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.

Management Oversight

QMS

System Reliability

Manufacturing Reliability

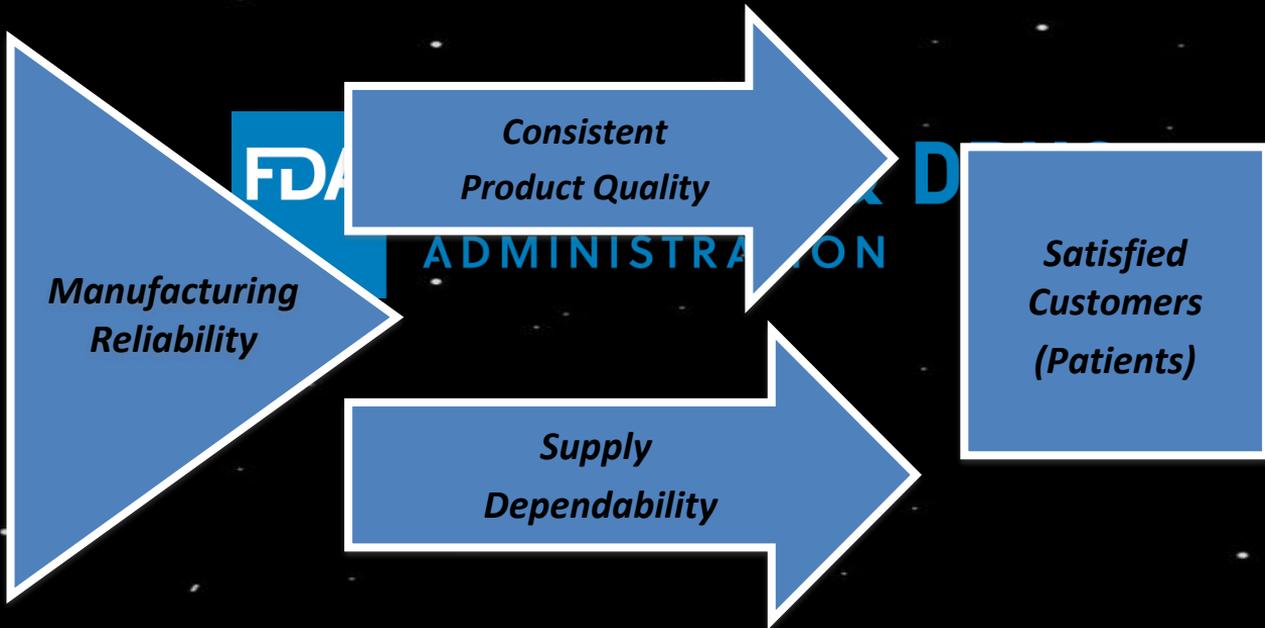# ISO 9001: 8 Principles of Quality Management

- 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
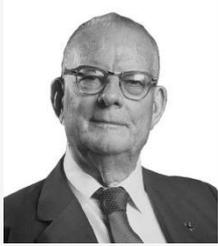
William Edwards Deming:
Reactive vs. Proactive Quality Culture

www.census.gov

"Uncontrolled variation is the enemy of quality."
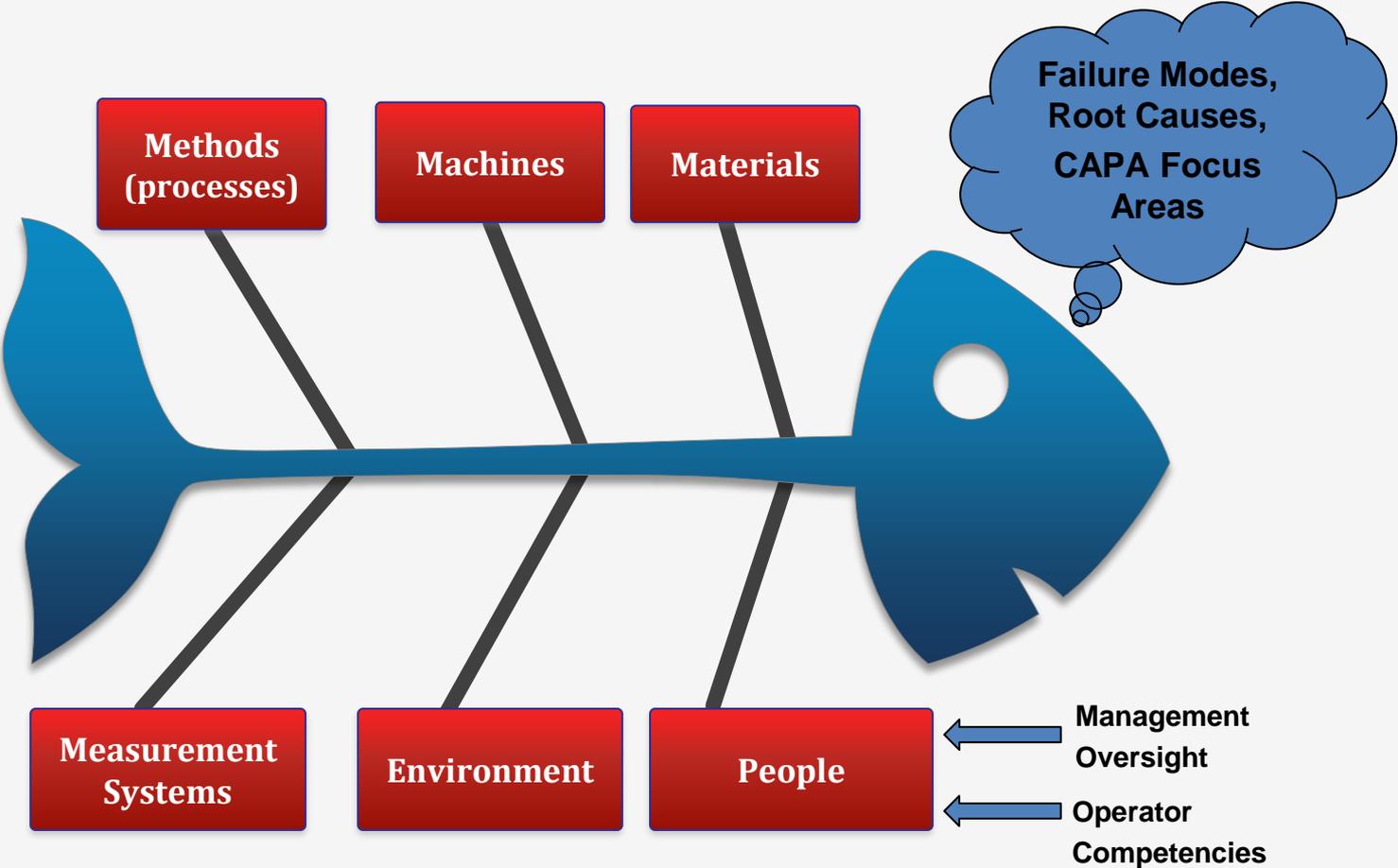
"Putting out fires is not improvement of the process."

Sources of Variability

- People

- Materials

- Methods

- Measurements

- Machines (Facilities and Equipment)

- Environment

Risk Management Tool to <u>Identify</u> Sources of Variability

Risk Management is Dynamic and Ongoing

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- 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.**

PIC/S QRM

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*?

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**."
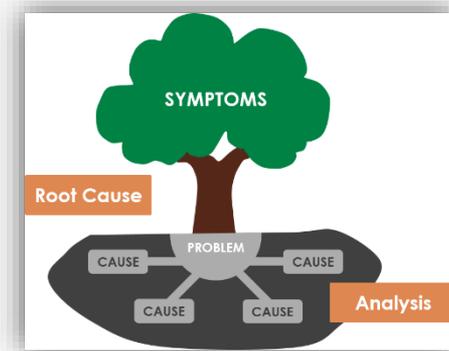
Change Management

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."

ICH Q10

In Some Cases, Very Substantial Changes Are Needed

FDA

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

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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

25

Quality Culture is Driven by Top Management

Leadership and the Corporate Quality Culture

Daily Decisions...

Quality/Compliance Path...

Choices

...influence your direction

Strong Corporate Quality Culture & Manufacturing Consistency

Unreliable Systems & Manufacturing Problems

Defects, Regulatory Actions, Business Failures

Adapted from Richard Davis

Quality Culture

High Quality & Compliance

Slippery Slope

Quality & Compliance Problems
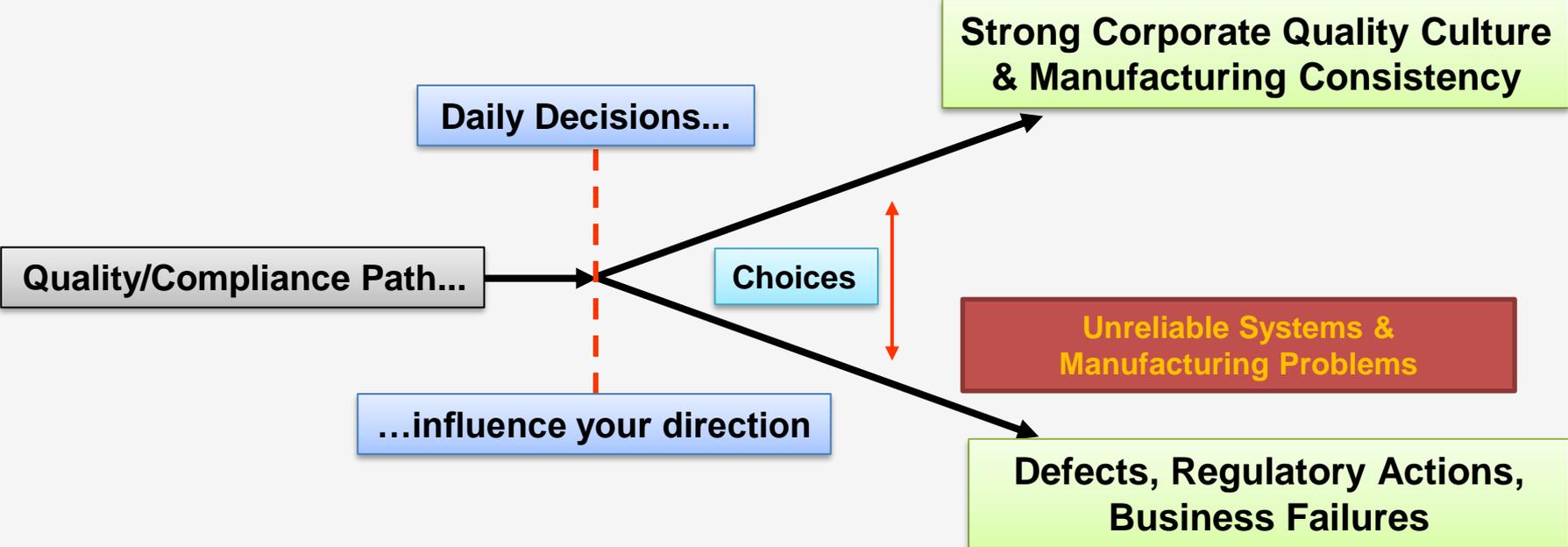
- Organizational Structures

- 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

Adapted from Richard J. Davis
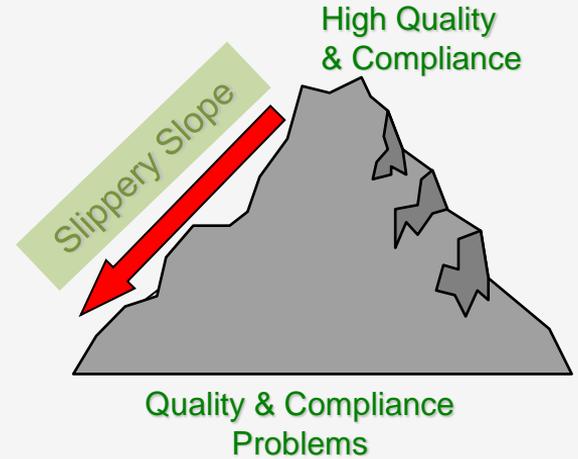
Teetering on the Border…
Sustainable compliance not attained by aiming for lowest standard

- The legal standard is the minimum or "floor."

- But, notably, minimum GMP requires <u>good</u> practices.

- This should not be confused with *"minimal"* ("do as little as possible") practices.
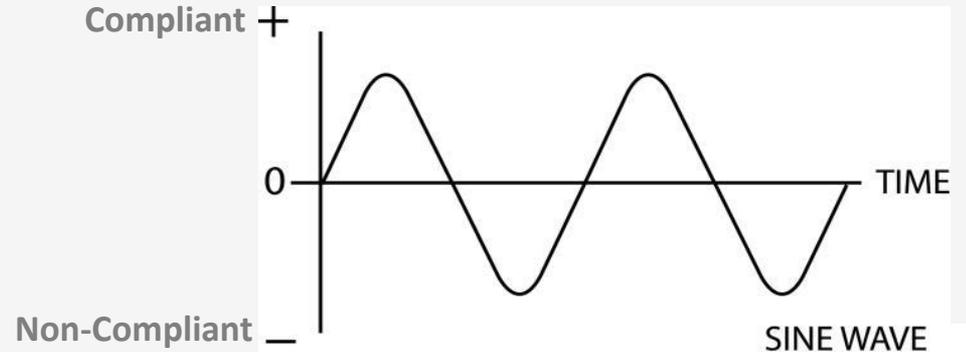
  – See word cloud on the right for synonyms for "good!"

- 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. <u>Teetering on the border</u> of compliance is not a recipe for robust quality or sustainable compliance.

worthy magnificent fine terrific acceptable satisfactory excellent splendid first-rate superlative outstanding fab first-class admirable superb marvelous superior hunky-dory agreeable wonderful

Compliant +

0 — TIME

Non-Compliant —

SINE WAVE

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!

0   Recalls

1   Batch Rejection

10   Major deviations

100   Deviations

1,000 Non-Q. focused behaviors

ATTACK THE BASE!
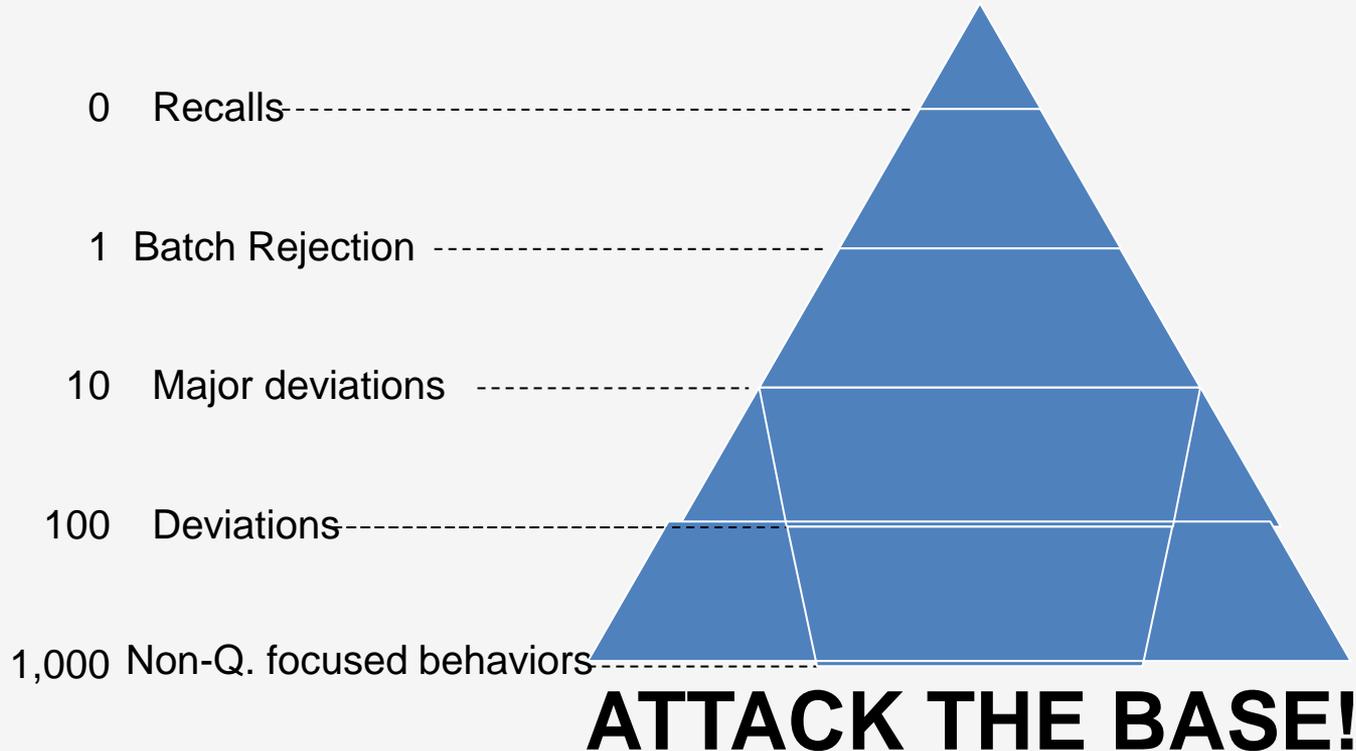
Quality Culture: Enterprise Transformation

ATTITUDE

Leader Behaviors

Culture

PERFORMANCE

- 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.

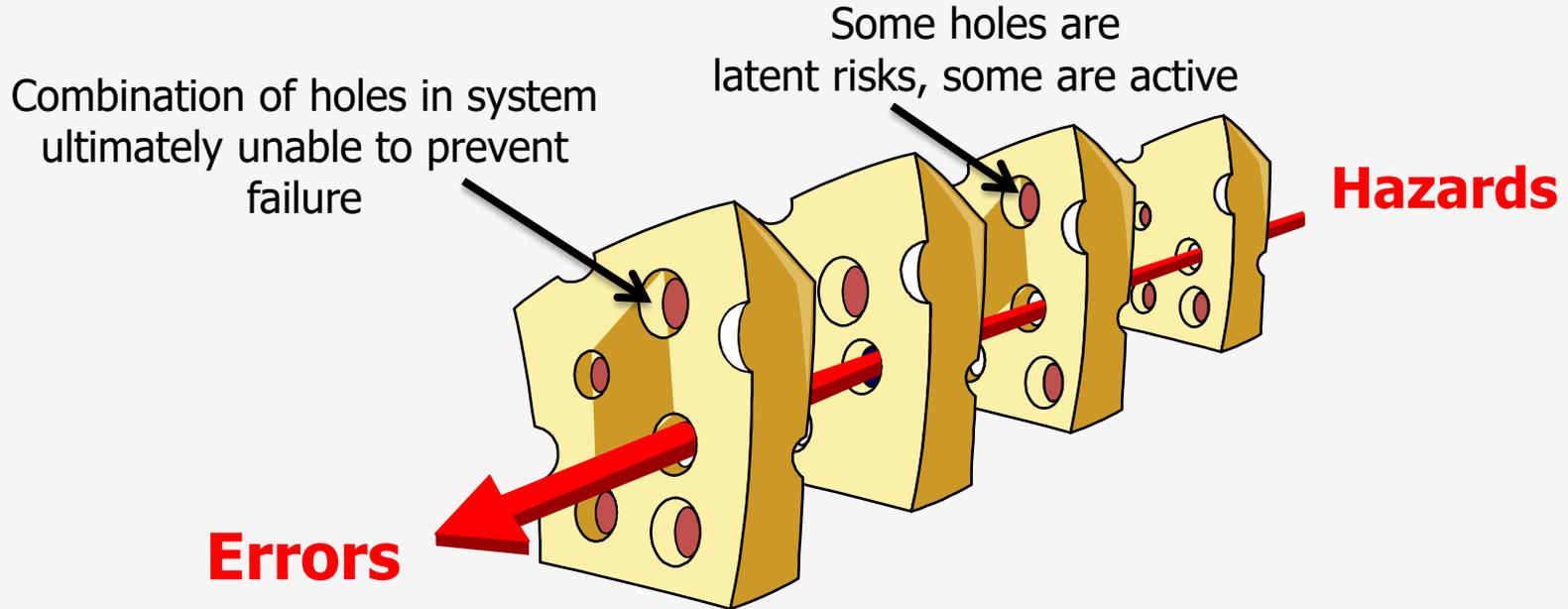# Producer Risk or Patient Risk?
A Strong Quality Culture Prioritizes the Patient

- "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

Combination of holes in system ultimately unable to prevent failure

Some holes are latent risks, some are active

Hazards

Errors

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

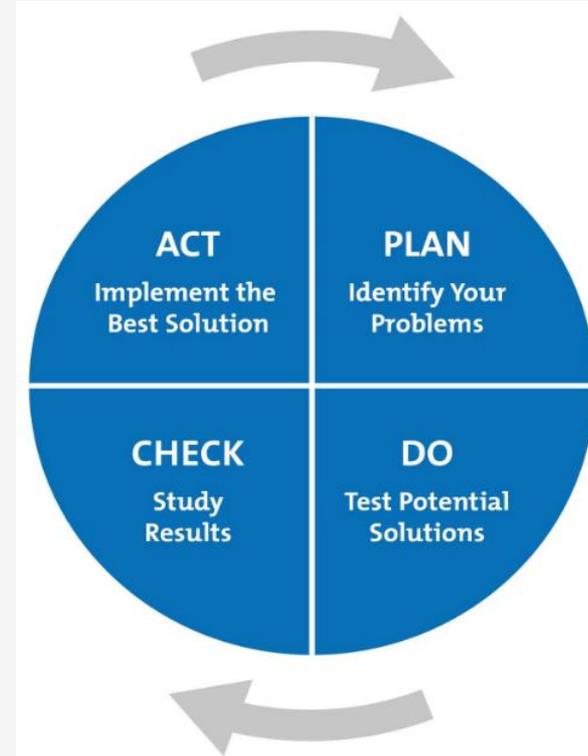**Facilitate Continual Improvement (ICH Q10, 1.5.3):**

- "**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..."

ACT
Implement the Best Solution

PLAN
Identify Your Problems

CHECK
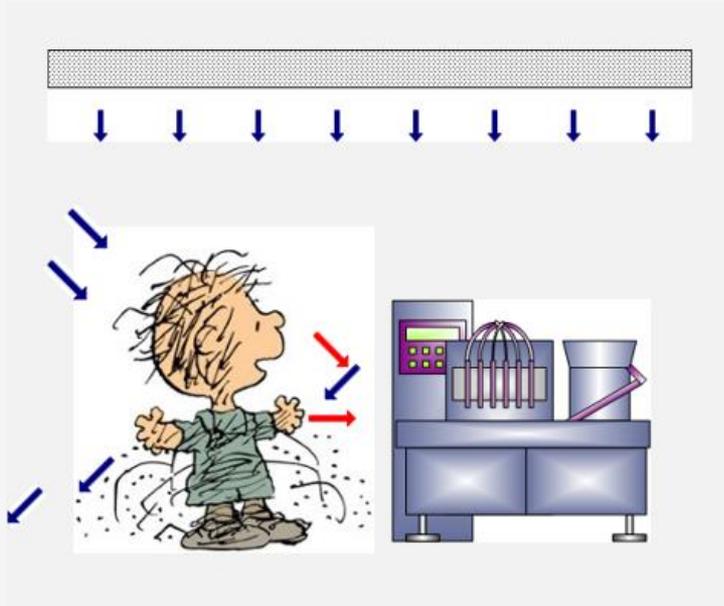Study Results

DO
Test Potential Solutions

Change Management:
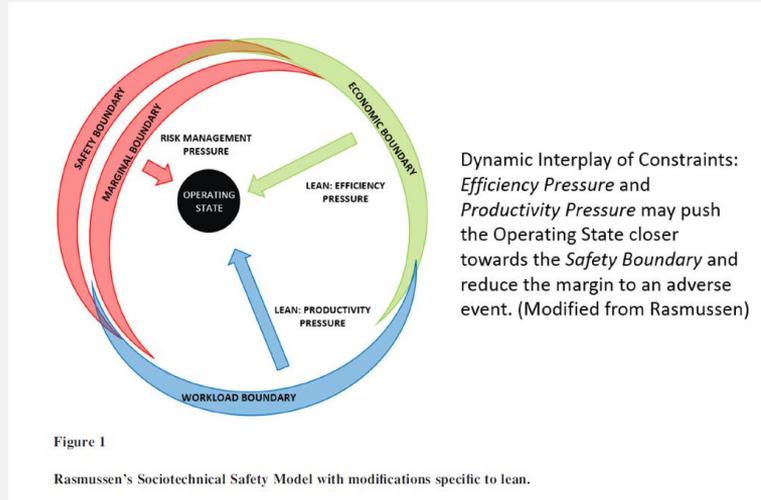# Manual vs. Automated Operations

- 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?

Pictures Courtesy of IPS

Current State – Human or System Fail?

Figure 1

Rasmussen's Sociotechnical Safety Model with modifications specific to lean.

Dynamic Interplay of Constraints: *Efficiency Pressure* and *Productivity Pressure* may push the Operating State closer towards the *Safety Boundary* and reduce the margin to an adverse event. (Modified from Rasmussen)

- 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."**

Berry C., at al. What Does It Really Look Like to Properly Address a "Human Error Problem" in Biopharma? The Human Performance Blue-Sky Description That Will Help Improve Industry Performance, *PDA J Pharm Sci and Tech*, 2019, *73(4)*
Wilson, A, et al. Changing the Performance Paradigm in Pharma/Biotech: Integrating Human Performance in Global Organizations, *PDA J Pharm Sci and Tech 2015, 69(5)*
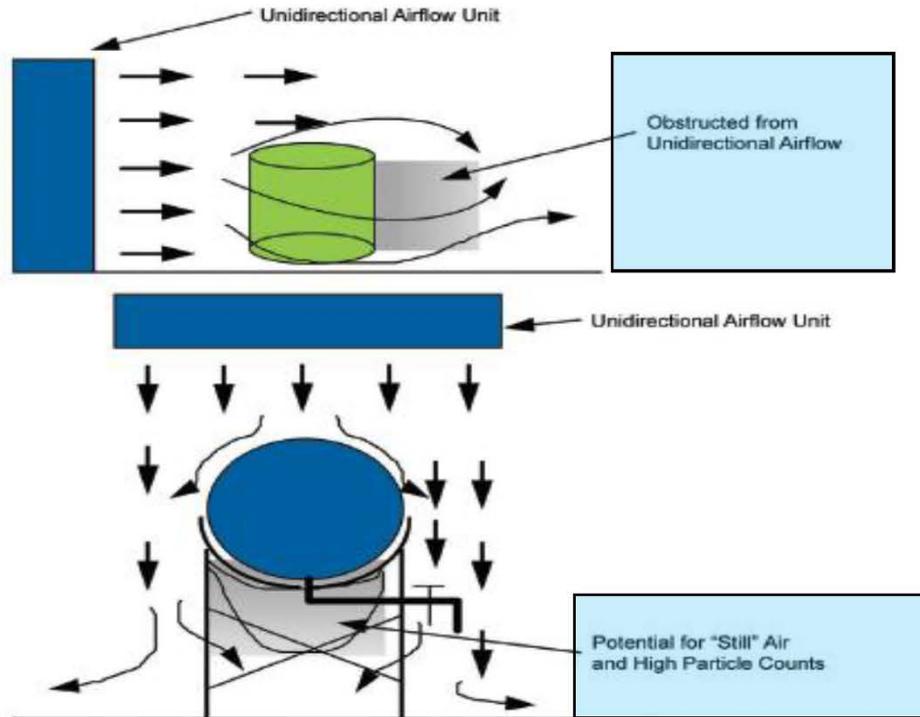
Is the inherent design risk from these obstructions acceptable?
Unidirectional Airflow "Shading"

ISPE Baseline® Guide:
Sterile Product Manufacturing Facilities

Figure 11.12: Unidirectional Airflow Shading

Unidirectional Airflow Unit

Obstructed from Unidirectional Airflow

Unidirectional Airflow Unit

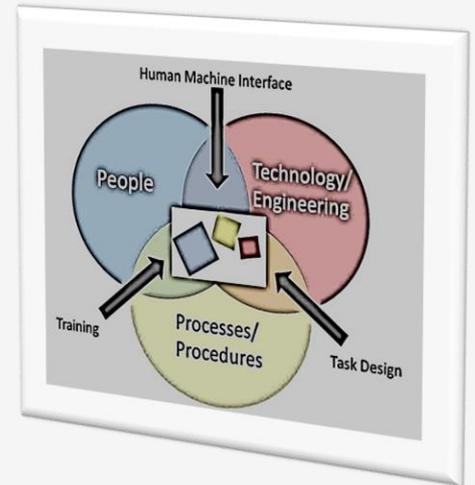Potential for "Still" Air and High Particle Counts

Production Risks:
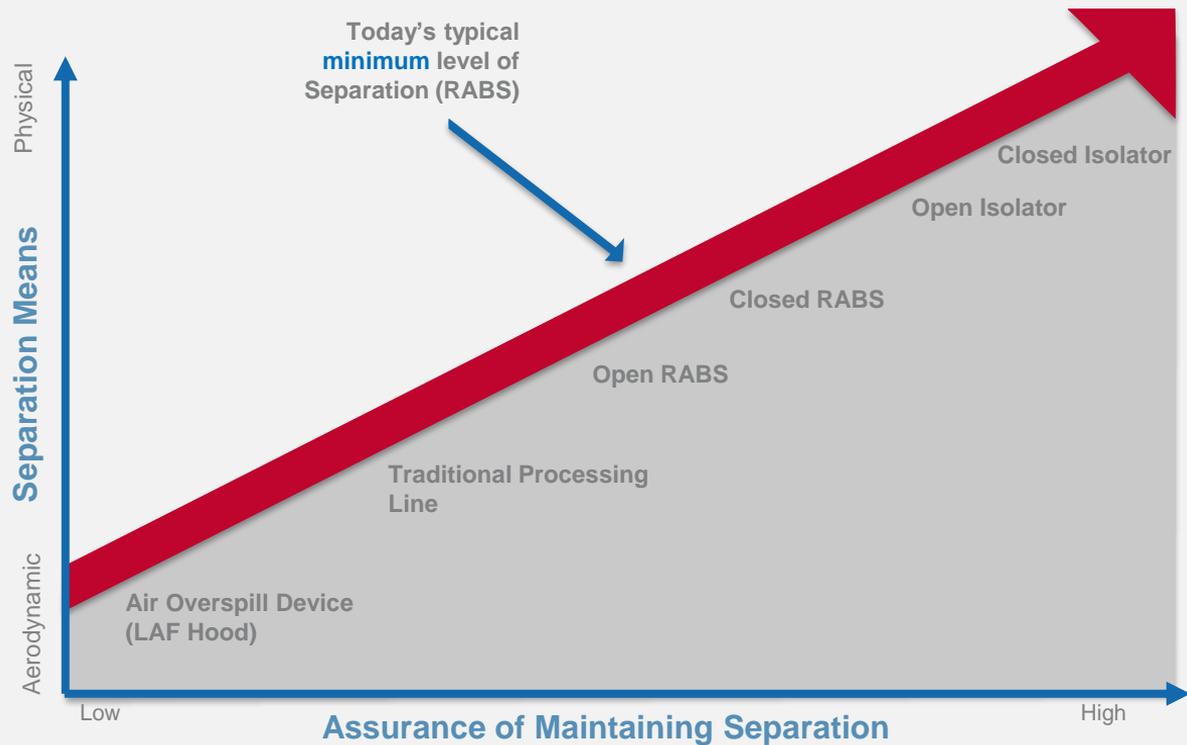# Human Factor Risks in Aseptic Manufacturing

Consider the <u>variability</u> 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?

Adapted from Farquharson, G. "ISO 14644…Part 7: Separative Devices,"
8th Pharmaceutical Isolator Conference Warwick, U.K.

Designing for Quality

FDA

- 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?

Prevention → Diet & Exercise

Correction → Medication

Remediation → Invasive Procedures

LOW COST LESS STRESS   HIGH COST   HIGH STRESS

FDA

Z. Kauffman, FDA/EMA/PDMA /PDA/ISPE/JPMA ICH Q10 Training Conferences

Summary

FDA

- 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