FIND

RISK MANAGEMENT

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TOPICS

1. What is risk management and why it is important
2. Risk documentation
3. Key terms and concepts
4. Illustration of risk management as a process
5. FMEA as a risk assessment tool; dFMEA, uFMEA, pFMEA
6. Common non-conformities

WHAT IS RISK MANAGEMENT?

- **Risk management is the set of activities** a manufacturer performs which are related to patients and operators from use of a medical device:

Identification

What can happen

Analysis

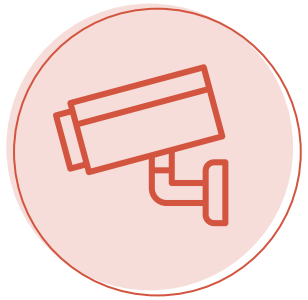
How can it happen

Evaluation

How severe is it (is it acceptable?)

Control

What can we/will we do about it?



Monitoring/ Surveillance

Is it sufficient/do we need to do it more?

WHY DO WE CONDUCT RISK MANAGEMENT?

- Ethical principles
- Legal or regulatory requirements
- Requirements from a standard
- Understanding indications for use and how the product will be used in the field helps to design a product that meets user needs the first time
- Anticipating failure modes and hazards helps to design a safer, more usable and robust product
- Prevention of product failures or recalls
- Prevention of litigation and reduction of liability

BACKGROUND OF LEGAL/ REGULATORY REQUIREMENTS

- There is a large element of trust in the IVD industry:

  A patient in an Emergency Room with chest pain will not be thinking about the risk of the IVDs used to diagnose their heart attack. They trust the healthcare professionals to determine how they will be diagnosed or treated, and unknowingly accept the risks of the devices used as part of their care.

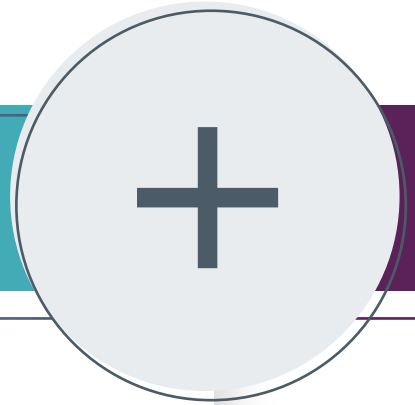
- Healthcare professional take **decisions** for the patient based on results of IVDs
- Manufacturers are obliged to **inform** the decision makers:
  - About the (claimed) performance and benefits of the device
  - About the (residual) risks of the device
- Anything that could compromise the physical integrity of the patient or impact their health and wellbeing requires a benefit that outweighs the risks

GOALS FOR RISK MANAGEMENT

A REGULATOR'S PERSPECTIVE

PRODUCT IS SAFE

- The product does not harm the patient, the operator, or the environment...
- … of if it does, the benefit still outweighs the risks.

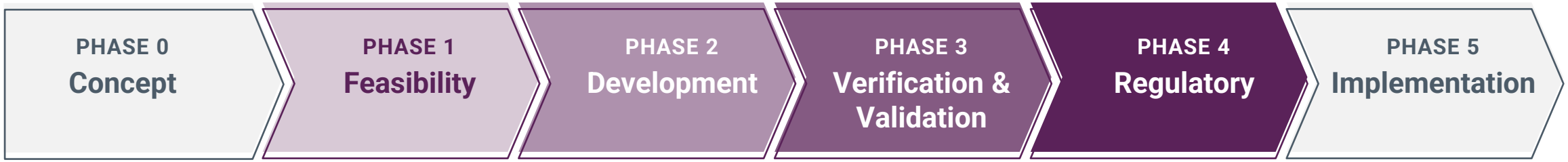


PRODUCT IS EFFECTIVE

- The product performs according to the manufacturer's claims
- What the product does has a medically significant effect.

RISK MANAGEMENT THROUGHOUT THE PRODUCT LIFE CYCLE

Risk Management is embedded throughout the entire Product Lifecycle. It is one of the first processes to start during product development and one of the last processes that ends upon decommissioning/withdrawal of the product. It is a continuous process that accompanies the product during all phases of its life cycle.



QMS Documentation:

Risk Management Plan:

- Policy
- SOP
- RM Team

Hazard Identification

Risk Evaluation

Risk Estimation

Risk Control:

Risk Analysis

Risk Effectiveness Evaluation

Benefit/Risk Analysis

Residual Risk Evaluation

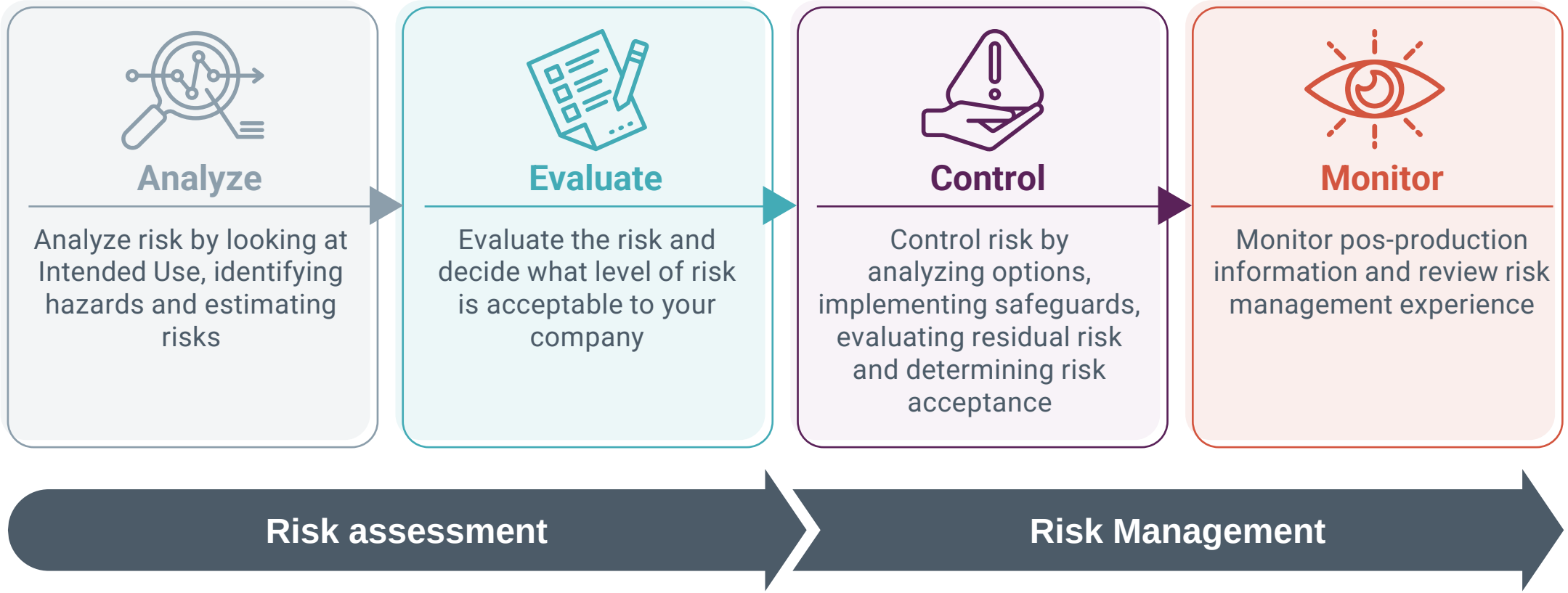
Risk Management Report

Production and Post-Production Information/Feedback

Risk Management Reviews

Risk Management File

RISK MANAGEMENT AS A PROCESS



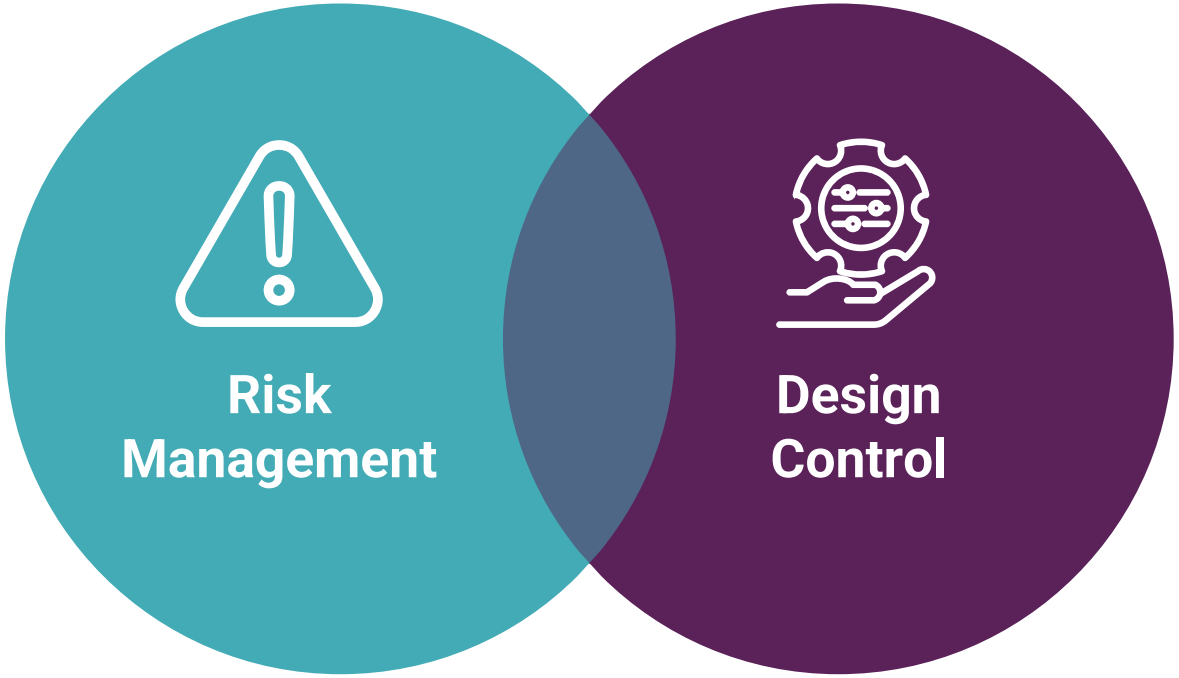
- **Risk Management:**

  Systematic application of… policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

RISK MANAGEMENT AND DESIGN CONTROL

There is a **strong correlation between Design Controls and Risk Management**; they both address design, development, and manufacturing of devices from slightly different perspectives. Both are critical to producing a safe and effective device, and both are needed.

- The product is safe (does not harm the user or patient)
- Benefits of use outweigh the risks
- Device performs as expected



- Address the needs of users and patients
- Designed to meet inputs and requirements
- Device is proven to meet acceptable standards
- Device meets performance criteria

GOVERNING DOCUMENTS

EN ISO 14971:2019 Medical Devices – Application of Risk Management to Medical Devices

- ISO 14971:2019 has been updated to include the new annex A11 2021 - is not considered to be a harmonized standard for the EU In Vitro Diagnostics Regulation (IVDR)

ISO TR 24971:2020

- 2020 revision has several updates from 2013 version, including the addition of several helpful new annexes:
  - *Annex D – Risk concepts*
  - *Annex F – Risk management for cybersecurity*
  - *Annex G – Risk management file*
  - ***Annex H - IVDs***

USEFUL REFERENCES

- “Implementation of risk management principles and activities within a Quality Management System”. GHTF/SG3/N15R8:2005.
- “Applying Human Factors and Usability Engineering to Medical Device", Guidance for Industry and Food and Drug Administration Staff, FDA, 03-Feb-2016
- “Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices”, Guidance for Industry and Food and Drug Administration Staff, FDA, 26-Feb-2020
- FDA Diagnostic templates for EUA (Emergency Use Authorization) submissions
- Regulation (EU) MSR 2017/745 and IVDR 2017/746 – Annex I – GSPRs (General Safety and Performance Requirements)
- “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications”, Guidance for Industry and Food and Drug Administration Staff, FDA, 30-Aug-2019

RISK MANAGEMENT PROCESS

Risk management plan

Risk analysis

- *Intended use* and *reasonably foreseeable misuse*
- Identification of characteristics related to *safety*
- Identification of *hazards* and *hazardous situations*
- *Risk estimation*

Risk evaluation

Risk assessment

Risk control

- *Risk control* option analysis
- Implementation of *risk control* measures
- *Residual risk* evaluation
- *Benefit-risk* analysis
- *Risks* arising from *risk control* measures
- Completeness of *risk control*

Evaluation of overall *residual risk*

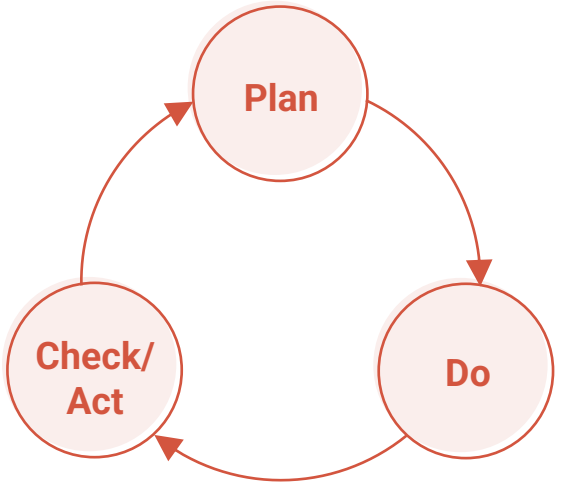
Risk management review

Production and *post-production* activities

- General
- Information collection
- Information review
- Actions

Risk management

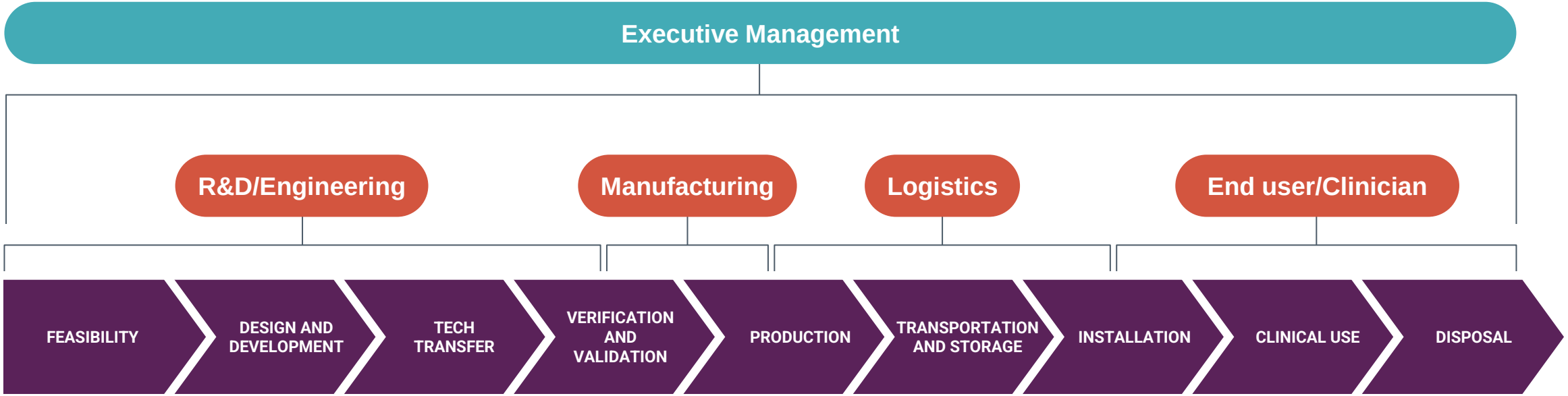
At the highest level:



The cycle repeats over and over throughout the product's lifecycle – NOT "One and Done"

MEMBERS OF THE RISK TEAM

RISK MANAGEMENT RESPONSIBILITIES



MEMBERS OF THE RISK TEAM

ROLE OF EXECUTIVE MANAGEMENT

- Executive management must be the cornerstone of a device manufacturer's risk management process. They:

1

Have responsibility for determining whether product risks are acceptable or not.

2

Are responsible for making sure there are adequate and appropriate resources for conducting risk management activities.

3

Are responsible for ensuring the company's risk management processes are adequate and effective and are described, documented and controlled as part of quality system procedures.

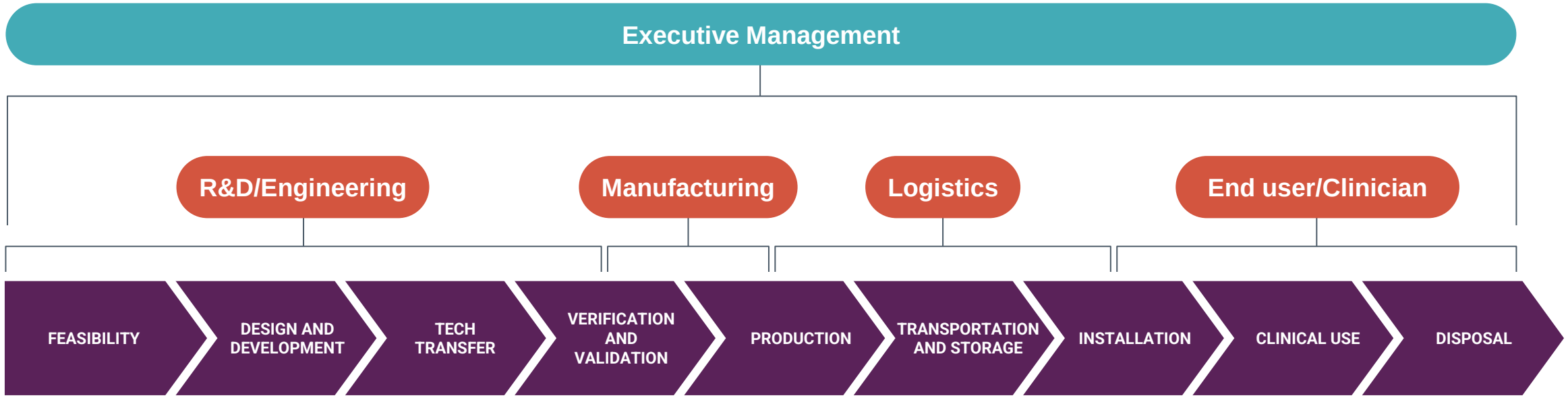
4

Are responsible for defining the company's risk management policy including determining the risk acceptability criteria and ensuring they are based on solid, objective evidence.

MEMBERS OF THE RISK TEAM

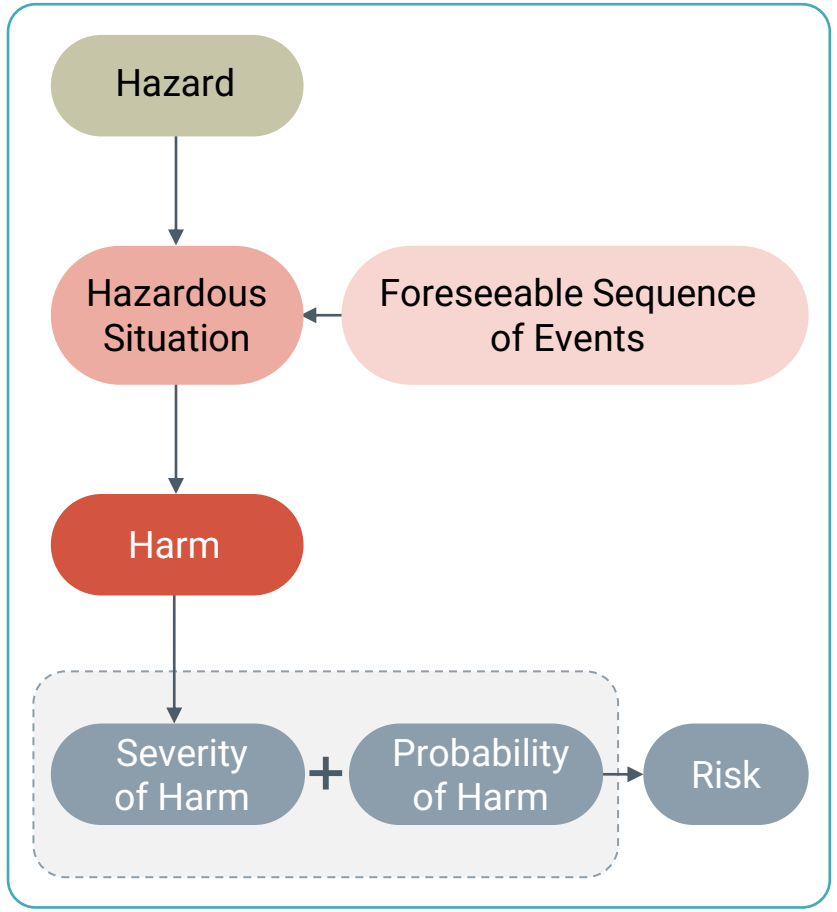
RISK MANAGEMENT PROCESS

- Risk management must involve more than just R&D
- Include end-users/clinicians, marketing, sales, quality, regulatory, manufacturing etc.
- They all provide different perspectives and experiences that are crucial to a holistic, comprehensive approach to risk management



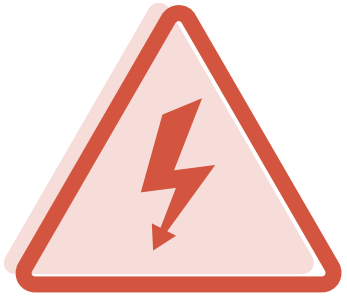
TERMINOLOGY

- **Hazard**
  - Potential source of harm
- **Hazardous situation**
  - Circumstance in which people, property, or the environment are exposed to one or more hazard(s)
- **Foreseeable Sequence of Events**
  - Events that need to happen for the hazardous situation to occur
- **Harm**
  - Physical injury or damage to the health of people, or damage to property or the environment

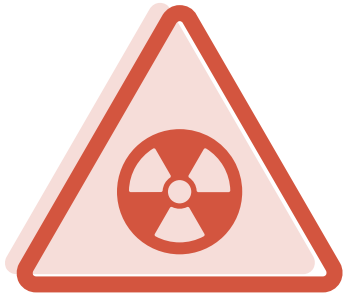


HAZARDS - EXAMPLES

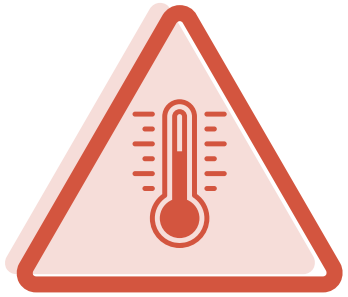
- **Anything that can cause (physical) harm to a patient, operator or the environment**



Electricity



Radiation
(optical, x-ray, radioactivity)



Thermal
(heat, cold)

Mechanical
(crushing, tearing, sharp edges, impacts)

Chemical/Biological
(exposure, infection)

No, or Inappropriate, Treatment

START FROM YOUR INTENDED USE

- When you start a hazard assessment for your device, use your documented **Intended Use Statement** to identify hazards and harms etc for routine use of the device.
- Also, identify any ways the device could be “reasonably foreseen” to be “misused” by the end user either intentionally (e.g. off-label use of the device) or unintentionally. Examples include:
  - Molecular IVD test using with incorrect software
  - IVD test used with a sample type not recommended by the manufacturer
  - Use of test components from different kit lots (same IVD OR different IVD from different manufacturers)
- Walk through every step need for the product to be used and identify any hazards and potential sources of harm

HAZARDS TO CONSIDER FOR IVDs

POTENTIAL HAZARDS TO PATIENT RESULTS:

- Chemical - Batch to batch inconsistency
- Biological - Common interfering factors
- Design - Inadequate test characteristics for intended use
- Transport and storage – Temperature stability of reagents
- Usability - Inadequate specifications (unclear Instructions For Use)
- Usability - over-complicated method
- Use - Carry-over effects
- Use – Errors in specimen collection, preparation, stability
- Use - Specimen ID errors

POTENTIAL HAZARDS FOR THE USER:

- Chemical - Toxic or other harmful ingredients
- Biohazard – Infectious materials
- Chemical or Biohazard - Potential contamination during handling operation and maintenance
- Physical - Packaging design (e.g. lancets - sharp object badly packaged)
- Energy-related equipment hazards

ISO 14971:2019 TABLE C2 – STARTING POINT

General category	Events and Circumstances
Requirements	Inadequate specification of: ▪ design parameters ▪ operating parameters ▪ performance requirements ▪ in-service requirements (e.g. maintenance, reprocessing) ▪ end of life
Manufacturing processes	Insufficient control of: ▪ manufacturing processes ▪ changes to manufacturing processes ▪ materials ▪ materials compatibility information ▪ subcontractors
Transport and storage	Inadequate packaging Contamination or deterioration Inappropriate environmental conditions
Environmental factors	Physical factors (e.g. heat, pressure, time) Chemical factors (e.g. corrosion, degradation, contamination) Electromagnetic fields (e.g. susceptibility to electromagnetic disturbance) Inadequate supply of power Inadequate supply of coolant
Cleaning, disinfection and sterilization	Lack of validated *procedures* Inadequate specification of requirements Inadequate performance of cleaning, disinfection or sterilization
Disposal and scrapping	No or inadequate information provided *Use error*
Formulation	Biodegradation Biocompatibility No information or inadequate specification provided Incorrect formulations *Use error*

General category	Events and Circumstances
Usability	Confusing or missing instructions for use Complex or confusing control system Ambiguous or unclear state of the medical device Ambiguous or unclear presentation of settings, measurements or other information Misrepresentation of results Insufficient visibility, audibility or tactility Poor mapping controls to actions, or of displayed information to actual state Controversial modes or mapping as compared to existing equipment Use by unskilled or untrained personnel Insufficient measurement and other metrological aspects Incompatibility with consumables, accessories, other medical devices Incorrect patient identification Slips, lapses and mistakes
Functionality	Loss of electrical or mechanical integrity Deterioration in performance (e.g. gradual occlusion of fluid or gas path, change in resistance to flow, electrical conductivity) as result of ageing, wear and repeated use Failure of a component due to ageing, wear of fatigue
Security	Unsecured data ports that are externally accessible (e.g. network, serial or USB ports) Data without encryption Software vulnerabilities that can be exploited Software updates without authenticity confirmation

Also: “Applying Human Factors and Usability Engineering to Medical Device", Guidance for Industry and Food and Drug Administration Staff, FDA, 03-Feb-2016

FORESEEABLE SEQUENCE OF EVENTS AND HARMS

- A hazardous situation is one where people, property and/or the environment is exposed to one or more hazard
- For a hazardous situation to occur, there has to be a “foreseeable sequence of events” to lead to it
- Once you identify a hazard, go through each foreseeable sequence of events that can results in a hazardous situation and ultimate harm
- Document each hazard/sequence of events, no matter how “obvious”

Hazard	Sequence of Events	Hazardous Situation	Harm
Biological reagent	1. Vendor obtains product (casein) from multiple sources without disclosing to manufacturer. 2. Lot to lot variability (casein) 3. Variable blocking of non-specific signal. 4. Increased frequency of false positive results.	False positive (e.g. HIV) result reported to clinician	Inappropriate treatment (e.g. patient started on anti-retrovirals)

TERMINOLOGY

- **Risk**
  - Combination of the **probability** of occurrence of harm and the **severity** of that harm

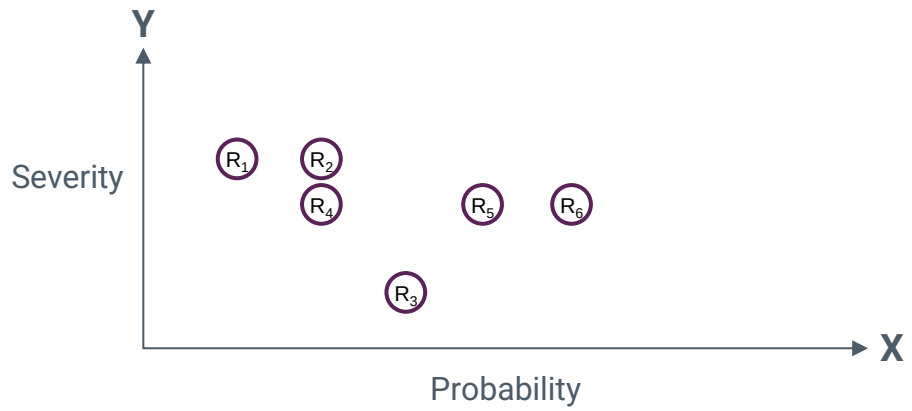
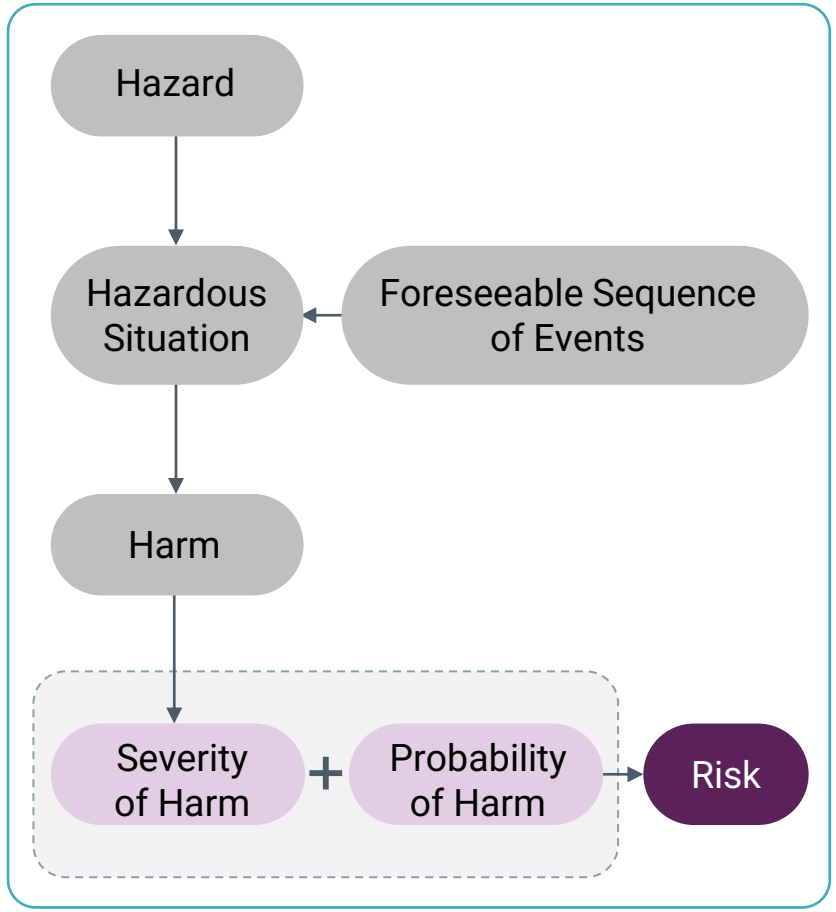


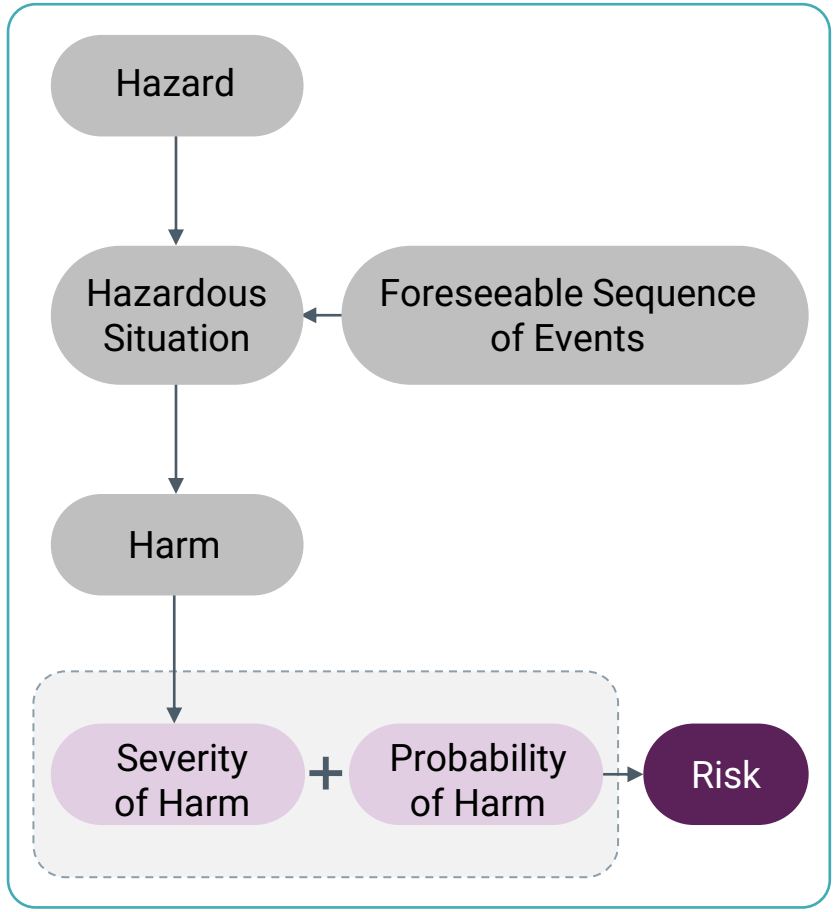
Illustration of Risk as a combination of severity and probability of occurrence of harm

- **Risk Management**
  - Systematic application of… policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk



EXAMPLE OF RISK CONCEPTS

- **Hazard**
  - Elevated temperature and humidity impacts test results
- **Hazardous situation**
  - Test left unpouched (undessicated) at 35’C for 24 hrs prior to use leading to deterioration of test cartridge
- **Harm**
  - E.g. HIV test – False Negative test result leads to case not detected leading to lack of treatment, suffering of patient and early death, and ongoing spread of disease
- **Severity**
  - High???
- **Probability**
  - ????



RISK EVALUATION

EXAMPLES OF SEVERITY LEVELS FOR IVDs

Severity	Harm*	Examples	Assigned Rank
Catastrophic/ Fatal	Results in death	False result where treatment was erroneously initiated or withheld – treatment (or lack thereof) results in death	5
Critical	Results in permanent impairment or irreversible injury	False result where treatment was erroneously initiated or withheld - treatment (or lack thereof) has severe health consequences	4
Serious/Major	Results in injury or impairment requiring medical or surgical intervention	False result where treatment was erroneously initiated or withheld and leads to further interventions	3
Minor	Results in temporary injury or impairment not requiring medical or surgical intervention	False result where treatment was erroneously initiated or withheld but does not lead to further interventions	2
Negligible	Results in inconvenience of temporary discomfort	Invalid test result* or missing test component	1

Severity levels should be chosen and justified by the manufacturer based on the harms that could result from a particular medical device. Note – even “Minor” or "Negligible" issues can become high risk if are frequent

** From ISO 24971*

EXAMPLES OF PROBABILITY SCORES FOR IVDs

Probability	Frequency of Occurrence*	Examples	Assigned Rank
Frequent	1 in 100	Reasonably likely to occur during a single test	5
Probable	1 in 1000	Likely to occur during 1,000 tests	4
Occasional	1 in 10,000	Likely to occur during a single batch/lot of 10,000 tests	3
Remote	1 in 100,000	Not likely to occur during 100,000 tests (10 lots)	2
Improbable	1 in 1,000,000	Not likely to occur during 1,000,000 tests (100 lots – this could be multiple years of production)	1

Probability scores should translate to the company's IVD manufacturing practices and scope/scale of production

- At least three levels should be identified
- Definitions of probability ranges can be the same OR different for different product families

** From ISO 24971:2020*

RISK EVALUATION

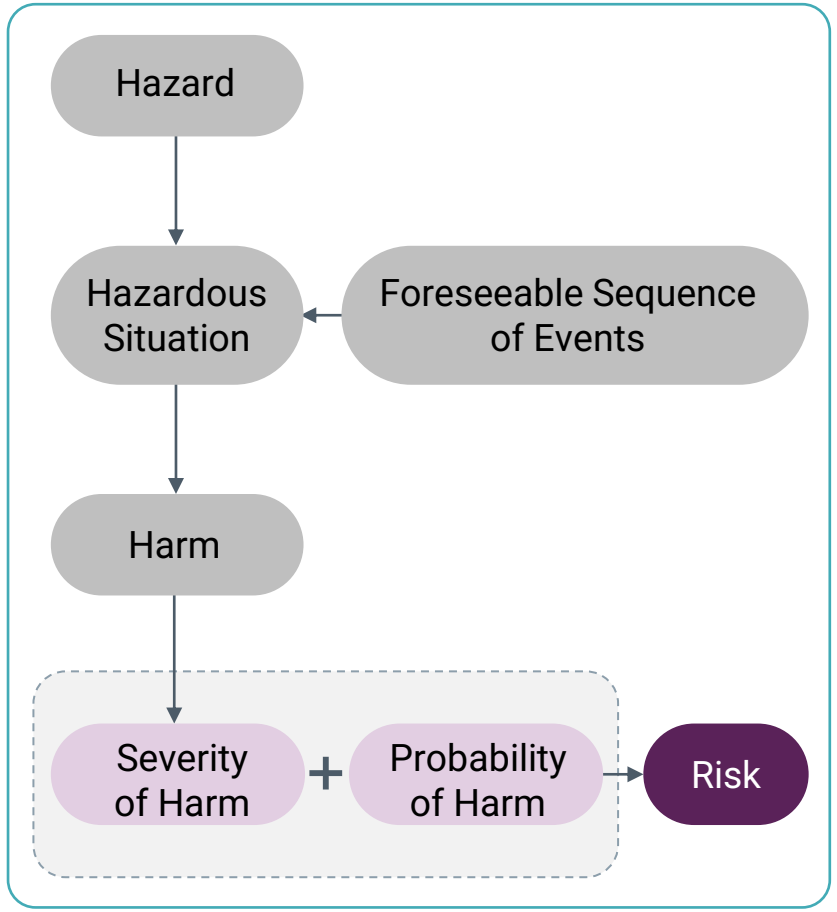
SEVERITY AND PROBABILITY

- There is no industry standard for severity and probability of occurrence.

When estimating severity and occurrence for harms, leverage objective evidence wherever possible to support your estimates.

Examples:

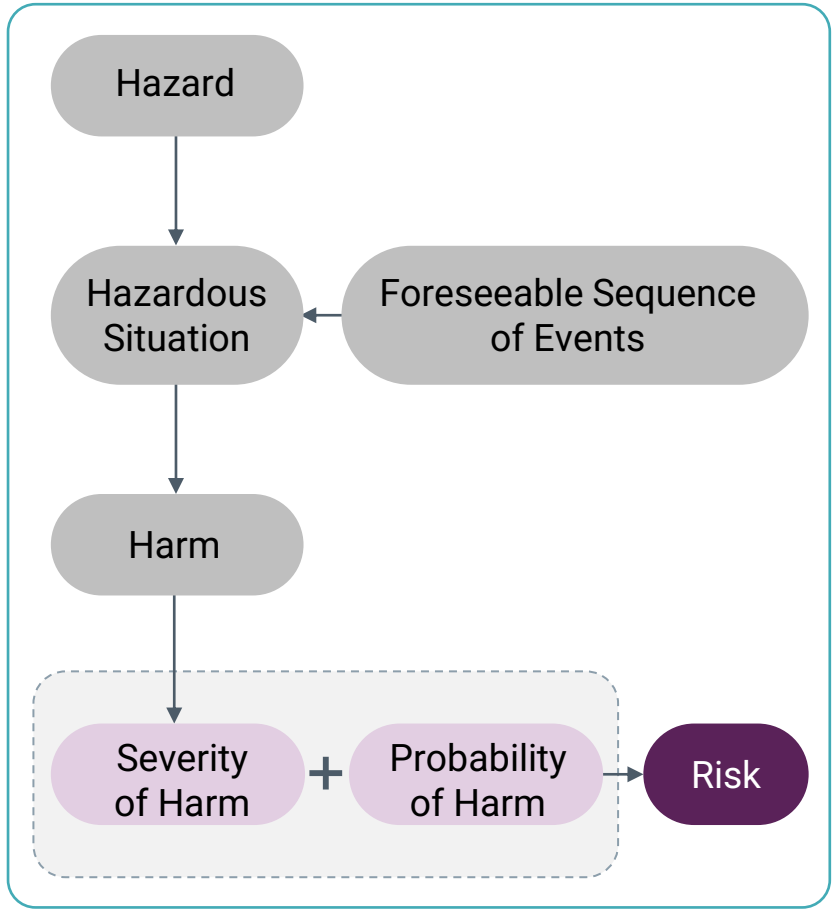
- Similar products
- Regulatory data (reported adverse events)
- Scientific white papers
- Industry standards
- End-user expertise
- Supporting test data



RISK EVALUATION

EXAMPLE OF RISK CONCEPTS

- **Hazard**
  - High temperature and humidity
- **Hazardous situation**
  - Test left unpouched (undessicated) for 24 hrs prior to use leading to deterioration of test cartridge
- **Harm**
  - E.g. HIV test – False Negative test result leads to case not detected leading to lack of treatment, suffering of patient and early death, and ongoing spread of disease
- **Severity**
  - Catastrophic /Fatal = 5
- **Probability**
  - Beginning of project – no IFU: Probable = 4



HOW TO DETERMINE RISK ACCEPTABILITY

Severity x Probability = Risk Priority Number

- RPN is a way of quantifying if the remaining (residual) risk is acceptable
- RPN drives your **Risk Acceptability Matrix**

RPN (Risk Priority Number)	Risk Grade	Description	Risk Reduction Required?	Benefit/Risk Required?
R1 ≤ 5	Low	Low level of risk. Further mitigations should be considered wherever practicable.	No	No*
R2 = [6 to 12]	Medium	Further mitigations required to **reduce the risk as far as possible**.	Yes	Yes
R4 ≥12	High	Every effort should be made to reduce the risk; technical practicability is balanced against risks and benefits, with the risk being reduced even at considerable cost.	Yes	Yes

** For IVDR, ALL harms require a benefit/risk analysis!*

RISK EVALUATION

RISK ACCEPTABILITY MATRIX

	Negligible No risk (1)	**Minor** Inconvenience or discomfort (2)	**Serious** Short term injury/impairment (3)	**Major** Severe/long-term injury, disability (4)	**Critical** Life-threatening injury/death (5)
Frequent 1 in 100 (1)	1	2	3	4	5
Probable 1 in 1000 (2)	2	4	6	8	10
Occasional 1 in 10,000 (3)	3	6	9	12	15
Remote 1 in 100,000 (4)	4	8	12	16	30
Improbable 1 in 1,000,000 (5)	5	10	15	20	25

- Are risk levels acceptable? (feedback from clinical/medical required, not just manufacturer)
- Is risk reduction required? **Yellow** and **Red** require Risk Reduction As Far As Possible

RISK EVALUATION – ACCEPTABILITY

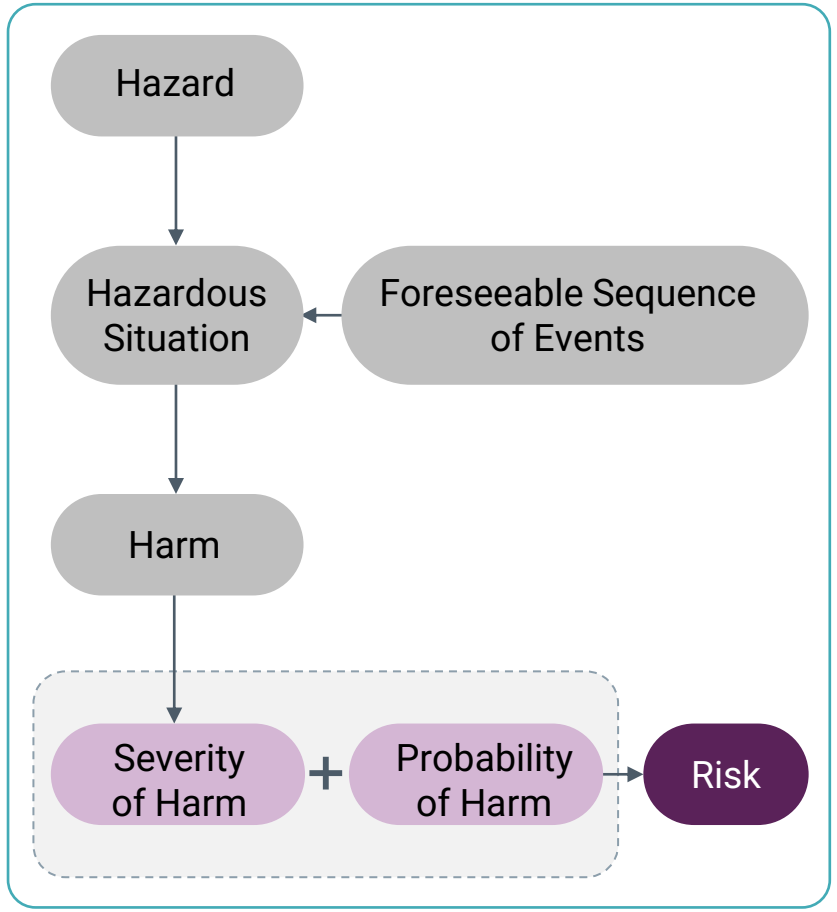
- **No** standards will define risk acceptability. This is the Manufacturer's responsibility.
- The manufacturer should evaluate risk acceptability for **each individual device or device family, dependent on its characteristics and intended use**
  - *Risk Acceptability is NOT "One and Done" – have to show you are thinking about the specific product!*
  - E.g. risk of a false positive result for an HIV test is different from a fertility prediction test
- **Explain** why each score category **is or is not acceptable** to the company for that product *(i.e. why a score ≤5 [green] is acceptable but a score 6-12 [yellow] vs >12 [red] is not?)*

RISK CONTROL

EXAMPLE OF RISK CONCEPTS

- **Hazard**
  - High temperature and humidity
- **Hazardous situation**
  - Test left unpouched (undessicated) for 24 hrs prior to use leading to deterioration of test cartridge
- **Harm**
  - E.g. HIV test – False Negative test result leads to case not detected leading to lack of treatment, suffering of patient and early death, and ongoing spread of disease
- **Severity**
  - Catastrophic/Fatal = 5
- **Probability**
  - Beginning of project, no IFU:
    Probable = 4 **RPN 5 x 4 = 20 = HIGH RISK !**

So now what do we do?



RISK CONTROLS (MITIGATIONS) AND RISK ARISING FROM RISK CONTROL

After risk is evaluated, if risk reduction is required, risk controls need to be applied = **how can you reduce the risk?**

Risk Control options (in order of preference):

- Directly, inherent safety by design
- Indirectly, protective measures *(for the device or for the manufacturing process)*
- By instruction – e.g. Information for safety *(product labelling as risk control is the least preferred option!)*

It is a best practice to include multiple Risk Controls to reduce risk.

Caveat: Instruction ≠ Information

Information by itself (e.g. warnings stating residual risks) is not enough to mitigate risks. However, warnings are commonly used to **emphasize instructions**.

E.g. Warning – Do Not Freeze. Device will produce an inaccurate result. Store device at 2 to 30 °C.

RISK CONTROLS (MITIGATIONS) AND RISK ARISING FROM RISK CONTROL

All risk control measures must be documented, and objective evidence identified to show the risk control was effective (Verification or Validation).

One you have implemented a Risk Control, you may not be done!
Go back and analyze to see if **new hazards** or hazardous situations (= new or changed risk) may have been introduced.

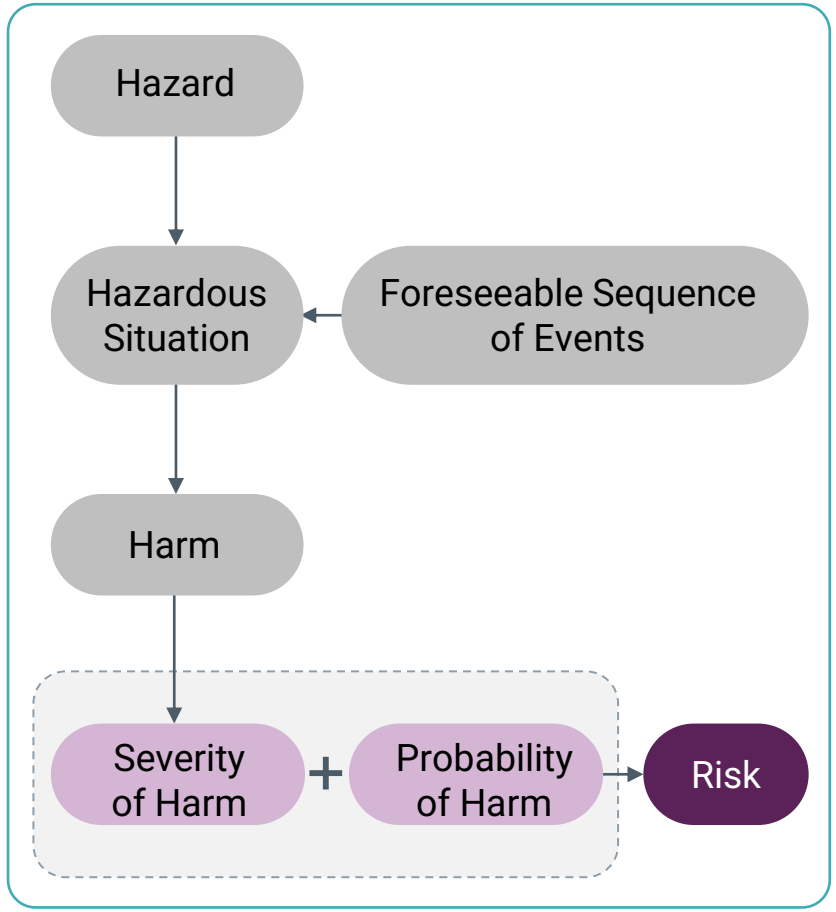
Already estimated risks for a hazards are affected by the introduction of the risk control measures (for IVDs, while it is possible to reduce the severity of an identified harm, a Risk Control will have the most significant impact on the probability of occurrence of harm).

It is best practice to identify specific Design Outputs, Design Verifications and/or Design Validations as your Risk Control measure, representing objective evidence that verifies Risk Control has occurred and is determined to be effective (or not).

RISK CONTROL

ILLUSTRATION OF RISK CONCEPTS

- **Hazard**
  - High temperature and humidity
- **Hazardous situation**
  - Test left unpouched (undessicated) for 24 hrs prior to use leading to deterioration of test cartridge
- **Harm**
  - E.g. HIV test – False Negative test result leads to case not detected leading to lack of treatment, suffering of patient and early death, and ongoing spread of disease
- **Severity**
  - Catastrophic/Fatal = 5
- **Probability**
  - Beginning of project, no IFU:
    Probable = 4 RPN 5 x 4 **= 20**
  - Implement IFU with warnings:
    Occasional = 3 **RPN 5 x 3 = 15 HIGH**



RESIDUAL RISK EVALUATION AND BENEFIT/RISK STATEMENT

Residual risk = the risk that remains after risk controls have been applied

If the residual risk is not acceptable, **further controls** shall be applied

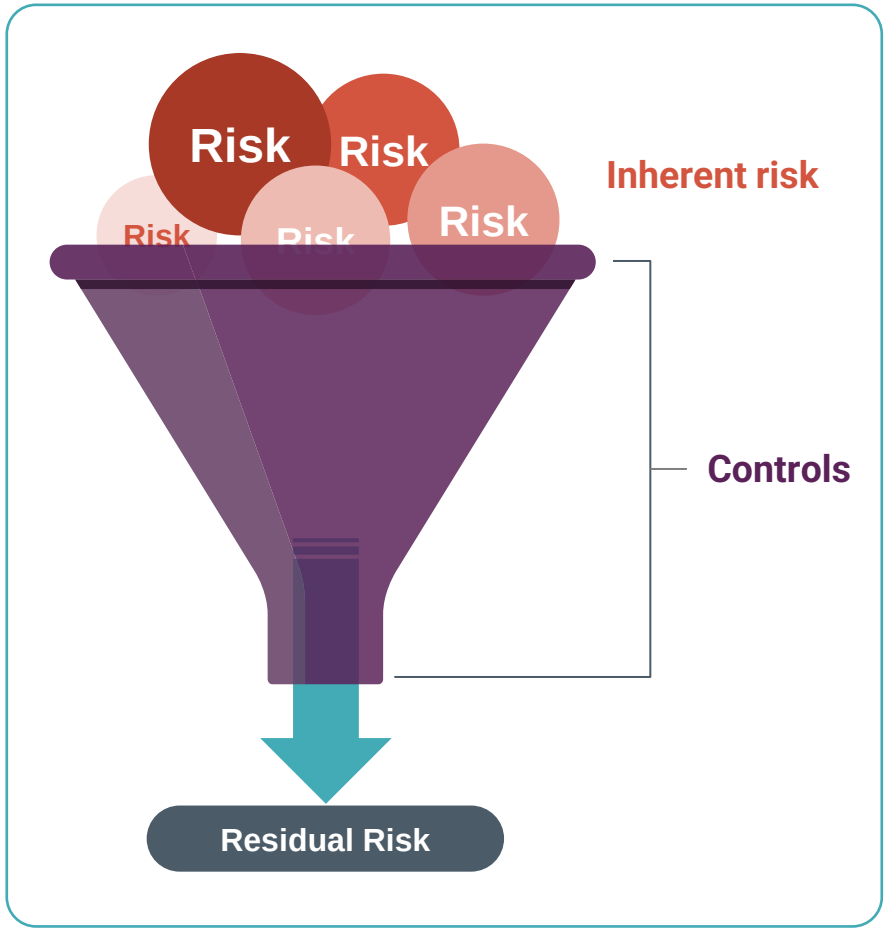


ILLUSTRATION OF RISK CONCEPTS

Probability

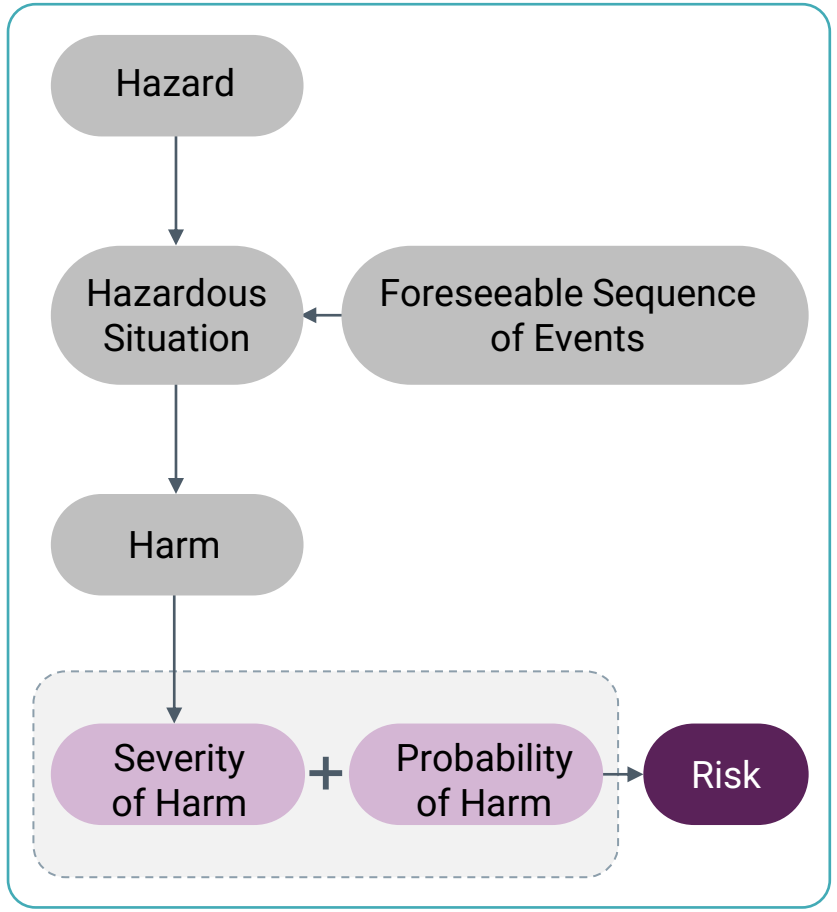
- Beginning of project, no IFU: Probable = 4 RPN 5 x 4 **= 20**
- Implement IFU with warnings: Occasional = 3 RPN 5 x 3 **= 15**

RPN is still unacceptable; can we do anything more?

Probability

- Before good IFU: Probable = 4 RPN 5 x 4 **= 20**
- After good IFU: Occasional = 3 RPN 5 x 3 **= 15**
- Implement an Operator Training program:
  Remote = 2 RPN 5 x 2 **= 10**

RPN is to reduce AFAP; so now what can we do?

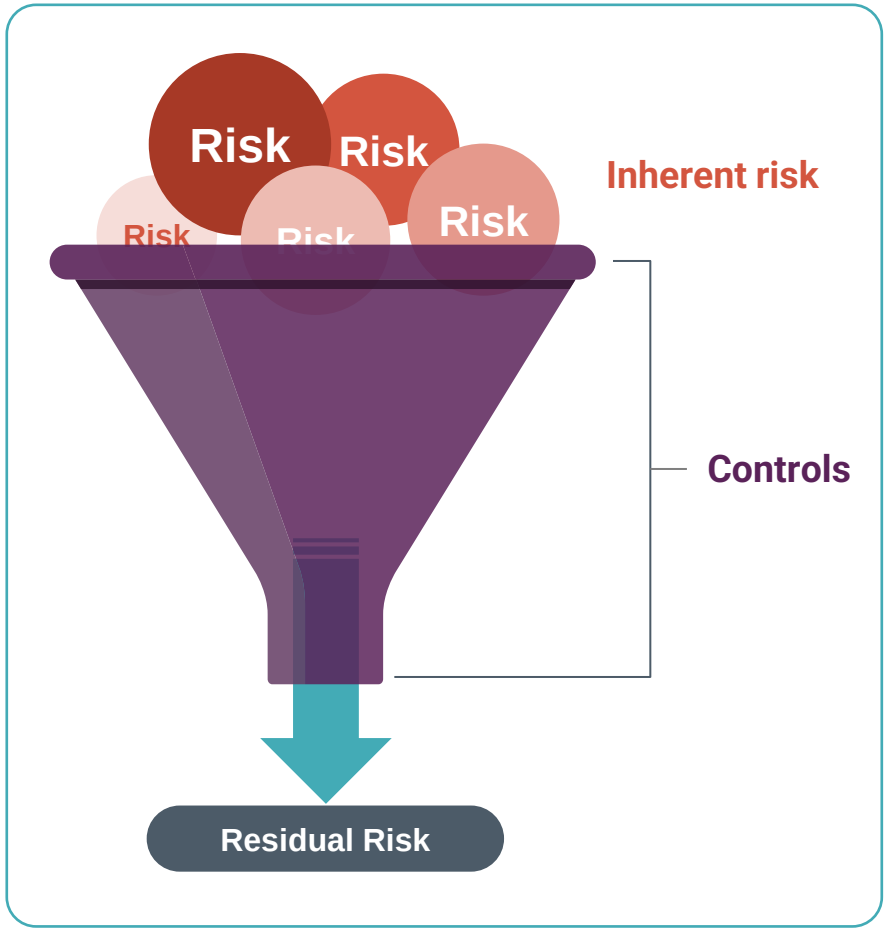


RESIDUAL RISK EVALUATION

Residual risk = the risk that remains after risk controls have been applied

Use the same severity, probability, risk level and risk acceptability criteria used throughout the process to determine if residual risk meets acceptable levels.

If the residual risk for one hazard is not acceptable, **every effort should be made to apply further risk controls**.

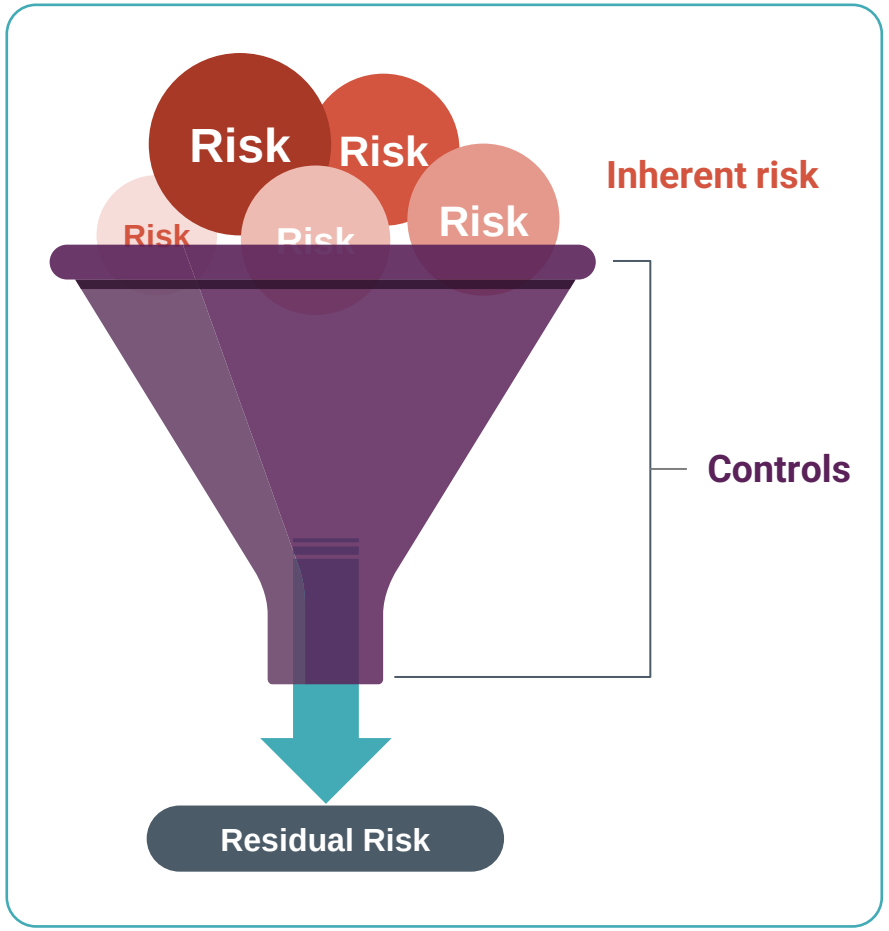


RESIDUAL RISK EVALUATION AND BENEFIT/RISK STATEMENT

There are times when risk can not be designed/labelled away.

If residual risk (for one hazard or for the entire device overall) is not acceptable and further controls not applicable, the manufacturer should determine **if the medical benefits of the intended use outweigh the residual risk**.

The manufacturer needs to conduct a **Benefit/Risk Analysis** and document the outcome in the Risk Management Report to clearly justify WHY the residual risk is determined to be acceptable.



HOW DO I KNOW IF RESIDUAL RISK IS ACCEPTABLE?

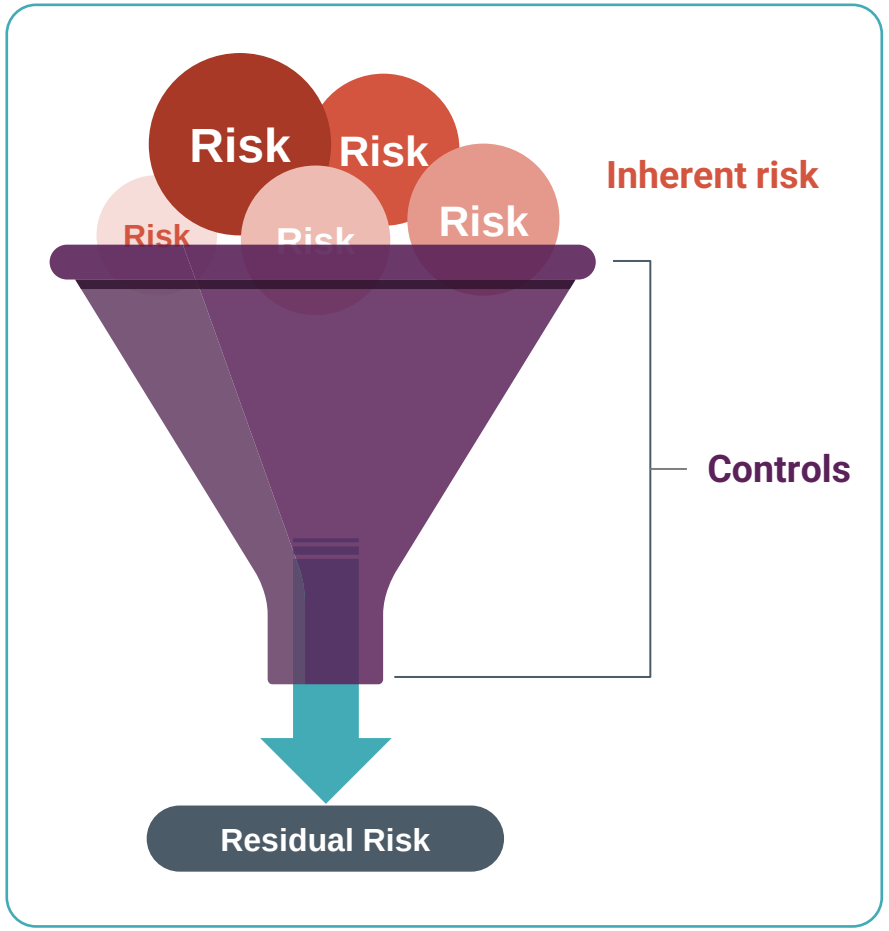
- [Use applicable international safety standards (e.g. IEC for electrical components testing) if available and applicable to the device
  - Compliance with such a standard can assume residual risks have been reduced to acceptable levels ***unless*** there is objective evidence to the contrary]
- Compare levels of known risks from similar devices already in use and the “state of the art” (publications, FDA warning letters)
- Discuss with external clinical experts and key opinion leaders (try to get >1 opinion) – is the risk acceptable in their opinion?
- Evaluate your Analytical and Clinical Performance data, Production data, Usability/Human Factors study data – is your probability estimate correct?

RESIDUAL RISK EVALUATION AND BENEFIT/RISK STATEMENT

- Example:
  - Cancer screening test has sensitivity of 50% for the biomarker, but is the only test that can be run in community health clinics
  - Consultation with clinicians/Key Opinion Leaders says it is better to have sensitivity of 50% than to not screen at all
  - Therefore this risk is acceptable

This statement/analysis should be signed by senior management

- For risks outweighed by benefits, the manufacturer shall decide which risk(s) to disclose
  - Warnings
  - Cautions
  - Contra-indications



Reference: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
https://www.fda.gov/media/99769/

ILLUSTRATION OF RISK CONCEPTS

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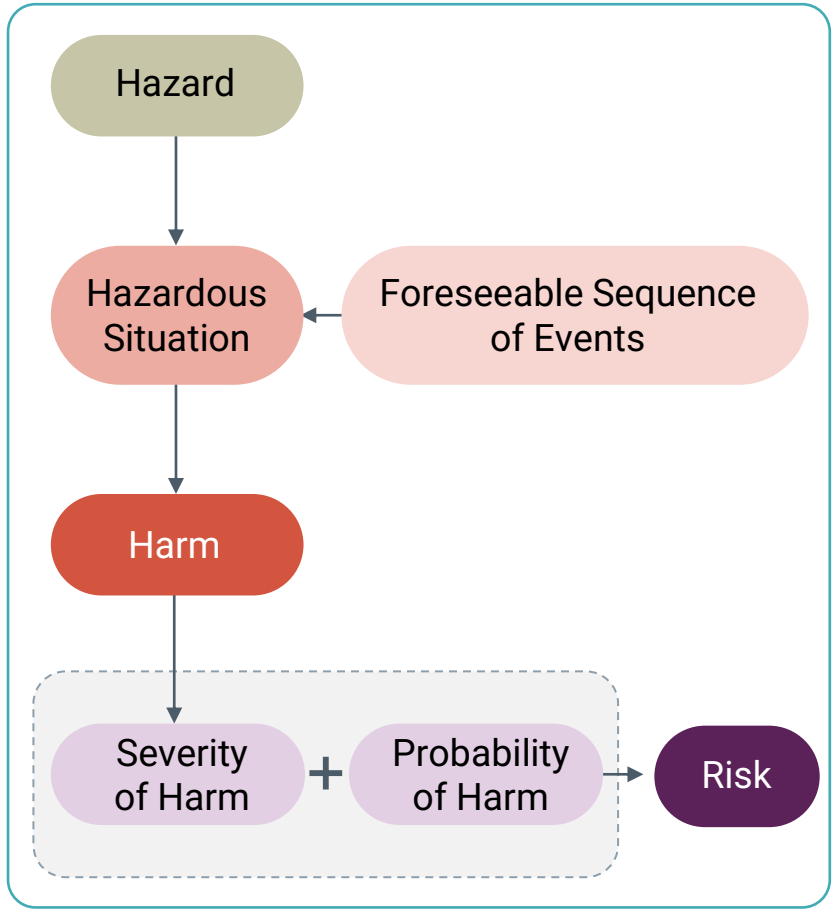
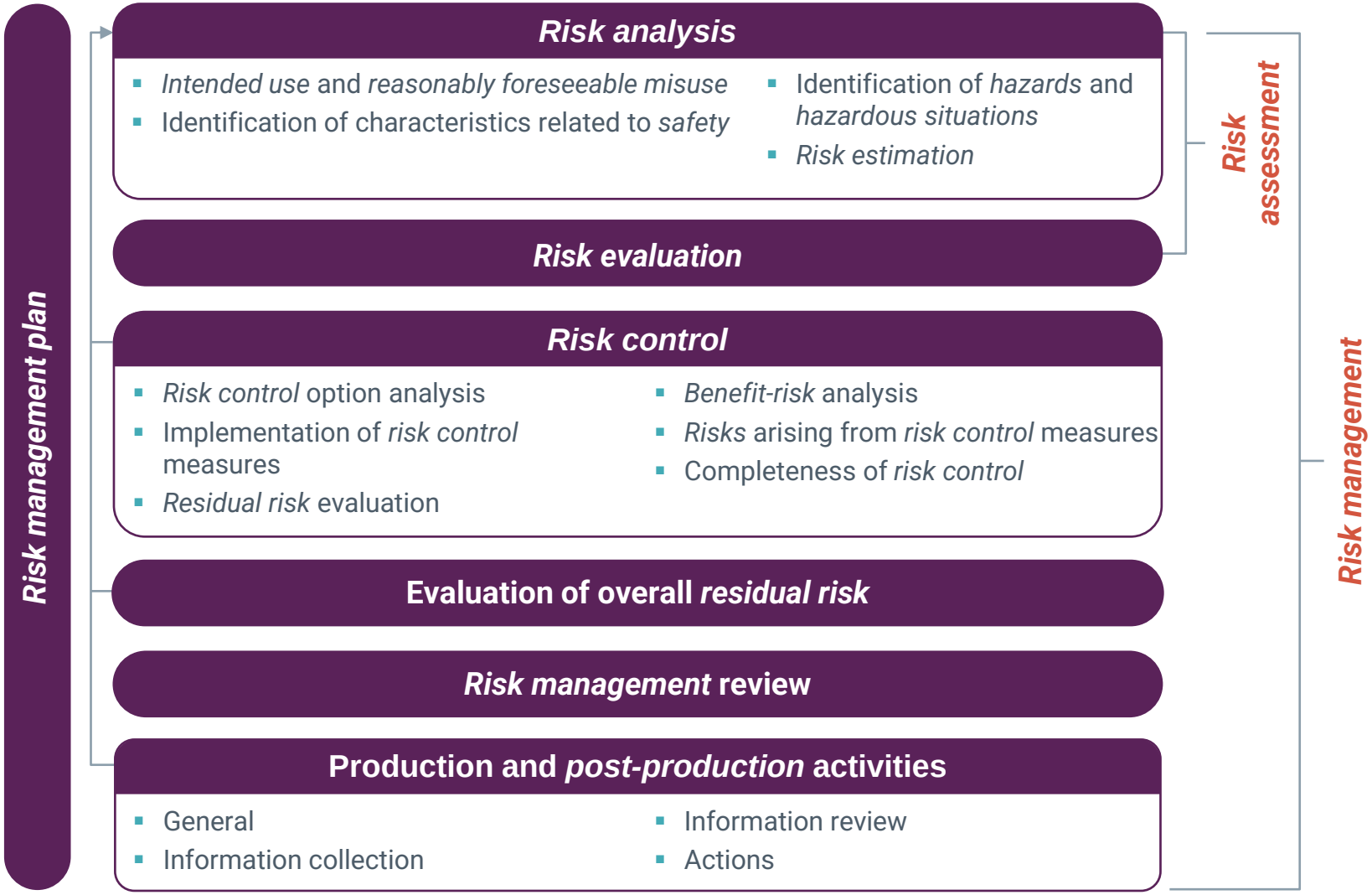
  Remote **= 2** RPN 5 x 2 **= 10**

Senior management determines risk is reduced as far as possible and signs off on risk report



RISK MANAGEMENT PROCESS



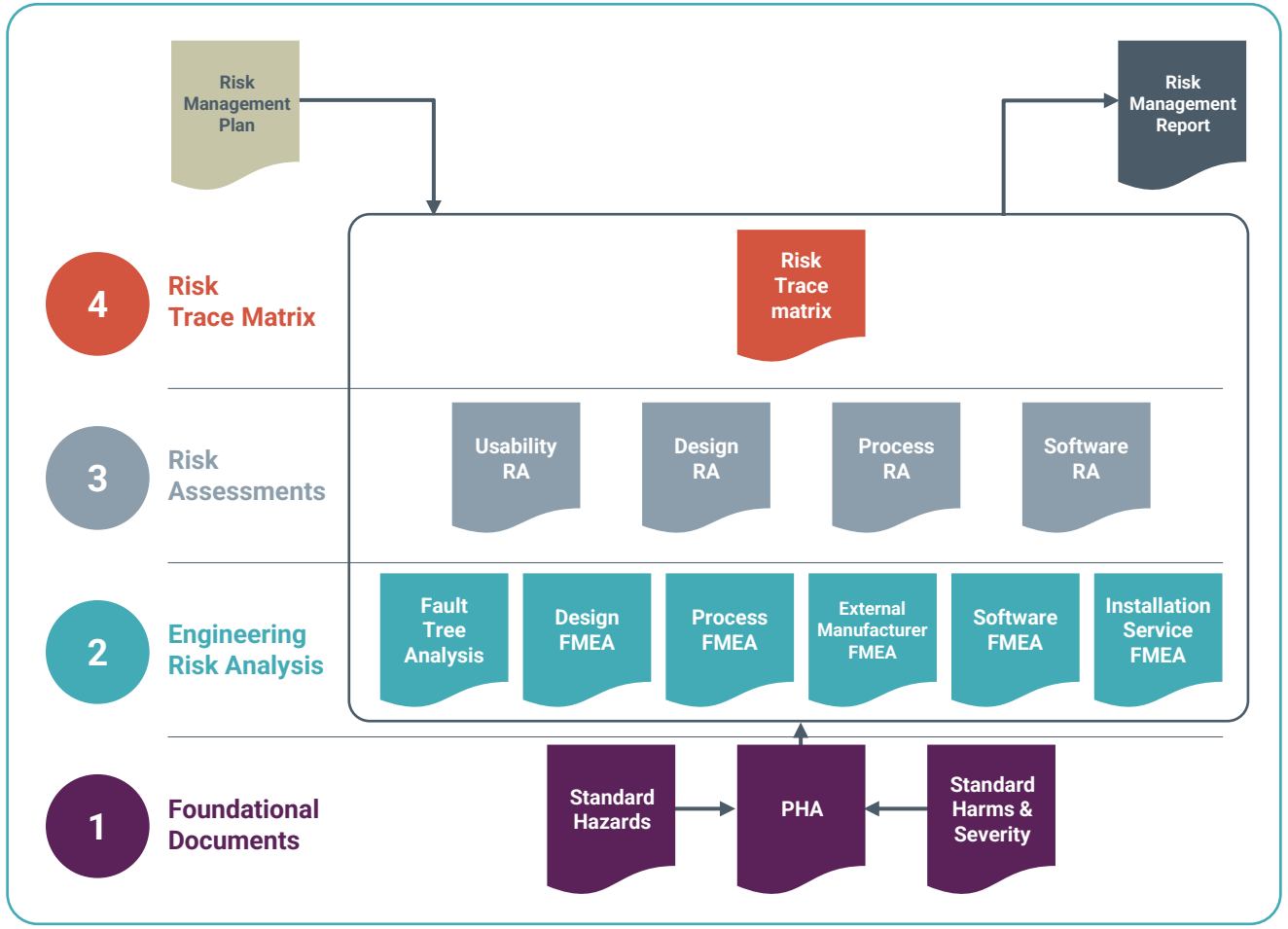
RISK MANAGEMENT FILE

A Living File for Each Device

Should contain evidence of:

- Risk Management Plan
- Risk Analysis (hazard identification)
- Risk Evaluation (severity, probability, RPN)
- Risk Controls (documented evidence)
- Determination of Risk Acceptability (signed statement)
- Risk Management Reviews
- Feedback on Production and Post-Production Risks

The Risk Management File will be inspected during audits and regulatory submissions. It must be kept up to date throughout the life of the product.



https://www.achievexl.com/blog/risk-management-file-structure-made-easy

GENERATING A RISK MANAGEMENT PLAN

- Define the scope – i.e. which product is included (may have multiple products in one plan)
- Describe the intended use of the product(s)
- Define your risk management process
- Identify all risk management activities that will be planned throughout the product life cycle
- Determine what references/harmonized standards you will apply
- Define critical terms
- Establish management roles and responsibilities
- Determine types of people needed on the risk team (diverse and suitable qualifications, including Subject Matter Experts familiar with the clinical use of the product, its technologies etc) and who will be reviewing and approving risk documentation
- Define how you will evaluate risk (severity and probability)
- Determine how you will verify acceptability of risk
- Determine frequency of risk management review
- Specify methods to verify Risk Control measures are implemented to reduce risk to pre-established acceptable levels
- Determine how you will evaluate production and post-production risks
- Document the plan (i.e. write an SOP)

RISK MANAGEMENT REVIEW

Before making a regulatory submission and/or before going to market, review the results of all steps in your risk management process to ensure completeness

Poor risk management is a common flaw in regulatory submissions

Risk should also be evaluated periodically post launch and the timeframe for evaluation defined in the Risk Management Procedure

PRODUCTION AND POST-PRODUCTION RISK MANAGEMENT

Much of the risk analysis and risk evaluation activities rely on experience and educated guesses of the risk management team…
… therefore we need to monitor how the device is working in real life over the long term and take actions where needed!

Establish a system to collect information about the device (e.g. Production/Quality Controls, Post-Market Surveillance activities)

- Internal audits
- External audits
- Non-conformities and Corrective/Preventive Actions
- Customer Complaints
- Production/Process Controls and Monitoring

The information gathered shall be evaluated for:

- previously unrecognized hazards
- already estimated risks are no longer acceptable

Additional Risk Assessments performed as needed

Risk Management File shall be reviewed/updated accordingly

RISK ANALYSIS TECHNIQUES

There are many ways to conduct a Risk Analysis; common techniques are listed below.

- Preliminary Hazard Analysis (PHA)
- Failure Mode and Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Event Tree Analysis (ETA)
- Hazard and Operability Analysis (HAZOP)
- Hazard Analysis and Critical Control Point (HACCP)

Reference: ISO 24971

RISK ANALYSIS TECHNIQUES

The intention of ISO 14971 is to use more than just FMEA for Risk Management; this is to ensure broad coverage of risks in both "normal" and "failure" user modes.

- Preliminary Hazard Analysis (PHA) → **Good technique to use early in the development process**
- **Failure Mode and Effects Analysis (FMEA)) → Industry standard for IVD risk analysis**
- Fault Tree Analysis (FTA)
- Event Tree Analysis (ETA)
- Hazard and Operability Analysis (HAZOP)
- Hazard Analysis and Critical Control Point (HACCP)

Reference: ISO 24971

RISK DOCUMENTATION

RISK ANALYSIS USING FMEA - FAILURE MODE AND EFFECTS ANALYSIS

Inductive technique asking the question: “What happens if?…”

Components are analyzed one at a time

FMEA may be done “bottom-up” or “top-down”

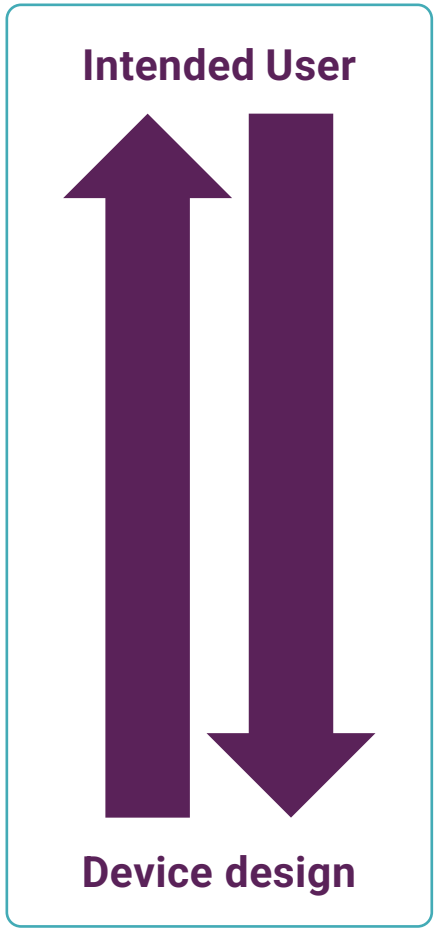
Strengths:

- Industry standard
- Can be used for design, manufacturing, intended use (usability), post-,market surveillance

Weakness:

- Analyses a single point of failure and not multiple failure points and how they may interact; effort should be made to consider double fault conditions

Three types of FMEAs: design (d)FMEA, use (u) FMEA and process (p)FMEA



DESIGN (D) FMEA

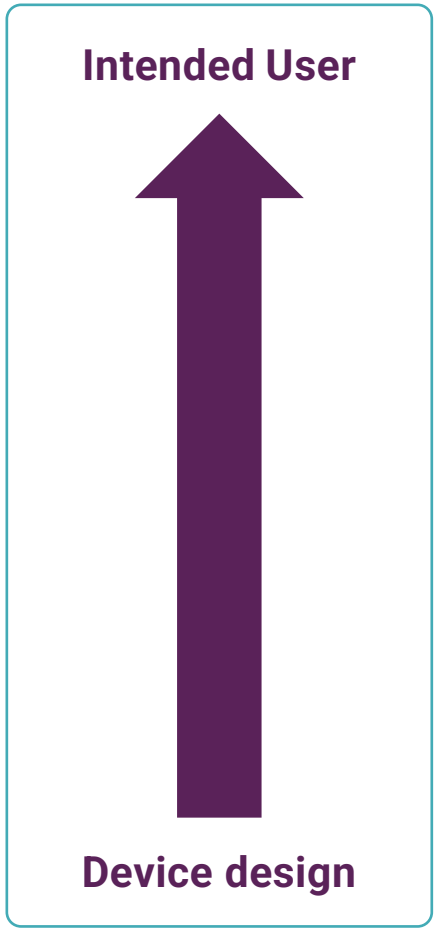
Design (d)FMEA - identifies, prioritizes, and mitigates the **device design** and assembly failure modes

dFMEA is a **bottom-up analysis** of possible failure modes:

How can this device fail based on how it was designed?

Driven by intended use and design inputs/requirements

- What is the effect on the end user in terms of potential harm?
- What are the possible causes of this failure?
- What is the anticipated percentage of patients who may be harmed by this failure?
- What actions can be taken to prevent or mitigate this failure mode?



USE (U) FMEA

Use (u)FMEA – Identifies, prioritizes, and mitigates the **product use** and functional failure modes.

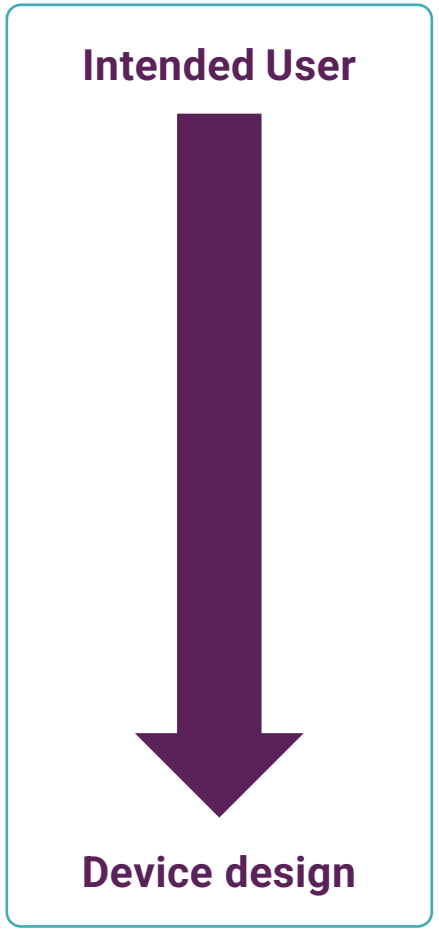
A use failure mode occurs when the design fails to perform as intended due to incorrect use by the consumer.

Incorrect use can occur when the user fails to follow the guidelines provided in the Instructions for Use (IFU).

uFMEA is a **top-down analysis** of failure modes: *How can the product fail when it is in use?*

Driven by product design and Instructions for Use

- What is the effect on the end user in terms of potential harm?
- What are the causes of this failure, including known misuses?
- What is the anticipated percentage of patients who may be harmed by this failure?
- What actions can be taken to prevent or mitigate this failure mode?



PROCESS (P) FMEA

Identifies, prioritizes, and mitigates the **process and equipment** failure modes

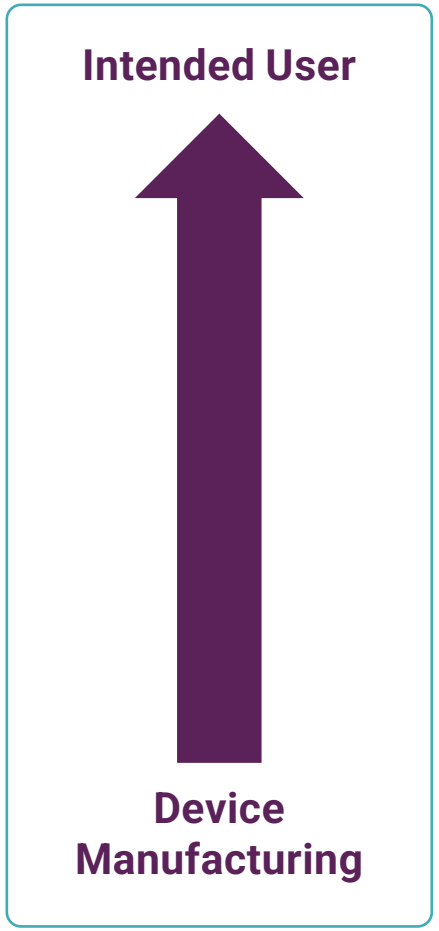
pFMEA analyzes the possible failure modes in each process, and it identifies how the process can affect the end user by failing to meet required specifications

pFMEA is caused by failure modes (identified in the Use or Design FMEA) related to the design's manufacturing processes

pFMEA is a **bottom-up analysis** of work instructions, equipment settings, material handling, and fixtures:

- What portions of the manufacturing process could be completed incorrectly?
- What is the impact of suppliers/reagents on the product?
- In what ways can a part be out of specification in each stage of operation?
- What are the effects of these possible risks on the process and product in terms of failure or design risk?
- What is the percentage of patients who may be harmed by this failure?
- What actions can be taken to prevent or mitigate identified failure modes?

Same iterative process used for other FMEAs; when add in **detectability** of failure and identification of **inspection method = Control Plan**



COMMON RISK MANAGEMENT NONCONFORMITIES

- ‘Old’ product – on market for 20 years
  - No product changes (design change or updated indications for use) therefore no RM update required is possible, but documented risk reviews should be carried out)
- No national regulatory requirements stated (but international sales?)
- No active surveillance of updates of regulatory requirements or revision of standards
- Poor understanding of the standards
  - No justification on how residual risks (benefit/risk evaluation) were deemed acceptable
- Personnel
  - Poor RM training/competencies
  - No medical/clinical representative or end user on Risk Team
- No management commitment
- Not following own procedure
  - Controls not carried out *(e.g. warnings, stability claims not in labelling / IFU; warnings on labelling but not in RM file)*

COMMON RISK MANAGEMENT NONCONFORMITIES CONT.

- Incomplete / inappropriate hazard identification
  - Not including end user risk in countries of sales of product (sub-Saharan Africa?), including stability in challenging environments
  - Foreseeable misuse not considered
  - Not including production / outsourcing risk
  - Not including full life cycle (including disposal)
- Documentation absent or incomplete
  - Especially RM report
  - No uFMEA/ evaluation of IFU
  - No statement of overall risk acceptability (only for individual risks)
  - No post-production/post-market updates procedure
- Inappropriate ratings (severity and probability scores, risk acceptability criteria)
  - Numbers ‘made’ to fall below action limits

KEY TAKEAWAYS

1

Risk management is critical to safe and effective device design

2

FMEAs are a useful tool for Risk Management of IVDs

3

Think “around” the product (d/u/pFMEA)

4

Good risk management takes time and effort but delivers on:

- Reduced product development costs
- Increased production efficiency and reduced waste
- Reduced customer complaints

5

Risk management does NOT end once your product gets to market

FIND

QUESTIONS & FEEDBACK