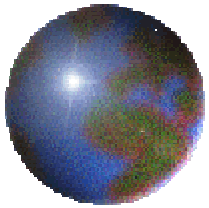

Best Practices:
Integration of Risk Management and Corrective and Preventive Action

Presented by:

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Cordis Corporation, a Johnson & Johnson company

The views expressed are those of the speaker and are not necessarily those of Cordis Corporation or Johnson & Johnson. The views are offered to provide an overview of issues related to Risk Management and Corrective and Preventive Action activities.

Agenda

- About Cordis Corporation
- What is Risk Management
- What is CAPA
  - Key Definitions
- Inputs and Triggers
- Root Cause Analysis
- Preventive Actions
- Continuous Improvement: Some Suggestions
- Q&A

About Cordis

- Cordis Corporation was established in Miami, Florida, in 1959 as a medical device corporation and rapidly gains recognition for being a pioneer in innovative devices and products for interventional vascular medicine and electrophysiology.
- In 1966, Cordis introduced the first full line of “Pre-shaped” Judkins catheters. These shapes become the industry standard.
- In 1990, Cordis introduced the first PTCA (percutaneous transluminal coronary angioplasty) balloon utilizing nylon balloon technology. This material becomes the industry standard.
- In 1996, Cordis Corporation merged with Johnson & Johnson Interventional Systems Co. to form Cordis Corporation, a Johnson & Johnson company with approximately 3,500 employees worldwide.

Source: http://www.cordis.com/logc_common/layout/showPage.jsp?article_name=includes/about_history.jspf&pageData=about_history.xml

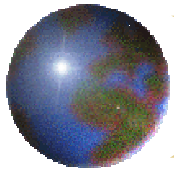
About Cordis - What did this mean??

- **In 2003, Cordis received FDA approval to market its CYPHER® Sirolimus-eluting Coronary Stent in the U.S., making it the first drug/device combination product for the treatment of restenosis.**
  - **As a combination device, what parts of CFR 210/211 apply?**
    - **Annual Product Review? Yes.**
    - **Stability Testing changes? Yes.**
  - **Impact of launch on:**
    - **Complaints System - Major**
    - **Regulatory Requirements - Major**
    - **Compliance Profile - Major**
    - **CAPA System - Major**
    - **Risk Management - Major**

RISK

- Probability of occurrence + severity of the hazard

Physical injury or damage to health of people or damage to property or the environment



What is Risk Management?

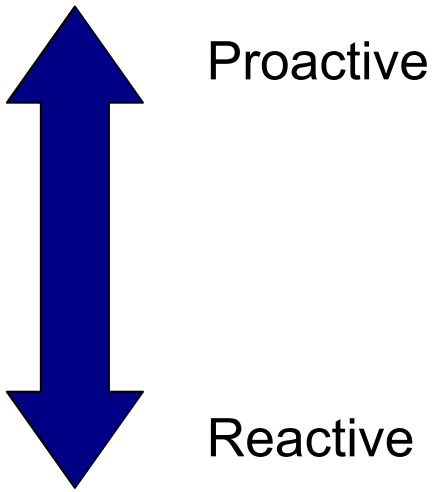
Companies want to know the impact (Risk) of decisions being made on the product.

Challenge

- "…each stakeholder places a different value on the probability of harm occurring and on the detriment that might be suffered on exposure to a hazard."

Systems of Feedback

- Design feedback
  - Customer Complaints
- Management Review
- CAPA Escalation and Risk Management
- Acceptable Risk



Risk Management

Challenges:

- No clear escalation from when an input reaches a threshold and when a CAPA is opened
- Risk assessment process/tool not established or well defined
  - Combination products (e.g., drug/devices) have shifted landscape
  - Adverse events due to the drug/device interaction
  - Procedural aspects of the case e.g., new techniques or uses, incorrect technique
- CAPA process not linked to risk management documentation (Design Controls documents, process and product FMEAs, etc.)
- Data not readily available to establish occurrence and therefore calculate risk

CAPA Escalation: Health Hazard Evaluations

- Complaint and MDRs provide inputs into health hazard evaluations (HHE) by characterizing:
  - Observed or potential harm to the patient
  - Relevant procedural issues
  - Contributing anatomical or pharmacological factors
  - Demographics of affected patients
  - Comparison of risks associated with same hazards for competitive products or alternate treatment modality

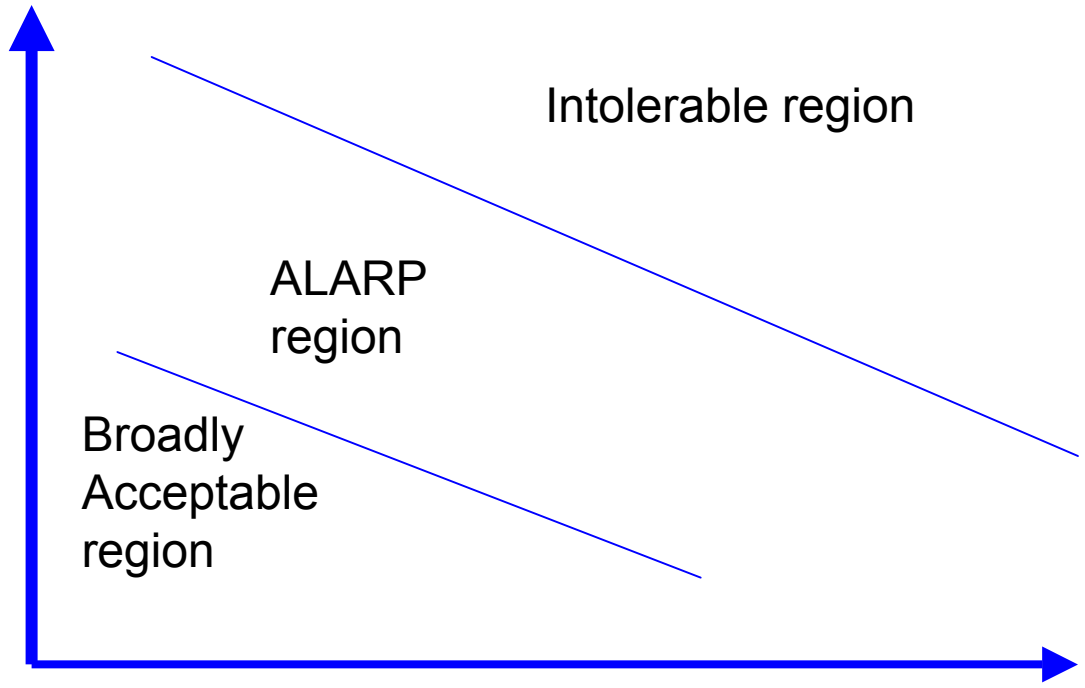
- Ultimately, HHEs act as a risk-benefit analysis for post-launch issues to characterize the necessity for a CAPA and the need for field action

Acceptable Risk

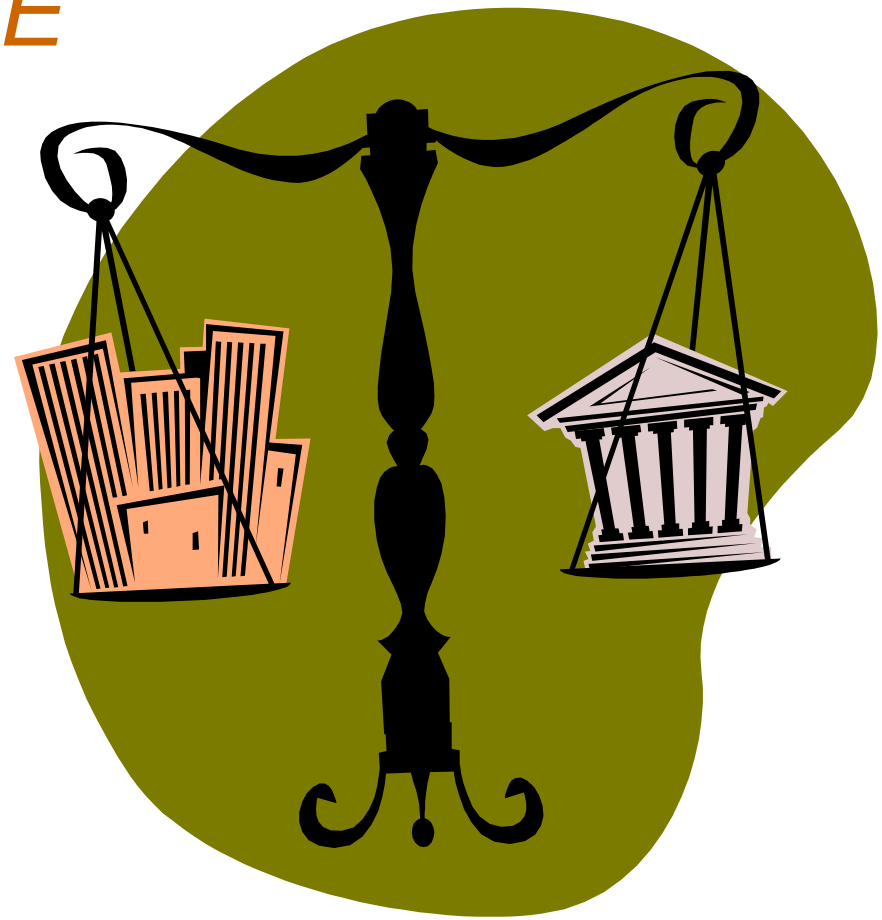
- What is the acceptable risk problem?

  A decision process (Fischoff, et. al. 1981) that
  - Specifies the objectives to measure the desirability or lack thereof
  - Defines possible options, including no action
  - Identifies the consequences of each option and likelihood of occurrence
  - Specifying the desirability of consequences
  - Analyzing the options and selecting the "most acceptable" option

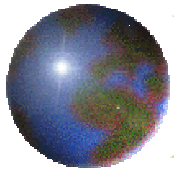
PLAN


Increasing Probability Of Occurrence
Intolerable region
ALARP region
Broadly Acceptable region
Increasing severity of harm

BALANCE



RISK **BENEFIT**



Why Risk as part of CAPA System?

- What is the impact of risk to the CAPA system?
- What hurdles will we encounter?

CAPA Escalation: Connecting Risk Management and Trending

- Critical questions that drive into the CAPA process and determine the depth of investigation/priority of CAPA:
  - Is this a new or unknown hazard?
  - Has the severity increased? Decreased?
  - Has the frequency of occurrence increased?
  - Have the causes of the hazard been confirmed?
  - Are there new causes of the hazard that have inadequate or no mitigation?

- Complaint and MDR investigations and trends provide answers to many of the questions above

Why is CAPA important?

88% of all FDA Warning Letters and 483's issued in 2003 were CAPA related

Key Definitions

Nonconformance (NC)

- Any noncompliance with the requirements of the Quality System (product and non-product).

Correction

- Repair, rework, or adjustment related to the disposition of an existing nonconformity. Corrections are typically one-time fixes.

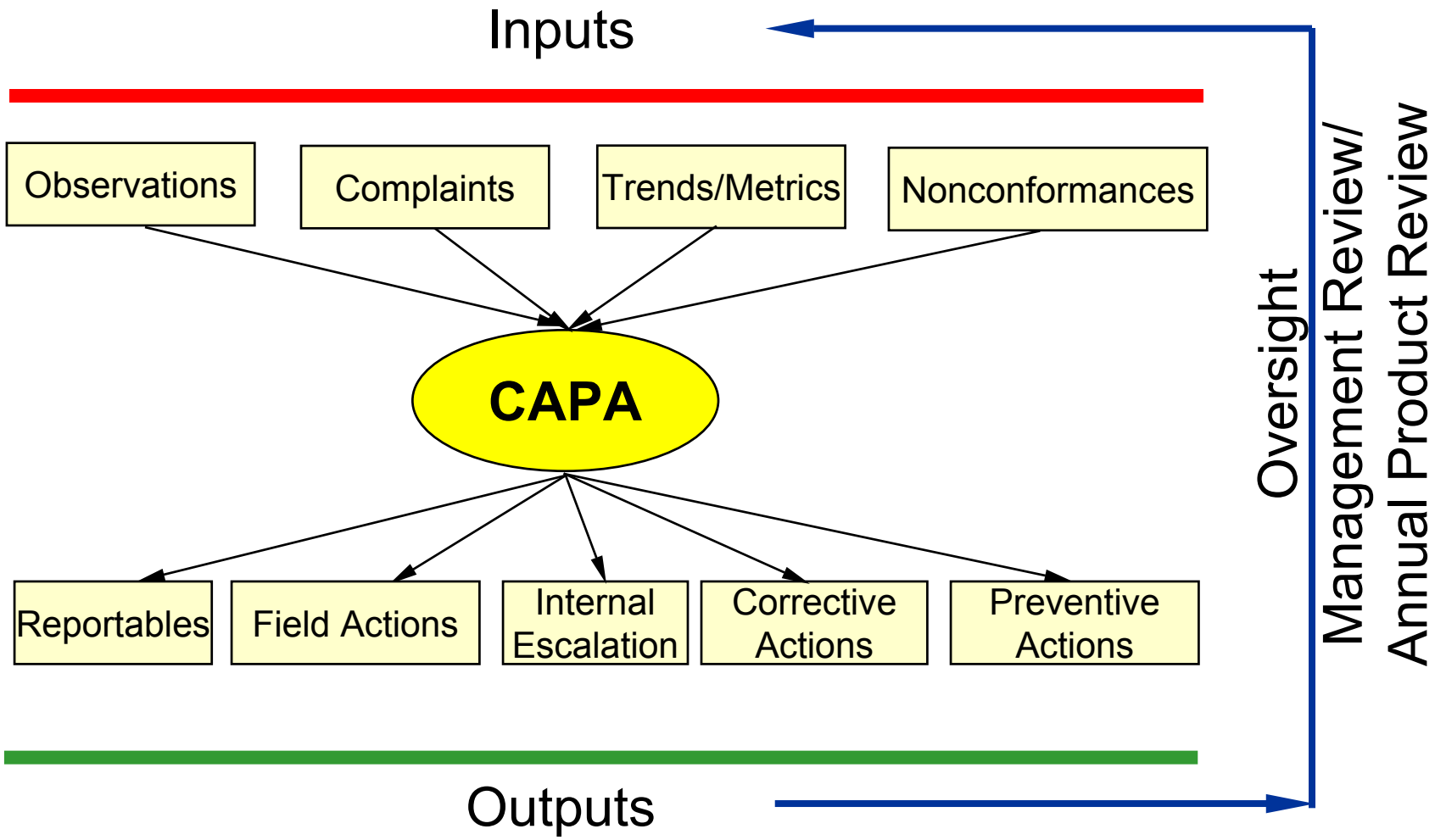
Corrective Action (CA)

- Action taken to eliminate the **causes** of an *existing* nonconformity, defect, or other undesirable situation in order to prevent recurrence.

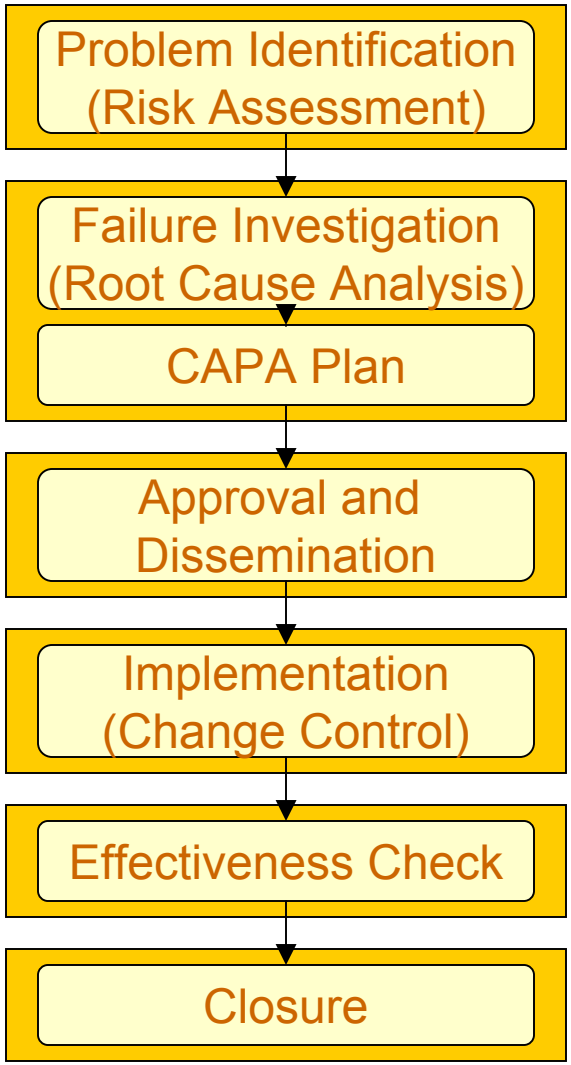
Preventive Action (PA)

- Action taken to eliminate the **cause** of a *potential* nonconformity, defect, or other undesirable situation in order to prevent occurrence and improve quality trends.

What is CAPA?


Inputs
Observations
Complaints
Trends/Metrics
Nonconformances
CAPA
Reportables
Field Actions
Internal Escalation
Corrective Actions
Preventive Actions
Outputs
Oversight
Management Review/
Annual Product Review

CAPA Process



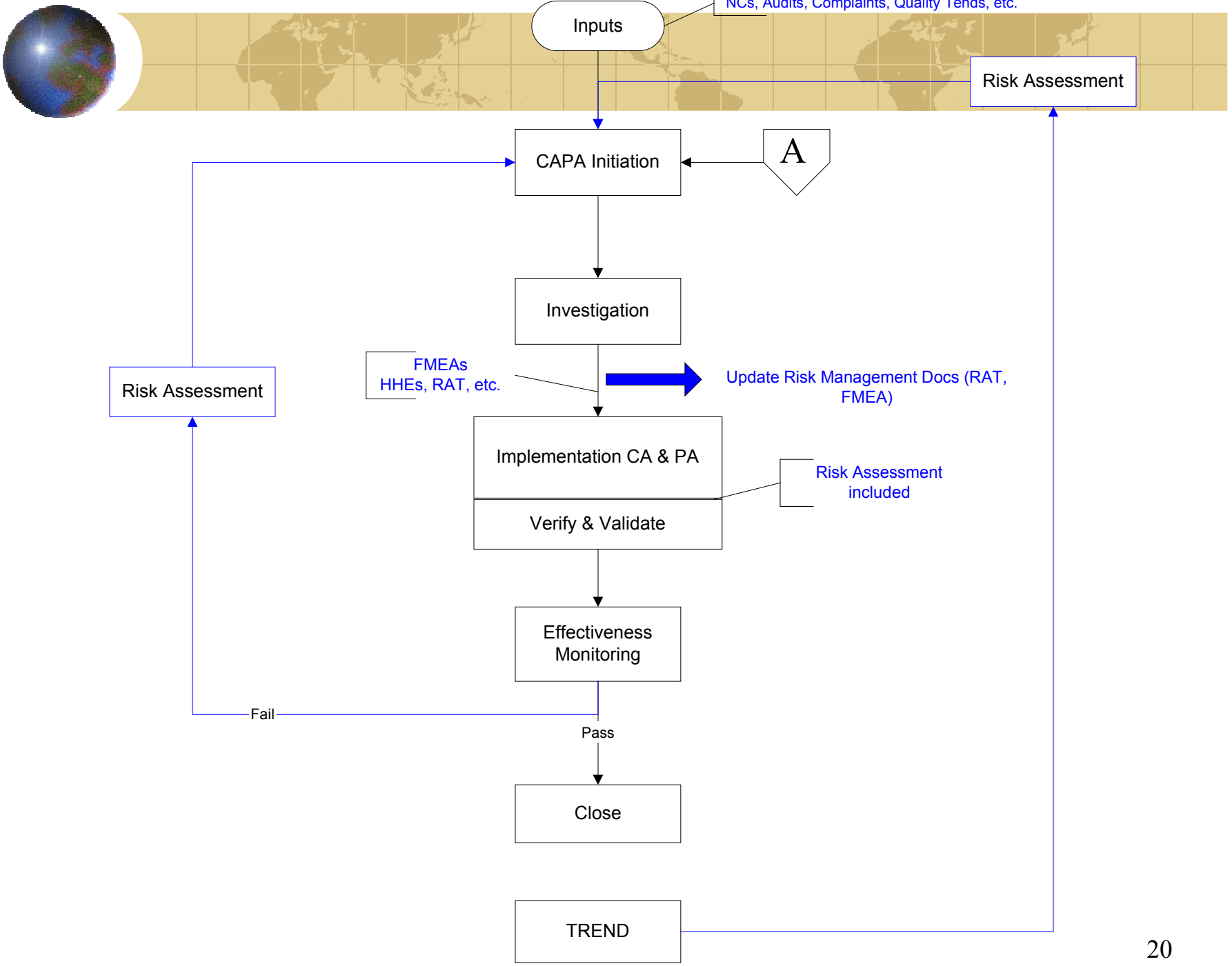
After root cause, revisit the risk.

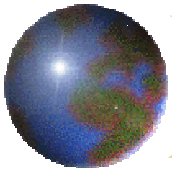
a) If >, need additional action

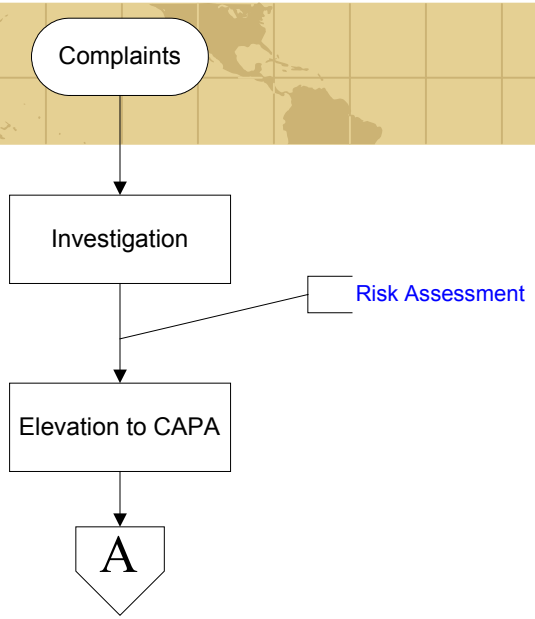
- Field Action
- additional CA & PA

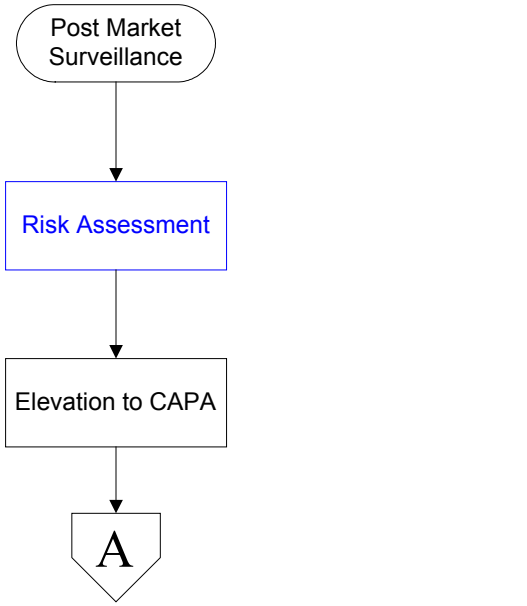
b) If <, can re-evaluate new risk.

- then decide intolerable to Broadly Acceptable, limited by resources


Inputs
NCs, Audits, Complaints, Quality Tends, etc.
Risk Assessment
CAPA Initiation
A
Investigation
FMEAs
HHEs, RAT, etc.
Update Risk Management Docs (RAT, FMEA)
Risk Assessment
Implementation CA & PA
Risk Assessment included
Verify & Validate
Effectiveness Monitoring
Fail
Pass
Close
TREND



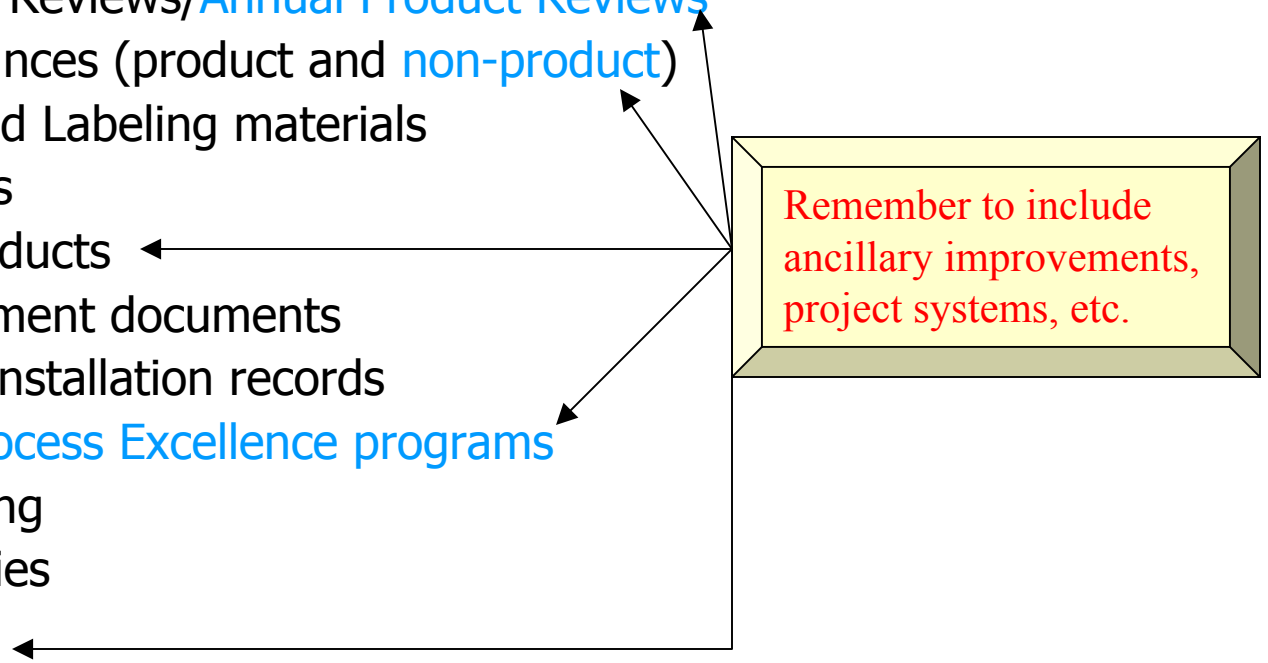

Complaints
Investigation
Risk Assessment
Elevation to CAPA
A


Post Market Surveillance
Risk Assessment
Elevation to CAPA
A

Inputs and Triggers

Internal Sources:

- Acceptance activities
- Calibration and Maintenance records
- Design Control system
- Management Reviews/Annual Product Reviews
- Nonconformances (product and non-product)
- Packaging and Labeling materials
- Quality Audits
- Returned products
- Risk Management documents
- Service and Installation records
- Six Sigma/Process Excellence programs
- SPC monitoring
- Stability studies
- And more…



Inputs and Triggers

External Sources:

- Customer complaints
- Customer feedback
- External Quality Audit reports
- FDA/ISO/EN/IVDD feedback
- Product warranty
- Recalls/field actions
- Identification of any other condition/issue that does not comply with:
  - Your own Quality System and/or
  - ISO/EN/IVDD standards (e.g., ISO 9001, ISO 13485, EN 46001, etc.)
  - FDA regulations (e.g., 21 CFR 820, 21 CFR 210/211, 21 CFR 600, 21 CFR Part 11, etc.)
- And more…

Remember to track & trend, use risk assessment tools

Inputs and Triggers

Challenges:

- Inputs not clearly defined or established
- Trigger thresholds not established
- Focus on reactive metrics (Nonconformances, Complaints, Audit Observations)
- Data not easily retrievable
- Data not easy to analyze for trends

Root Cause Analysis

Challenges:

- Poor/lack of technical skills to conduct root cause analysis
- Poor/lack of writing skills in documenting root cause analysis
- Poor/little business knowledge in conducting root cause analysis across processes, systems, product lines, and Quality Systems

Preventive Actions

Challenges:

- When everything is corrective, how can the organization assign resources to address Preventive Action?
- Risk assessment may not be designed to address elevation to CAPA for a potential issue or improvement (Preventive Action).
- CAPA metrics tend to focus on closure rates, cycle time, number of open CAPAs, etc. Preventive Actions are, in most cases, longer-term solutions across processes, systems, product lines, and Quality Systems and will take more time to close.

From Corrective to Preventive – some suggestions:

Inputs and Triggers

- Clearly define inputs and establish thresholds
- Implement predictive metrics/indicators
- Routinely review and act on sources of product and quality data
- Make data reporting available and easy to users and management

From Corrective to Preventive – some suggestions:

Risk Management

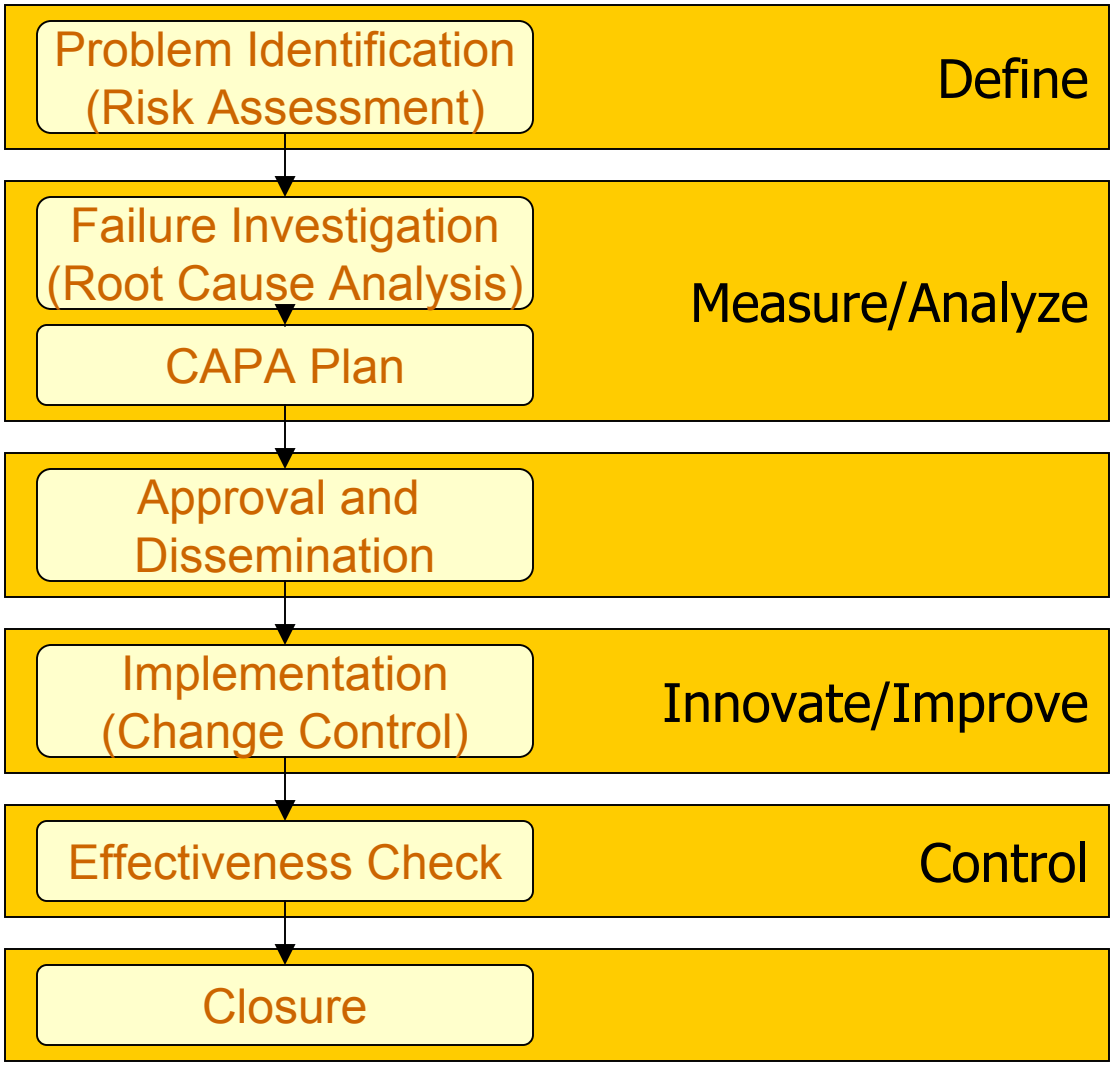
- Establish elevation mechanisms to CAPA
- Use a risk assessment process to allow prioritization of CAPAs and elevation to Management
- Use a risk assessment process that allows CAPAs for Preventive Action
- Link CAPA to Risk Management documentation (e.g., FMEAs, Design Control documents)
- Make data reporting available and easy to users and management

From Corrective to Preventive – some suggestions:

Root Cause Analysis

- Establish clear roles and responsibilities for conducting investigation
- Increase technical skills on root cause analysis tools
- Improve writing skills
- Use team approach to conduct investigation to increase business and technical knowledge
- Align with Six Sigma/Process Excellence

CAPA Process and Six Sigma (DMAI²C)



From Corrective to Preventive – some suggestions:

Preventive Action

- Implement predictive metrics/indicators
- Routinely review and act on sources of product and quality data
- Use a risk assessment process that allows CAPAs for Preventive Action
- Improve linkage between CAPA into Design Controls
- Take a holistic view of issues
  - Can it link to other Quality Systems, product lines, systems, and/or processes?

From Corrective to Preventive – some suggestions:

CAPA Process

- Integrate, integrate, integrate across business solutions and across sites
- Streamline/Lean your CAPA process
- Implement a global process for all sites
- Establish technical and user support for your CAPA system
- Leverage sister companies for design and experience (lessons learned)
- Establish joint partnership between business/system owner and Information Technology for continuous improvement efforts
- Project team (business and Information Technology) need to be experts in the process as well as the software solution
- Take a holistic view of the CAPA process
  - Does it link to other Quality Systems and business systems?

From Corrective to Preventive – some suggestions:

Software Solution

- Integrate, integrate, integrate across software solutions and sites
- Implement a global software solution
- Establish technical and user support for your CAPA system
- Leverage sister companies for infrastructure and validation
- Ensure that the hardware is reliable and support users needs including connection time, processing speed, 24x7 availability, etc.
- Increase technical expertise and involvement from your software vendor during initial design and implementation phases
- Project team (business and Information Technology) need to be experts in the process as well as the software solution
- Take a holistic view of the CAPA process and software solution
  - Can/does it link to other Quality Systems and business systems?

From Corrective to Preventive – some suggestions:

Management Support and Oversight

- Ensure Management oversight and commitment
- Align CAPA with company, departmental, and individual goals and objectives
- Create rewards and recognition programs
- Establish joint partnership between business/system owner and Information Technology for continuous improvement efforts
- Align metrics from departmental to corporate level

Annual Product Review - Requirements

Does it apply to devices? Yes, for combination devices such as, drug/device, biologics/device, etc..

- Written records subject to this review include, but are not limited to, the following:
  - Manufacturing and quality records from lots or batches of drug/device combination products manufactured within the previous year, including:
    - receiving inspection
    - in-process
    - final release testing results
    - deviations
    - investigations
    - change control records
    - quality system trends

Annual Product Review *(continued)*

- Post market quality records such as:
  - complaints
  - Medical Device Reporting (MDR)
  - adverse events
  - field actions
  - product corrections
  - regulatory submissions
  - returned or salvaged products
  - product stability data

Conclusions - Annual Product Review

- Covers the product cradle to grave. Presents management a view of product and process behavior over time.
- Is influenced by all aspects of the Quality System - including in process and release testing.
- Supports decisions related to design control, process validation and control as well as user drift.
- Identifies trends/opportunities across mfg lines or sites.

BIG Lesson Learned

Process Owner (Users)

+

System (Procedures + Software)

=

Sustainability

Leads to Cultural Change

Q&A

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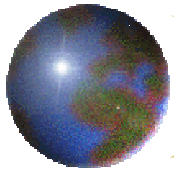

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