Practical Application of ISO 14971:2019

- Risk Management Across the Medical Device Lifecycle -

FMMC Symposium

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Presented by:

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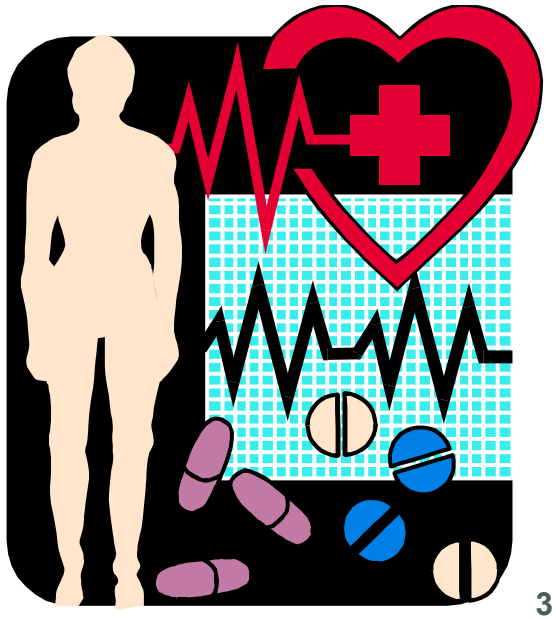
Agenda

A. Overview of Risk Management and the Application of 14971:2019
B. Practical Application Of Risk Management During Product Development
C. Monitoring Risk in On-Market Product
D. Using Risk Data in Decision Making and within the QMS
E. Decommissioning



ISO 14971:2019 → An FDA Recognized Consensus Standard

- What is a Standard?

  "...document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines, or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context." (*ISO/IEC Guide 2 Standardization and related activities - General vocabulary.)*

ISO International Organization for Standardization

Declaration of Conformity (DoC) to a Consensus Standard

- Conformity with FDA-recognized standards facilitates the premarket review process
  - DoC to a consensus standard means all the requirements of the standard have been met
  - Can reduce the documentation needed for marketing approval of a medical device (i.e., least burdensome approach.)
- While manufacturers are encouraged to use FDA-recognized consensus standards in their premarket submissions, conformance is voluntary, unless a standard is '*incorporated by reference*' into regulation.

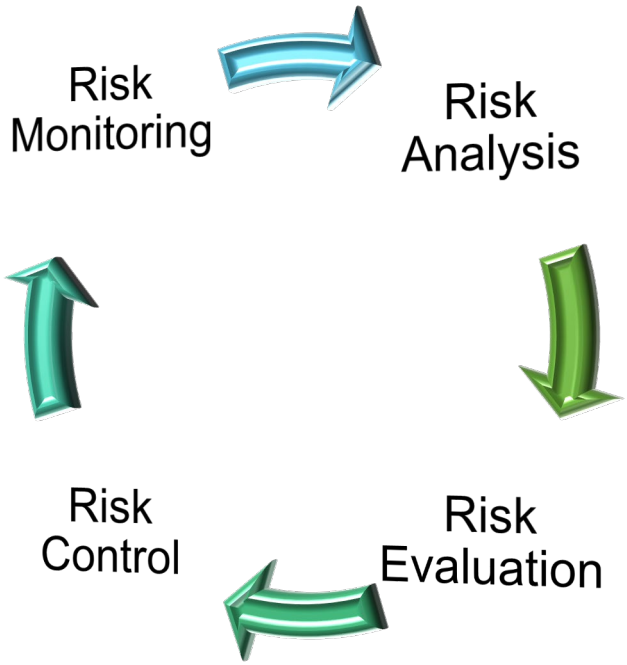
See: Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff, issued September 2018.

EUMDR
Annex I - General Safety and Performance Requirements

- Manufacturers shall establish, implement, document and maintain a risk management system. Risk management shall be understood as a **continuous** iterative process **throughout the entire lifecycle** of a device, requiring regular systematic updating.

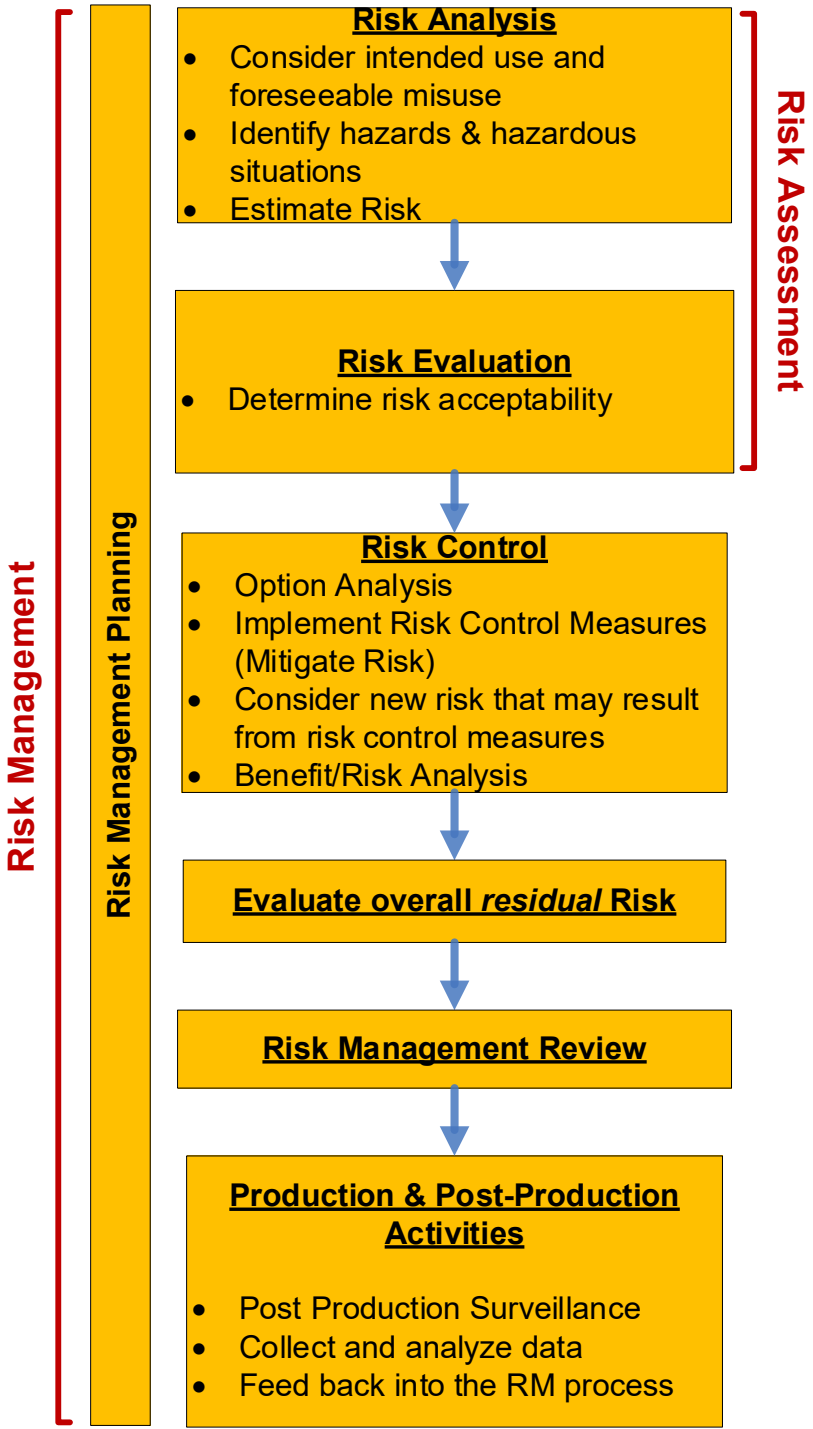
ISO 14971-2019, Scope

- Delineates a systematic approach for identifying the hazards associated with medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.
- Establishes risk management principles & process that will lead to more consistent science-based decision-making across the **life-cycle of a product.**
- Risks associated with a medical device, such as risks related to biocompatibility, data and systems security, electricity, moving parts, radiation, and usability.

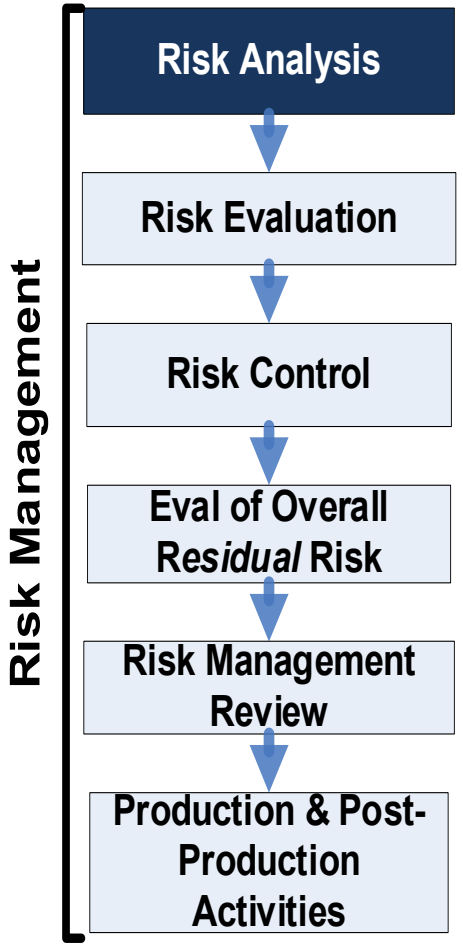


ISO 14971:2019 Does NOT …

- …apply to clinical decision making (i.e., the decision to use a device in the context of a specific medical procedure.)
- …specify acceptable risk levels.
- …require that the manufacturer have a quality management system in place. However, risk management can be an integral part of a quality management system.
- …business risk management


Risk Management
Risk Management Planning
Risk Analysis
Consider intended use and foreseeable misuse
Identify hazards & hazardous situations
Estimate Risk
Risk Evaluation
Determine risk acceptability
Risk Assessment
Risk Control
Option Analysis
Implement Risk Control Measures (Mitigate Risk)
Consider new risk that may result from risk control measures
Benefit/Risk Analysis
Evaluate overall residual Risk
Risk Management Review
Production & Post-Production Activities
Post Production Surveillance
Collect and analyze data
Feed back into the RM process

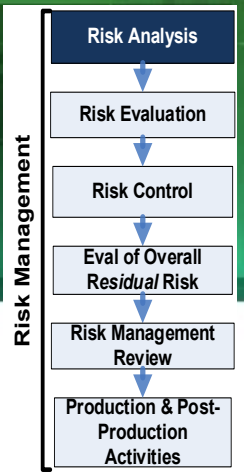
Risk Analysis



Tools for Risk Analysis

- HAZARD Analysis
- FTA
- FMEA
- FMECA
- HACCP
- HAZOP

Documentation to support Risk Analysis

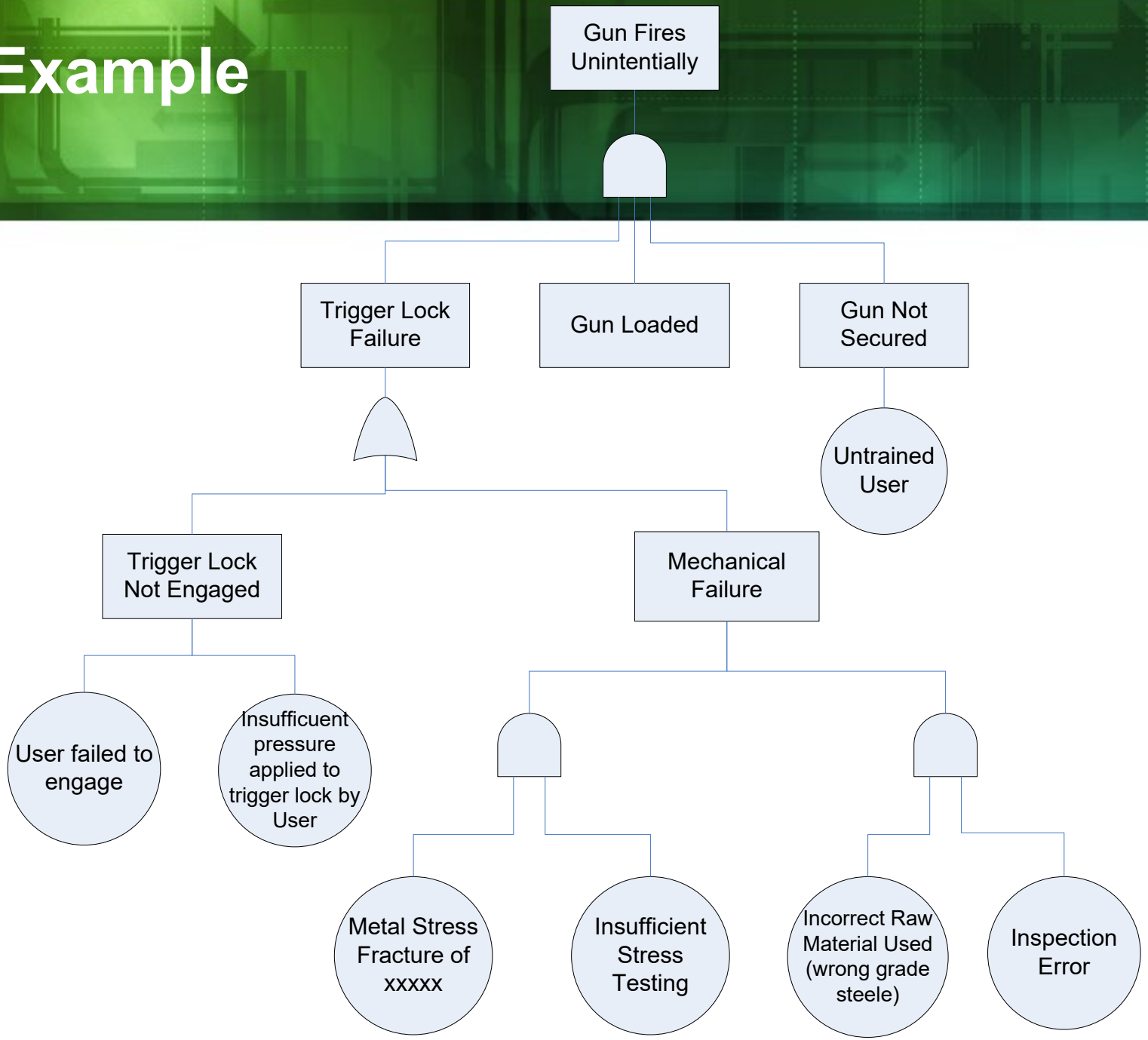


- Master Harms List (or Harms & Hazard List)
  - Documents the predictive harm in relation to hazards/hazardous situations.
  - Severity is assigned to the harm based on the input of clinical and medical personnel in the company.
  - Developed and maintained by Clinical/Medical Affairs, not Engineering. Used by Engineering and QA in the development of HA, FMEAs, Ad Hoc Risk Assessments, etc.
- Hazard Analysis (or Risk Analysis) is the "**Parent**" Risk Document
  - Hazard Analysis Determines Hazards, Sequences of Events, Hazardous Situations, Probability, Harm, Severity and RISK
- FMEA's/FTAs are "**Children**" Supporting the HA –
  - Design FMEA
  - Process FMEA
  - Usability FMEA
  - Software Hazard Analysis
  - Cybersecurity Hazards Analysis

Tools for Risk Analysis-FTA

- **Fault Tree Analysis (FTA) Top down approach**
- **Supplements an FMEA**
- **Shows interrelations between various fault conditions.**
- **Graphically shows the various combination of events that lead to the top-level undesirable event.**
- **Focuses on identification of root causes (this can feed into the FMEA)**

FTA Example



FMEA/FMECA

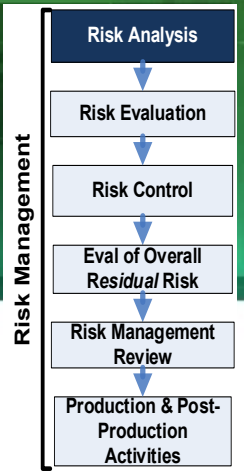
- FMEA is a specific, quantitative process that identifies risks, evaluates their potential impact, and tracks risk reduction in cases when it is necessary to diminish an unacceptably high risk-level.
  - FMEA can be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence and their detectability, … becoming a Failure Mode Effect and Criticality Analysis (FMECA).
  - The criticality or risk associated with different failure modes are quantified using an algorithm that assigns pre-defined numerical values to relative levels of severity, frequency, and detectability.

RPN

- **Quantitative risk value is referred to as the Risk Priority Number (RPN)**
- **RPN typically expressed as a quantitative value based on the degree of severity X Probability**

RPN= Severity X Probability

Hazard Analysis



- Identify Hazards
- Identify the sequence of events leading to the hazardous situation and define the hazardous situation.
- Link the hazard to a severity level based on the associated Master Harms List (Harms & Hazards Document.)
  - Needs medical/clinical input.
  - Once established any/all downstream evaluation of a hazard should always report the same severity level.
  - Team should not re-determine (guess) severity levels in a vacuum for different analysis they perform, FMEAs, Ad Hoc Risk Analysis etc..
- Consider normal and fault conditions.
- Consider use error and/or reasonably foreseeable misuse.

Understanding Hazards and Hazardous Situations

- Go to List of Hazard Types

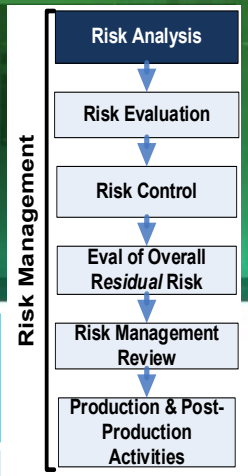
Hazardous Situations

Can be caused by:

- **Random Faults** (contamination, discrete component failure).
- **Systematic Faults** (a combination of inputs and/or environmental conditions that systematically cause failure that otherwise would have been latent).
  - Design/software defects
  - Labeling inadequacy
- **Security Vulnerability** (loss of data, data integrity, confidentiality)
- **Sequence or Combination of Events**

EXAMPLES

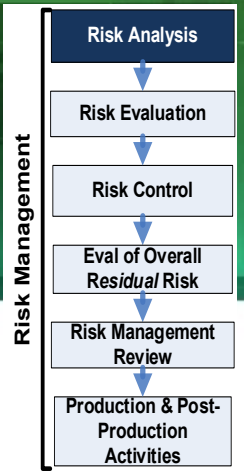
Hazards → Seq. of Events → Hazardous Situation → Harm



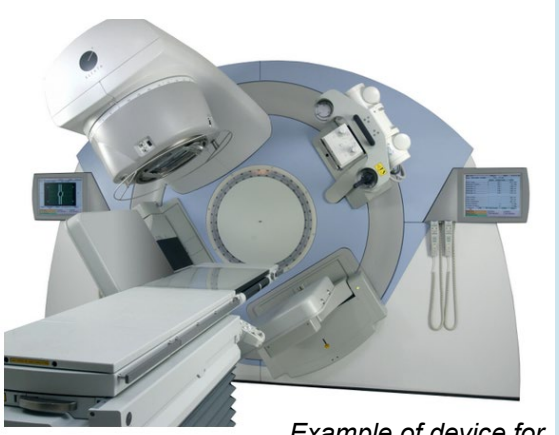
Hazard	Sequence of Events	Hazardous Situation	Harm
Overexposure to ionizing radiation	1. Nitinol wire stored in uncontrolled heat/humidity. 2. Integrity of Nitinol wire is compromised. 3. Nitinol wire is stressed over several uses 4. Alarms intended to detect radiation after wires retracted fail to function or are disregarded.	Nitinol wire containing Cesium seeds breaks-off in patient during and remains in the patient.	Significant tissue damage, ulceration, death

EXAMPLES

Hazards → Seq. of Events → Hazardous Situation → Harm



Hazard	Sequence of Events	Hazardous Situation	Harm
Overexposure to ionizing radiation	1. Software Testing did not consider the impact of null characters when entering treatment plan into LINAC. 2. Transition from one data entry field to the next, physicist hits "TAB" on keyboard to move from one data entry field to next. 3. TAB key defaults to a "zero" in the megavoltage (kilogray) delivery field. making intended treatment plan of 10 MV now = 100 MV	Megavoltage delivered during radiation treatment exceeds that intended by treatment plan.	Localized 3rd degree burn.



Example of device for illustrative purposes, not intended to represent a particular device brand.

EXAMPLES

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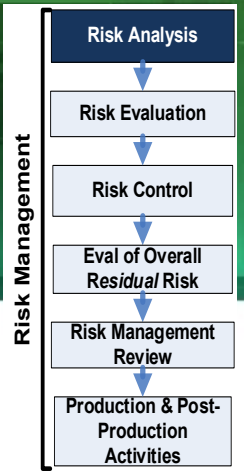
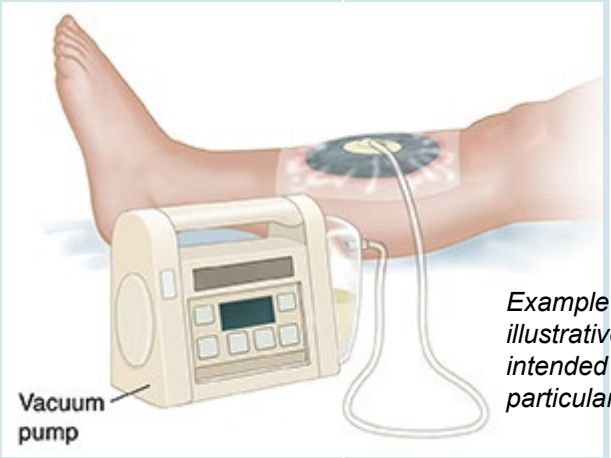


Hazard	Sequence of Events	Hazardous Situation	Harm
User error	**1. Health Care Provider, fails to evaluate depth and severity of a Stage 4 decubitus ulcer with signs of tunneling.** **2. Decubitus ulcer located on spine.** **3. HCP places wound suction device on decubitus ulcer on spine and initiates wound suctioning at default setting, 125 mmHg.** **4. High vacuum pressure enables wound care system to extract spinal fluid with exudate.**	**Extreme loss of cerebrospinal fluid**	**Death**



Example of device for illustrative purposes, not intended to represent a particular device brand.

Hazard Analysis

- Go To Hazard/Risk Analysis Template

User Error and Foreseeable misuse

"Reasonably" Foreseeable Misuse

- use of the device in a manner not intended by the manufacturer but which can be readily predictable human behavior.
  - User error (unintentional mistake)
  - Intentional acts of misuse
  - Intentional use of the device for an application for which it was not intended (off-label use.)

User Error

User action or lack of action that was different from that expected by the manufacturer and caused a result that

(1) was different from the result expected by the user and

(2) was not caused solely by device failure and

(3) did or could result in harm.

Abnormal Use

intentional act or intentional omission of an act that reflects violative or reckless use or sabotage beyond reasonable means of risk mitigation or control through design of the user interface

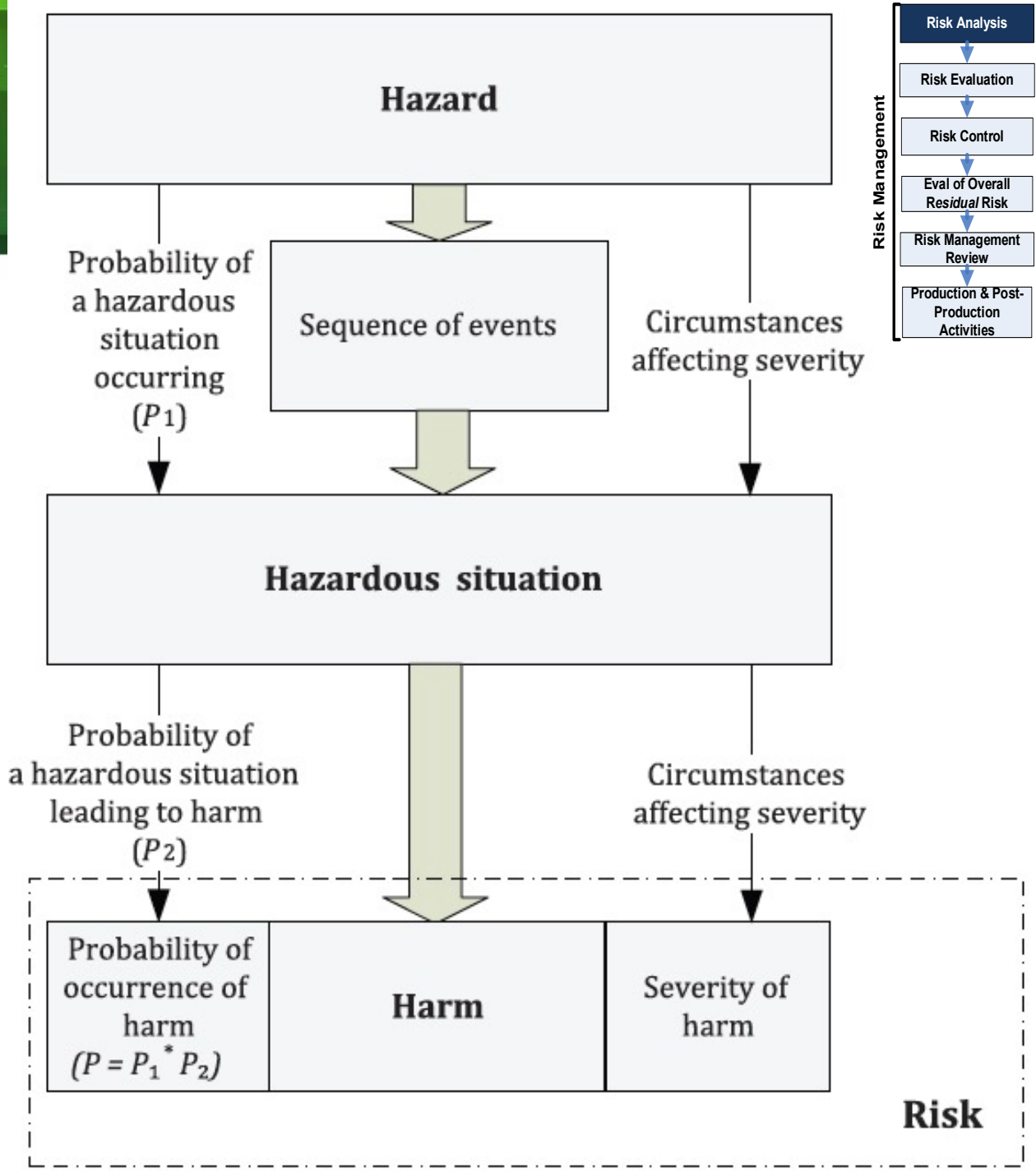
FDA – Applying Human Factors and Usability Engineering to Medical Devices, 2016

Human Factors Engineering/Useability Engineering

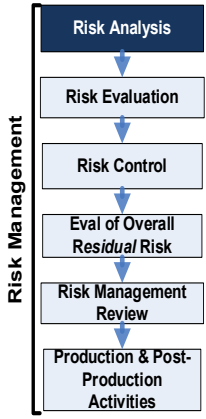
- Following published guidance will help identify, in a systematic manner, the user errors.
- Key Activities in HFE/UE that will help control user related risk
  - Understand and document User population and characteristics of population, User environment, User interface
  - Conduct a Task Analysis
  - Perform formative study with prototypes during design verification
  - Identify points reasonably foreseeable error (based on formative study and review of clinical data, adverse event databases, etc.)
  - Based on defined tasks and subtasks, execute a uFMEA.
  - Map User Failure Modes to the Hazard Analysis (ref. Haz ID#)
  - Based on severity assigned – classify “critical tasks”
  - Implement risk control measures, translate risk control measures into design requirements and provide traceability.
  - Perform a summative study with final design and labeling to validate efficacy user related risk controls.

Estimating Risk

- A Hazard could be attributed to multiple hazardous situations (with different probability of occurrence.)
- A Hazardous situation can lead to different Harms. Focus on most severe harm.
- Considering P1 and P2 is *"not mandatory"*, it is OK to estimate overall Probability (P).

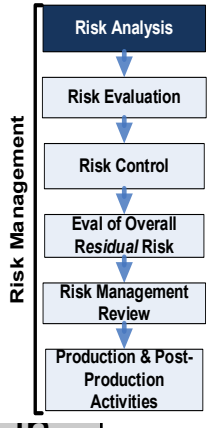


Estimating Risk – Severity Example



- There is no standard scale or industry standard cut-off value for concepts such as "Acceptable risk" or "Unacceptable risk".
- Neither the FDA nor any other regulatory body establishes the scale for use in quantifying risk. It is up to each company to define their numerical scales and definitions for severity and probability.
- This information must be in the Risk Management Plan.

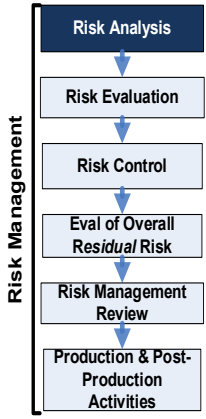
Estimating Risk – Severity Example



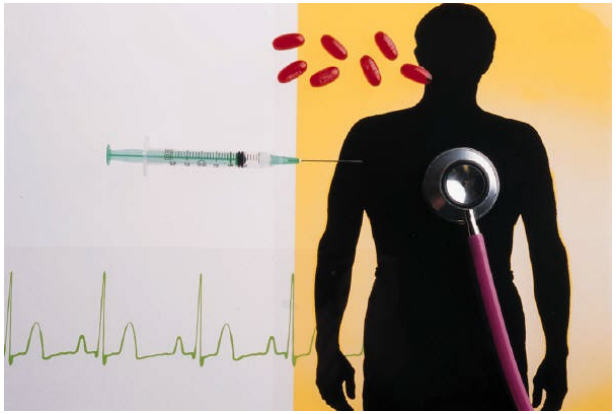
Severity Level	Description
1 – Negligible	Inconvenience or temporary discomfort. In significant delay in in procedure that does not require professional medical intervention.
2 – Minor	Results in temporary injury or impairment that does not require professional medical or surgical intervention
3 – Major	Results in serious injury or illness that requires medical or surgical intervention to prevent permanent impairment of a body structure or function.
4 – Critical	Results in permanent impairment of a bodily function, permanent damage to a body structure, short of death. (e.g., loss of limb.)
5 – Catastrophic	Death

* Where does this wording come from?
* Avoid the use of 10 points scales, 4-5 levels is sufficient.

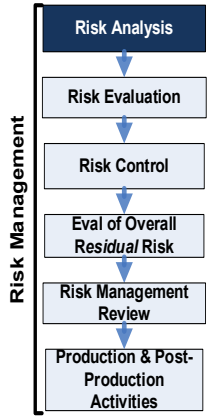
Estimating Severity



- **Assign a quantitative value to the possible clinical outcome or effect resulting from the failure mode.**
- **In all cases, make a conservative estimate of severity, cautioning on the side of patient safety.**
- **Severity of the hazard is estimated based on the EFFECT it may have on the patient or user**



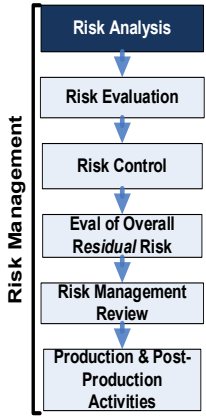
Estimating Risk – Probability Example



Qualitative Estimation

Probability Level	Description
3 – High	Likely to happen. Could be expected several times in the lifetime of the device. Expected.
2 – Moderate	Can happen, but not expected to be frequent. Could be expected to occur a few times in the life of the device.
1 – Low	Unlikely, rare, remote. Not expected to occur in the lifetime of the device.

Estimating Risk – Probability Example

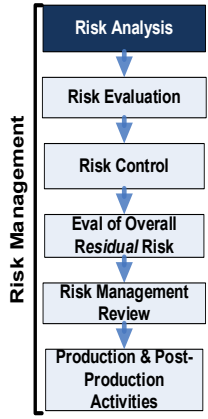


Quantitative Estimation

Probability Level	Description
5 – Frequent	$\geq 10^{-3}$
4 – Probable	$< 10^{-3}$ and $\geq 10^{-4}$
3 – Occasional	$<10^{-4}$ and $\geq 10^{-5}$
2 – Remote	$<10^{-5}$ and $\geq 10^{-6}$
1 – Improbable	$<10^{-6}$

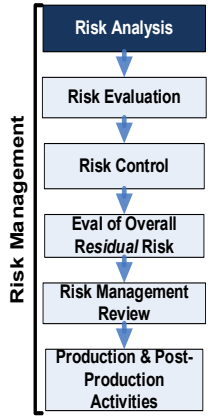
When would we use qualitative vs. quantitative probability scales?

Estimating Risk



- Align severity definitions to terminology used by regulators in describing injury, serious injury, etc.

Estimating Risk – Probability Example



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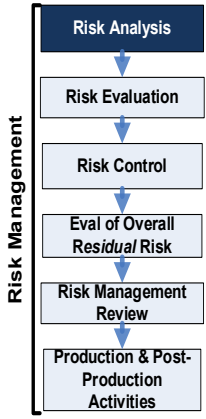
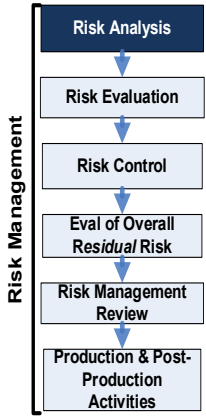
When would we use qualitative vs. quantitative probability scales?

Estimating Risk



- Probability levels assigned during product developmen and used is estimating risk during initial 1-2 years are market are naturally predictive. Over time, as data becomes available and the confidence in that data improves, the probability levels should be re-evaluated (part of surveillance/post market risk management)
- Points where probability are particularly difficult to estimate include:
  - Software failures
  - Abnormal use
  - Novel/New hazards where little is known (e.g., Covid vaccine unable to affect transmission rate of rare new variant.)
  - Toxicological hazards where it is inherently difficult to determine/measure the safe exposure limit.

Estimating Probability

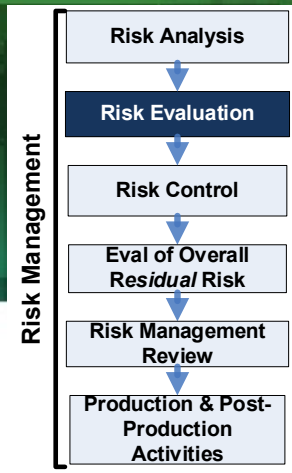


Can be very difficult to do…

- Consider historical data with similar processes/products
- Inherent design limitations
- Trend analysis (failures, NCRs, etc.)
- Common sense approach
- The first time through hazard analysis estimate probability without controls such as validation and in-process monitoring, finished product testing.

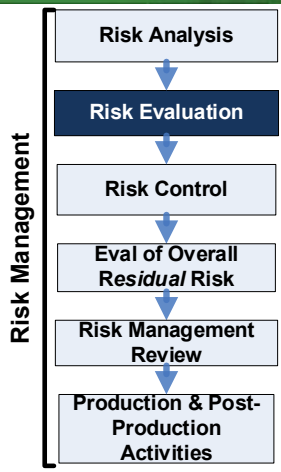
Risk Evaluation

Risk Evaluation



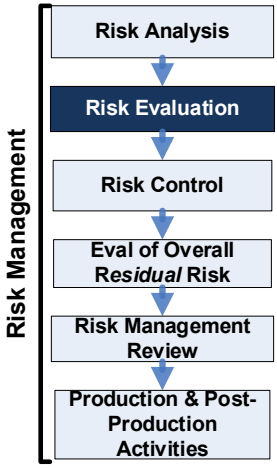
- The requirement in EUMDR Annex I is to reduce risks as far as possible, meaning the reduction of risks as far as possible, without adversely affecting the benefit-risk ratio.

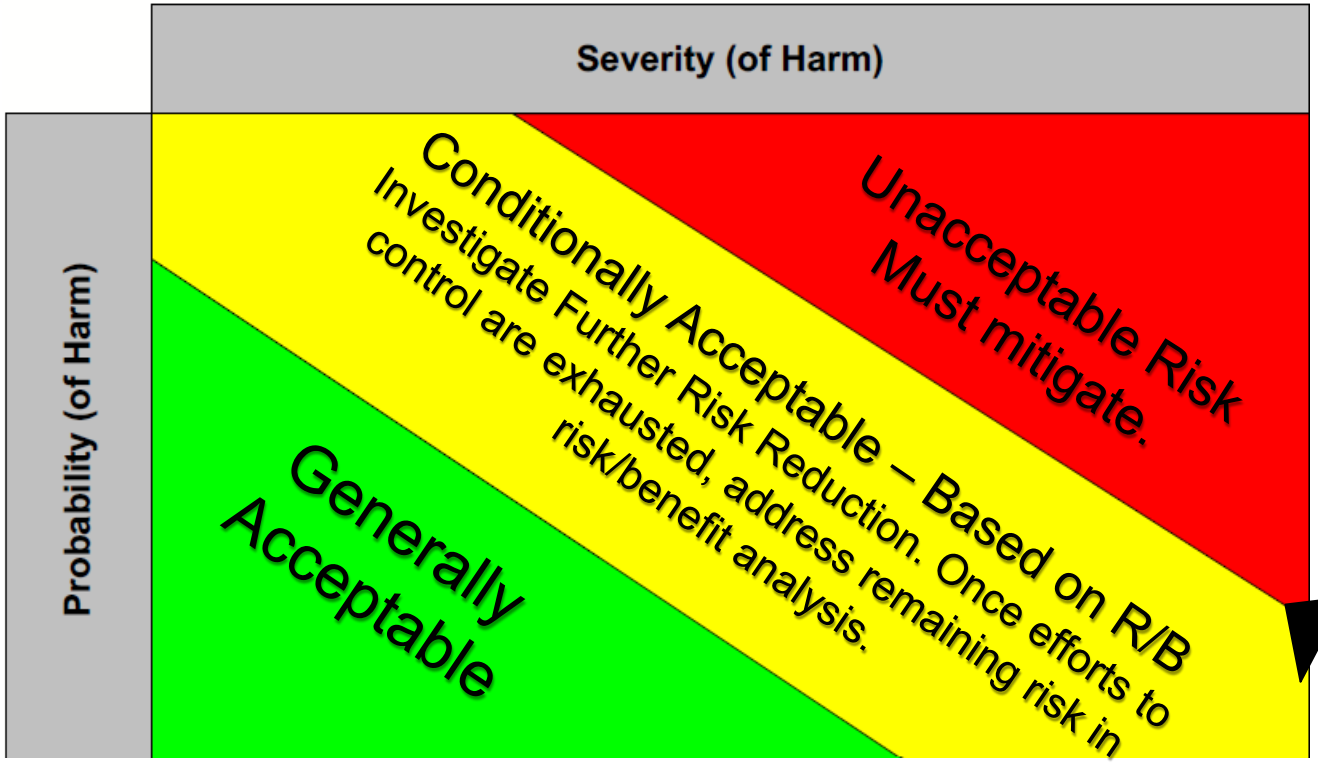
Risk Evaluation



- The evaluation of risk to product, process or quality should be based on scientific knowledge and ultimately link to the ***protection of the patient.***
- Manufacturer must define the risk acceptance criteria prospectively in the Risk Management Plan.
  - Determine the threshold where the risk level is not acceptable and further risk controls must be investigated.
  - Determine when a hazardous situation should be subject to benefit/risk analysis.
  - Clearly document expected action to take for different risk levels.
- Compare estimated Risk to Risk Acceptance Criteria.
- Evaluate risks of each hazardous situation
  - If acceptable, the estimated risk treated as residual risk
  - If unacceptable, then implement risk control measures

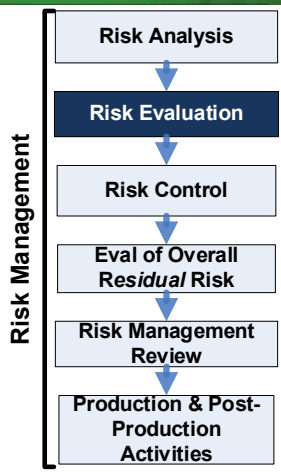
Risk Evaluation





Where do you draw the line?
When do you do a benefit/risk analysis?

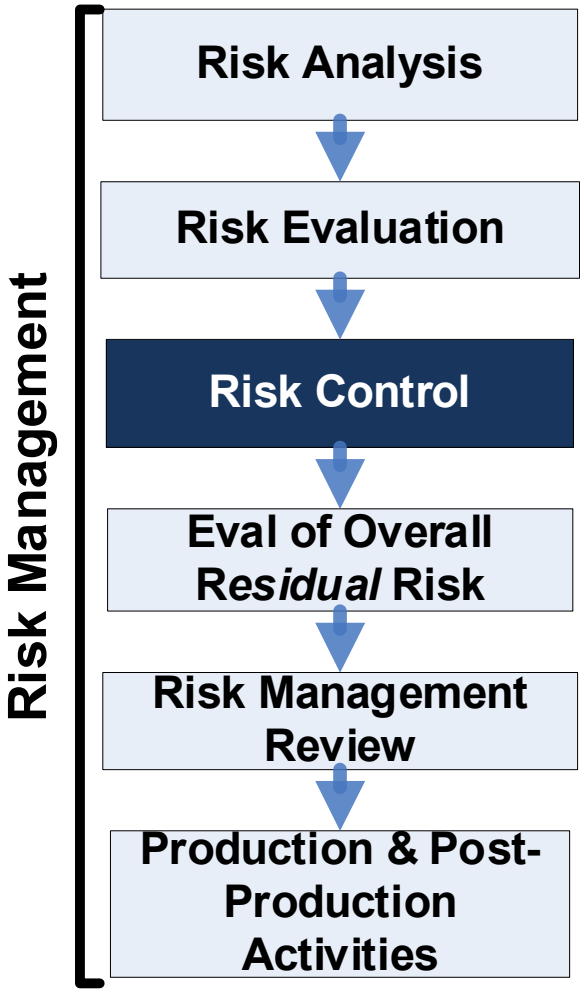
Risk Evaluation



Likelihood \ Severity	Negligible	Minor	Moderate	Significant	Severe
Very Likely	Low Med	Medium	Med Hi	High	High
Likely	Low	Low Med	Medium	Med Hi	High
Possible	Low	Low Med	Medium	Med Hi	Med Hi
Unlikely	Low	Low Med	Low Med	Medium	Med Hi
Very Unlikely	Low	Low	Low Med	Medium	Medium

The risk acceptability criteria may be different for different product lines. This is why the RMP needs to define the criteria for each product line.

Risk Control



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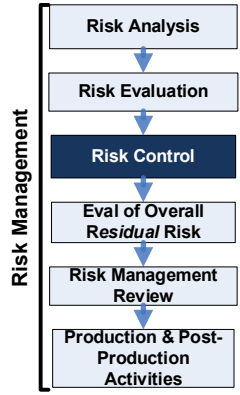
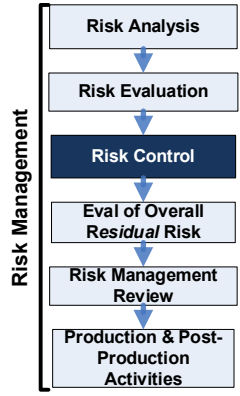


ISO 14971:2019	EUMDR Annex I
Manufacturer shall determine risk control measures hat are appropriate for reducing the risk to an acceptable level.	Risk mitigation must consider reducing risk as far as possible (AFAP), and take into account generally acknowledged State of the Art.

- Risk mitigation should be implemented in this order of preference:
  - Design/redesign so that the design is inherently safe
  - Add protective measures in the device or production process
  - Information to users, i.e., warnings in labeling

(This is in the ISO standard and EUMDR, Annex 1).

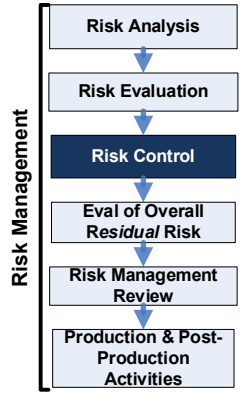
Risk Control



Risk Control Type – Enter into the Hazard Analysis Template using Acronyms.

- Inherent safety by design (IBD)
- Protective measures in the medical device itself (PMD)
- Protective measures in the manufacturing process (PMM)
- *Software Process Quality (SWPQ)*
- Information for safety (IFS)

Risk Control



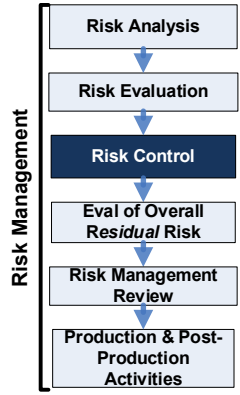
State of the Art

- International Standards are considered to represent “state of the art”.
- Standards define safety requirements, protective measures, and information for safety.
- Complying with a product’s relevant standards provides a means of reducing risk to what would be considered an acceptable level.

Recognized Consensus Standards:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

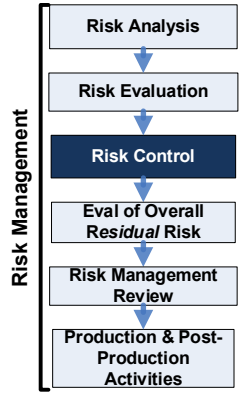
Risk Control



- Implementation of risk control measures means TRANSLATING the risk controls into Design Inputs/Design Requirements.
- Risk Controls are verified to be effective through design verification and design validation (Simulated and/or actual use testing.)
- Risk Controls related to the manufacturing process are verified effective through process validation.
- Risk Control related to user errors are verified to be effective through Usability Testing, (Formative and Summative.)
- Evaluation of a risk control and it's effectiveness must take into consideration the potential for additional new hazards or hazardous situations to be introduced.

There must be traceability between risk control measures and the design inputs that implement them. (Should be forward and backward via Design Traceability Matrix.) This ensures that you can readily demonstrate with objective evidence that the risk control measure was implemented and it was effective.

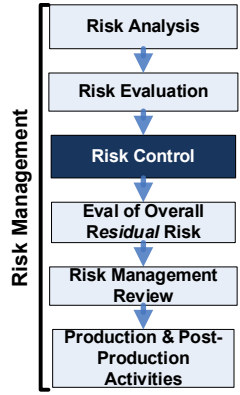
Risk Control



Points to consider in using published international standards as a means of documenting risk control and product safety:

- Where a standard provides for safety measures, design or testing requirements that mitigate a hazardous situation, *compliance to it is a means of risk control.*
- In the hazard analysis, the risk control section would reference the Standard to which the manufacturer is stating compliance. *("Compliance with ISO-XXXXX as it relates to XXXXX testing".)*
- If only a portion of the standard is followed, met, or applicable to the device, the exceptions must be clearly stated in the DHF (See Requirements Traceability Matrix) and the Technical File (see GSPR Checklist)
- The Hazard Analysis would show reference to the Design Req. ID# that translates that risk control into a design requirement. (i.e., the Design Req ID# that states requirement to comply to a particular standard.)

Risk Control

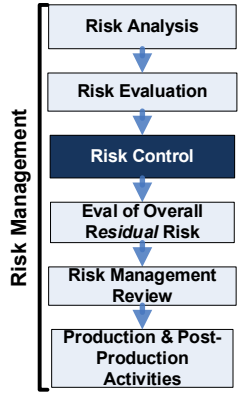


- Per EUMDR, Annex I:
  - In eliminating or reducing risks related to use error, the manufacturer shall:

    (a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

    (b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

Risk Control

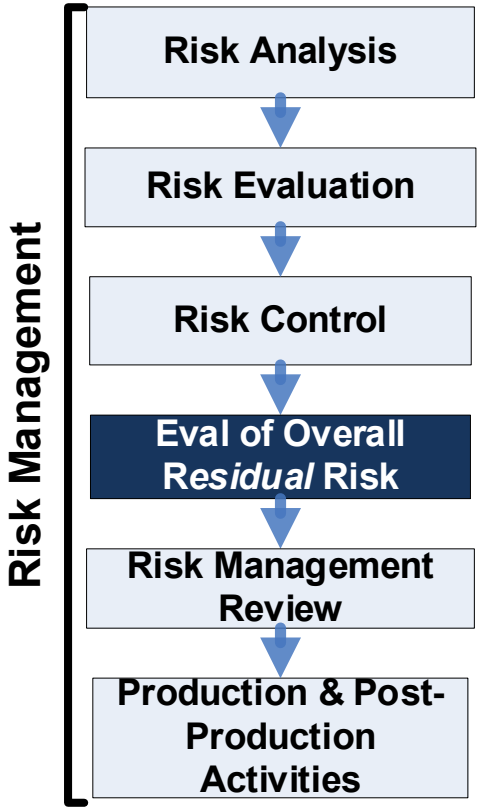


- Concurrent with identifying and implementing risk control measures, complete a Checklist of GSPRs (General Safety and Performance Requirements) to meet design and risk management requirements of EUMDR Annex I. This will be part of the Technical File.

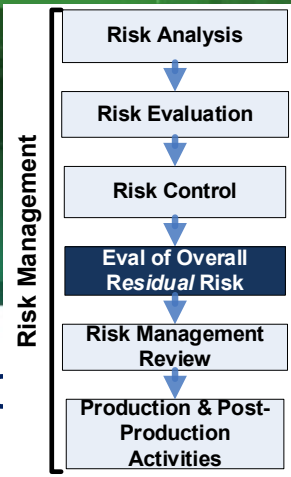
[GO TO CHECKLIST EXAMPLE]

If a particular GSPR does not apply to the device, do NOT indicate N/A. Must explain why the requirement does not apply (i.e., provide rationale.)

Evaluation of Residual Risk

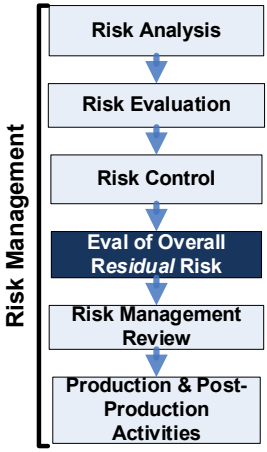


Evaluating Residual Risk



- Residual risk is the risk remaining after implementatic risk controls.
- Residual risk is evaluated against the same risk acceptance criteria used to evaluate initial risk. (Per RMP.)
- If residual risk is not acceptable investigate for further risk reduction.
- If risk cannot be reduced to "Acceptable Level" and remains in the "Conditionally Acceptable Level" include in a benefit/risk analysis.
- Per EUMDR Annex I, Manufacturers shall inform users of any residual risks. Per ISO, …inform users of significant residual risks.

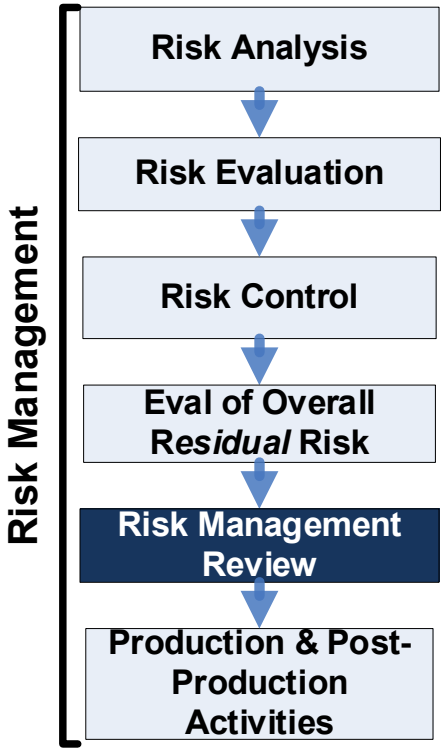
Evaluating Residual Risk



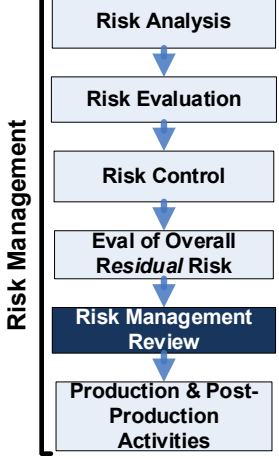
Benefit/Risk Analysis

- EU MDR Annex I, GSPRs:
  - All known and foreseeable risks, and any undesirable side-effects, shall be minimized and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.
- ISO 14971:2019:
  - Perform a benefit/risk analysis for those risks where further risk control is not practicable
- Weighs the risks against clinical / medical benefits.
- Should be established and approved by multidisciplinary team that involves one or more persons with Medical / Clinical Knowledge. Use clinical data, published literature, etc., to support.
- Benefit Risk Analysis cannot be used to compare product risk to business or economic advantages.
- If the benefit does not outweigh risk, must consider changing design or the intended use.

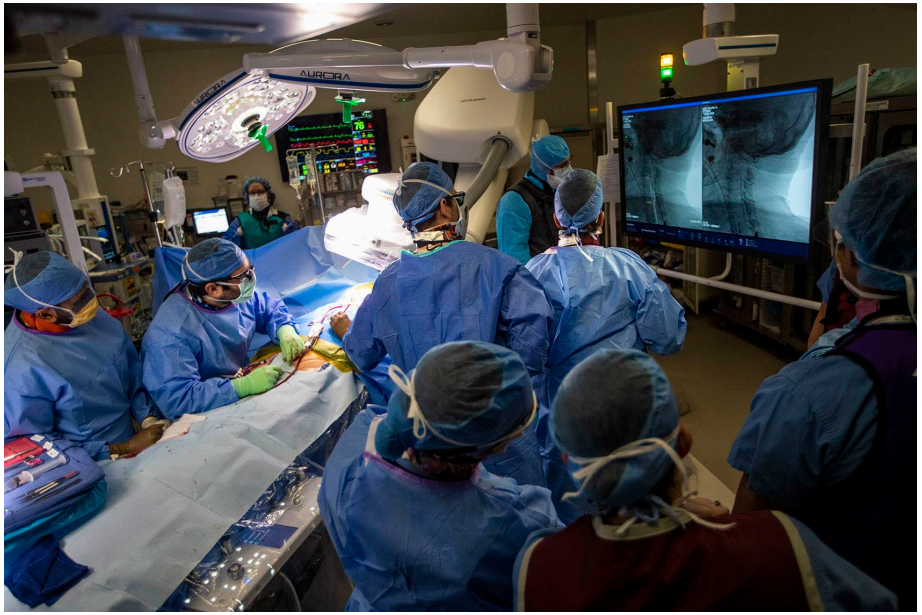
Risk Management Review

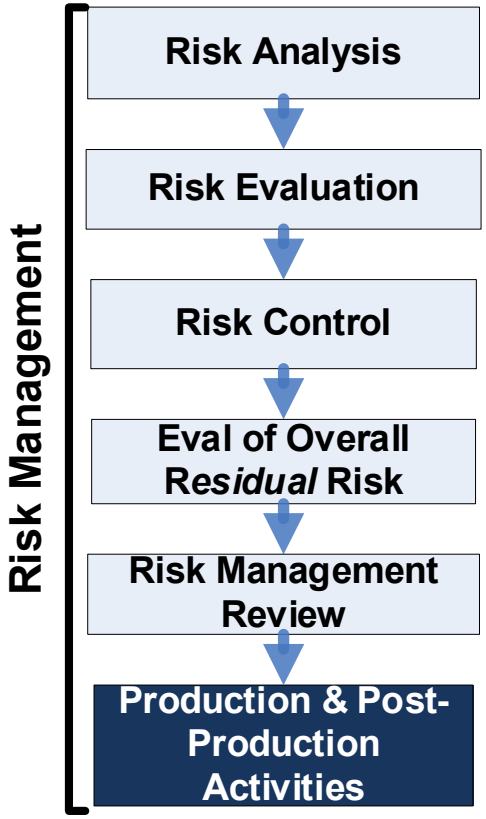


Risk Management Review



- Generate a Risk Management Report to document
  - A review of the overall residual risk,
  - the execution of risk analysis, eval, and control against the Risk Management Plan (Where there any deviations from plan.)
  - Provide reference to the objective evidence of the execution of the risk management plan
  - Verify the methods, procedures, systems are in place for managing risk in production and post-production (post market surveillance methods to be used for continually identifying new hazard, haz situations, and harms.





Production & Post-Production Activities

(Monitoring Risks for Product On Market)

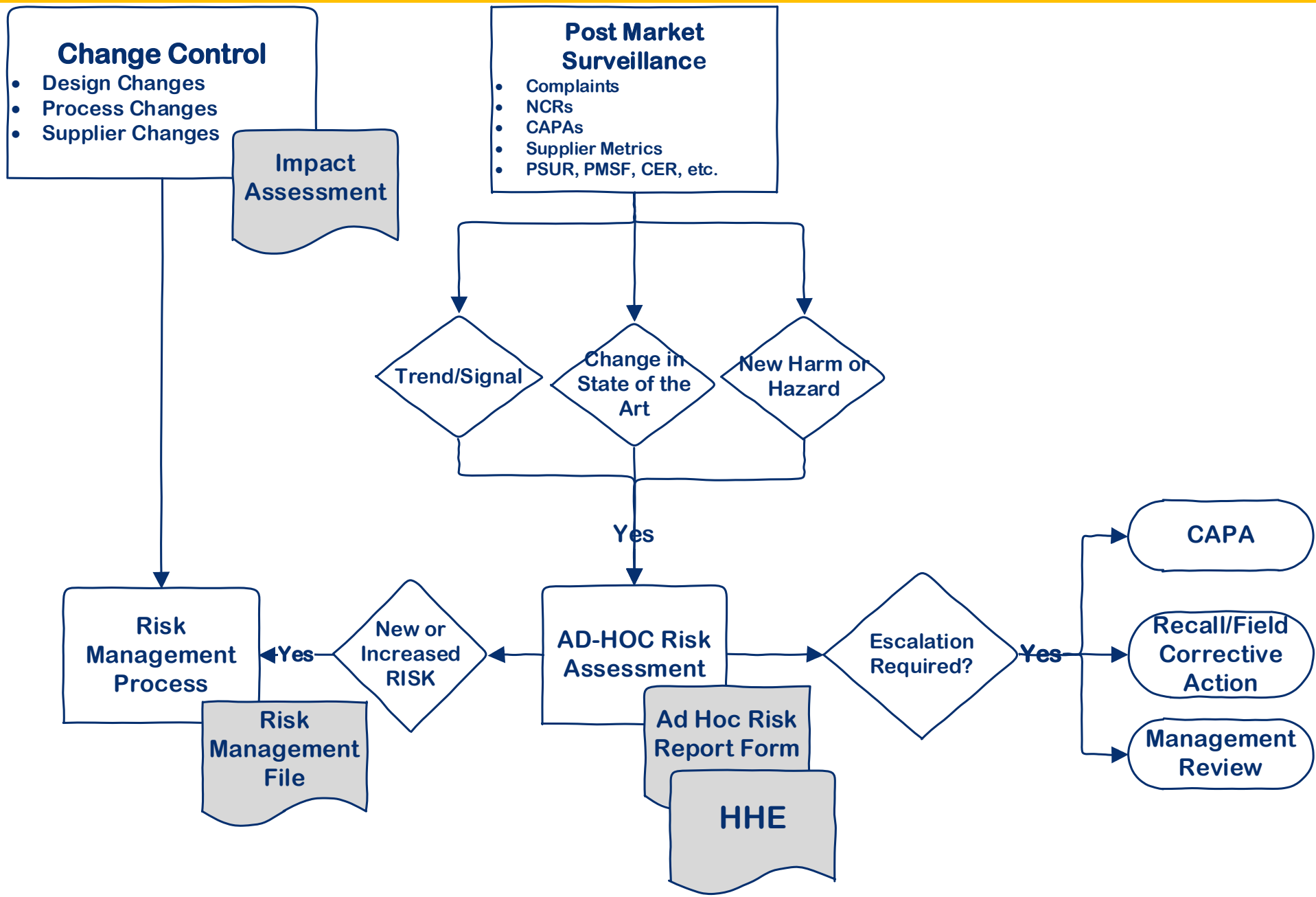
Production and Post Production Risk Management

- Manufacturers must establish and maintain systems for actively collecting and reviewing information relevant to the medical device in production and post-production phases.

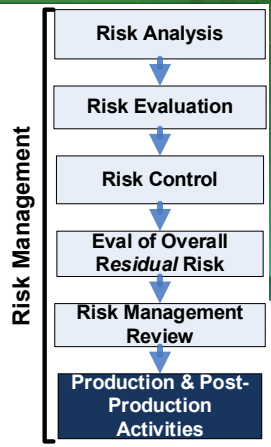
Objectives for Monitoring Post-Market Data Monitoring

- Identify new, previously unpredicted hazards that have not been assessed for risk.
- Identify new or unexpected harms resulting from use of the product in the post-market environment.
- Identify when risk level for on-market product is no longer acceptable so that actions can be taken in a timely manner to eliminate or reduce that risk.
- Ensure clinical risks identified within clinical evaluations and clinical investigations are monitored throughout the life of the product.
- Maintain product technical documentation and
- Cooperate with the regulators and national competent authorities in charge of vigilance and market surveillance activities.

Post Market Risk Management

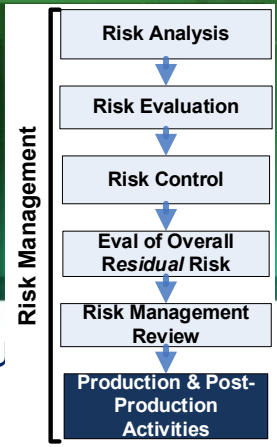


Data to be monitored



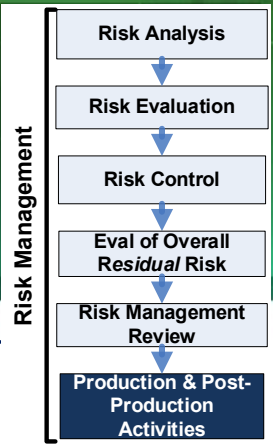
- Post market surveillance data generated by the user, customers, and distributors; specificall complaint data, service/repair data.
- Adverse events and malfunctions that may cause or contributed to death or serious injury or serious incidents. (This includes the monitoring of Vigilance reports and Medical Device Reports.)
- Production and process monitoring data, such as deviations and nonconformances arising from failure of product to meet specifications and rework.
- Supply chain data, including supplier and contract manufacturer performance metrics and component/raw material rejects.
- Public information relevant to the product or similar on-market products such as information published within professional journals, product reviews, professional meetings and social media.
- Regulatory Agency databases such as MAUDE for MDR reports.
- Information submitted to manufacturer by regulatory authorities regarding on-market product problems reported to- or identified by- them.
- Design and manufacturing process changes that may impact product risk and require update of risk management files.
- Information that may indicate a change in the generally acknowledged state of the art for the product.

Ad-Hoc Risk Analysis is warranted when:



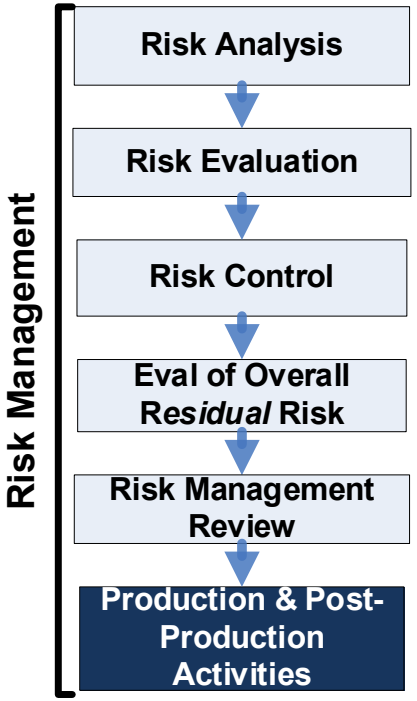
- A **new** hazard, hazardous situation or harm cannot be disconfirmed throu evaluation/investigation.
- Investigation of an individual quality event identifies that the severity of an alleged harm is higher than previously reported in the Risk Management File.
- An investigation of a quality event may identify a new cause of the hazard that may require an additional risk control measure to reduce risk.
- Statistical trend analysis indicating a hazard or hazardous situation is occurring at a frequency above that predicted in the Risk Management File.
- Review of Periodic Safety Update Reports (PSUR) and Post Market Clinical Follow Up (PMCF) provide information that may identify changes in the generally acknowledged state of the art which may impact the acceptability of a product's benefit-risk ratio..

Ad-Hoc Risk Analysis- Content

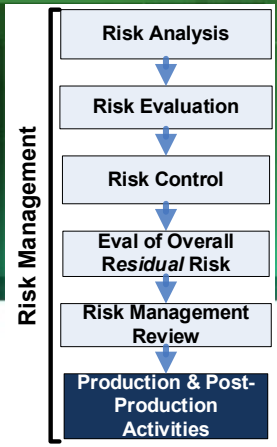


- An Ad-Hoc Risk analysis is typically completed using a form or template wh to assign a Severity with rationale.
- Hazard, Hazardous situation, and Harms are identified with appropriate background data and context.
- Data is compiled to establish a probability with rationale.
- Labeling review.
- Risk Priority Number, or risk index value is assigned and analyzed to determine if the risk is in an acceptable level.
- Risk Controls are identified with reference to any investigations, etc., that led to discovery of the risk control measure.
- This document is reviewed/approved by Clinical/Medical, Product Development.
- Approved Ad-Hoc risk analysis is filed in the RMF and used as the basis for updating the Risk Analysis, Harms List, etc. (referenced in the Engineering Change Order or change request)

Risk-Based Decision Making & Application of Risk Management in a Quality Management System



Assume…

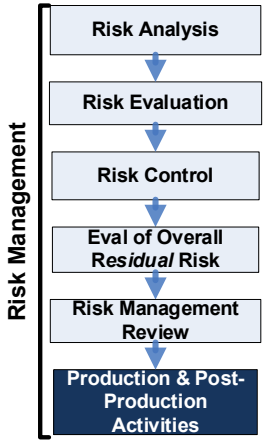


- You have a Master Harms List which provides Severity ranking to Hazards.
- You have a Design FMEA which allows you to correlate a failure mode to a hazardous situation and harm. This provides a severity rating.
- You have a Process FMEA which assigns relative risk values to specific process defects or failures that may occur.

Q: What can we do with this information?

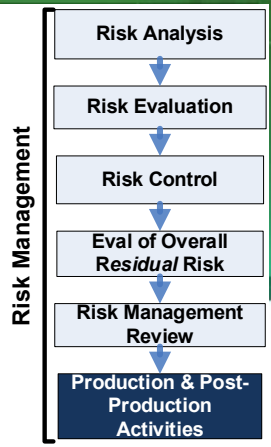
A: Use it to provide rationales for quality-related decisions and updating the risk management file.

Routine Quality Related Decisions



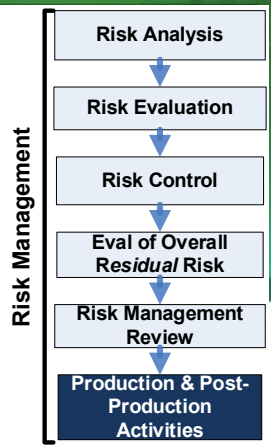
- What are the potential process variables that I should characterize/optimize as part of process development?
- How many samples should I select and test during process validation?
- How many samples should I pull for in-process and finished product testing?
- How tight should a tolerance be for a specific product specification?
- What kind of AQL/Sampling Plan should I use for incoming inspection of components and raw materials?
- What level of effort should I apply to qualifying a vendor?
- Should I invest resources into opening an investigation (root cause analysis) for a specific complaint?
- Should I investigate resources into performing an investigation of a specific non-conformance?

Justifying Decisions and Resource Allocation



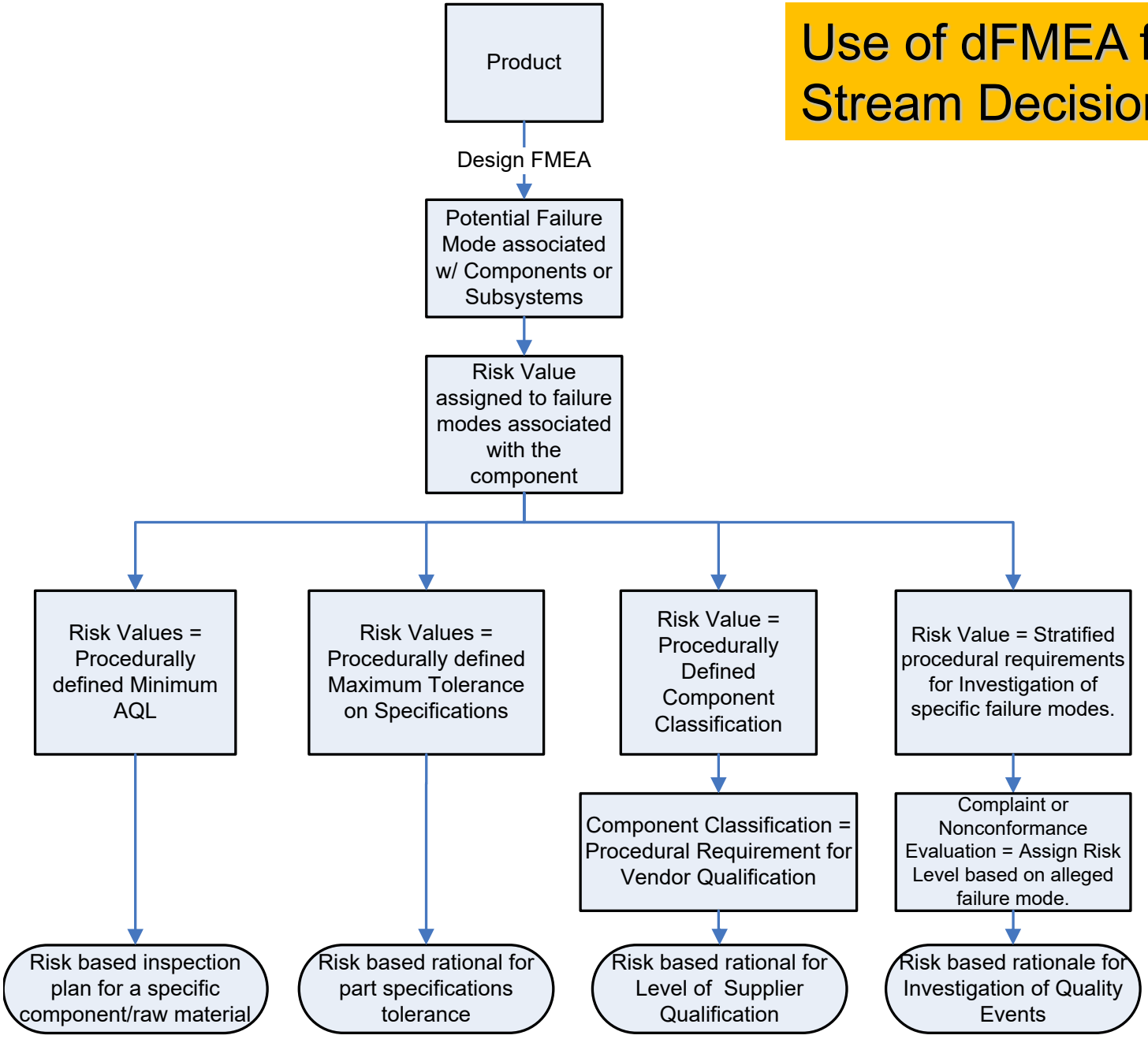
- If we know the risk level associated with specific events or failure modes, we can leverage this information in making quality-related decisions.
- Risk Analysis information can be effectively leveraged in several areas; for example:
  - Process Validation,
  - Establishing Quality Control inspection plans and process monitoring plans,
  - Determining level of supplier controls that are necessary for purchased materials and services.
  - Determining the need for and extent of investigation required for quality events as they occur.

Why is all this important?

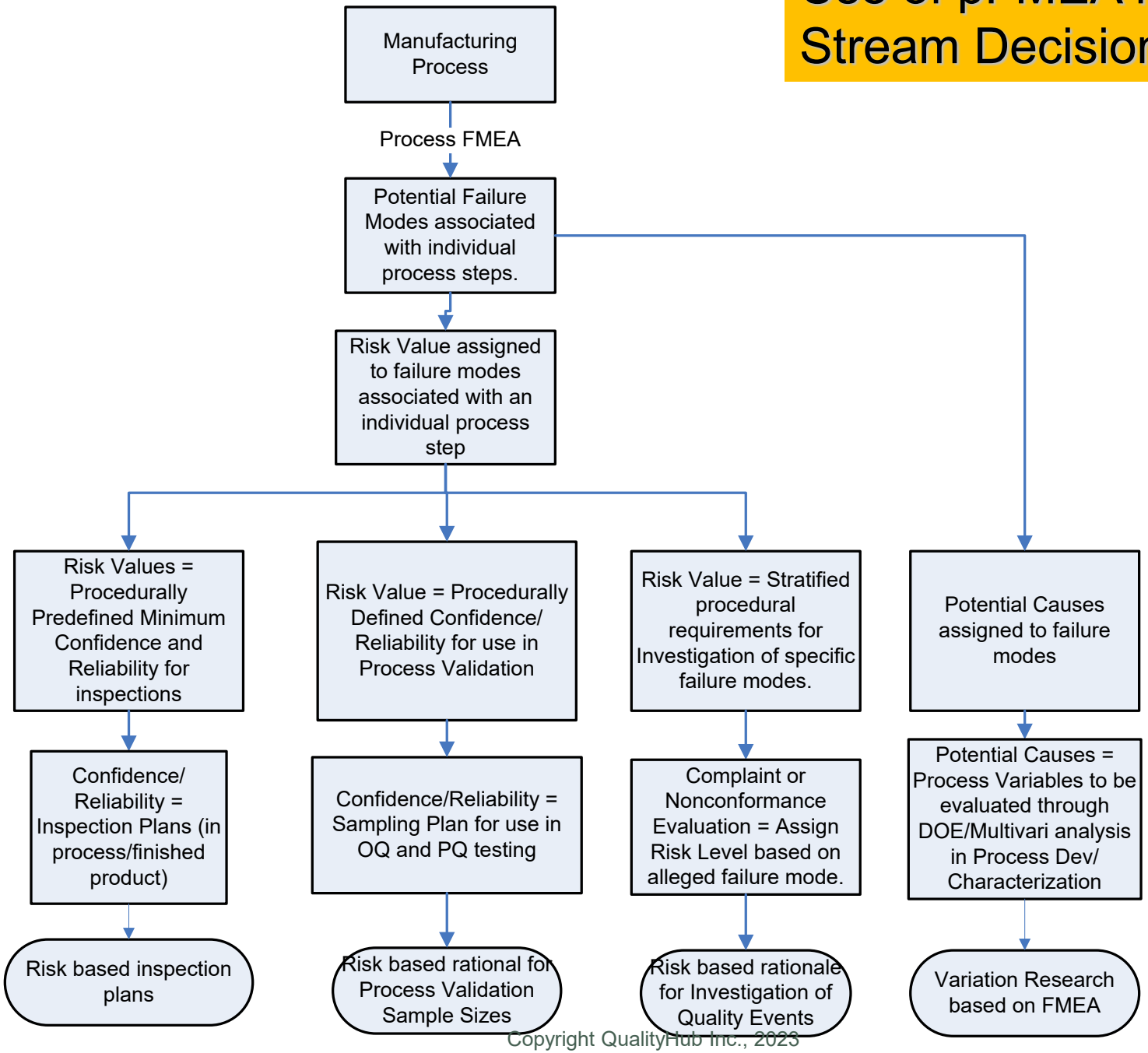


- Integrating risk analysis into quality decision making helps management put resources where they will add the most value and have the biggest impact on quality and customer satisfaction.

Use of dFMEA for Down-Stream Decision Making



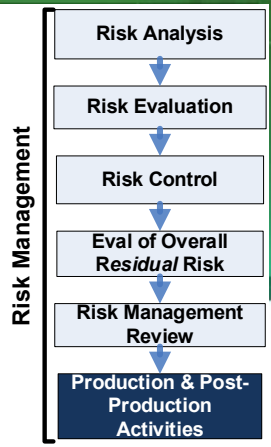
Use of pFMEA for Down-Stream Decision Making



Process Controls Based on Calculated RPNs

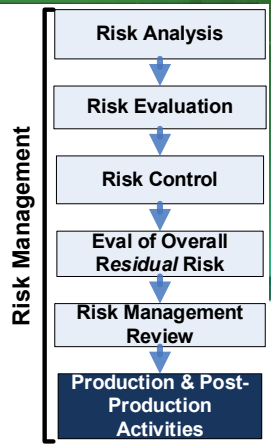
RPN	Description	Action Required to control process
>27	Intolerable risk.	• Must be validated. • Where Cpk is applicable, target is ≤2. • Evaluate additional Tests/Inspections • AQLs at least 0.60 • Evaluate possibility for process re-engineering.
13-27	Unacceptable risk / must be reduced	• Must be validated • Where Cpk is applicable, target is ≤1.33 • Evaluate additional Tests/Inspections • AQLs at least 1.0
5-12	Tolerable risk if the technical and economic resources required for correction would exceed the benefits.	• Should be Validated, unless appropriate justification is provided. • Where Cpk is applicable, target is ≤1.33 • Evaluate additional Tests/Inspections • AQLs at least 1.5
1-4	Negligible risk.	• Verification vs. May be Justified • Set Cpk and AQL based on business risks

Application of Risk Analysis in CAPA and CAPA Feeder Systems



- The principles of risk analysis are applied to quality related events to determine the need for investigation, the scope of investigations and corrective/preventive actions, the prioritization of investigation and corrective/preventive actions.

Risk Analysis in CAPA and CAPA Feeder Systems

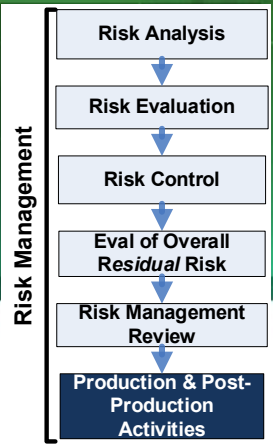


The FDA Perspective…

- FDA agrees that the degree of corrective and preventive action taken to eliminate or minimize actual or potential nonconformities must be appropriate to the magnitude of the problem and commensurate with the risks encountered.

What are CAPA Feeder Systems?

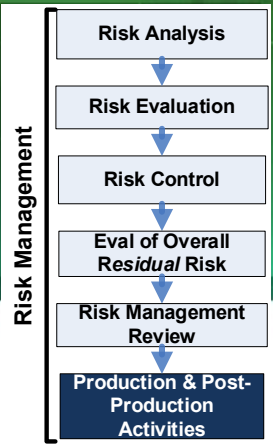
Risk Analysis in CAPA and CAPA Feeder Systems



The FDA Perspective…

- FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, but **FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment.**

Use of Risk in Complaint Handling, Nonconformance Control



- In order to allow statistical trend analysis complaints and NCRs should be “coded”.
- To effectively use risk analysis to determine the level of investigation that is appropriate it is IMPORTANT that that coding is aligned with hazards and failure modes in risk management file that allow assignment of a Severity level to the event.
  - Contamination
  - Particulate
  - Leak prior to injection
  - Under filled vial
  - IFU Missing
  - Sterility Failure
  - Battery/Power Failure

See IMDRF.ORG

Consultation documents

IMDRF Terminologies for Categorized Adverse Event Reporting: terms, terminology and codes DOCX (218.14 kb) PDF (325.49 kb)

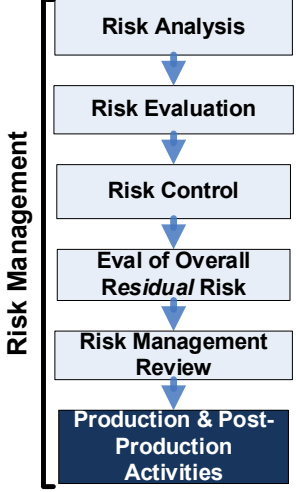
Annex A - IMDRF Terminologies for Categorized Adverse Event Reporting: terms, terminology and codes XLSX (64.04 kb)

Reference Mapping - IMDRF Terminologies for Categorized Adverse Event Reporting: terms, terminology and codes XLSX (45.85 k

Please use the comments template to provide comments on the Proposed Document and email comments to imdrf-aewg-chair@pmda.go.jp.

Comments - IMDRF Terminologies for Categorized Adverse Event Reporting: terms, terminology and codes XLSX (15.57 kb)

Coding Quality Events

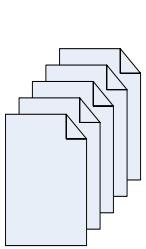


- Properly coding allows “grouping”
- Grouping can increase ability to identify risk:
  - Increases detectability of rare events
  - Increase detectability of statistical trends/signals in aggregate data.
  - Provides more reliable estimates of magnitude over time.

Determine appropriate action to take, based on the results of evaluation and risk analysis:

Non-Conformance/Failure Mode Risk Table		
Complaint /Nonconformance Code	**Severity from Hazard Analysis**	**Investigation Required**
Contamination of xxxxxx.	4	Level III
Visual inspection failure for particulate in xxxxxxxxx.	2	Level I
Sterility Failure	4	Level III
Underfilled vial	1	Level I
Leak test failure on xxxx	3	Level II
Power/Battery Failure	3	Level II
Needle Bent	1	Level I

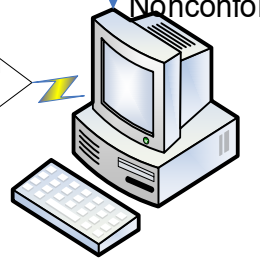
Using Risk to Drive the Level of Investigation



Hazard Analysis
UFMEA
DFMEA
PFMEA
Risk Analysis Docs

Non-Conformance/Failure Mode Risk Table		
Event/ Non Conformance	**Severity from dFMEA/pFMEA**	**Investigation Required**
Contamination of xxxxxx.	4	Level II
Visual inspection failure for particulate in xxxxxxxxx.	2	Level I
Sterility Failure	4	Level II
Underfilled vial	1	NA- monitor
Leak test failure on xxxx	3	Level II
Etc….		

Pre-determined risk drives Decision Trees in Complaint and Nonconformance Database



Investigation Required?

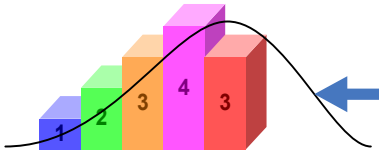
Risk I
No Investigation/ Surveillance (Document Rationale)

Risk II
Routine Preliminary Investigation

Risk III
Root Cause Investigation

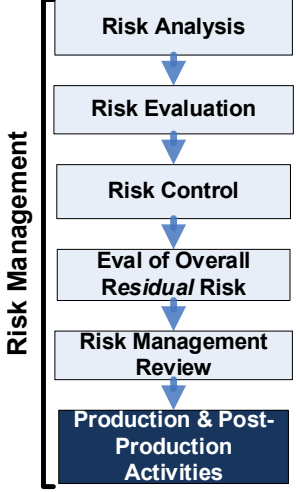
CAPA (if required)

Review/Close Event Record



Statistical Analysis of Aggregate Quality Data

A Note about Medical Device Reporting (MDR) and Risk

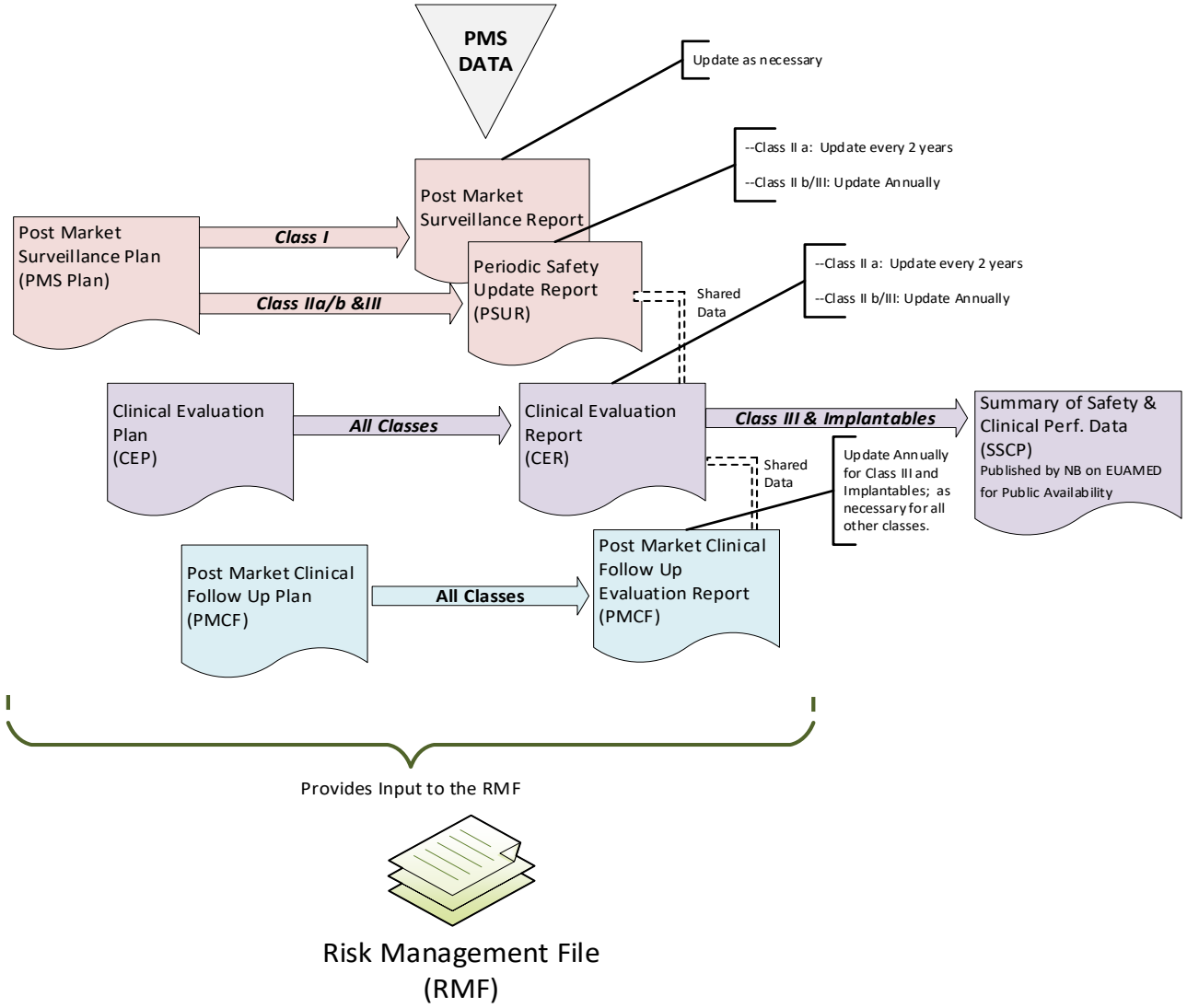


- MDR required if:
  - The device caused or contributed to a death or serious injury.
  - The device malfunctioned and if that malfunction were to recur, it could lead to death or serious injury.
- Requires us to understand “serious injury.”
- Requires us to understand whether or not specific malfunctions could lead to a hazardous situation.
- Required us to understand when a hazardous situation could lead to death or serious injury (i.e., SEVERITY)

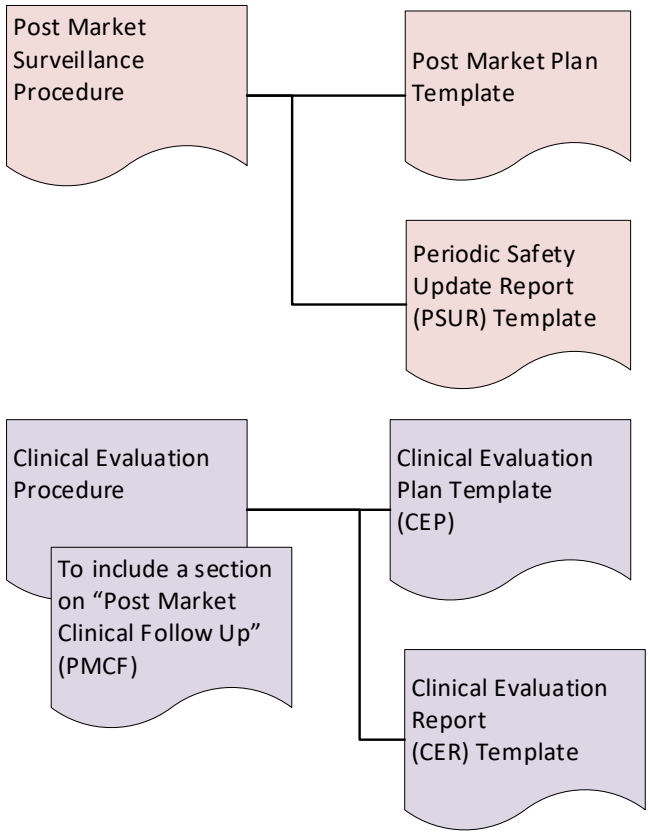
The decision to submit and MDR (or not) should not contradict Severity ratings in the Risk Management file.

qualityhub

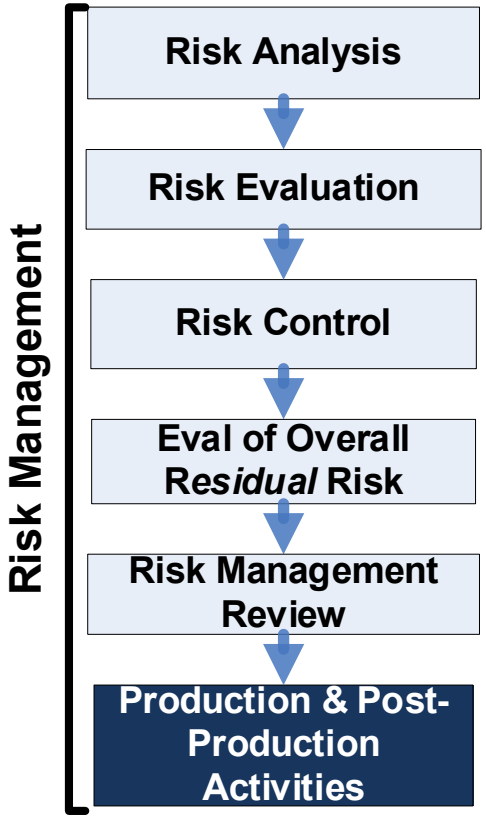
EUMDR
Post Market Surveillance Requirements | Ver. 3



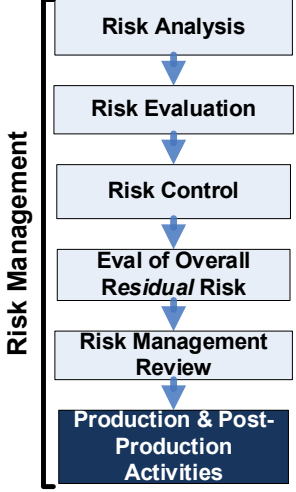
EUMDR
Post Market Surveillance Requirements | Ver. 3



Risk Considerations in Decommissioning

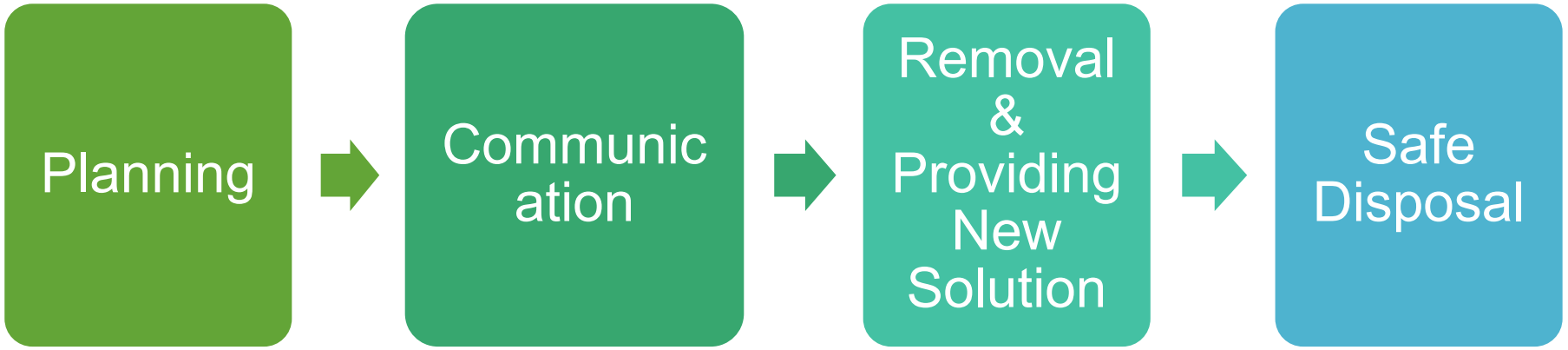


Decommissioning Medical Devices



- Decommissioning devices is a decision that is made to reduce risk to Users. (There are also business considerations.)
- Timing is important and is based on information regarding
  - Device Reliability
  - Component and system stress testing
  - Availability of correct parts, ability to properly support ongoing service & repair
  - State of the Art – Availability of newer/better technology.
  - Benefit/Risk Analysis

Decommissioning Medical Devices



- Cross functional team
- Budget
- How/when to communication
- Options to provide users
- Protocol for destruction or salvage

- Patients/Users/ Health Care Community/Re gulators
- Allow plenty of time for Users to Plan.
- State regulations

- Manage & Monitor Logistics.
- Carefully record disposition of each device by S/N. Note, must record destruction.

- Consider protection of patient data and potential need to preserve data.
- Environmental/Ch emical Hazards
- Contamination Control, Radiation Safety
- Gov. regulations

Bibliography

- ISO 14971:2019, Medical Devices – Application of risk management to medical devices. Edition 3, December 2019.
- ISO/TR 24971:2020, Medical Devices – Guidance on the application of ISO 14971. Edition 2, June 2020.
- Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff. February 3, 2016.