Risky Business? *Quality Systems and Drug Lifecycle Risk Management*

Edmund Mrak
Investigator, Pharmaceutical Inspectorate
US FDA, New England District
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Connecting a World of Pharmaceutical Knowledge

Adapted from a presentation provided by:

Richard L. Friedman, M.S.
Deputy Director, Science and Regulatory Policy
Office of Manufacturing & Product Quality
FDA/CDER/OC

Agenda

- Risk Discussion
- Reliable Manufacturing = Reliable Supply
  - State of Control and Lifecycle QRM
- Senior Management Oversight
  - Quality Culture
  - Manufacturing Infrastructure (process/facility design)
  - Data Integrity

Risky Business?

Risk is the potential of losing something of value.

Is anything free of risk?

What are some big risks in Pharmaceutical Manufacturing? Who is affected by risk?

Push the envelope here!!!

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Not here!!!

Who is at risk??

Bode can tolerate significant risks in Alpine Ski Racing – but even Bode has well programmed systems for risk mitigation: Fitness Conditioning; Equipment Preparation; Training; Coaching and Support on course; and more.

Who is at Risk??

- What do your customers (patients) expect when they receive your drug product??
- Can your customers (patients) accept risk?
- Lower risk - Operate within the product Design Space.

The Patient is the Customer

- **Voice of the Customer: Quality should be patient-focused**
  - Decisions include understanding of intended use of the ingredient/product
  - Emphasis on minimizing consumer risk (See ICH Q9)
- **Quality is achieved through a strong Quality System**
  - Includes Senior Management Commitment, Quality Risk Management (QRM), and Knowledge Management (KM)
  - Quality is better assured when management recognizes and leads with the understanding that upstream controls (e.g., this applies to both robust processes and supplier management programs) make good business sense
  - QRM and KM are used to identify and control variability in materials, facilities, processes, and the supply chain throughout the lifecycle
  - A Quality Assurance (proactive) culture will then supplant the antiquated Quality Control (reactive) paradigm

Types of Risk: Potential for Tension between Commercial and Public Health Interests

- "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 are based on "inspecting and scrapping good product" or "the costs of shipping bad product."

[Jim Colton, Quality Digest, Dec., 2011 "Statistical Tools for Pharmaceutical Manufacturing"]

By bringing an objective analysis to subjective issues, vested interests (e.g., "silos") can begin to diminish. **Quality risk management works best when it is used proactively and should not be used to justify a bad decision.** When new information becomes available that can impact a prior quality risk assessment, iterative processes can ensure the quality assessment is not static.

Pharmaceutical Technology, "FDA's Pharmaceutical Quality Initiatives: Implementation of a Modern Risk-based Approach," May 2008

FDA Warning Letters

- Drug Manufacturing and Product Quality Warning Letters issued by FDA in 2015 call for risk assessments.
  - "A risk assessment of the potential effect of the observed failures on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution"

CGMP Objective: Assure the Quality of Every Batch, Every Day

"We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality… We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug *will continue to be safe and effective and perform as described in the label*."

- Janet Woodcock, M.D.

QC Release and QRM: Should a Quality System Rely on QC Alone to Detect Variation & Defects before Distribution?

- Test of a firm's Quality System is if it will promptly catch a problem in a batch ***vs***. discovering only after it is marketed.
  1. Mistakes are, in many cases, not caught by the individual making the error, but instead through final inspection or QC test!!
  2. And… QC tests and inspection methods intended to assess a chemical, microbiological, or physical attribute are of limited sample size (or sensitivity).
  3. To avoid detecting mistakes or defects only after a drug product has been distributed:
     - Use Redundancy of Controls, or PAT

Risk Reduction Through Innovation: Modern Pharmaceutical Manufacturing

"…Significant opportunities exist for improving development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control."

Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (2004)

"Unit dose uniformity performed in-process (e.g., using weight variation coupled with near infrared (NIR) assay) can enable real time release testing and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards."

ICH Q8, Pharmaceutical Development

Risk Reduction Through Innovation – ICH Q10

"Innovation" found 11 times in *ICH Q10, Pharmaceutical Quality Systems*

–**Glossary: "**Innovation **-** The introduction of new technologies or methodologies."

–**Introduction: "**Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement"

–**Change Management (3.2.3)**: "Innovation, continual improvement, the outputs of process performance and product quality monitoring, and CAPA drive change."

–**Knowledge Management (1.6.1): "**Sources of knowledge include, but are not limited to… manufacturing experience; innovation…" KM assures a lifecycle awareness of new opportunities for innovation, including identification of useful advanced technologies (manufacturing, analytical).

–*etc.*

Risk Reduction Opportunities
"very" common causes…

1. Deficient Facilities and Processes

- Old Manufacturing Platforms (antiquated facilities, inefficient/unstable processes)
- Unpredictable manufacturing can lead to quality problems, defects, and supply shortfalls
- Many firms do not take advantage of contemporary technology
- Many processing lines require frequent starts and stops to correct problems and to pull samples
  - e.g., Tablet, Sterile manufacturing lines
- Open *vs*. Closed Processes (Also, Unit Operations *vs*. Integrated)
- Manually Intensive Operations vs. Automation
  - **Human Error still very prominent root cause…**

Risk Reduction Opportunities
"very" common causes… (cont'd)

1. Deficient Facilities and Processes (cont'd)

- Human Error is cause of substantial variation across the industry
- Can be prevented by analyzing process for failure modes and increasing automation. A lifecycle QRM opportunity…
  - "Human Error Analysis" – HE training allows for "deeper insights into the underlying causes of human error in order to identify and avoid its sources" *[Miglaccio, et al, Chapter in* **The Pathway to Operational Excellence***, 2010, ECV Publishing]*

2. Ingredient Variability

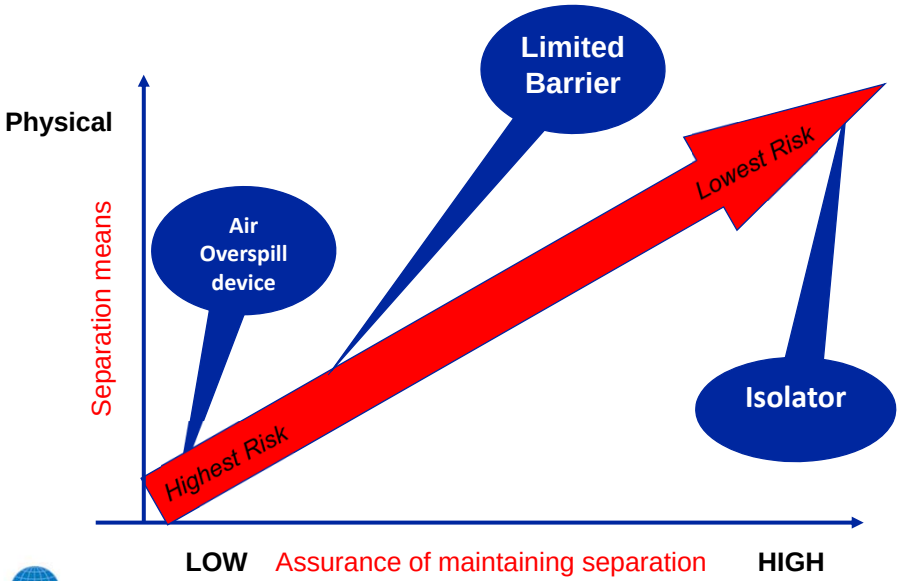
- Excipients: FDA's *Recall Root Cause Research* findings
- Most excipients are naturally-derived
- Use of QRM for supplier selection, monitoring, and management

Risk Control: Addressing Very Low Detectability

- It is difficult to reliably detect:
  - Changes in a drug that is not "well-characterized"
  - Non-sterility in a finished parenteral/topical product
  - Adventitious Virus Contamination of a Biotech Drug Substance
- A sound QRM approach takes this into consideration, and includes very stringent and redundant production controls: "*Additional emphasis on process controls should be considered in cases where products cannot be well-characterized and/or quality attributes might not be readily measurable due to limitations of testing or detectability (e.g., microbial load/sterility).*"

[ICH-IWG Points to Consider, Criticality]

Aseptic Line Risk Reduction: Open *vs*. Closed Systems

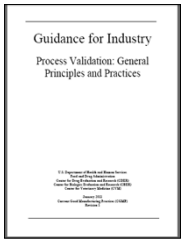


[Adapted from Farquharson, G. "ISO 14644…Part 7: Separative Devices," 8th Pharmaceutical Isolator Conference Warwick, U.K. December, 2004.]

State of Control = Daily Quality Assurance

ICH Q10 Definition of State of Control:

A condition in which **the set of controls consistently** provides assurance of continued process performance and product quality. (ICH Q10)



FDA PV Guidance on State of Control:

"After establishing and confirming the process, **manufacturers must maintain the process in a state of control over the life of the process,** even as materials, equipment, production environment, personnel, and manufacturing procedures change."

PV Overview

- In the final revised 2011 guidance, process validation is defined as…

"The collection and **evaluation** of data, from the process design stage through commercial production, which establishes **scientific evidence** that a **process is capable** of **consistently** delivering quality product."

Continual Improvement: Science & Risk-Based

- Quality system elements and management role to allow for "use of **science- and risk-based** approaches at each lifecycle stage, thereby promoting continual **improvement** across the **entire** product lifecycle."
- **QRM** is part of the PQS and includes "a proactive approach to identifying, **scientifically evaluating, and controlling potential risks** to quality. It facilitates continual improvement of **process performance and product quality** throughout the product lifecycle."

[ICH Q10]

Good Measurements = Good QRM

- Poor metrics can drive poor decisions/behaviors, undermine performance, and may fail to detect problems
- "Reevaluate the measures you are using."
  - The right metrics will drive the right change, and promptly detect problems (new or emerging risks).
- Monitor for OOT instead of waiting for OOS…

Mauboussion, M. "The True Measures of Success," Harvard Business Review, Oct, 2012

cGMP-Compliance (Quality Assurance)?

The manufacturer routinely *reacts* to production failures by making corrective actions, but does not take any preventive actions.

Putting out fires is not improvement of the process

- W. Edward Deming

Prevention and Correction
Mitigates Product Risk

- See 21 CFR 211.192, 211.22, 211.110, 211.180(e), other regulations
- *Prevention* (of contamination, loss of process control, errors, defects, etc.) is basic theme and purpose throughout the CGMP regulations and ICH Q7
- An effective CAPA program will decrease process variation and improve product quality (ICH Q10, 3.2.2)

cGMP-Compliance (Quality Assurance)?

You are the owner and applicant for a parenteral (LVP) product, and learn that your contract manufacturer has received recurring complaints of leaking containers regarding two batches. This contract manufacturing site produces batches for you when you can't meet demand at your site. The two lots have already been distributed. Your investigation of the complaints includes testing retains, and you learn from testing that three other in-date lots produced over the last two years also have leakers. You had qualified the facility solely by testing the first three lots it produced. Was this qualification sufficient?

Managing Outsourced Activities: FDA Regulation on Contract Relationships

Sec. 200.10 Contract facilities…

(b) The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer's own facility.

(c) The FDA reserves the right to disclose to the pharmaceutical manufacturer, or to the applicant of a new drug application (NDA) or to the sponsor of an Investigational New Drug (IND) Application, any information obtained during the inspection of an extramural facility having a specific bearing on the compliance of the manufacturer's, applicant's, or sponsor's product with the Federal Food, Drug, and Cosmetic Act…. FDA does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility.

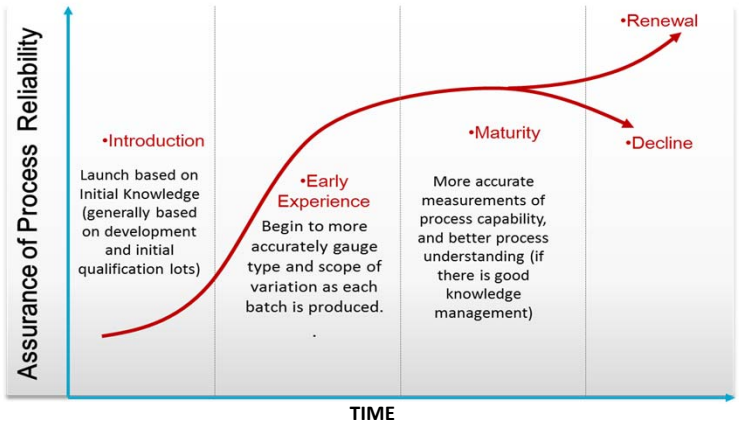
[40 FR 13996, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

- Also see 211.22 and other relevant regulations

Managing Outsourced Activities: ICH Q7 API GMP Guideline

- There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.
- Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.
- The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.
- Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.
- Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.
- etc.

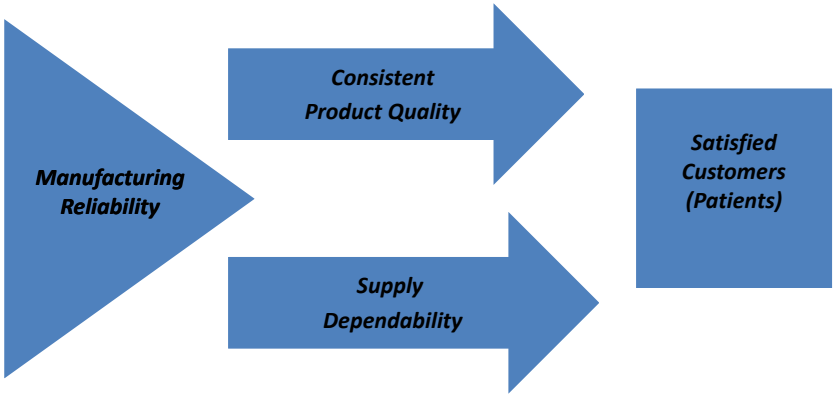
Product Life Cycle Curve



Continued Process verification:

- ✓Evaluate variation as process experience is gained, and more accurately measure process capability
- ✓Provide objective data relating to process performance and product quality
- ✓Provide assurance that the process remains in a state of control

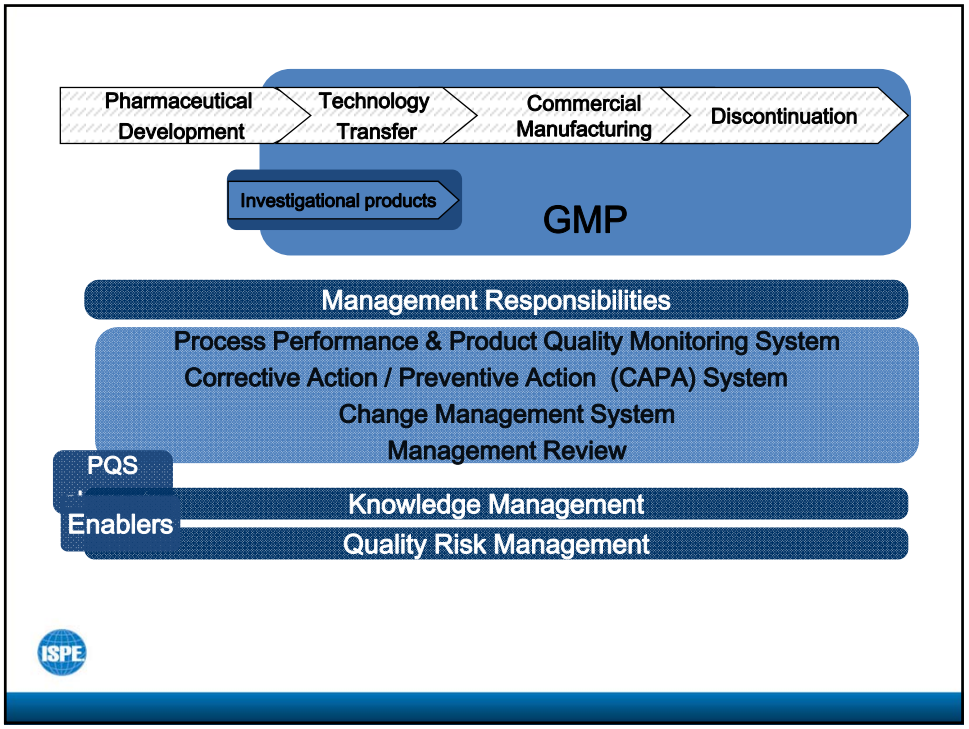
Goals



Commercial Lifecycle: Oversight of Manufacturing and Quality

Robust Quality System = State of Control

- The Pharmaceutical Quality System:
  - **Drives Sound Lifecycle Decision-making**
  - **Uses Scientific and Risk-Based Approaches**
  - Establishes and Maintains a **State of Process Control**
    - Monitors process performance & product quality
    - Assures reliable processes and products
    - **Creates real "fixes" to problems (long term, systemic)**



PQRI: Process Robustness (2006)

"When the product is transitioned to Manufacturing, it will most likely encounter a much wider range of variation on the parameters than seen in development. For example, attribute variability may increase due to a wider range in incoming raw material parameters that cannot feasibly be fully studied in R&D. **It is upon transfer to Manufacturing that assessment of the true process capability and robustness** as well as any process improvement or remediation **will begin."**

Process Robustness- A PQRI White Paper," PharmEng, May 2006

FDA Guidance on Quality Systems

- ICH published a final harmonized quality systems guideline in 2009**:**
  - ***ICH Q10, Pharmaceutical Quality Systems***
  - Official guidance in US, EU and Japan
- FDA guidance (2006) also provides further information on quality systems expectations:
  - ***Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations***

Definition of "cGMP" Explicitly Includes Management Oversight of Manufacturing to Ensure Quality

ENHANCING THE SAFETY AND QUALITY OF THE DRUG SUPPLY.

July 2012 - Section 501 (21 U.S.C. 351) is amended by adding:

"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."

"All firm's must manage risks each day appropriately to meet basic cGMPs, as per the Act. That is a fundamental responsibility of management." *(R. Friedman)*

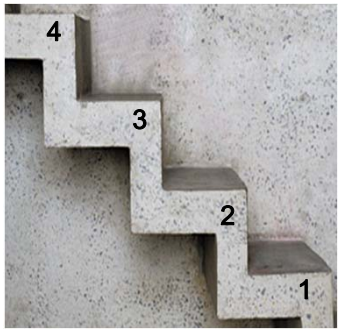
How mature is your quality system?

Level 1: Small problems ultimately snowball into larger ones, and management becomes aware only when there is a crisis.

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

Level 3: More proactive. *Increasingly* detects emerging adverse trends, surfaces major issues, and makes lasting manufacturing & system improvements.

Level 4: *Routinely* acts preventively as described in level 3. Fully institutionalizes and reinforces (rewards) a vigilant culture so that making lasting manufacturing & system improvements is habitual and expected.



Gradual Industry Changes…

- **Current facilities** have been **built "using technologies and processes from the 1950s and 1960s"**
  - Inefficient
  - Not always capable
- Needed **Capabilities:** Modern facilities and technologies, as well as relevant staff competencies
  - "A more **highly skilled** manufacturing organization will be required to deal with the new technologies; however the **improved automation and process control** should bring staff [FTE] cost savings."

ILF GPS Document, Published by ISPE, May 2012

Management Responsibility

Suitable Manufacturing Facilities and Processes

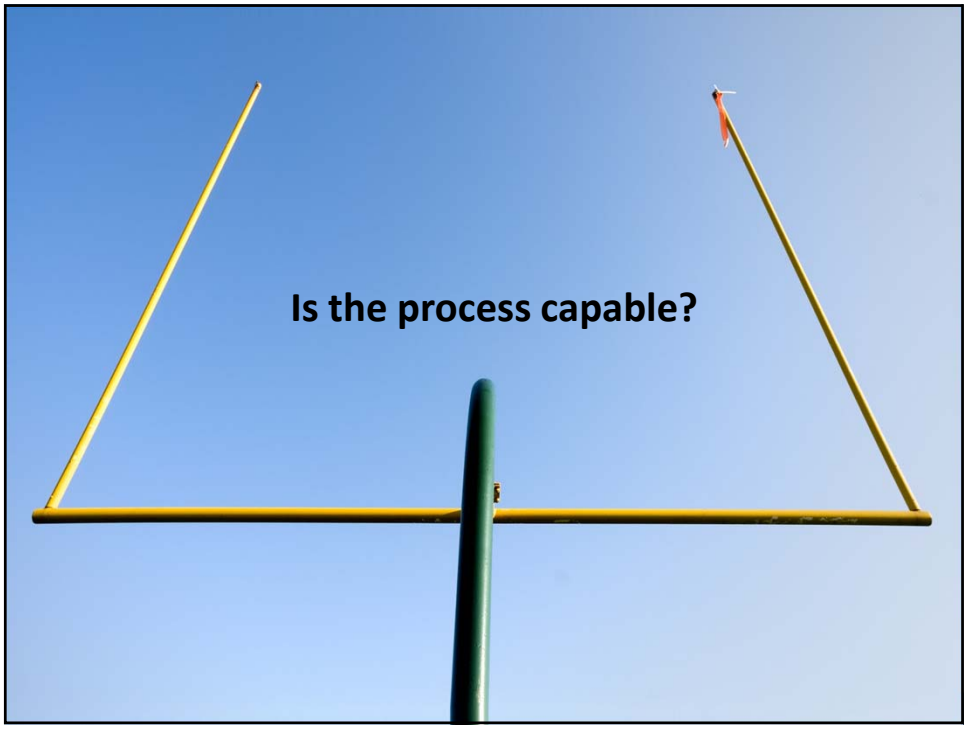
- Inadequate manufacturing capability is a frequent cause of drug defects and critical drug supply shortfalls
  - For example, ISPE's industry survey cited lyophilization and sterile manufacturing as two areas in need of improvement.
- "Some…inspections have found operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized."

Janet Woodcock, M.D., CDER Center Director (December, 2013)

Mitigating Risk in the Legacy Facility

"A master plan presents the opportunity to develop a vision for the future. For a legacy facility, the master plan can establish a direction to reinvent a facility that will remain sustainable, viable, productive, successful, and profitable. The master plan provides the comprehensive evaluation of the strengths and weaknesses of the legacy facility and seeks to identify opportunities within constraints. From the analysis of the legacy facility, the master plan will identify specific improvements that will best implement the goals of streamlining materials flows, personnel circulation, and improving the condition of critical utilities. "

ISPE, The Link, 02/25/2014 - Master Planning Legacy Facilities: Dealing with the Issues of a "Band-Aid" Approach - Co Authors: Eric Bohn, AIA, and Magdalena Nogalski Krapf AIA, LEED AP BD+C with Jacobs Wyper Architects



PQMS – How good is your trending program?

Does it identify off-center processes?

Does it shed light on intra and inter-batch trends?

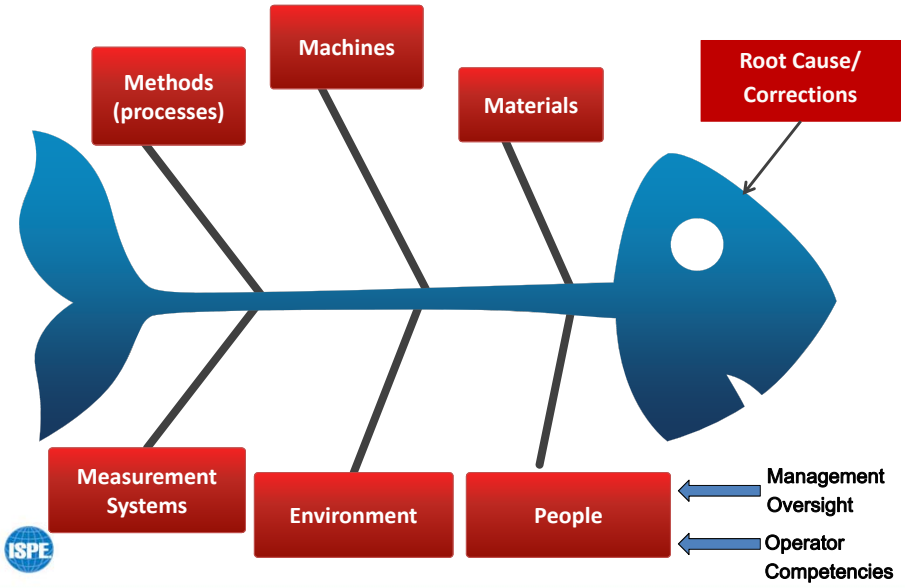
Knowledge Management: Connecting the Dots

Ubiquitous IT: Better Data Management Leads to Better Control

- **Improved systems to manage data** will be required to ensure patient safety, product quality**,** and cost containment.
  - The Pharmaceutical Quality System must be able to collect, **analyze**, ***trend***, and **store** data generated from **process control** instrumentation and applications.
  - For advanced manufacturing, the PQS must be able to to update and support periodic calibration and maintenance of **NIR models.**

ISPE Global Positioning Strategy, ILF Document, 2012]

Getting to Root Causes



Quality-Loss Function (Taguchi on Cost of Poor Quality)

- Concept: *as variance from the targeted quality levels increases, quality is reduced and the customer receives less value.*
- Lifecycle Goal: Minimizing Variation.
  - e.g., includes mistake proofing against special causes, such as human errors
- Minimize Variation → Minimize Cost

Adapted from Duane Bonig, MIT, Control of Manufacturing Processes (SMA6303)

Lifecycle QRM Question: How Robust is your process?

- Learn and apply knowledge from commercial experience
- What assumptions were made about your process, and what has manufacturing (includes raw materials) experience revealed?
- How sensitive is your process to:
  - Material variability?
  - Environmental factors?
  - Human-machine interactions? etc.
- Variation may not be constant throughout an operation. At what points is the process most vulnerable to variation?

Warning Letter: *"GMP-Compliant Quality System"*

Please note that a **cGMP-compliant quality system** supports a sustainable **state of control.** This includes but is not limited to systems to ensure **proper raw materials**, **vigilant quality monitoring [PQMS],** and **appropriate corrective and preventive [CAPA] actions.** FDA expects your firm to perform a comprehensive assessment of manufacturing operations to ensure that drug products conform to FDA requirements.

Why is Data Integrity Important?

Data integrity breaches:

- undermine assurance of pharmaceutical quality (and potentially safety and efficacy)
- break down basic trust with regulator and public
  - *The regulatory system largely relies on trusting people to routinely do the right thing (i.e., when the regulator is not there watching)*
- **are a fundamental failure of the Quality System**

Data Integrity (e.g.)

- Laboratory
  - The system for management of electronic data permitted unauthorized changes; digital computer folders and files could be easily altered or deleted.
  - Data deleted or altered, with no audit trails.
  - Backdating; rewriting or destroying lab notebooks.
  - Password sharing.
  - Selection of only passing results from HPLC and GC (gas chromatography) data, while failing test results are disregarded, ignored, and not investigated. This practice was noted during the testing of raw materials, finished drug release and stability studies.

Data Integrity (e.g.)

- Manufacturing
  - Torn Batch Production Records found in a trash can. Upon further follow-up, we found that batches had failed blend uniformity testing
  - Records (e.g., batch, training) fabricated during the inspection.
  - Shadow/Show factories; equipment and records removed during inspection.
- Management Oversight
  - Senior Management informed FDA investigators that they were unaware of the data breaches
  - *Your Senior Management, at the local and corporate levels, is responsible for assuring that strict corporate standards, procedures, resources, and communication processes are in place to detect and prevent breaches in data integrity, and that such significant issues are identified, escalated, and addressed in a timely manner.*

Moving from QC to QA

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.

Remember: "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."

Discussion