

A person wearing a white protective suit, a white face mask, and blue gloves is holding a magnifying glass over a white surface. The person's eyes are visible through the mask. The background is a light, neutral color.

FDA

**U.S. FOOD & DRUG
ADMINISTRATION**

Establishing a Culture of Quality

Rick Friedman, Deputy Director Office of
Manufacturing Quality Office of Compliance
Center for Drug Evaluation & Research FDA

***FDA CoE Conference
September 2021***

Agenda



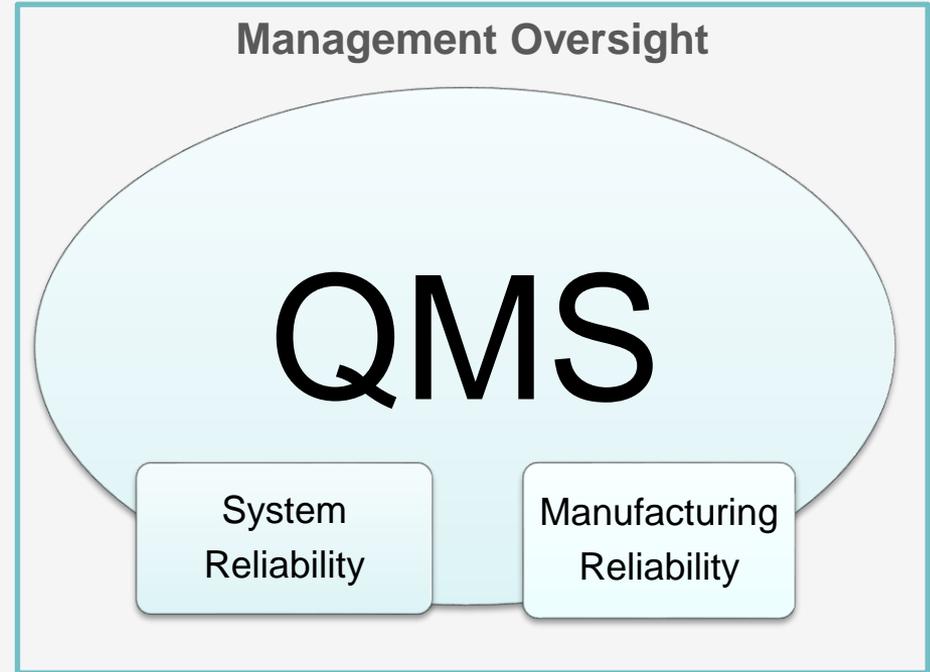
- Effective Quality Management Systems (QMS)
 - *The foundation for quality assurance*
- The Patient is the Customer
 - *Manufacturing, quality, and patient risk*
- Management Oversight of Drug Quality
 - *The Ishikawa Fishbone*
 - *QMS Elements (Process & Quality Monitoring, CAPA, Change Management, Management Review)*
- Quality Culture is Driven by Top Management
 - *Executive oversight and decisions define the culture*
- The Facility Lifecycle



Effective QMS

Effective Quality Management Systems

An effective QMS (“quality system”) establishes and maintains a state of control throughout the product lifecycle via systems that vigilantly oversee process performance and product quality.



ISO 9001: 8 Principles of Quality Management

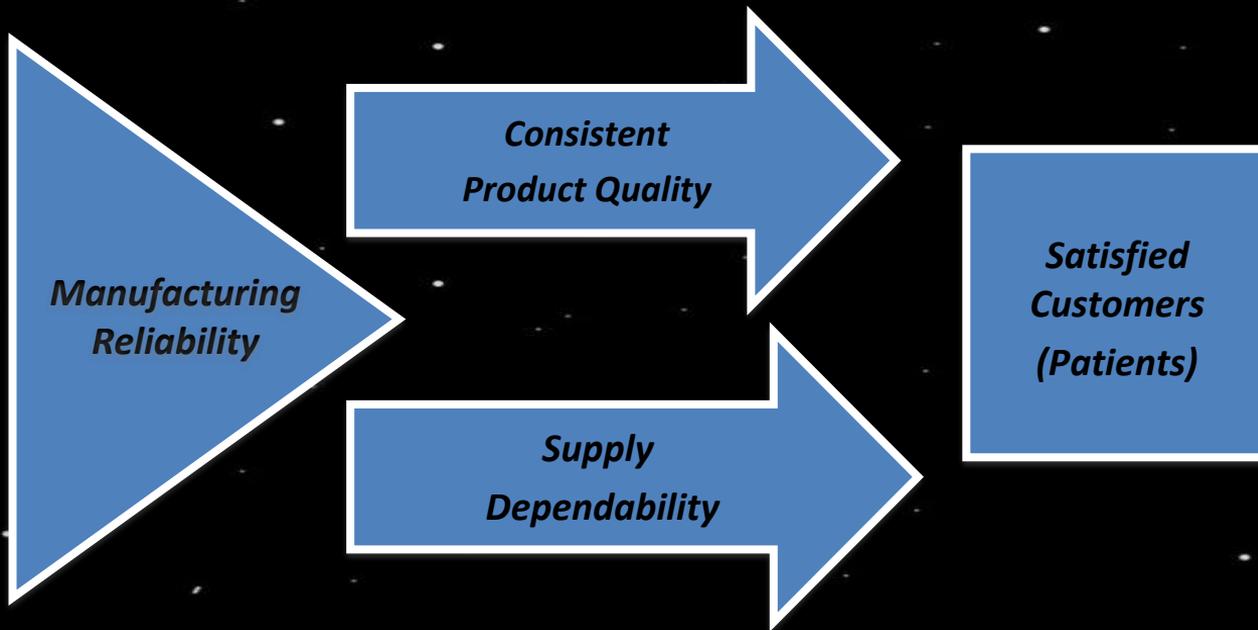
- Leadership
- **Customer focus**
- Process Performance
- Systems Management
- Continual Improvement
- Involvement of People
- Factual approach to decision making
- Strong supplier relationships

**The Patient is the
Customer**

The Patient is the Customer



- Voice of the Customer: Quality is customer-focused
 - *e.g., Is process designed to assure quality? Are the ingredients suitable for their intended use?*
- Quality is achieved (and consumer risk minimized) by a strong QMS, which requires Senior Management Commitment.
- In a strong QMS, senior management recognizes and leads with the philosophy that:
 - *Quality Assurance activities avoid problems by good design and early detection (proactive). Reliance only on Quality Control leads to problems that are detected too late (reactive).*
 - *Robust supplier relationships and oversight programs are essential to identify and address variability in materials and processes.*





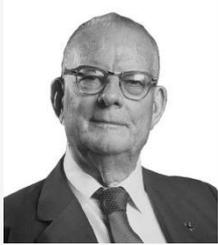
Benefits of Better Quality Performance

A quality-focused organizational culture yields many benefits:

- Early problem detection.
- Enhanced process stability drives productivity and performance.
- Fewer major deviations, failures, and investigations...leading to more efficient QA release of batches.
- Low likelihood of costly emergency remediations or non-compliance.
- Minimizes significant customer complaints/returns.
- Protection of brand, more competitive (Deming Chain Reaction).



Management Oversight of Drug Quality



www.census.gov

William Edwards Deming: *Reactive vs. Proactive Quality Culture*

“Uncontrolled variation is the enemy of quality.”

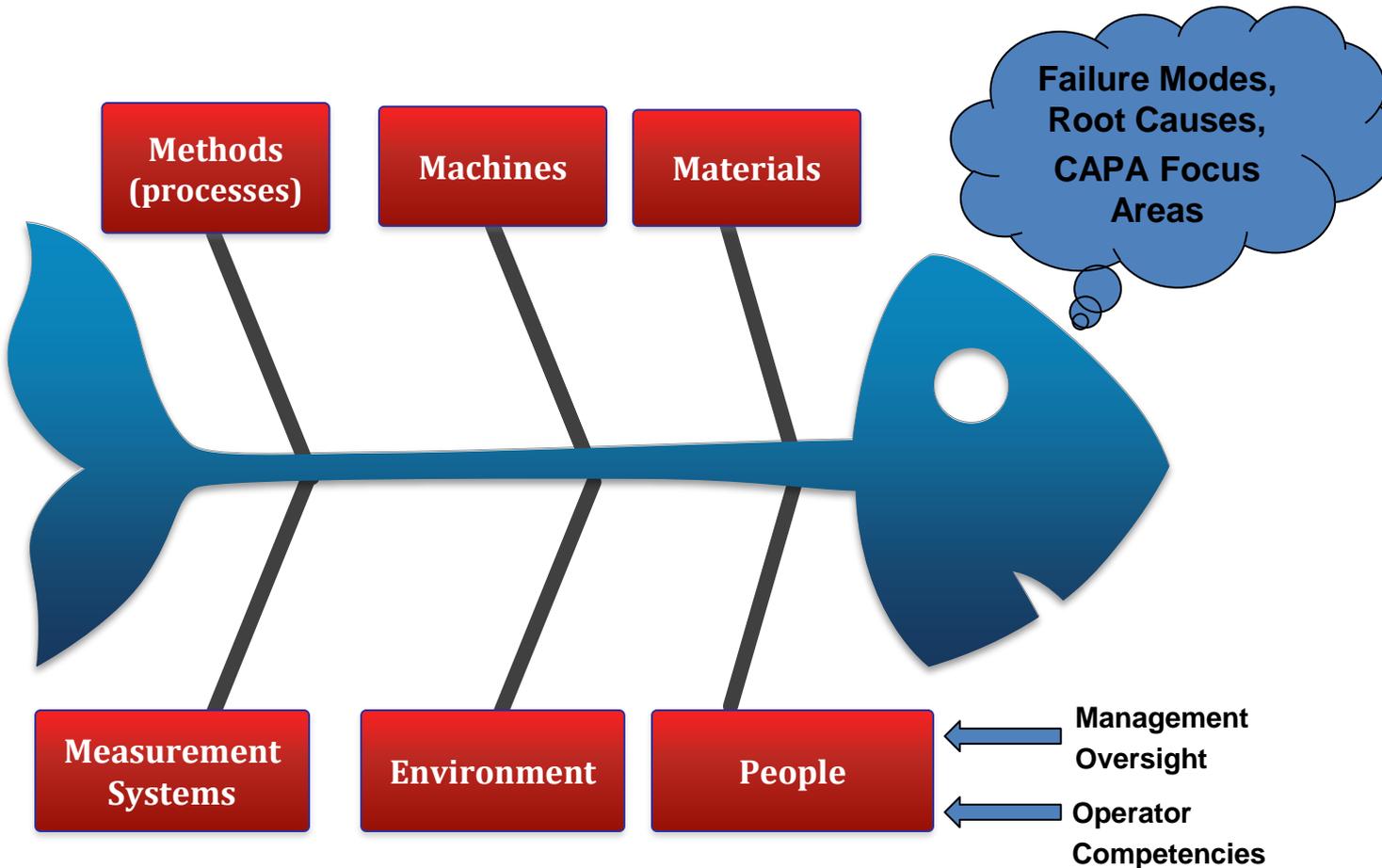
“Putting out fires is not improvement of the process.”



Sources of Variability

- People
- Materials
- Methods
- Measurements
- Machines (Facilities and Equipment)
- Environment

Risk Management Tool to Identify Sources of Variability



Risk Management is Dynamic and Ongoing

- CGMP necessitates ongoing vigilant management of these risks, and enables continual learning and improvement.
 - Some think that risk assessment is a one-time thing...
 - Risk management is **an iterative, lifecycle endeavor**.
 - Risk management activities will not be sustainably effective if they are **Static**.
 - Notably, more information is available after product launch and through extensive batch manufacturing experience than was available through early experiments. **This new knowledge inevitably identifies new risk management opportunities.**



Process Performance and Product Quality Monitoring



PPPQMS Inputs

May Trigger Risk Review, CAPA, and/or Change Management

- Nonconformances, discrepancies, deviations, failures, recalls
- Product Quality Data
- Process monitoring results (e.g., batch data, trend analysis)
- Equipment or Facility issues (e.g., malfunctions, maintenance)
- Raw Material Issues
- Regulatory Findings (local or at another site)
- Audits and self-inspections
- Complaints/Returns
- Stability Testing results

Managing Risks: Do you *connect the dots*?

FDA

Complaints

Rejections

Feedback
from "Shop
Floor"

Maintenance
Issues

Deviations

Returned
goods

OOS
Results

Stability
Results

Current
Staff
Competencies

Raw
Material
Data

Results of
Audits &
Inspections

Process
Trending
Data

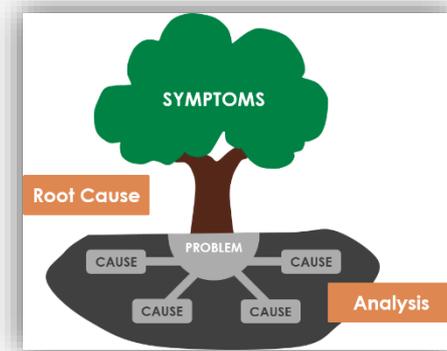


CAPA

Corrective Action and Preventive Action (CAPA)



“The pharmaceutical company should have a system for **implementing corrective actions and preventive actions** resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A **structured approach to the investigation process** should be used with the objective of determining the **root cause.**”





Change Management



Change Management

Timely and Effective Actions

- The change management system ensures corrections and improvements are undertaken in a timely and effective manner.
- “Implement appropriate product **quality improvements, process improvements, variability reduction, innovations** and pharmaceutical quality system enhancements.”

In Some Cases, Very Substantial Changes Are Needed



OOS results may indicate a flaw in product or process design

- Lack of robustness in product formulation
- Inadequate raw material characterization or control
- Substantial variation introduced by one or more unit operations of the manufacturing process
- Or a combination of these factors
- *“In such cases, it is essential that redesign of the **product** or **process** be undertaken to ensure reproducible product quality.”*



Management Review



Management Responsibility

- Quality policy & planning
- QMS effectiveness and ongoing state of control
- Management commitment to quality and safety
- Internal communications
 - *supports surfacing of issues by staff as a norm for prompt problem identification and continual improvement*
 - *escalating major issues to top management, whenever needed*
- Resource management
- Extends beyond local site or corporation to the supply chain
 - *Outsourced activities (CMOs)*
 - *Quality of incoming materials (includes changes in raw material supplier or quality)*

Risk, Science, Law, and the Consumer

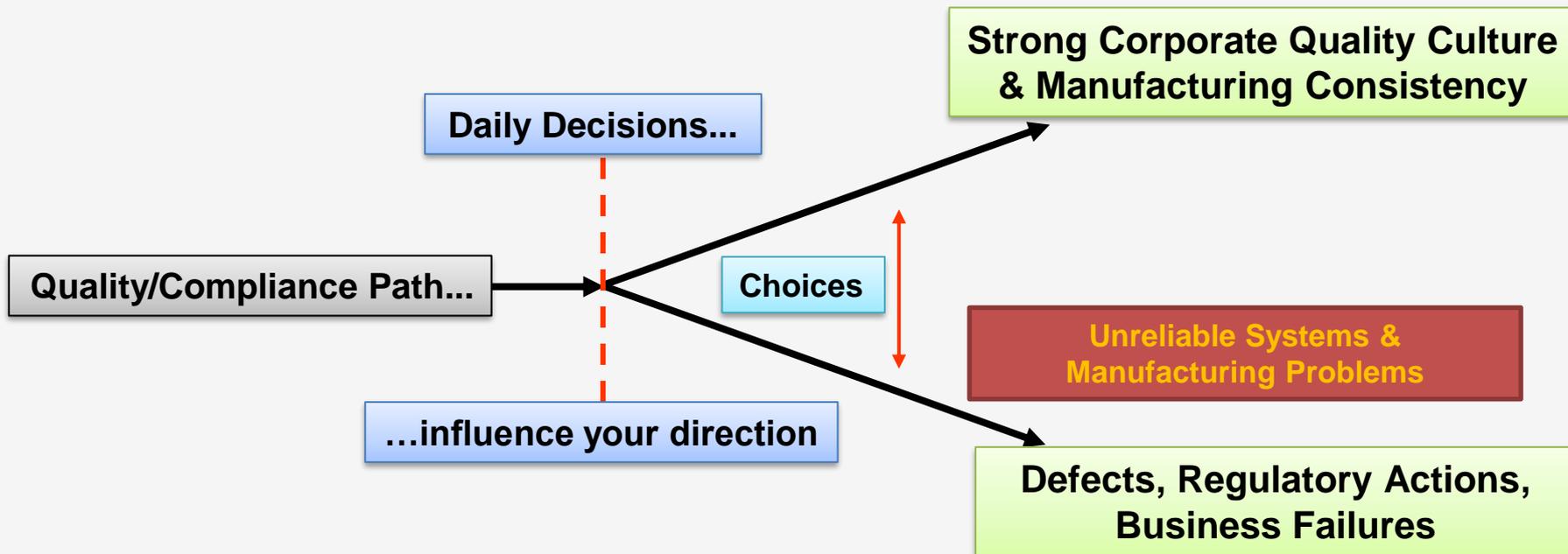
In 2012, the FDASIA legislation amended FD&C Act 501 (21 U.S.C. 351) as follows:

“For purposes of paragraph (a)(2)(B), the term ‘current good manufacturing practice’ includes the implementation of **oversight** and **controls over the manufacture of drugs to ensure quality**, including **managing the risk** of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”

Section 711 of FDASIA: Enhancing the safety and quality of the drug supply

Quality Culture is Driven by Top Management

Leadership and the Corporate Quality Culture



Quality Culture



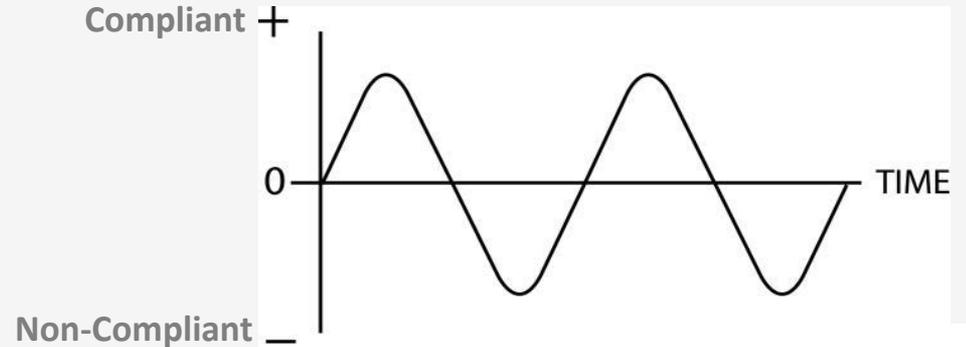
- Organizational Structures
- Actions More Than Words
- The Quality of the Work You Accept Becomes Your Standard
- Support for the Quality Organization
- Investments in Quality
- Quality Involved in Business Decisions

Teetering on the Border...

Sustainable compliance not attained by aiming for lowest standard



- The legal standard is the minimum or “floor.”
- But, notably, minimum GMP requires good practices.
- This should not be confused with “*minimal*” (“do as little as possible”) practices.
 - See word cloud on the right for synonyms for “good!”
- Companies who strive for nothing more than minimum performance leave no margin for error. This does not support a robust state of control, and instead the facility will likely vacillate between good and substandard quality. Teetering on the border of compliance is not a recipe for robust quality or sustainable compliance.



Compliance and Quality Assurance



- Solely “checkbox” approaches to CGMPs are not effective
- Instead, the foundation of compliance is an ongoing commitment to **quality assurance** which:
 - *Facilitates sound daily decision-making across the product and facility lifecycle (quality risk management)*
 - *Promotes iterative learning (knowledge management)*
 - *Leverages today’s technologies which often also have Total Cost of Ownership benefit*
- This level of quality management maturity enables **sustainable compliance** and **consistently high-quality drugs**
- Less capable operations generally receive increased inspectional scrutiny

Quality Culture: How mature is your Quality Culture?

Level 1: Small problems often snowball into larger ones. Management becomes aware only when there is a crisis.

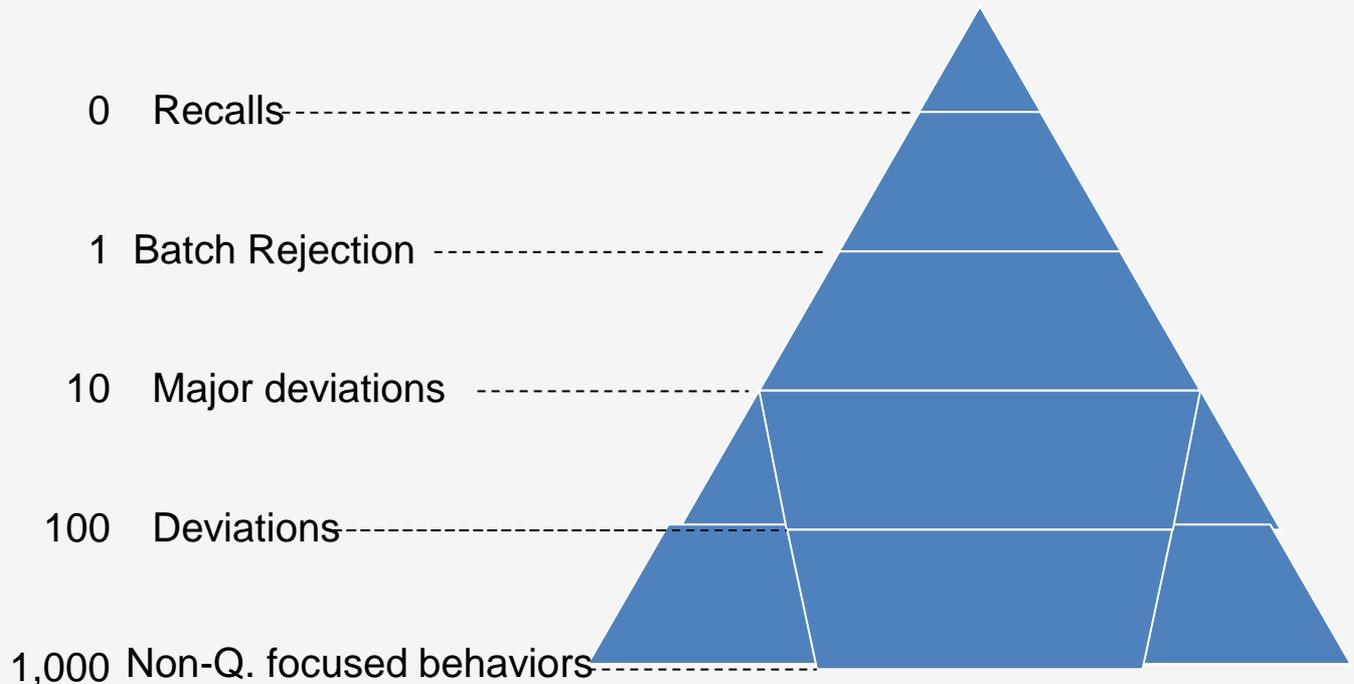
Level 2: Nearly always reactive. Patchwork corrections are the norm, but there might be some willingness to change.

Level 3: More proactive. Increasingly surfaces major issues and makes some lasting systemic improvements.

Level 4: Acts preventively and rewards improvement. Implementing meaningful process and system improvements is routine practice in the organizational culture.



A proactive quality culture... attacks the base!



ATTACK THE BASE!

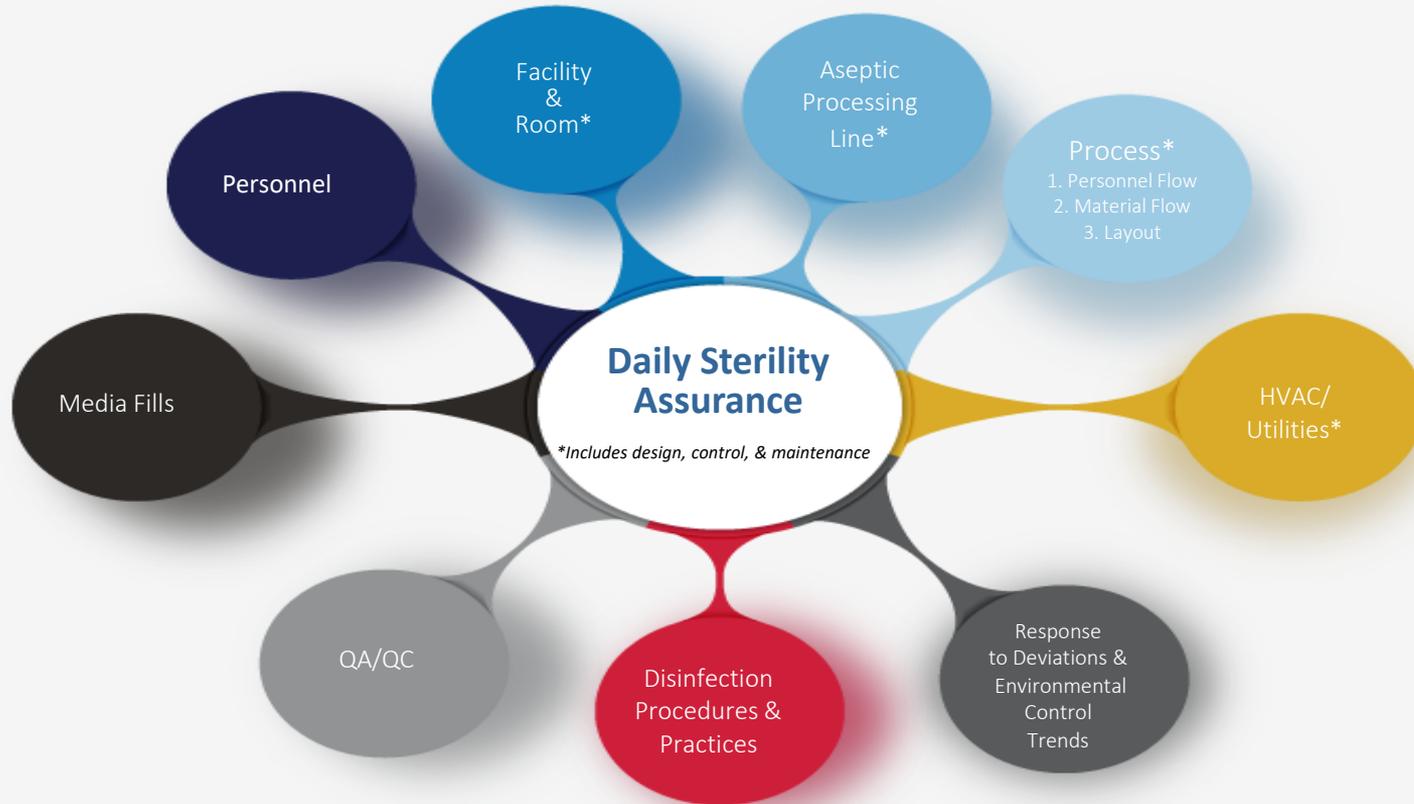
Quality Culture: Enterprise Transformation



- Shared accountability and transparency
- Cross functional teamwork and collaboration
- Listening and learning
- Benchmark and continual improvement
- Coaching and developing others
- Business integrity



The Facility Lifecycle



Management Decisions Create the *de facto* Culture



A drug manufacturer is responsible for implementing **dependable daily operations** that assure consistent drug quality.

Management's **daily decisions** on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will ultimately determine the **quality** of the drugs that are shipped from a given facility.

The Facility Lifecycle

Oversight of Operational Suitability



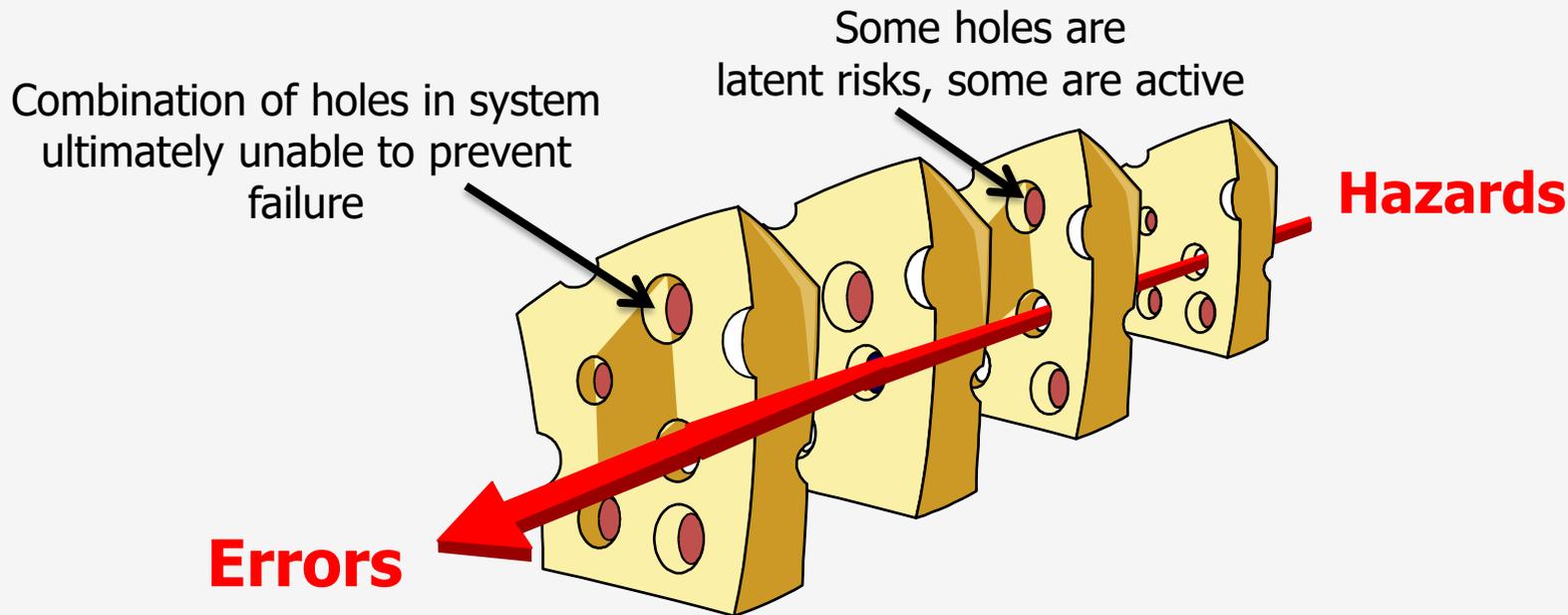
- **Senior management has a critical ongoing oversight role to ensure suitability of operational design, control, and maintenance. For example, infrastructure may be...**
 - *unreliable or low capability from outset*
 - *not appropriate for new product demands*
 - *or, equipment/facility degradation (aging facility) may have occurred over time*
- **Key Leadership Principle: You cannot shirk your individual responsibility if you expect a system to work.** (Leaders rightly emphasize that everyone is responsible for assuring quality.)
- This principle is a good one for both the leaders and those they lead. Senior leaders need **to allocate resources for major infrastructure upgrades** when operations are deficient.

Producer Risk or Patient Risk?

A Strong Quality Culture Prioritizes the Patient

- “The probability alpha, also known as the **producer's risk**, is the risk that adequate product is rejected. The probability beta is known as **the consumer's risk** because defective product is accepted.”
- The associated risk probabilities will depend on “scrapping good product” or “the costs of shipping bad product.”

Reason's "Swiss cheese" model of error causation



Successive layers of defenses, barriers and safeguards. Are they sufficient, or are there dangerous holes in the manufacturing operation or system?

Executive Management Role: Facility

Facilitate Continual Improvement (ICH Q10, 1.5.3):

- “**Implement** appropriate product quality improvements, process **improvements**, variability reduction, innovations and pharmaceutical quality system enhancements.”

Resource Management (ICH Q10, 2.4):

- Management should determine and **provide** adequate and appropriate resources (human, financial, materials, **facilities, and equipment**) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

Change Management (ICH Q10, 3.2.3):

- “The change management system ensures continual **improvement** is undertaken in a **timely and effective**” manner...”

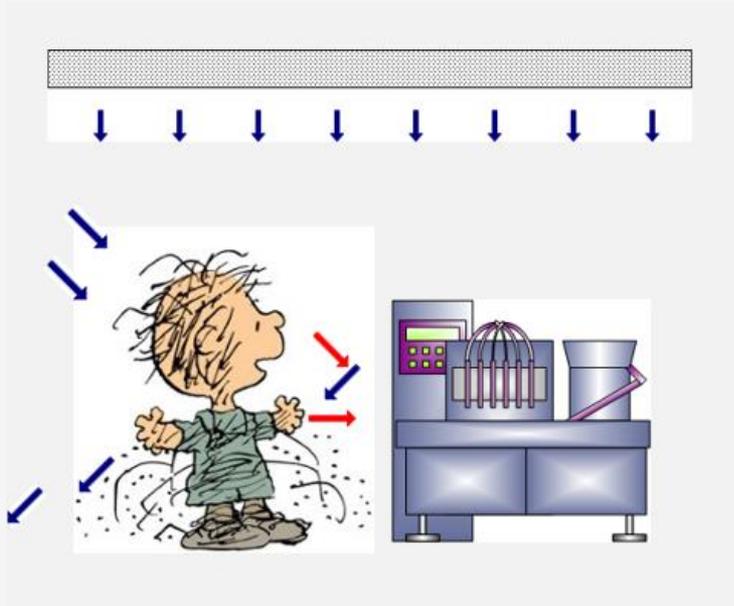


Change Management: Manual vs. Automated Operations

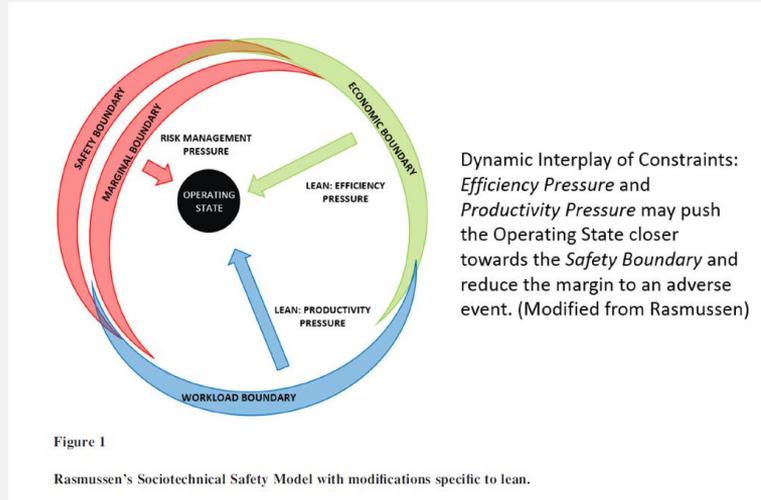
- Modern outsourcing facilities use automation and separation technologies (e.g., RABS, isolators) to protect the ISO environment from contamination risks.
- But many lower capability facilities still include manually intensive aseptic processes, and deficient facility layouts and process flows. These facilities are less effective at mitigating the various operational variables that pose risks to product sterility. There is significant potential for improvement at such facilities.
 - “When production line operators **perform manual activities near an insufficiently protected product**, they raise the risk of microbial contamination.”
 - “**If equipment is not well designed or is poorly maintained**, repeated or extensive **manual** interventions often occur.”

Risk Management Decision in 2021

Should humans directly interact with the aseptic line?



Current State – Human or System Fail?



- Since 2012, BioPhorum Operations Group has researched how to improve operational performance. They “recognized our common ‘human error problem’ and began efforts to address this critical issue.”
- “50% of deviations are attributable to human error. We have found internally that despite our best efforts the human error rate has been constant over several years.”
- Some “continue to consider human error as a **cause** and not as a **symptom** of the problems within our system.” The belief “is difficult to shake as an industry, for reasons both cultural and institutional.”
- “Relying on a reductionist approach is an incomplete solution” to preventing recurring problems that have more complex system origins. We need to “continue to work on improving **systems.**”

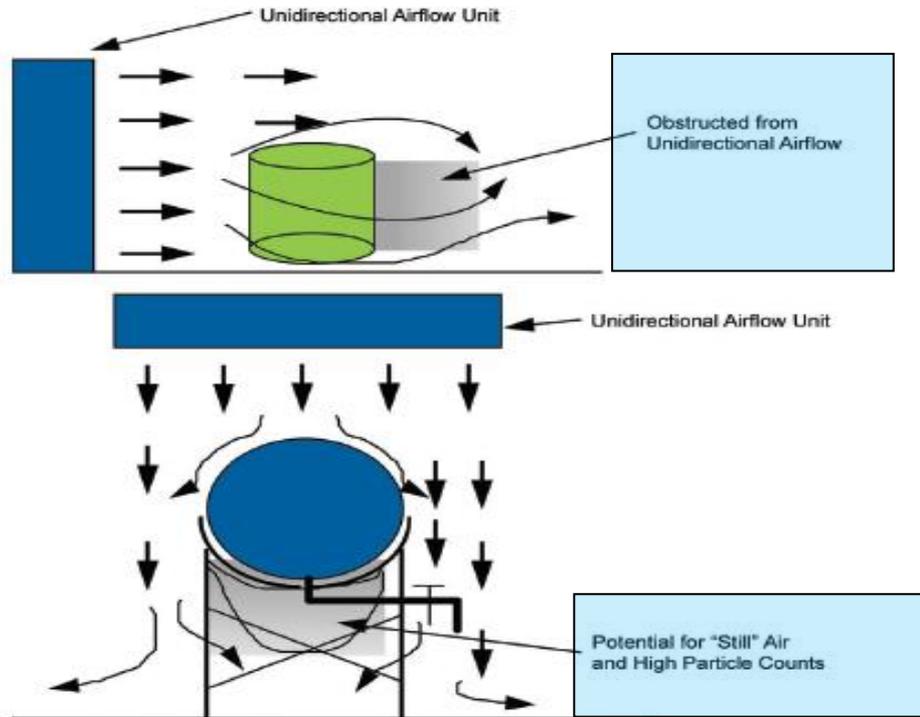
Is the inherent design risk from these obstructions acceptable?

Unidirectional Airflow "Shading"



ISPE Baseline® Guide:
Sterile Product Manufacturing Facilities

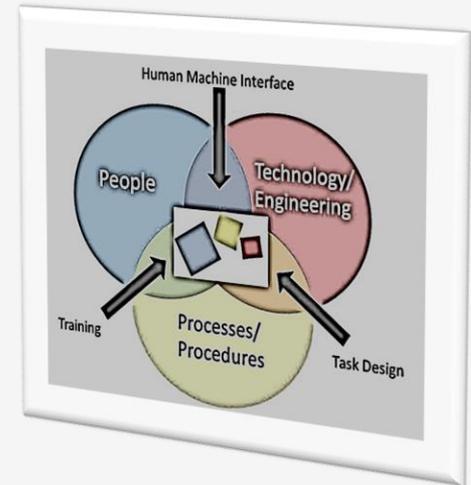
Figure 11.12: Unidirectional Airflow Shading



Production Risks: Human Factor Risks in Aseptic Manufacturing

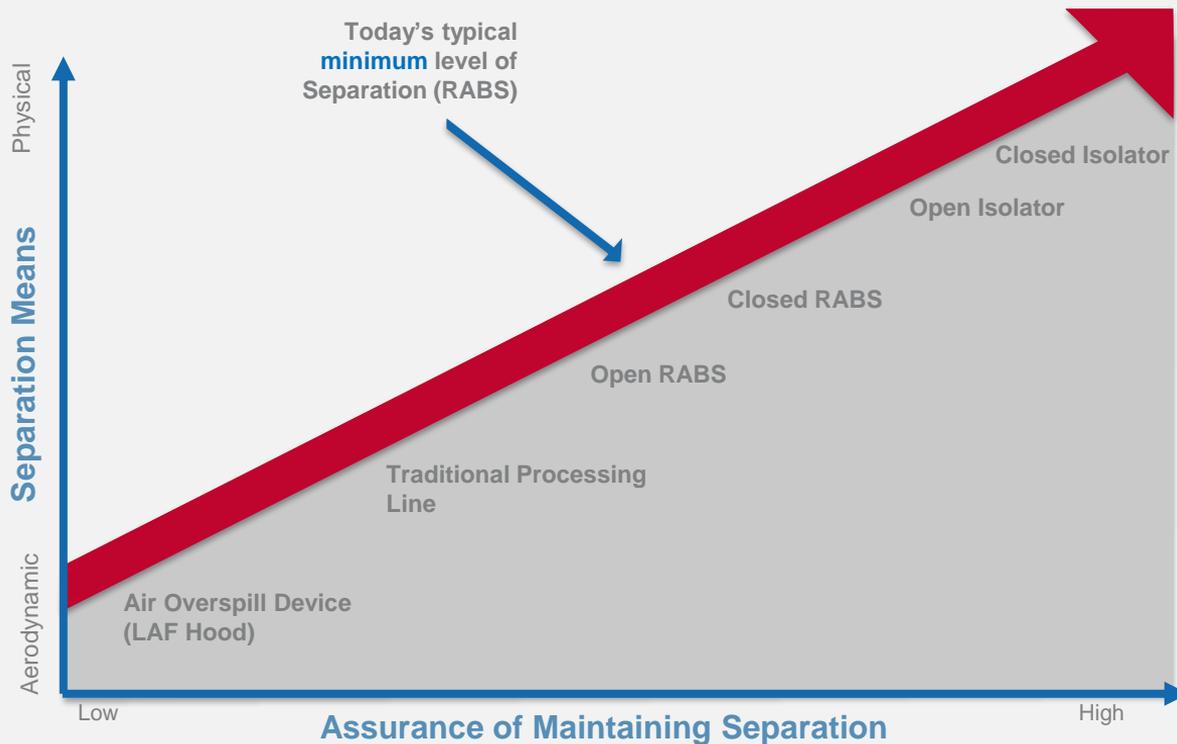
Consider the variability in these Critical Human-Machine Interactions:

- **Setup** of equipment (Stopper Hopper, BFS Machinery, etc.)
- **Routine** Interventions
- **Non-Routine** Interventions: Fixing a Vial Jam or equipment malfunction
- **Charging containers or closures** onto a filling line
- **Aseptic connections**
- **Aseptic addition** of a non-filterable ingredient
- **Wrapping parts and equipment** for porous autoclave load
- **Disinfection** of processing line and room
- **Transfer of product** (transfer/loading of half-stopped vials to lyophilizer)
- **Clearance of specified number (or all) units on the aseptic processing line** because of major/extended intervention



Equipment & Facility Risks:

Is Line Designed to Reduce Hazard Posed by People?



Designing for Quality



- Separation (prevents Mixups, Contamination)
- Automation (eliminates manual variability)
- Integration (minimizes risks from manual transfers between unit ops)

Also:

Advanced Testing/Analytics - better tests and informatics to automatically adjust when anomalous conditions are detected in on-line testing, detect adverse trends, and diagnose root causes



Summary

How Do You Know If Your Quality Culture is a Healthy One?





Summary

- A robust quality culture is:
 - Vigilant and Proactive
 - Patient-focused
 - Science and risk-based
 - Able to identify issues while they are still small
 - Readily meets Good Manufacturing Practice
 - Responsible for assuring any supplier or contract site is qualified to do the function, and performed it satisfactorily
 - Supportive of business needs because assuring quality creates higher yield, dependability, and sustainability
- It should not be:
 - Reactive or defensive (issues should be surfaced)
 - Solely a procedural approach (only “plan-do,” without “check-act”)



U.S. FOOD & DRUG
ADMINISTRATION