validaton) Alarms and protections: activated immediately Warning: detailed, evident warnings and symbols foreseen in label/IFU	0.2

RCM impact assessment - example

- Device supplied sterile to avoid risk of use before sterilization by third parties/ users
  - Requires qualification of sterilization source
  - Requires revision of expiry date evaluation
  - Lowers risk of infection, contamination
  - Increases risk of materials mix-up in the company

Risk Index \ RCM Index	0,2	0,4	0,6	0,8	1	1,5	2
1	0,2	0,4	0,6	0,8	1	1,5	2
2	0,4	0,8	1,2	1,6	2	3	4
3	0,6	1,2	1,8	2,4	3	4,5	6
4	0,8	1,6	2,4	3,2	4	6	8
5	1	2	3	4	5	7,5	10
6	1,2	2,4	3,6	4,8	6	9	12
8	1,6	3,2	4,8	6,4	8	12	16
9	1,8	3,6	5,4	7,2	9	13,5	18
10	2	4	6	8	10	15	20
12	2,4	4,8	7,2	9,6	12	18	24
15	3	6	9	12	15	22,5	30
16	3,2	6,4	9,6	12,8	16	24	32
20	4	8	12	16	20	30	40

Risk after RCM

- Measures level of risk after the RCM is implemented and verified

$$RI_{after}=RIxR$$

- Keep same levels for acceptability, for easiness of use (RCM Index is a fraction when effective)
- If risk is higher,
  - new RCM may be required and/or
  - the RCM under evaluation may be discarded as not feasible

RCM impact assessment- example

- Color code introduction
  - Impact on product BOM
  - Requires update of raw materials sourcing SOP, manufacturing SOPs,…
  - Lowers connection/ assembly misuse
  - May increase risk of information overload

Overall evaluation and risk approval

- Set acceptable percentage of yellow risk in the analysis
- NO red risk should be accepted before the overall risk-benefit evaluation

		Severity			
		Minor	Major	Critical	Catastrophe
Occurrence		1	2	3	4
Very High	5	5	10	15	20
High	4	4	8	12	16
Moderate	3	3	6	9	12
Low	2	2	4	6	8
Remote	1	1	2	3	4

Benefit evaluation

- As compared to state of the art
- As per intended use and expected results
- As compared to the patient clinical state, life expectancy, quality of life
- Usually is difficult to express in quantitative terms, relative to many factors

Risk- benefit analysis

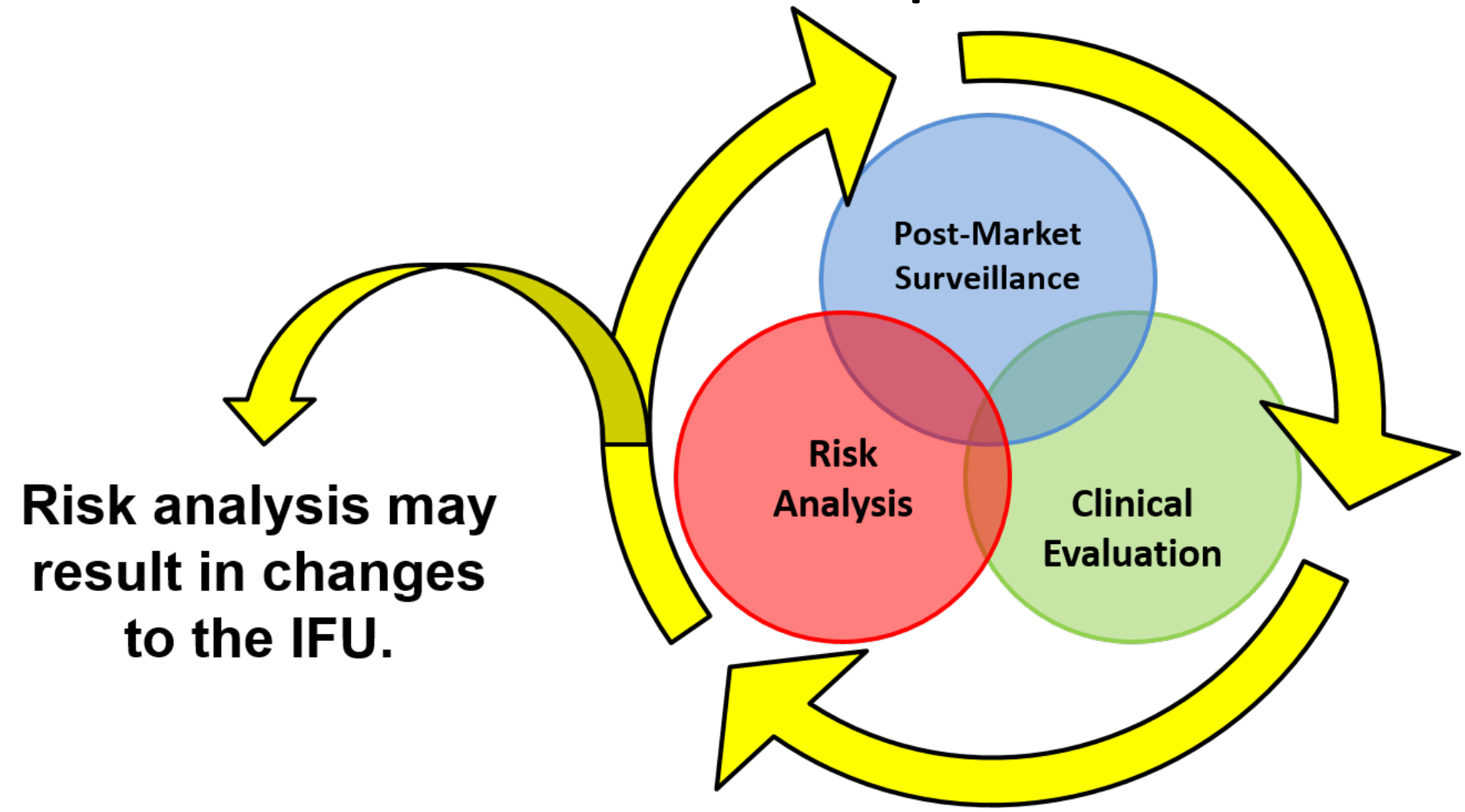
- Confirm that all available RCMs are in place
- Evaluate all risks, regardless of “color level”
- Evaluate overall risk-benefit and implement additional protection measures

Overall risk-benefit evaluation

- All device characteristics
- Expected (or proven) benefit
- State of the art

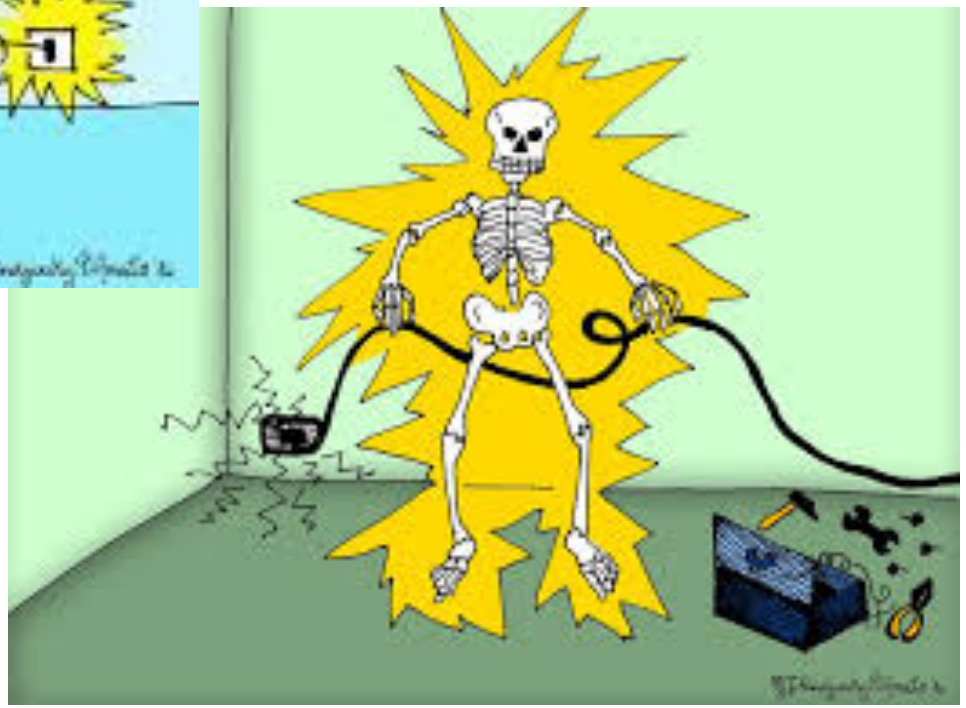
Device can be accepted
if the overall expected benefit of use
exceeds the risk involved

Non finisce qui!



Risk analysis may result in changes to the IFU.

workshop



Example Annex E: device sold sterile

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	RCM Index	RI after
Cleaning, disinfection and sterilisation								
Lack of, or inadequate specification for, validated procedures for cleaning, disinfection and sterilization.	device is forwarded to sterilization in an unproper condition leading to unproper sterilization	4	cleanroom manufacturing environment is not controlled	1	4	Design control SOP and device tech file (manufacturing environment definition); SOPs for cleaning and cleaning records; SOPs for cleanroom access control and training records	0,2	0,8
	device is not sterilized	4	sterilization is not validated	1	4	SOP for sterilization validation and validation report	0,2	0,8

Example Annex E: device sold sterile

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	RCM Index	RI after
Inadequate conduct of cleaning, disinfection and sterilization	device is forwarded to sterilization in an unproper condition leading to unproper sterilization	4	cleanroom manufacturing environment out of specification	2	8	Cleaning SOP and cleaning records; cleanroom access control SOP and training records; manufacturing control SOP and records	0,4	3,2
	device is not sterilized	4	sterilization cycle is out of specification	1	4	lot release control SOP and records	0,4	1,6

Example ER 8.2 Device with animal tissue

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
Use of raw materials with BSE prions	contamination of patient with consequent illness	4	unproper qualification of raw materials	1	4	Design control SOP and device tech file (for raw material identification); raw material qualification and supplier selection SOP and records; incoming material control SOP and records	0,2	0,8

Example ER 9.1 (measuring) device used in combination

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after	RCM	R	RI after
interference, lowers capability to measure vital parameter	Device not effective in detecting vital parameter alarm levels	4	Missing definition/ validation of use in combination; missing information on forbidden devices	5	20	Design control SOP and device tech file (for definition of possible associated devices)	0,2	4	Advertences on labelling	0,6	2,4

Sequence of RCM

- It is REQUIRED to implement additional RCMs
- Usually the design RCMs are completed and backed-up by alarms/protection or by information in label and IFU
- Extra warnings in label are always advisable….

Example question C2.18 device requiring maintenance

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
Maintenance not performed	Sudden mechanical failure	3	Deterioration of parts for normal tear and wear	5	15	SW routine not allowing operation after maintenance due date	0,2	3
Pipes maintenance by unskilled personnel with unproper tools	Leaking	3	Connectors and pipes not properly tightened	3	9	Loss alarm activated after loss of 1%	0,4	3,6

Example question C2.29.7 special needs users

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
Device too heavy	Device not used	5	Device too heavy for elderly people	2	10	Design lighter case	0,2	2

ALTERNATE RCM:

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
Device too heavy	Device not used	5	Device too heavy for elderly people	2	10	Add indication of weight on case	0,6	6

Residual risk still “yellow”: comments

- The risk remains in the “ALARP” area even after RMC
  - Search for “higher level” or “more effective” RCM
  - Implement additional RCM
  - Restrict intended use

  OR
  - Accept risk level as the lowest possible option (given the state of the art, design development step,…)

Risk Table- level 2

Functional group	Description of the functional group and its function	Hazard	Harm	S	failure modes/ causes	O	RI	RCM	R	Riafter
Unique identification as per BOM or other means	As regards of safety features	What happens if….	How each stake-holder is affected		Sources of the hazardous situation		Sx O	Reference to RCM definition, implementation, effectiveness verification		

Example: a closure cap

Functional group	Description of the functional group and its function	Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	Ri after
Cap n.5 of BOM	Closes the packaging, tamper proof	Not properly connected	Liquid leak	3	Un-proper assembly by operator/ machine	2	6	Assembly instructions	0,6	3,6
	Closes the packaging, resealable	Sudden crack	Loss of liquid	4	Raw material defect	1	4	Raw material qualification and control SOP	0,2	0,8

Example: a sensor

Functional group	Description of the functional group and its function	Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	Riafter
Sensor A	Detects vital parameter, unique sensor	Not properly connected	Wrong reading	4	Un-proper assembly by end user	2	8	Assembly instructions	0,6	4,8
		Sudden detachment	Loss of signal	4	External event	1	4	Immediate alarm	0,2	0,8

RCM: if the risk is still high

- Evaluate technical availability of more RCMs
- Evaluate feasibility and effectiveness of implementing additional “lower level” RCMs
  - Protections and alarms
  - Warnings
- Evaluate overall risk-benefit of use of device
- Evaluate clinical availability of restricting intended use

RCM: impact

- Use RCM as input of the FMEA table

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
RCM required use of heavy shield for un-intended radiation	Device can harm operator/ patient if falls	2	Device is hit during use and falls	4	8	Device is stabilized with protruding feet	0,2	1,6

RCM: negative impact

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
RCM required use of extra alarm	Device will start 2 alarms at the same time	3	Operator may solve only 1 faulty situation	4	12	Alarms with different sound	0,2	2,4

RCM with negative impact/ alternate

Hazard	Harm	S	Failure modes/ causes	O	RI	RCM	R	RI after
Faulty condition in system	Patient in danger	5	Output out of specification	2	10	Immediate Alarm	0,2	2
						Alarm starting with other sound/light alarms	1,5	15