MEDICAL DEVICE CONSULTANTS, INC.

Risk Analysis in Design and Development of Medical Devices

ASQ BOSCON 2007
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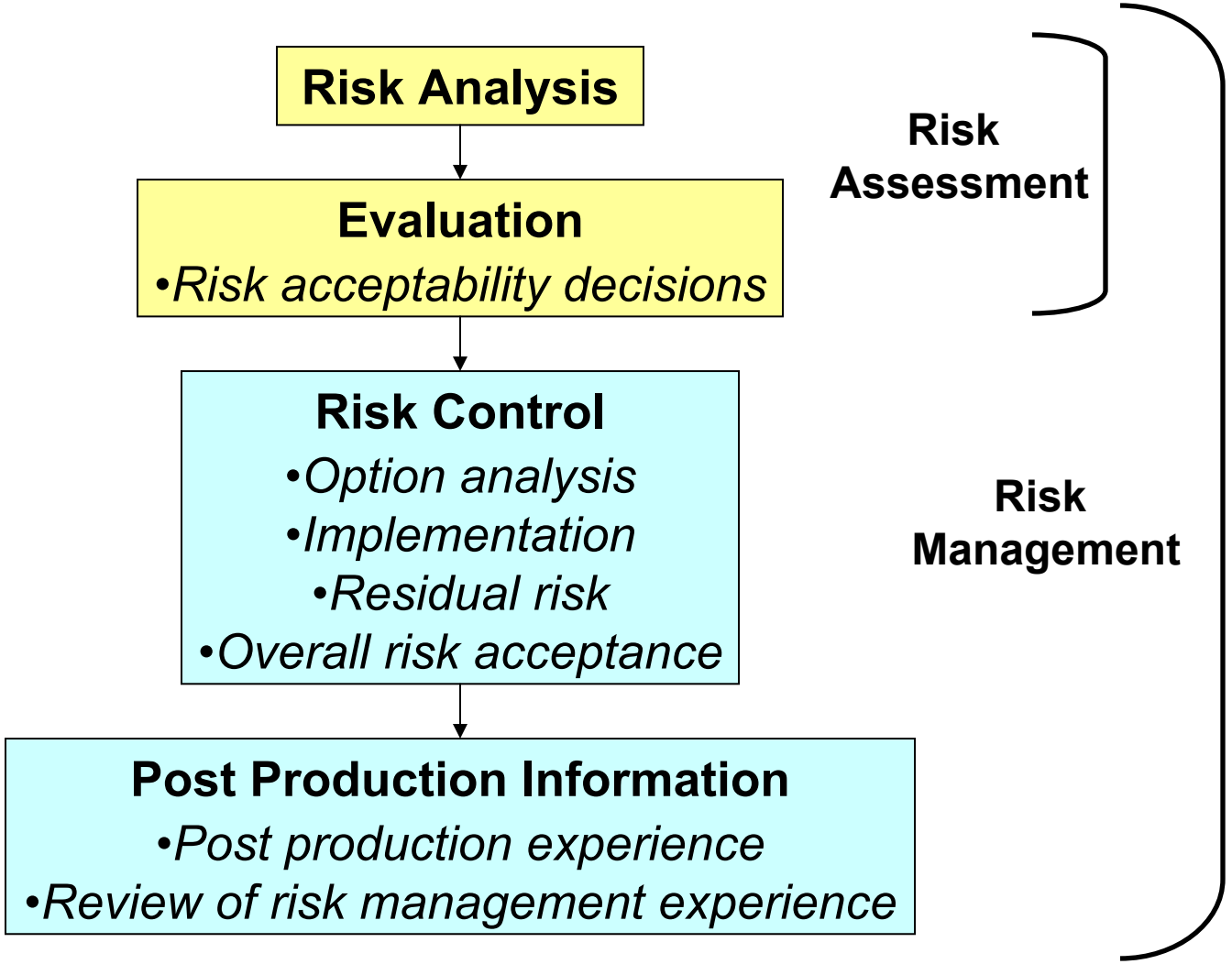
ISO 14971:2000

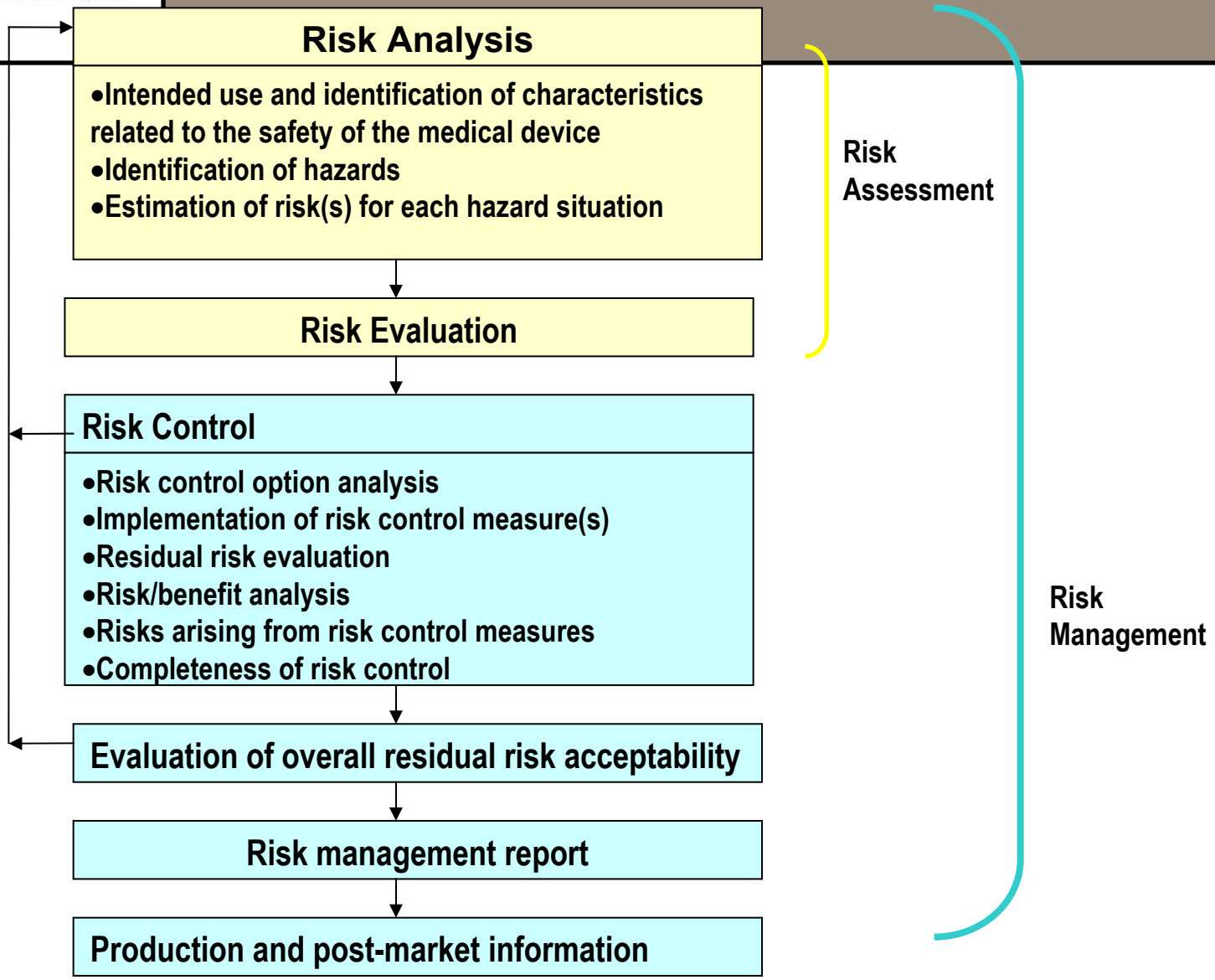
- **Current Standard ISO 14971:2000**
- **Amendment ISO 14971:2003 - Rationale for requirements**

ISO 14971:2007

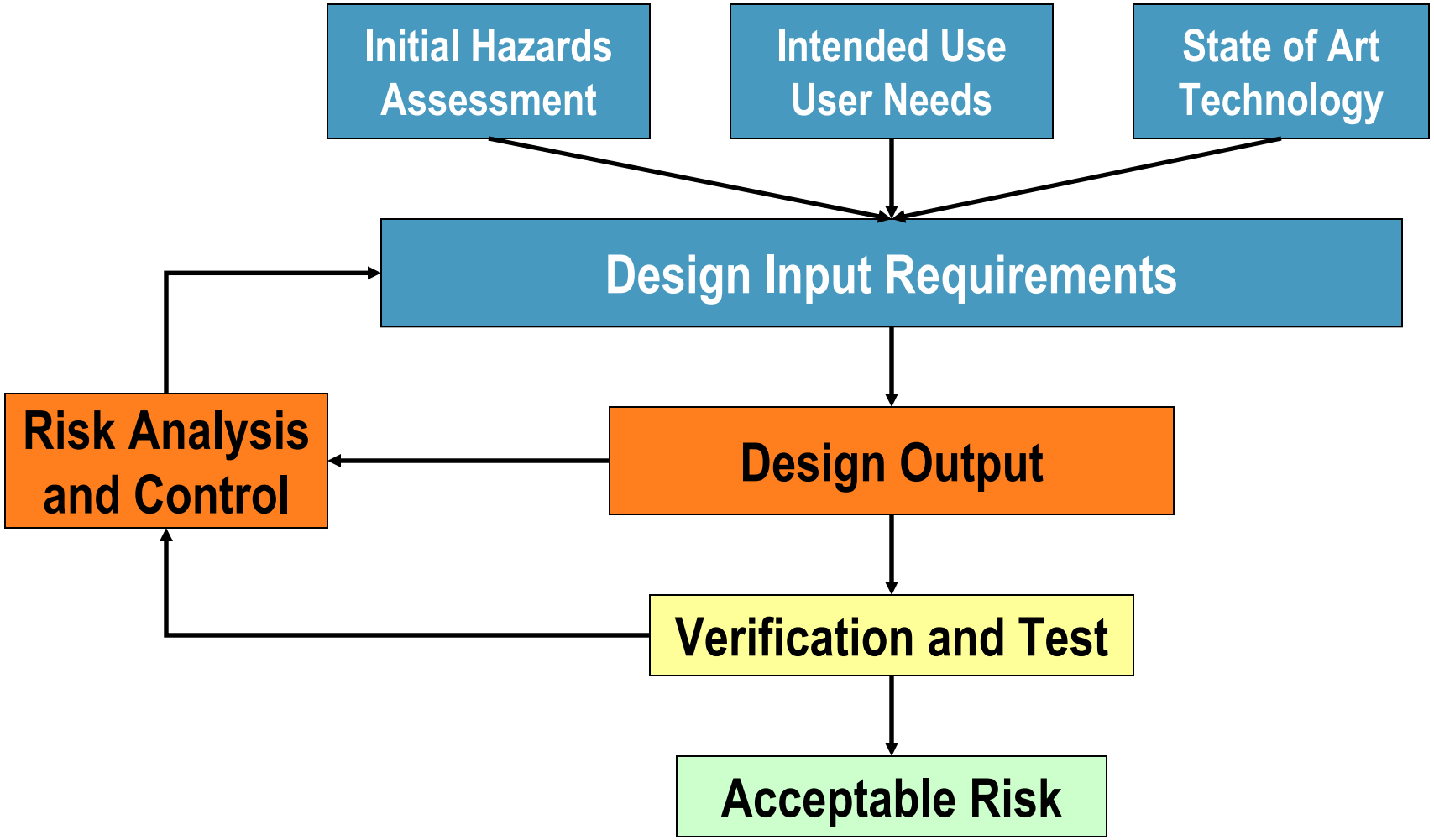
- **ISO 14971:2007 – Issued in February**
- **Contains expanded Annexes with more examples**
- **Includes the 2003 amendment – Rationale for requirements**
- **Some notable changes/additions**
  - Risk arising from control measures
  - Estimation for risk for each hazardous situation
  - Overall residual risk acceptability

ISO 14971:2000



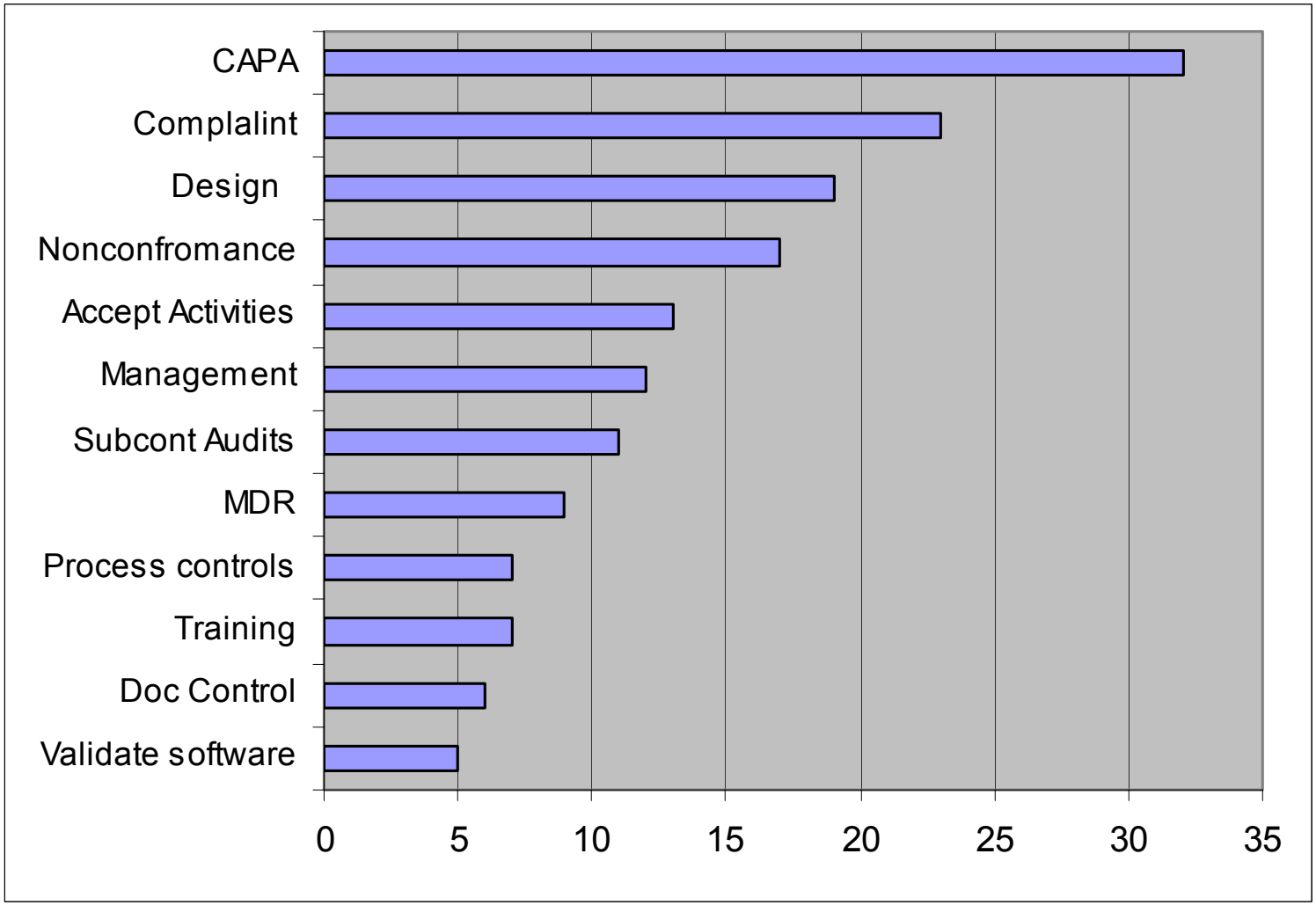


Interaction Between Risk and Design



Why is Understanding Risk Important?

Warning Letters



Recall for Unrecognized Risk

- **Baush & Lomb initiated an investigation that evaluated the manufacturing facility environmental records, a review of batch records and testing of retain samples for numerous produced lots. All of the records indicated there were no anomalies that could have been related to the report, there were no fusarium recoveries from the facility environmental monitoring program of the aceptic processing areas, and all product release sterility evaluations met criteria. Product retain sample testing …..and indicated that all chemical and biocidal performance was effective against microbial challenges as required. The conclusion of this investigation is that some aspect of the moistureloc formula may be increasing the relative risk of fusarium keratitis in unusual circumstances**

FDA's Response to Unacceptable Risk

FOR IMMEDIATE RELEASE
P07-69
April 17, 2007

FDA Seizes All Medical Products From N.J. Device Manufacturer for Significant Manufacturing Violations

"The deficiencies may compromise the safety and effectiveness of the products, particularly their sterility"


RISK PLAN

Risk Plan (ISO 14971:2007 Annex F)

- **Risk Management begins with a plan**
  - Assignment of responsibilities – Risk Team
  - Requirements for review of activities
  - Define criteria for risk acceptability
  - Define verification activities – effectiveness of risk control
  - Define methods of obtaining post production information up during product design.

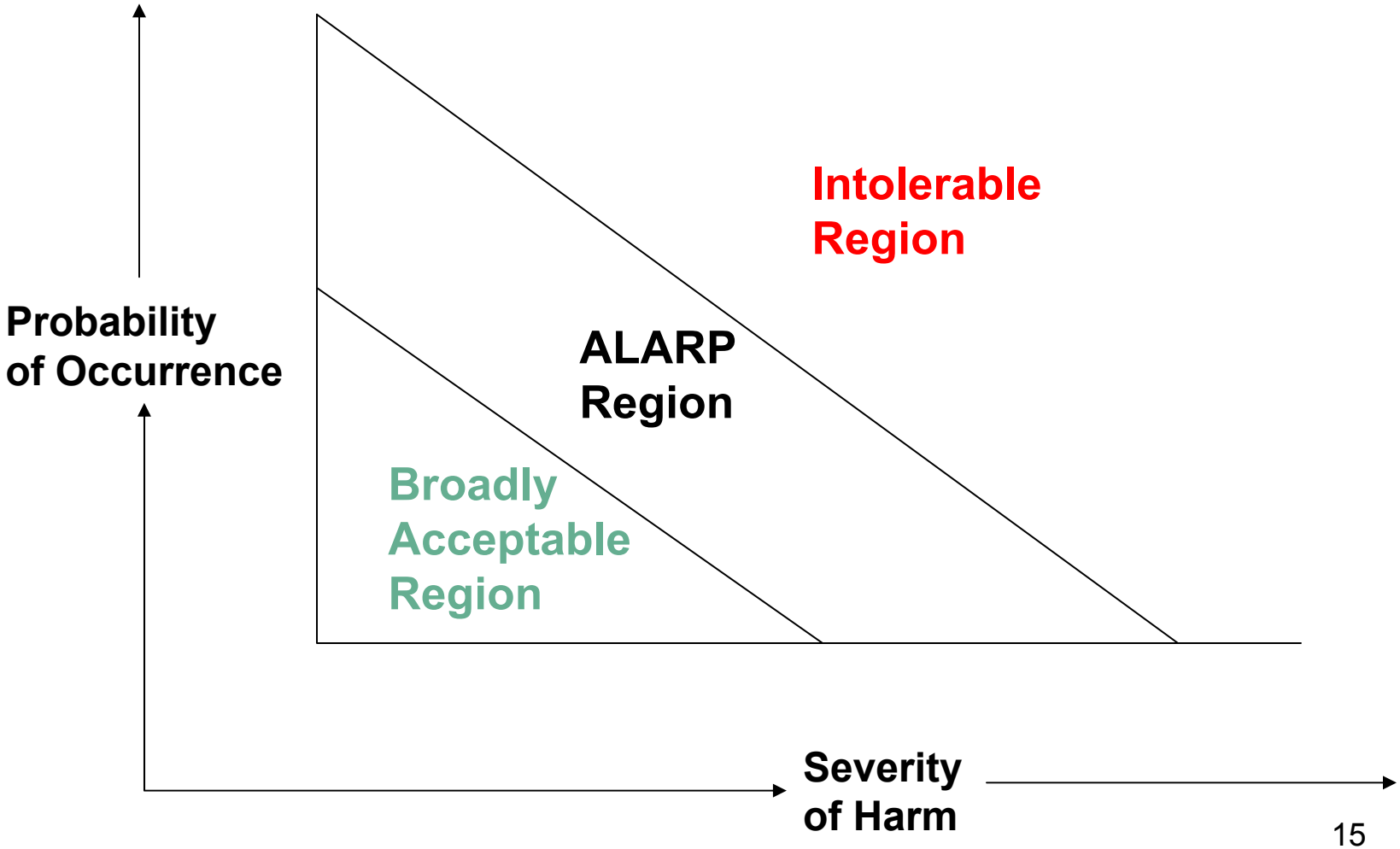
Acceptable Risk

- **The standard does not specify acceptable risk – the manufacturer must decide acceptable risk for each device.**
- **Determination of acceptable risk includes**
  - Compliance to applicable standards
  - Comparing risk levels to similar products
  - Clinical study data, especially for new technology

Acceptable Risk

- **Perception of risk may need to be considered**
  - Public/patient perception of what is acceptable
  - Medical professionals
  - Regulators
- **Public vs patient risk**
  - Packaging for safe shipment
  - Environmental exposure on disposal

Risk Evaluation



Qualitative Risk Chart
ISO 14971:2007

Frequency / Severity	*Negligible*	*Marginal*	*Moderate*	*Critical*	*Catastrophic*
Frequent	R1				
Probable		R2		R3	
Occasional					
Remote				R4	
Improbable			R5, R6		

Acceptable
Unacceptable

Severity (Cosmetic Implant)

Class	***Severity***
Negligible	Inconvenience to user
Marginal	Temporary Discomfort
Serious	Cosmetically unsatisfactory
Critical	Minor long term discomfort

Severity (Life Saving Device)

Class	***Severity***
Negligible	Temporary discomfort
Marginal	Minor injury
Serious	Serious injury
Critical	Death

Frequency of Occurrence (Reusable Equipment)

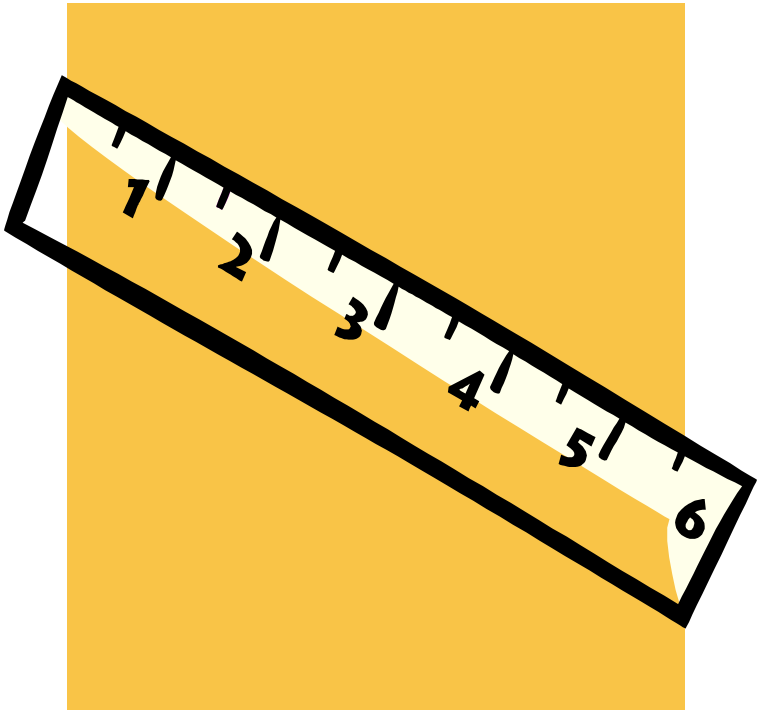
Class	***Frequency***
Improbable	Once during 5-year life
Unlikely	Once a year
Occasional	Less than once a month
Frequent	More than once a week

Frequency of Occurrence (Diagnostic Test)

Class	***Frequency***
Improbable	Once every 100,000 tests
Unlikely	Once every 10,000 tests
Occasional	Once every 1,000 tests
Frequent	Once every 100 tests

Compliance with Standards

- **Compliance with harmonized standards assumes acceptable risk**
  - IEC 60601 series (electro mechanical)
  - ISO 10993 series (biocompatibility)
- **Identify all the standards that apply**



Standards

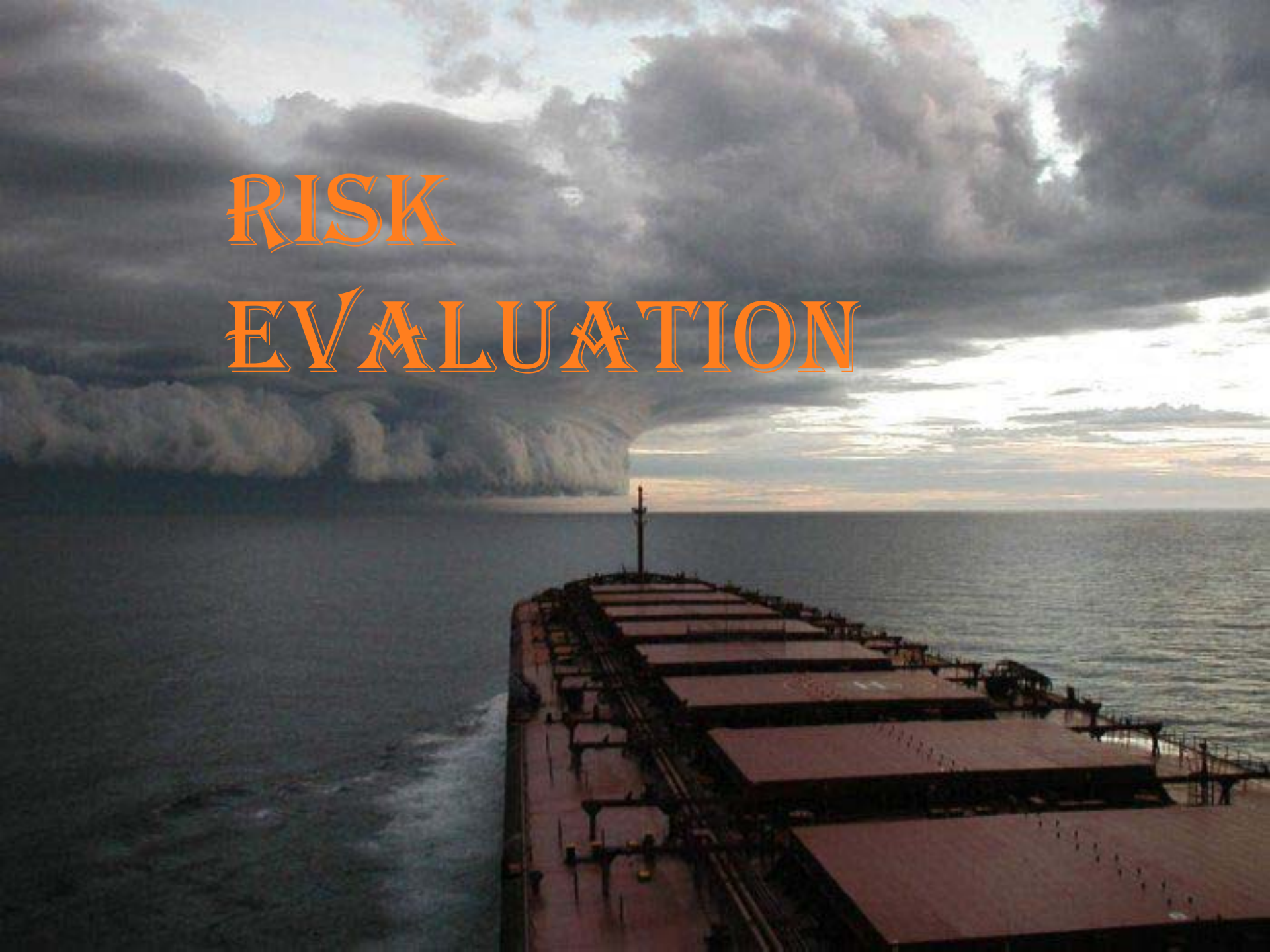
- **Ensure you have identified all appropriate standards**
  - http://www.newapproach.org/
  - www.ansi.org
  - http://www.iso.org/iso/en/prods-services/ISOstore/store.html
  - http://www.bsi-global.com/en/Standards-and-Publications/
  - http://www.meddev.info/

Post Market Risk

- **Define methods of obtaining post production information up during product design.**
- **How would you go about defining post market risk?**

Post Market Risk

- Critical components – critical suppliers
- Critical manufacturing processes
- Areas for misuse
- Label warnings


RISK
EVALUATION

Hazard Identification

- **Identify Hazards and potential hazardous situations**
  - Checklists to assist in hazard identification are found in the Annexes to ISO 14971
  - Using the questions in Annex A
    - These questions are aids to ensure that all possible sources of risk are identified.
    - They are not intended to be answered as questions individually
    - For each question that has a “Yes” answer, there should be at least on assessment of the risk your device poses to patient or user.

Hazard Identification

- **A.2.13 Are there unwanted outputs of energy or substances?**
  - Current leakage – ISO 60601?
  - Waste disposal for diagnostic test liquids – what are the hazards?
- **A.2.28 Is the device intended to be mobile or portable?**
  - Is there a risk the device will be dropped?
  - How can this be mitigated by design?
  - What kind of testing should be conducted to ensure appropriate durability for expected drop hazards?

Risk Evaluation – Harm

- **Once all the hazards have been identified, the harm associated with the hazard can be accessed.**
- **For example the risk posed by current leakage may have greater consequences for a device used in intensive care that for a device used in a diagnostic laboratory**

Risk Evaluation - Probability

- **The occurrence of some risks cannot be estimated**
  - Software failure
  - Tampering or sabotage
  - Poorly understood hazards
  - Certain toxicological hazards
    - Genetoxic carcinogens
    - Sensitizing agents

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Occasional					
Remote				R4	
Improbable			R5, R6		

Acceptable
Unacceptable

Qualitative Risk Chart
ISO 14971:2007

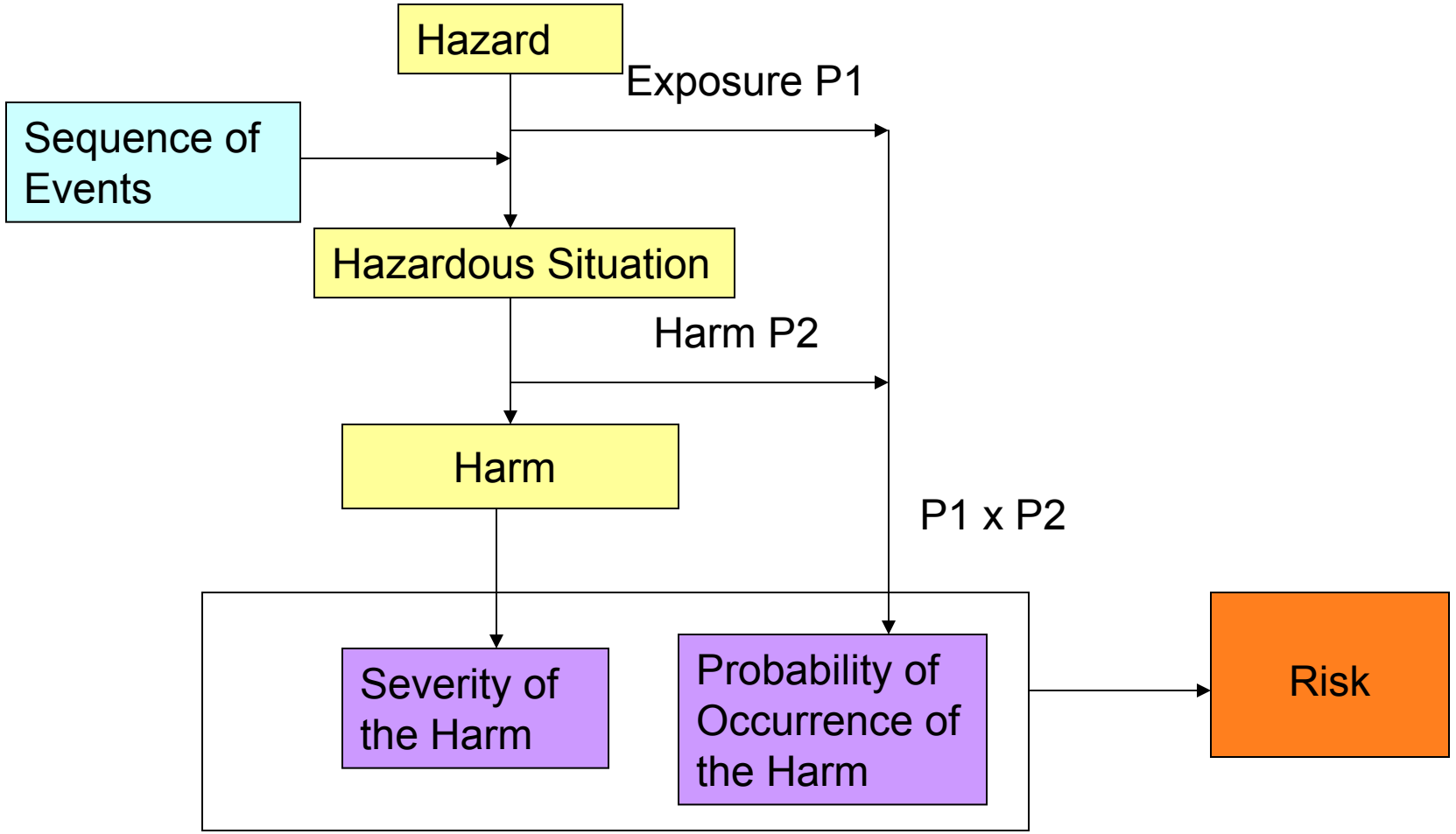
Frequency / Severity	Negligible (1)	Marginal (2)	Moderate (3)	Critical (4)	Catastrophic (5)
Frequent (5)	5	10	15	20	25
Probable (4)	4	8	12	16	20
Occasional (3)	3	6	9	12	15
Remote (2)	2	4	6	8	10
Improbable (1)	1	2	3	4	5

Acceptable
Unacceptable

Foreseeable sequence of events

- **Incorrect result in diagnostic test**
  - Patient receives the improper or no treatment
  - Condition worsens
  - Patient injury or death
- **Failure to properly validate useable shelf life of re-useable device**
  - Repeated steam sterilization causes deterioration
  - Device failure
  - Patient death or injury

Hazard and Harm

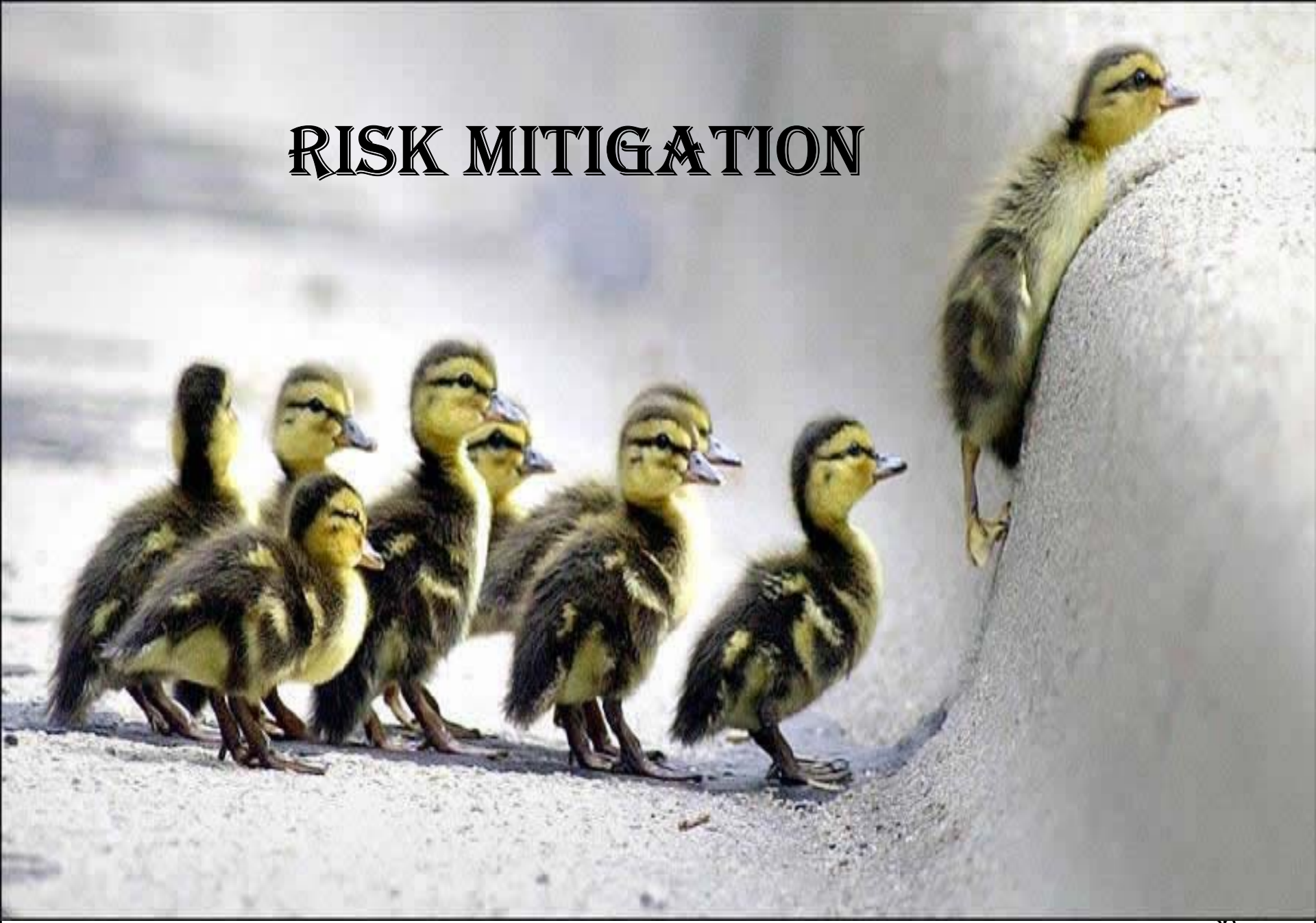


Assess risk before any mitigation

Source of Harm	Hazardous Situation	Harm Caused	Severity	Probability of Occurrence	Risk Number

Risk Number	Mitigation	New Severity	New Probability of Occurrence	Verification of Mitigation	New RPN

RISK MITIGATION



Risk Control

- Inherent safety in design
- Protective measures in the device such as alarms, locks outs etc.
- Protective measures in the production process.
- Information for safety

Risk Control

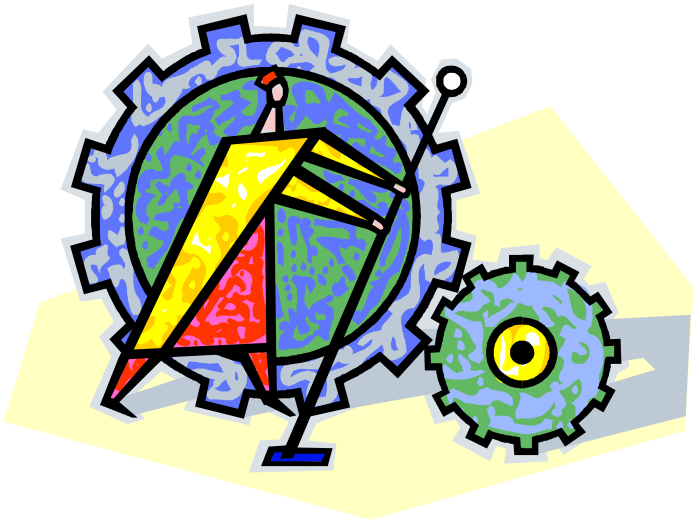
- **Each risk control measure shall be verified.**
- **Often this takes the form of testing to a standard, design validation or production validation.**
  - Biocompatibility testing
  - Clinical trial data
  - Process validation – sterile process validation

Risk Mitigation in Design

- **Electrical Safety**
- **Biocompatibility**
- **Human Factors Analysis**

Risk Control in Manufacturing

- **Sterilization Validation**
- **Controlling the cleaning process to ensure manufacturing materials are removed**
- **Validating software controlled processes**
- **In-process inspection points for critical processes**



Risk Control in the Device

- **Failure Alarms**
- **Back up batteries**
- **Manual back up availability**

Risk Benefit

- **In general if all practicable risk control measures are insufficient to satisfy the risk criteria the design shall be abandon.**
- **The standard allows for greater risks if these risks can be justified.**
- **An important consideration in the acceptability of risks are**
  - Is there an alternative design solution or therapy that avoids the risk
  - A review of further risk reduction should be considered before a risk/benefit analysis is considered

As Low as Reasonably Practicable

- **Option for risk analysis**
- **Useful for those risks for which the probability cannot be estimated**
- **Practicability considerations**
  - Technical
  - Economic

Technical Practicability Reduction regardless of cost

- **Pitfalls may be**
  - So many warnings that use is hampered
  - Multiple alarms that create confusion
  - Communicating so many residual risks that it is difficult to determine which are really important
  - Creating a procedure so complex that the intended use is compromised.
  - Risk control measures that comprise intended use (reducing laser level in surgical instruments so low that the do not function for their intended use.

Economic Practicability

- **Cost and availability are important considerations – a device that is so expensive it is not used is not useful**
- **However cost alone should not be used as a rationale for acceptance of unnecessary risks.**
  - Risks in the unacceptable range should be reduced even at considerable costs
  - Already low risks that could be reduced further, but a considerable cost might justifiably be left unmitigated if the cost is very high.

Acceptable Risk

- **20% probability of second degree burns in use of an emergency defibrillator**
- **5% experience of long term discomfort in cosmetic implant resulting in a 50% explant rate.**
- **2% False negative rate in a rapid (30 minute) test for a high transmissible infection disease. The gold standard culture has a false negative rate of 0.01% but takes 3 days to run**

RISK REPORT

Risk Report

- **A risk report must be completed prior to release for commercial distribution**
- **A review management process shall ensure**
  - The risk management has been appropriately implemented
  - The overall residual risk is acceptable
  - Appropriate methods are in place to obtain relevant production and post-production information

Summary

- **Risk Management is a integral part of the design process**
- **Design risk should guide the efforts of post market risk monitoring**
- **A well conducted risk assessment can reduce problems in the field by addressing them in design**

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Thank you

For more information:

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