Risk Management

FDA Regulated Industries

Balanced Quality Systems and Regulatory Compliance

PathWise

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Introduction

- Risk Management has become an important component of activities in companies regulated by FDA
- FDA expects companies to be making risk-based decisions
- FDA provides little direct guidance for risk management activities, but relies on international standards and guidances

Introduction to Standards

- The only current standard available for risk management for **medical devices** is ISO 14971

Introduction

- ISO 10993-1Biocompatability standard is being updated to incorporate risk management its processes
- IEC 80002 is being created as a guidance for incorporating risk management in software lifecycles as described in IEC 62304
- A general business risk management standard is under development by ISO and will be part of the ISO 31000 series

Introduction

- ISO 13485 Medical device quality system standard requires a risk management process be implemented as part of the quality system
- IEC 60601-1 general safety standard for electro-medical devices requires the use of a risk management process **complying with ISO 14971**

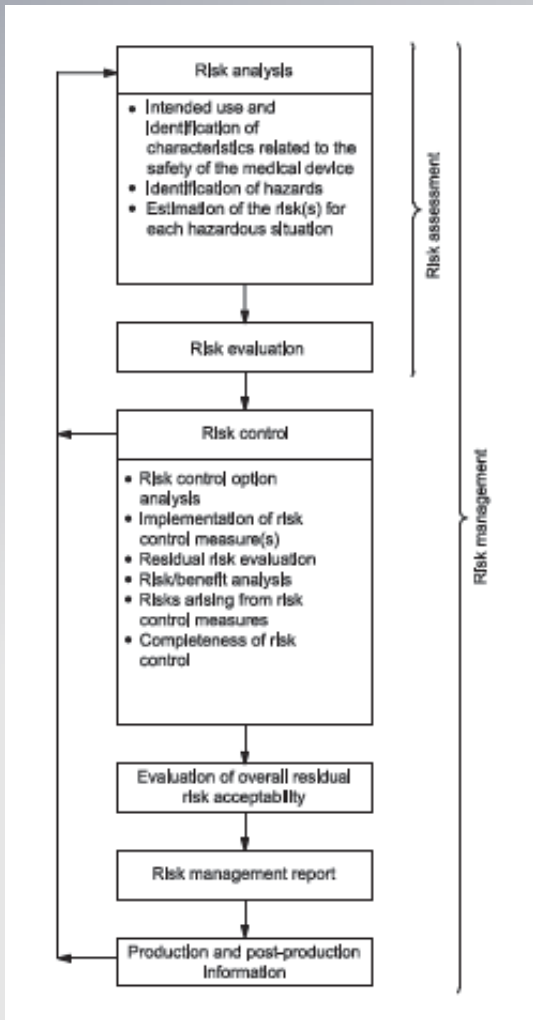
Introduction

- Global Harmonization Task Force Study Group 3 provided guidance, *Implementation of risk management principles and activities within a Quality Management System*

Introduction

- ISO 14155 clinical trials standard is being revised to further incorporate risk management
- Additional work is being done on many medical device standards to incorporate risk management

ISO 14971 Risk Management Process



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Risk Management in the Product Life Cycle

- Pre-production
- Production
- Post Production

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Definitions

- **Harm:** Physical injury or damage to the health of people, or damage to property or the environment.
- **Hazard:** Potential source of harm.
- **Hazardous situation:** Circumstance in which people, property, or the environment are exposed to one or more hazard(s).

Risk

- “All stakeholders need to understand that the use of a Pharmaceutical or medical device entails some degree of risk.”
- What is risk?

  Risk has two components:

  - The probability of harm occurring;
  - The consequences of that harm, i.e., severity.

Definitions

- **Risk analysis** – “systematic use of available information to identify hazards and to estimate the risk”
- **Risk estimation** – “process used to assign values to the probability of occurrence of harm and the severity of that harm”
- **Risk evaluation** – “process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk”
- **Risk control** – (old term-mitigation) “process in which decisions are made and measures implemented by which risk is reduced to and maintained within specified levels”
- **Residual risk** – “risk remaining after risk control measures have been taken”

Risk Management Process

The International Standards specifies a process where the manufacturer can

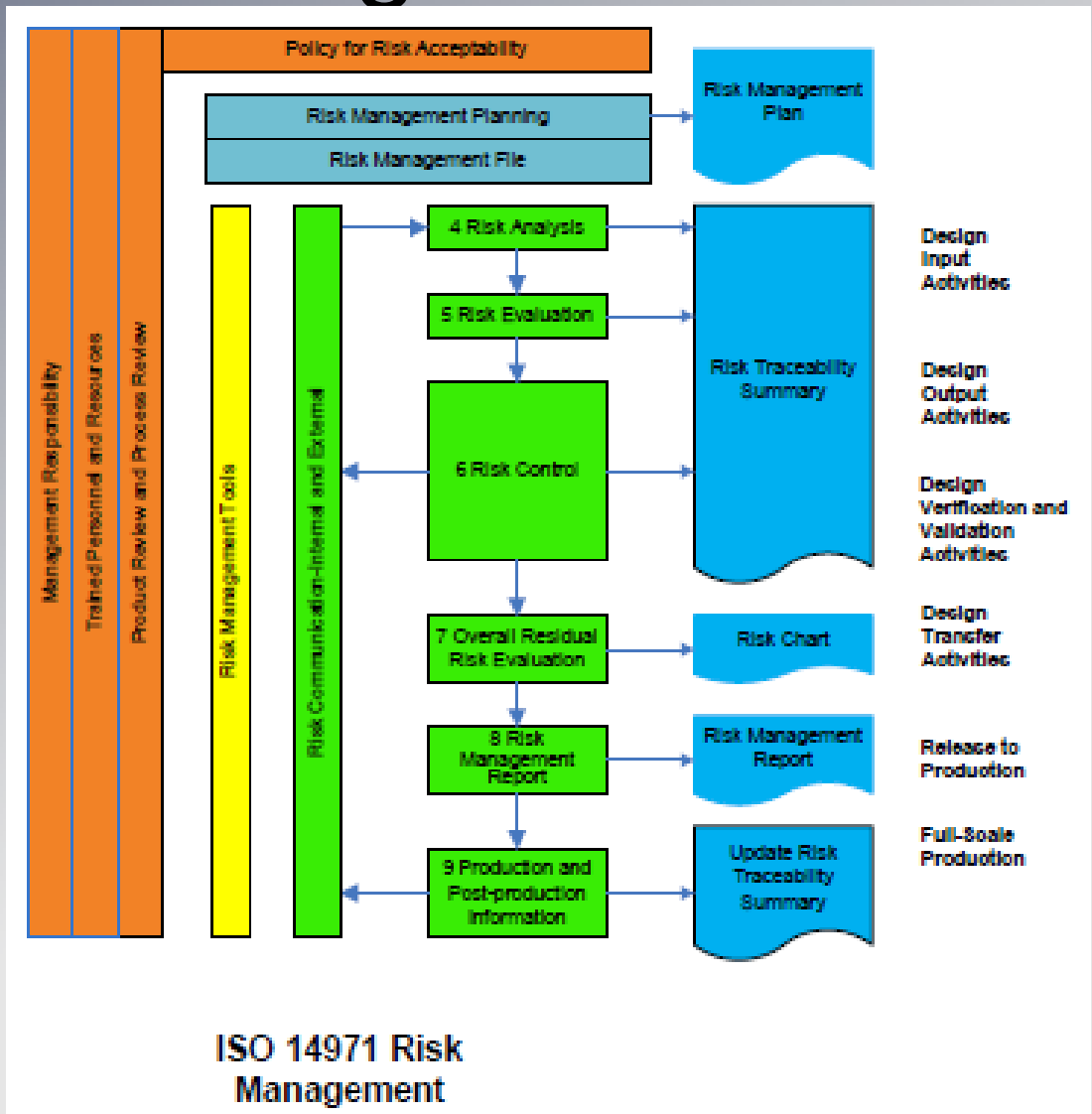
- identify hazards,
- estimate and evaluate the risks,
- control these risks, and
- monitor the effectiveness of the control.

Identification of Hazards Specific to IVDs

The following aspects should be considered identifying potential hazards for the patient or the person subjected to examination:

- **batch in-homogeneity, batch-to-batch inconsistency;**
- **common interfering factors;**
- **carry-over effects;**
- **specimen identification errors;**
- **stability problems (in storage, in shipping, in use, after first opening of the container);**
- **problems related to taking, preparation, and stability of specimens;**
- **inadequate specification of prerequisites;**
- **inadequate test characteristics.**

Risk Management Process



Risk Planning

- ISO 14971 3.4 Risk Plan shall include
  - Scope of planned activities including describing the product and lifecycle
  - Assigned responsibilities and authorities
  - Requirements for review of risk activities
  - Criteria for risk acceptability
  - Verification activities
  - Review activities of production and post-production information

Scope of Plan

- Risk Management Plan identifies the process to be used and the product to which the plan applies as well as the product lifecycle to which it applies
- The plan helps identify when the process has reached its goals

Scope of Plan

- In cases where the development and production are distributed among a number of activities or even several firms, the plan scope identifies who is responsible for each activity

Probability of Occurrence Definitions

Classification/ Ranking	Harm Occurrence Definitions
Frequent	> 1/100 or >1%
Probable	< 1/100 thru 1/1,000
Occasional	< 1/1,000 thru 1/10,000
Remote	< 1/10,000 thru 1/1,000,000
Improbable	> 1/1,000,000

Probability of Occurrence Definitions

- Probability of Harm per use?
- Probability of Harm per device?
- Probability of Harm per hour of use?
  - How often is device used?
  - What is lifetime of device?
  - Who is user and who is patient?
  - How long and how is patient exposed?

Probability of Occurrence Definitions

Classification/ Ranking	Harm Occurrence Definitions	Qualitative Definitions (preferred unless data supports Quantitative Definitions)
Frequent	> 1/100 or >1%	Likely to occur regularly to an individual product, continuously experienced throughout product population
Probable	< 1/100 thru 1/1,000	Likely to occur several time during the life of an individual product, frequently during product population
Occasional	< 1/1,000 thru 1/10,000	Likely to occur sometime during life of an individual product, several times during entire product population
Remote	< 1/10,000 thru 1/1,000,000	Unlikely to occur but possible during the life of an individual product; unlikely but possible reasonably expected expected to occur in the product population
Improbable	> 1/1,000,000	Extremely unlikely to occur to an individual product; possible for product population

Severity Definitions

Classification /Ranking	Description based on Product End Effect
Critical	Potential for Death
Severe	May cause permanent impairment to patient or user.
Moderate	May cause significant but recoverable injury to patient or user.
Limited	May cause transient, self-limiting illness or injury to patient or user.
Negligible	No adverse health consequence to patient or user. inconvenience to user.

Harm Definitions?

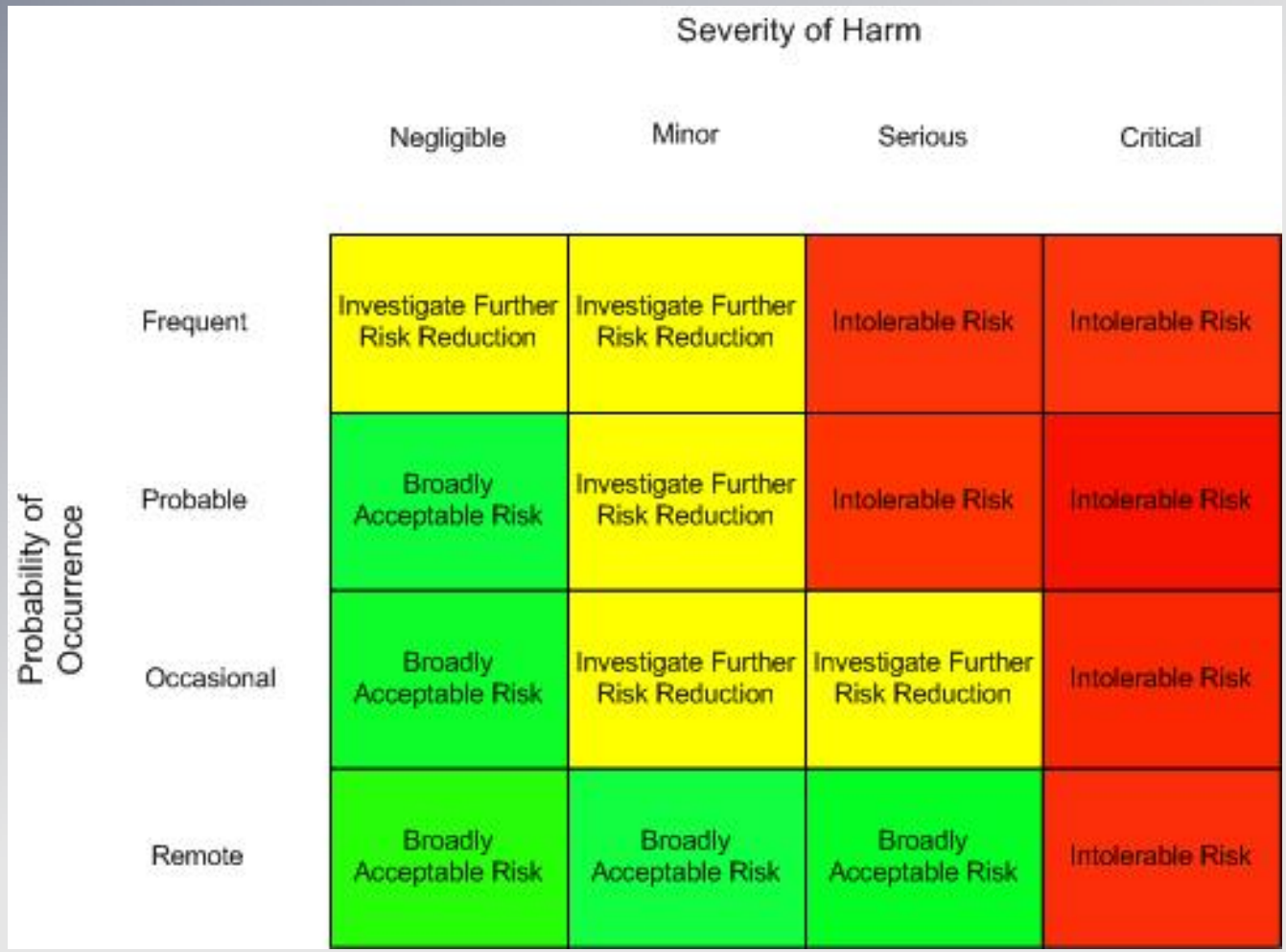
- Consider Vigilance terms in definitions
  - Death
  - Serious injury requiring medical intervention
  - Injury not requiring medical intervention
  - No injury

Risk Estimation Specific to IVDs

In estimating the risk for each hazard, the following aspects should be taken into account:

- **extent of reliance on the analytical result (contribution to the medical decision);**
- **plausibility checks;**
- **availability and use of controls;**
- **quality assurance measures/techniques applied in medical laboratories;**
- **detect ability of deficiencies/errors;**
- **situations of use (e.g., emergency cases);**
- **professional use/non-professional use;**
- **method of presentation of information.**

Example Risk Chart



Risk Chart

- Risk Level is established at the intersection of the Severity of Harm and Probability of Occurrence of Harm
  - Example –"Occasional" occurrence of "Serious" Harm results in a Risk Level of "Investigate Further Risk Reduction"

Risk Management File

- Risk management file has been revised to include a traceability requirement formerly in the Risk Management Report
  - Note indicates the Risk management file can be in any form or medium (such as electronic files)

Risk Management File

- Risk management file-traceability must be shown from each hazard to the risk analysis, risk evaluation, implementation and verification of risk control, and assessment of residual risk acceptability
- A Risk Summary Table is a good tool to fulfill this requirement

Traceability Summary

Product Name/Model | Document Number | Revision Level | Date

System Risk Analysis

Cause	Specific Cause	Harm Severity	Probability of Harm	Premitigation Risk Class	Mitigation	Risk RqtID	Risk Mitigation Verification Protocol	Risk Mitigation Verification Report	Post-Mitigation Harm Severity	Post-Mitigation Probability of Harm	Post-Mitigation Risk Class	Risk Mitigation Effectiveness Protocol	Risk Mitigation Effectiveness Report
1.0 Overdose Delivered													
1.1 Overdose Delivered Unexpectedly-Device													
1.1.1	Pump overrun due to microprocessor lockup	Critical	Remote	Investigate for further Risk Reduction	a) Blocking capacitor limits pump on time to a maximum of one second b) (Barcode Option) Delivery rate encoded in prescription barcode; user prompted to scan patient bracelet and confirm settings	Hardware Spec ID 1.2.3 Hardware Spec ID 4.6.1 Software Spec ID 3.2.5	Verification Protocol P345.1	Verification Report R345.1	Critical	Improbable	Insignificant	Product Validation Plan P67.2	Product Validation Report R67.2
1.1.2													
1.1.3													
1.2 Overdose Delivered Unexpectedly-Operator													
1.2.1	User setup error	Critical	Occassional	Intolerable	a) Alphanumeric display shows delivery rate and units b) Watchdog timer interrupts power to pump	Hardware Spec ID 5.7.9 Software Spec ID 6.7.2	Verification Protocol P345.2	Verification Report R345.2	Critical	Improbable	Significant	Product Validation Plan P67.21	Product Validation Report R67.22
1.2.2													
1.2.3													

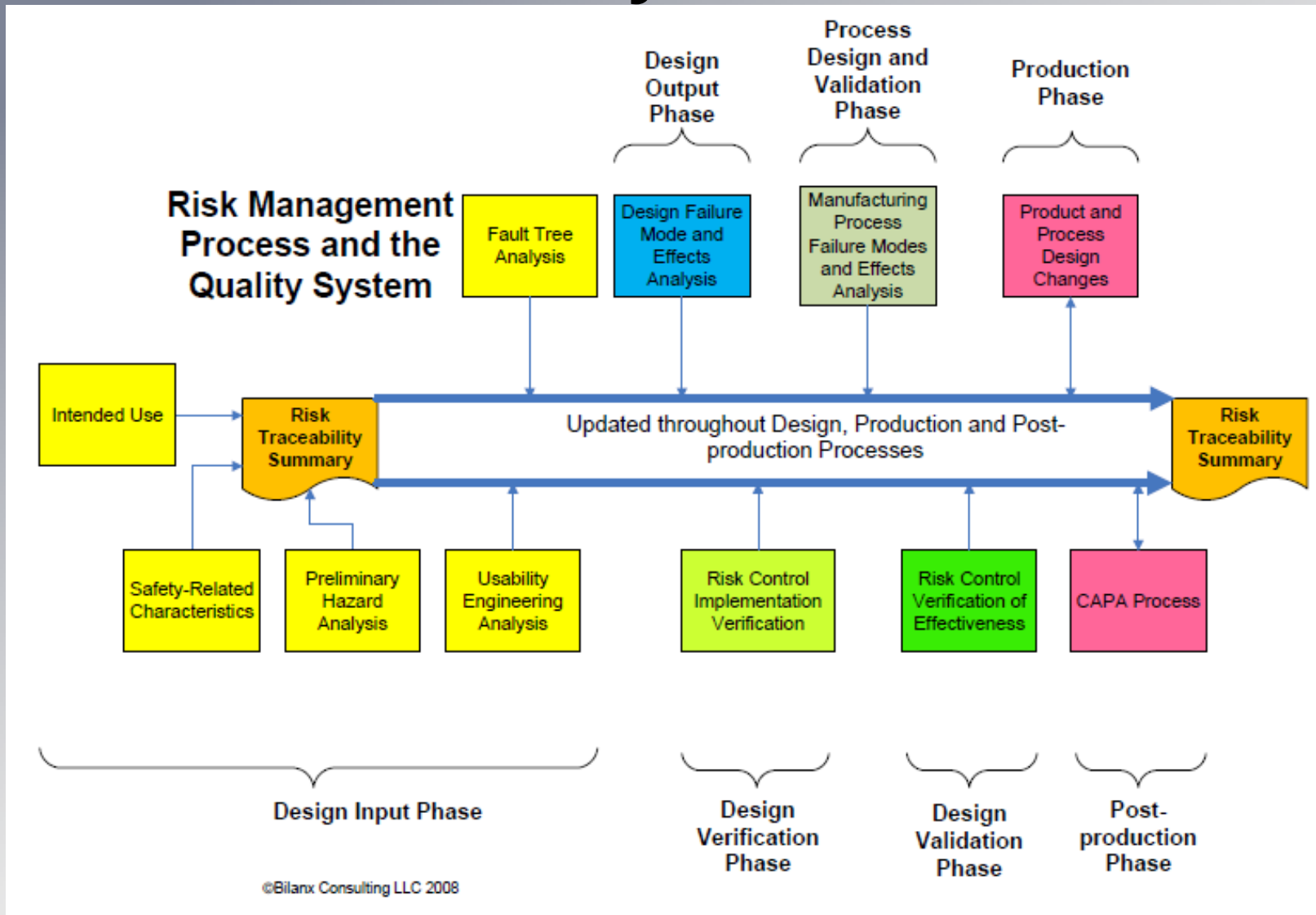
Summary

- For each project:
  - Each product/product family must have a risk management plan with acceptability
  - Each product/product family must have a risk management file
    - Can be an index
  - Each risk management file must contain a traceability summary

Summary

- Management must provide a risk management process, resources to implement the process, and a policy for establishing risk acceptability criteria
- Management must monitor the effectiveness of the process

Risk Analysis View



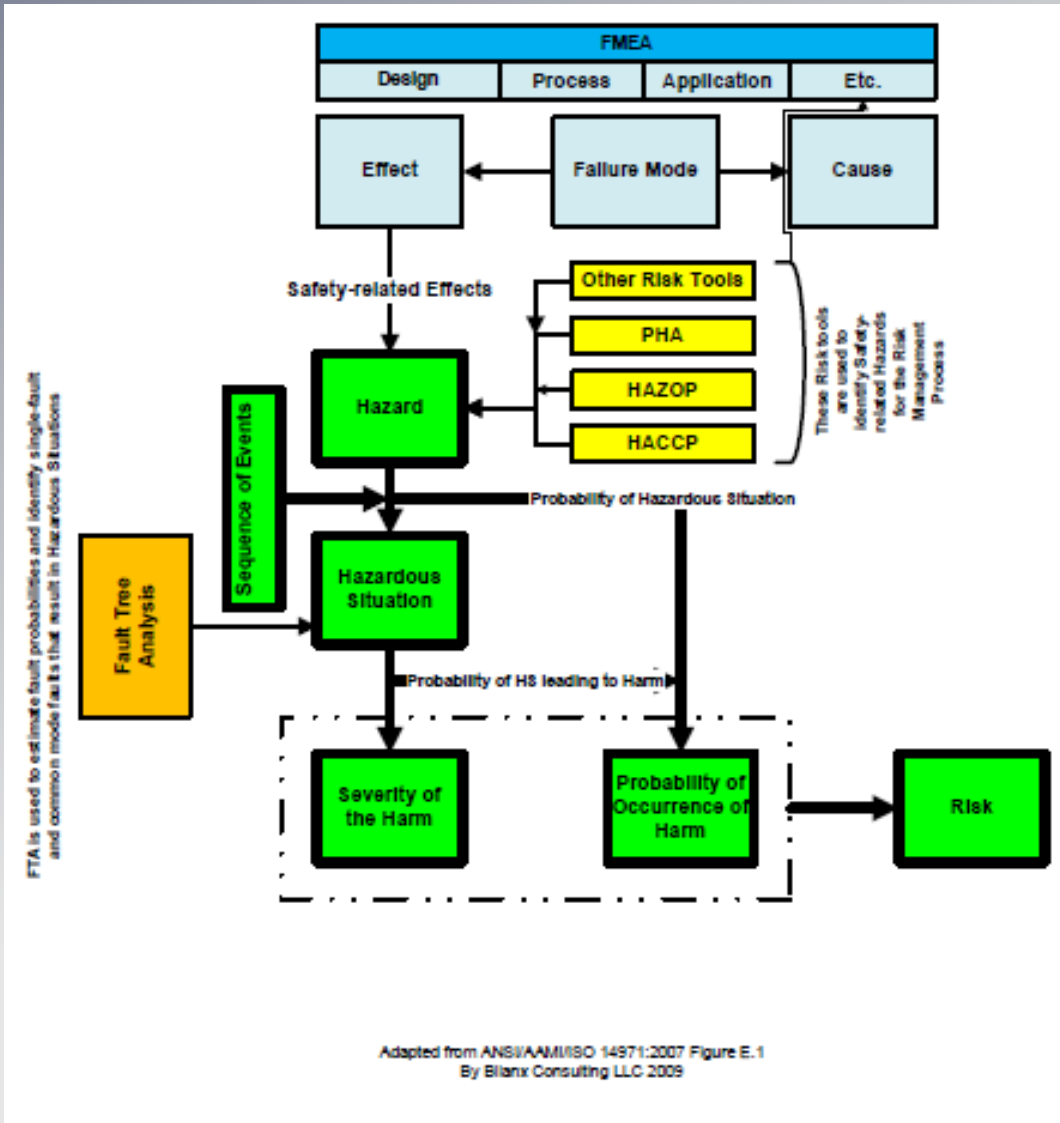
Review of Common Tools

- **Failure Mode and Effect Analysis (FMEA)**FMEA is primarily a qualitative technique by which the consequences of an individual component fault mode are systematically identified and evaluated. It is an inductive technique using the question "What happens to the output if . . .?"
- **Fault Tree Analysis (FTA)** FTA is a means of analyzing hazards identified and starts from a postulated undesired consequence, called a "top event." In a deductive manner, the possible causes or fault modes of the next lower functional system level causing the undesired consequence are identified. Following stepwise identifications of undesirable system operations to successively lower system levels will lead to the desired, usually the component fault mode.
- **Hazard and Operability Study (HAZOP)**

  HAZOP is similar to an FMEA. HAZOP is based on a theory that assumes accidents are caused by deviations from

  the design or operating intentions

Use of the Tools



Production and Post Production

- Outline of Concepts and Activities
- Review of Tools

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Clause 9-Production and Post-production information

- **Clause 9**, Title of "*Production and post-production information*" to emphasize that there is information available during production which is important to Risk Management
- Adds a requirements for systems collecting and reviewing device information

Clause 9-Production and Post-production information-Summary

- This is an important clause that has not been well implemented in industry
- Requires continual access throughout product life to Risk Analysis documents with periodic updates when new risk information obtained

Clause 9-Production and Post-production information-Summary

- Requires all changes to product and production process be evaluated for impact to Risk Analysis
- Risk Management File must be accessible until final product has been removed from the market

Changes and Corrective Actions

- Changes to the production process require a review for impact to the risk analysis (Process FMEA)
- Any corrective action to the process must also be reviewed for impact to the risk analysis

How Does Risk Management Connect to CAPA

- CAPA-Corrective *and Preventive* Action
  - Companies use Complaints as one input into CAPA-Corrective Actions and Corrections follow
  - World Class companies use pro-active feedback on products to take Preventive Actions before incidents and complaints occur

Monitoring Process

- CAPA processes collect information from monitoring activity for analysis and potential action

Risk Analysis-Measurement Standard

- How can company take action without knowing action is needed?
- Risk Analysis provides a standard to compare data from complaints and proactive data gathering
- Is the frequency and severity of events predicted in Risk Analysis reflected by actual incidents?

Data Analysis

Some Sources of Quality Data

- **Quality Audits**
- **Customer Complaints**
- **Service Delivery Data**
- **Customer Requirements/Contract Data**
- **Customer and User Surveys**
- **Inspection and Test Data**
- **Beta Testing of New Product**
- **Non-conforming Product Data**

More Sources of Quality Data

- **Warranty Parts Usage Data**
- **Process Monitoring Results**
- **Supplier Data**
- **Management Review Data**
- **Published Literature**
- **Comparative Product Data**
- **Returned Product**
- **Rework Data**
- **SPC Data**

Data Analysis

- Develop a process for systematic review of quality data related to product and process
- Systematic review should compare various data that relate such as the supplier, process performance, inspection and test data, failure data and complaint data on a single component or characteristic

Data Analysis

- Watch for information relating to the “Essential Characteristics”
- How do you identify these “Essential Characteristics”?
- Use of Risk Management techniques such as FMEA. FTA, HAZOP is valuable in identification of Essential Characteristics

Data Examples for Analysis

- Supplier performance over time
- Non-conformances by part # per supplier
- Root causes of non-conformances
- Scope, extent, and quantity of changes
- Root causes of product failures per model; failure rates per model and product family
- Quality system failure types (based on root causes) and failure rates
- Root causes of product failures per model; failure rates

Data to Information

- Convert data into information
- Be systematic
- Use “data mining” techniques
  - http://www.statsoft.com/textbook/stdatmin.html for a complete discussion

Decision-Making

Risk Based Decisions

- Relies on availability of Risk Management information
  - Product and process design risk management information must be accessible for review during entire product lifecycle
  - Risk Management information is updated as new information about product and process risk is learned

Prioritizing Decisions

- Decisions are prioritized based on the Risk Management results
  - If the Risk Process identifies characteristics of components or assemblies, subassemblies, software and operation of the product, that affect the safety or effectiveness of the product or the process, then these are identified as Essential Characteristics in product/process design documentation

Prioritizing Decisions

- If items that are identified as Essential Characteristics of the Product or the Process in Risk Management, are determined to not meet requirements, then a High Priority for Investigation is Assigned
- These issues may have an effect on product or process safety and should be investigated as soon as possible

Prioritizing Decisions

- If a review of the Risk Process indicates a potential for Product Recall to prevent Injury or Death, then Investigation should begin Immediately to determine cause and propose action
- An immediate review for a decision on stopping the production process should be made

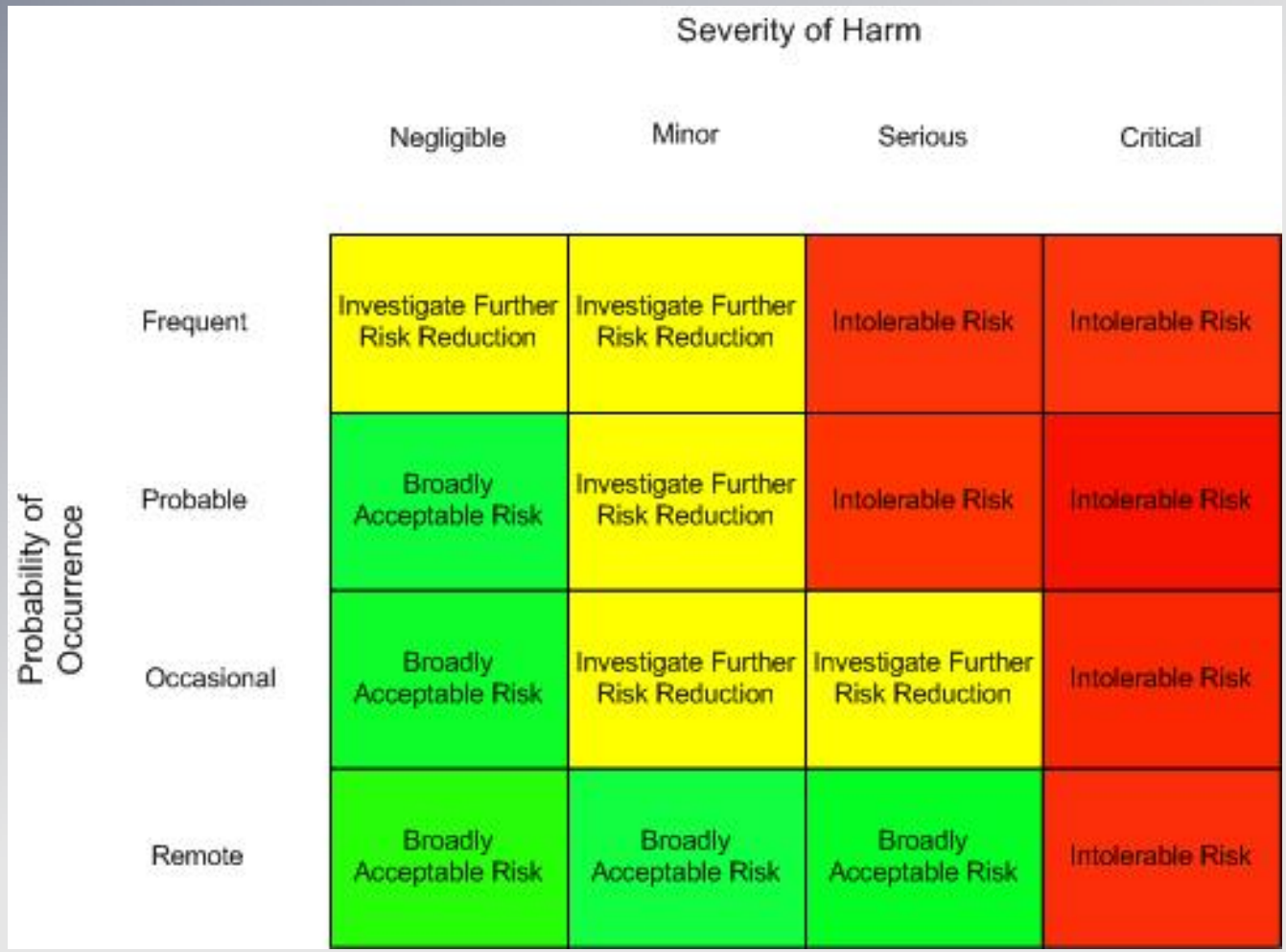
Prioritizing Decisions

- If there is a moderate risk to use of the product or process that does not result in risks of harm to individuals or property, then the investigation is assigned a Moderate Priority and is undertaken following Immediate and High Priority investigations

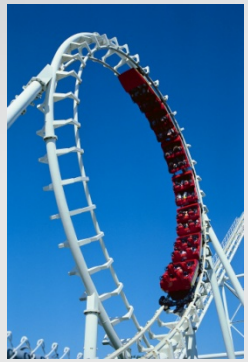
Prioritizing Decisions

- For issues that do not relate to Essential Characteristics (do not have a Safety Risk) such as Customer Preference, Priority for Investigation is established as Lower Priority

Example Risk Chart



Closed-Loop Risk-Based CAPA Process



GHTF CAPA System