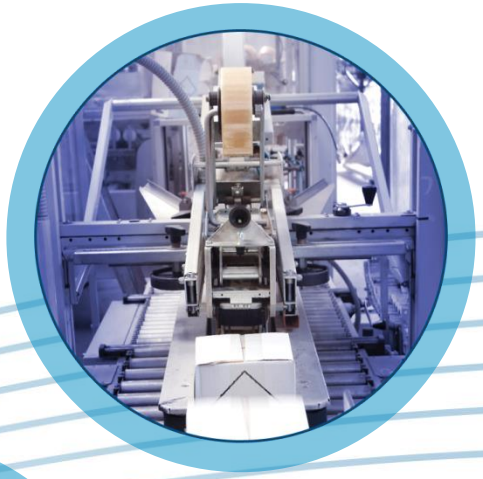
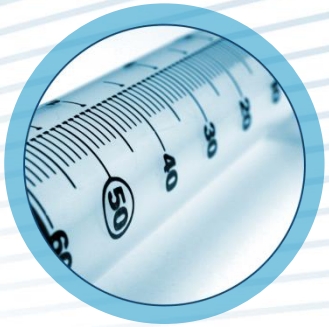
Connecting People, Science and Regulation®

Data Integrity – Focus on Quality Culture



Wallace I. Torres Ph.D.
VP Manufacturing
Amgen
May 2020



Singapore Chapter

Agenda

- **What Is data Integrity & Why is Important**
- **Pharma industry Issues**
  - 2012 to 2017
  - 2019 trends
- **Quality culture**
  - Why Now
  - Benefits
  - Trends
- **PDA Tool**
  - Key attributes
  - Data Integrity & Quality Culture
- **Examples**
  - Implementing in Manufacturing operations
  - Quality culture and Suppliers

What is Data Integrity?

- **Complete, consistent, and accurate data to assure patient safety and product quality.**

- Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a ‘true copy’, and accurate (ALCOA).

- Good Documentation Practices for Static and Dynamic Records.

- Data integrity should be maintained throughout the data life cycle, including, but not limited to data creation, processing, archiving and disposition after record’s retention period.

Source: FDA CAPT Sharon K. Pederson (Thoma), PharmD - Data Integrity Issues & Concerns - PDA Meeting Kansas City, MO August 21, 2017

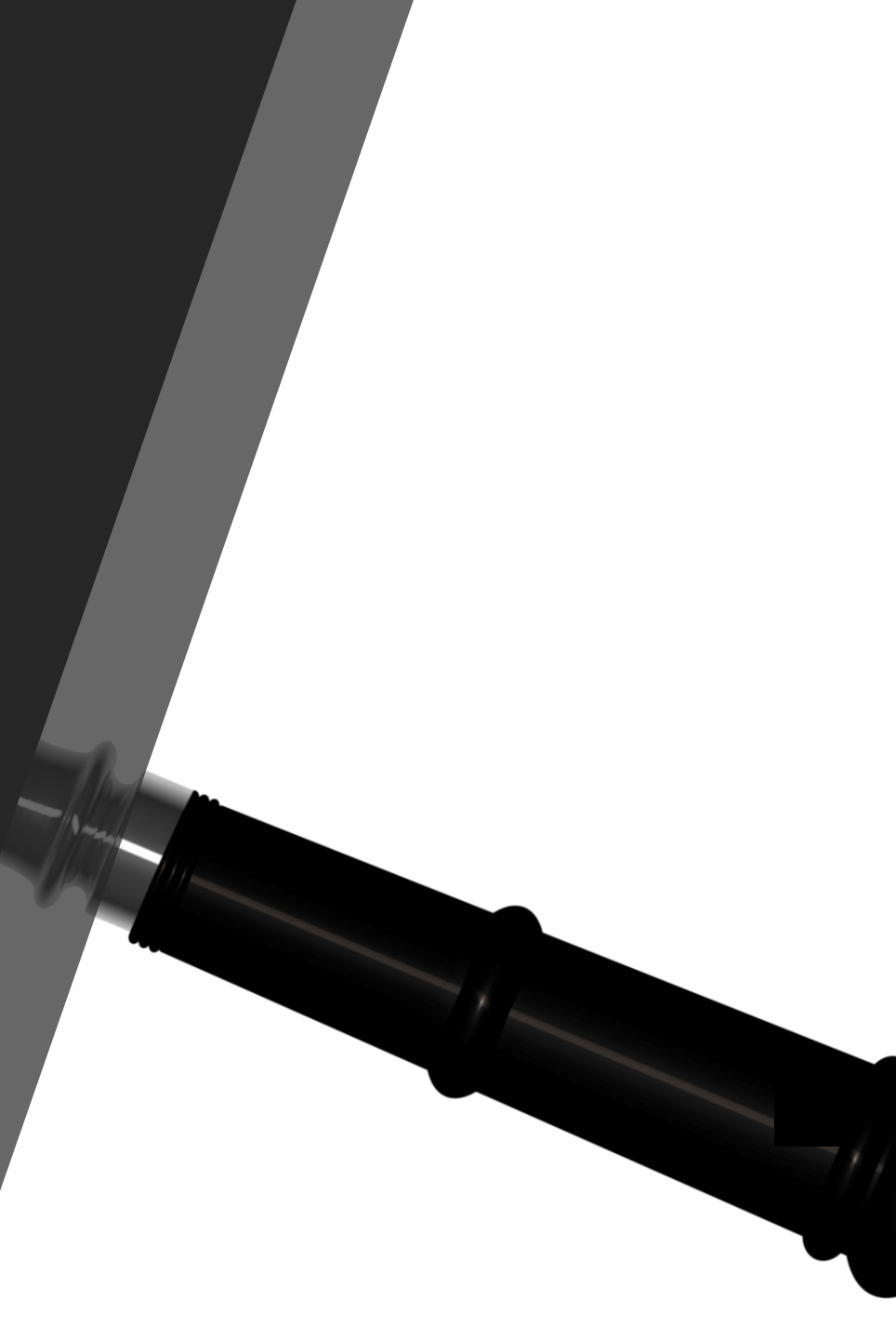
Why Data Integrity is important?

- ***Lack*** of ***integrity*** undermines the assurance and confidence in a drug's ***Safety***, ***Efficacy*** and ***Quality***
- Data integrity problems ***break trust***
- Data integrity problems can ***severely impact*** your ***business***

Without data, you are just another person with an opinion – *W.E. Deming*

Source: FDA CAPT Sharon K. Pederson (Thoma), PharmD - Data Integrity Issues & Concerns - PDA Meeting Kansas City, MO August 21, 2017

Data Integrity Issues 2012 to 2017



Data Integrity – Issues in Industry 2012 - 2017

1. **Failure to perform Required testing** – records generated but sampling or testing activities not performed. Regulators cited firms for failing to perform these activities while Certificates of Analysis (COA) indicate the final testing had been conducted.
2. **Falsification of critical data** – Falsification of sampling information or test results in worksheet/logbooks/test reports including fabricating results or passing results when original data failed to meet specifications.
3. **Deletion of data** – deletion or overwriting of electronic data of laboratory results.
4. **Deficiencies in deviation reports and investigation of data integrity issues** – deficiencies cited such as inadequate root causes, limited scope of investigations not extending to data integrity issues, lack of action plans to address deficiencies and how the Quality unit will avoid recurrence and lack of comprehensive assessment of all products manufactured or to support applications.
5. **Failure to Validate analytical methods** – reported in 2 FDA Warning letters

Source: PDA Technical report 80 – Section 3.0 Regulatory trends for data integrity in Pharmaceutical Laboratories

Data Integrity – Issues in Industry (cont.) 2012 - 2017

6. **Falsification of CGMP records** – include modifications of records, omission, or reporting inaccurate results.
7. **Failure to ensure that laboratory records included complete data** – regulators found that companies failed to maintain critical test results pertaining to product tested and release. Some excluded Out-of-Specifications (OOS) results or not reported/investigated these tests. Some times testing was repeated and not reported.
8. **Failure to configure computerized systems to meet the requirements for the security and control of data** - include unauthorized system access including the deletion of raw data and failure to configure, enable or review audit trails. Refenced in more than 15 FDA citations between 2012 to 2017.
9. **Failure to document lab Records Contemporaneously and/or deliberate falsification of manual records** – inconsistencies when comparing lab documentation records against electronic data files
10. **Performing unreported sample test injections** – included in Four Warning letters. Unauthorized testing outside the quality systems

Source: PDA Technical report 80 – Section 3.0 Regulatory trends for data integrity in Pharmaceutical Laboratories

Data Integrity 2019 Trends

Data Integrity – 2019 trends

Notable Warning Letter Trends

1. **Supply Chain**
   - *Insufficient Impurity Profiles (e.g., genotoxic impurities)*
   - *Repacking (unknowns in the chain)*
2. **Microbial Contamination of Non-sterile Drug Products**
3. **Aseptic Processing Line Design**
4. **Data Integrity: Underlying Causes**
   - *A primary root cause is computer system vulnerabilities…*

Source: R. Friedman MS (FDA) – 2019 PDA/FDA Regulatory Conference / Sept 16 -18 / Washington, DC

Data Integrity – 2019 trends

Warning Letter
Data Integrity & Poor Laboratory Controls

- The ***audit trail feature was disabled*** on instruments you use for quality control testing of your API, including your HPLC system.
- Your analytical systems also lacked controls to prevent users from deleting or altering electronic data.
- For example, a quality assurance manager, ***who also performed your analytical tests,*** *had* ***administrator access to each system***.

Source: R. Friedman MS (FDA) – 2019 PDA/FDA Regulatory Conference / Sept 16 -18 / Washington, DC

Data Integrity – 2019 trends

Data Integrity
Outright falsification

"You were not able to provide analytical test data for three batches of [redacted] spray and one batch of [redacted]. We found that you created certificates of analysis for these four batches before they were manufactured and tested."

FDA sampled the OTC product at the border and found it was out of specification.

Source: R. Friedman MS (FDA) – 2019 PDA/FDA Regulatory Conference / Sept 16 -18 / Washington, DC

Quality Culture

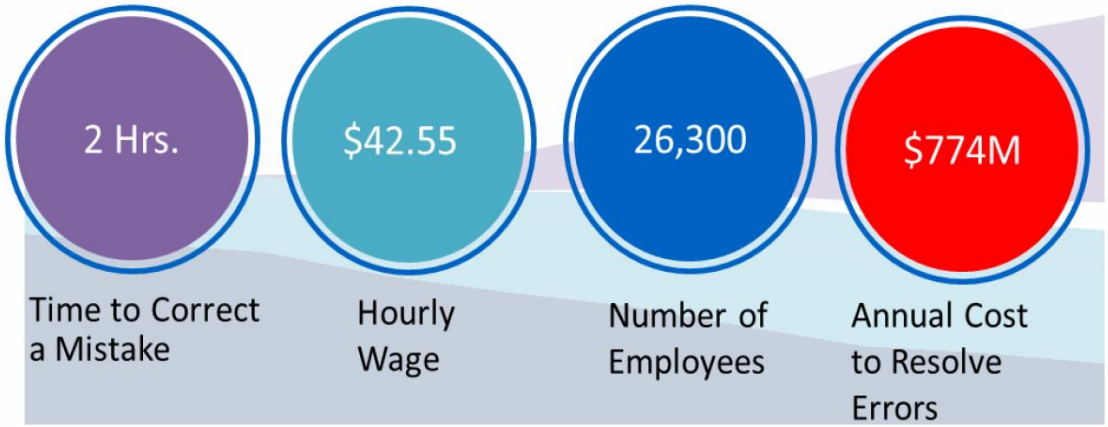
Why Now In The Pharma Industry ?

- Pharma focus on manufacturing cost and productivity
- Rising regulator scrutiny on quality & their focus on metrics
- Regulators are beginning to assess quality culture
- Rising consumer scrutiny (i.e. social media)
- Research has shown a positive ROI for strong quality culture

Harvard Business article outlines research on the positive financials

Source: C. Chen & S. Mendivil – 2019 PDA/FDA Regulatory Conference / Sept 16 -18 / Washington, DC

Benefits of a robust Quality Culture



For every 5,000 employees, moving from the bottom to the top quintile would save a company $67 million annually

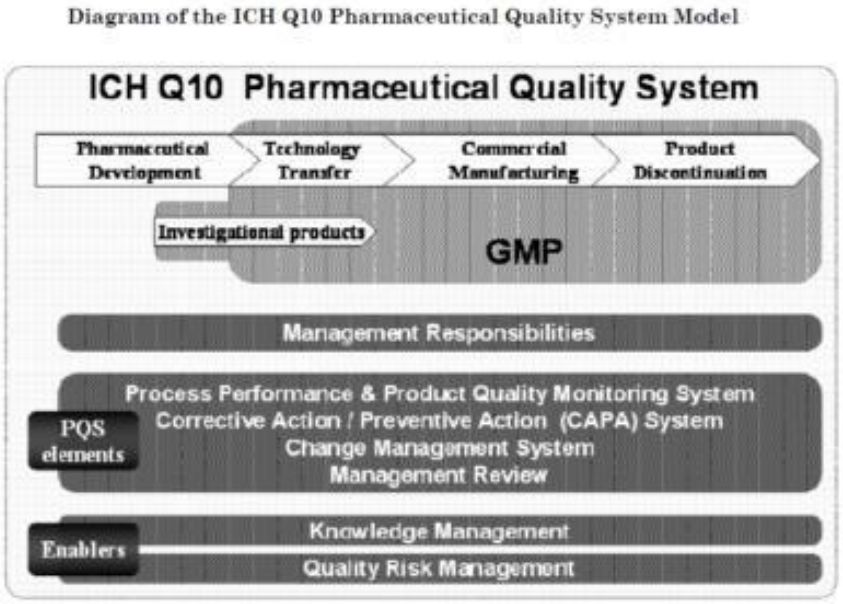
Harvard Business Review April 2014 "Creating a Culture of Quality"
CEB (Corporate Executive Board) Results of Two Years of Research

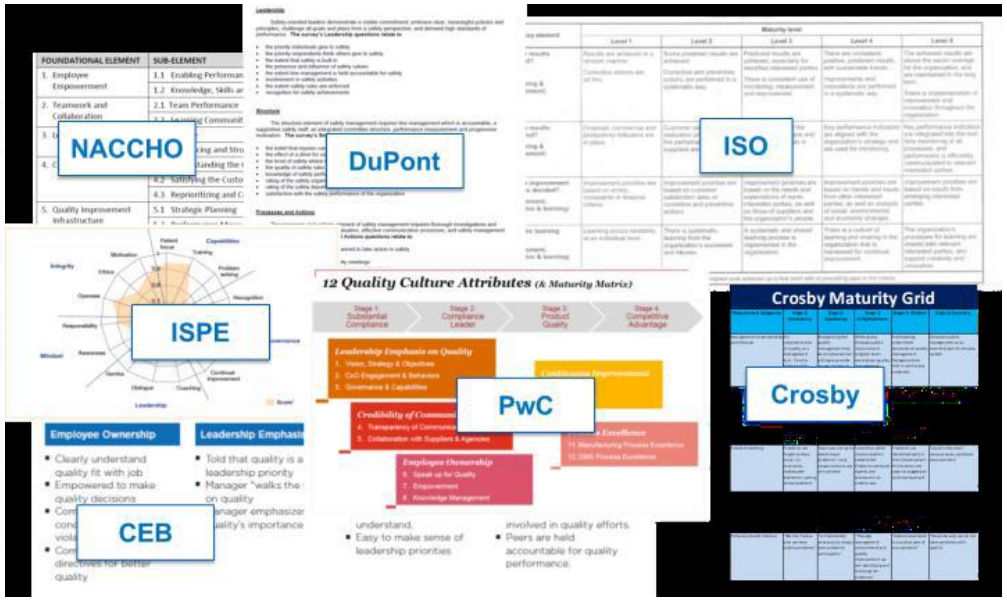
Employees in the top-quintile culture of quality saw 75% fewer significant mistakes than those in the bottom quintile.

Building a strong quality culture results in significant savings

Quality Culture *PDA Tool*

PDA Tool - Foundations





Developed based on key attributes in ICH Q8, 9, 10, 11 and other Maturity Models

Quality Culture is a Journey

Need to assessed what is going well and what may need some additional focus

Pre-Assessment Questionnaire

- One set of answers per site to pre-score and plan the on site interviews in the most efficient way possible

Quality Culture Self Assessment Tool

- Independent assessment via interviews with staff and leadership at the site
- focused on mature quality attributes

Quality Culture Behavior Staff Wide Survey

- Administered confidentially by PDA; blinded results returned
- Used to collect input from staff at the site

Quality Culture Data Analysis & Action Plan

- Review the survey results and comments to identify areas of focus and have activities currently in progress on site to address areas of opportunity

Require a structured implementation of the PDA methodology

PDA Tool – 5 Attributes

Leadership Commitment

- Commitment to Quality
  - Accountability and Quality Planning
- Enabling Capable Resources
  - Safety Program
  - Rewards and Recognition
  - Feedback & Staff Development

Communication & Collaboration

- Quality Communications
  - Quality Communications
- Management Review and Metrics
  - Management Review
  - Metrics
- Internal Stakeholder Feedback
  - Internal Stakeholder Feedback
  - Quality Culture Survey
- Collaboration with Assessors (*optional*)
  - Operations Readiness & Knowledge

Employee Ownership and Engagement

- Understanding Quality Goals
  - Impact on Product Quality
  - Patient Impact
- Staff Empowerment and Engagement
  - Process Ownership & Engagement
  - QMS Processes

Continuous Improvement

- CAPA robustness
  - Root Cause
  - Human Error
- Clear Quality Objectives and Targets
  - Continuous Improvement

Technical Excellence

- Utilization of New Technologies
  - Manufacturing Technologies
- Maturity of Systems
  - Training
  - Business Conduct
  - Quality Risk Management

Mature quality attributes that highly correlates to positive behaviors

Source: C. Chen & S. Mendivil – 2019 PDA/FDA Regulatory Conference / Sept 16 -18 / Washington, DC

Data Integrity & Quality Culture

Importance of Data Integrity

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Attributes of Quality Culture

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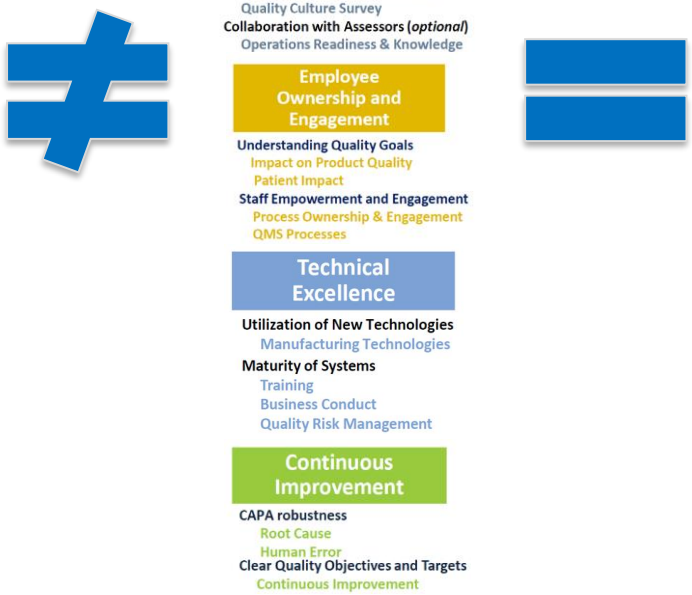
Deficiencies

Data Integrity & Quality Culture

Lack integrity

Break trust

Business Impact



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8. Failure to configure computerized systems to meet the requirements for the security and control of data
9. Failure to document lab Records
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Manufacturing Facility

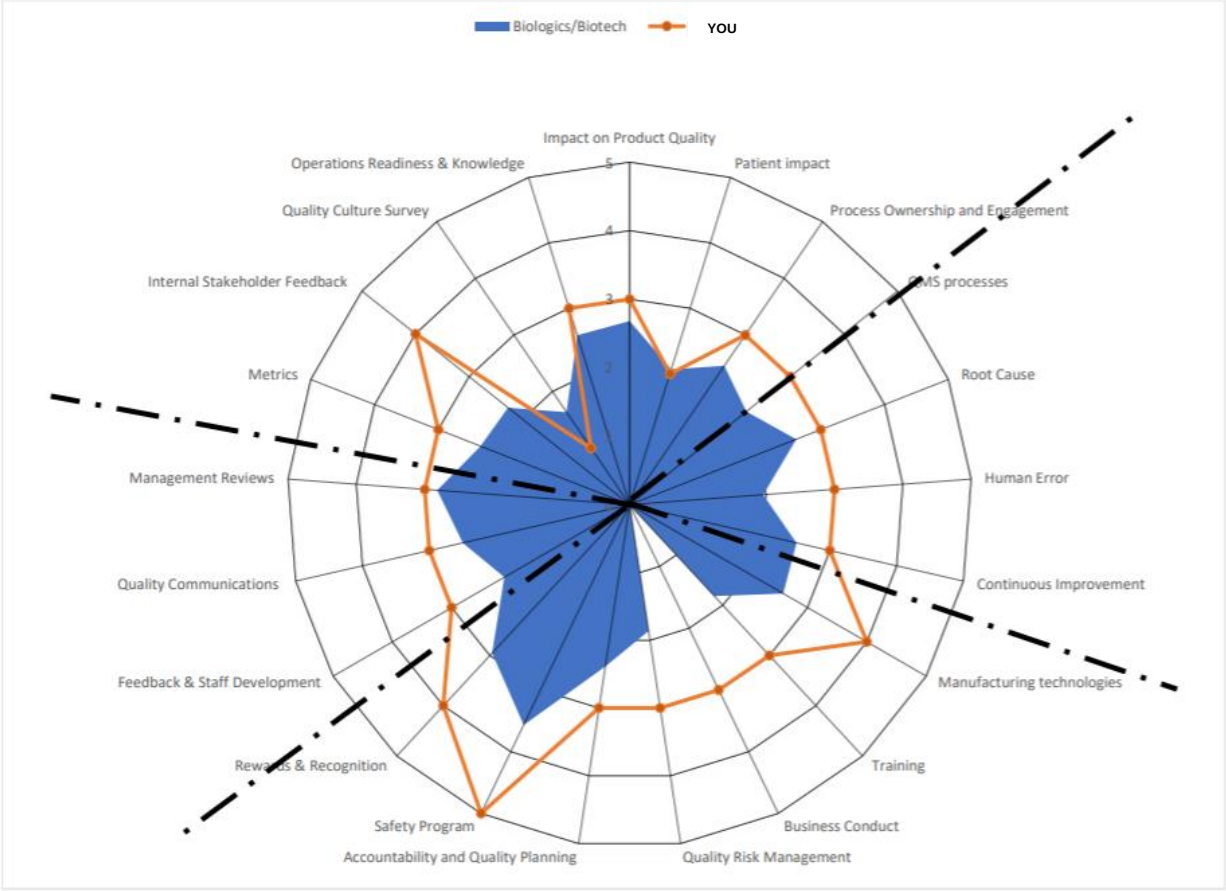
What are potential signals?

In-process controls are okay but final testing results are Out of Trend (OOT) or Out of Specifications (OOS)

QC results okay but Stability indicators failing

Repeated investigations due to missing or wrong information in the batch records

Start with a self assessment



Knowing your baseline is key to your success

How to implement a robust Data Integrity/Quality Culture

1. ***Define baseline*** - Measure compliance as starting point with a questionnaire or survey

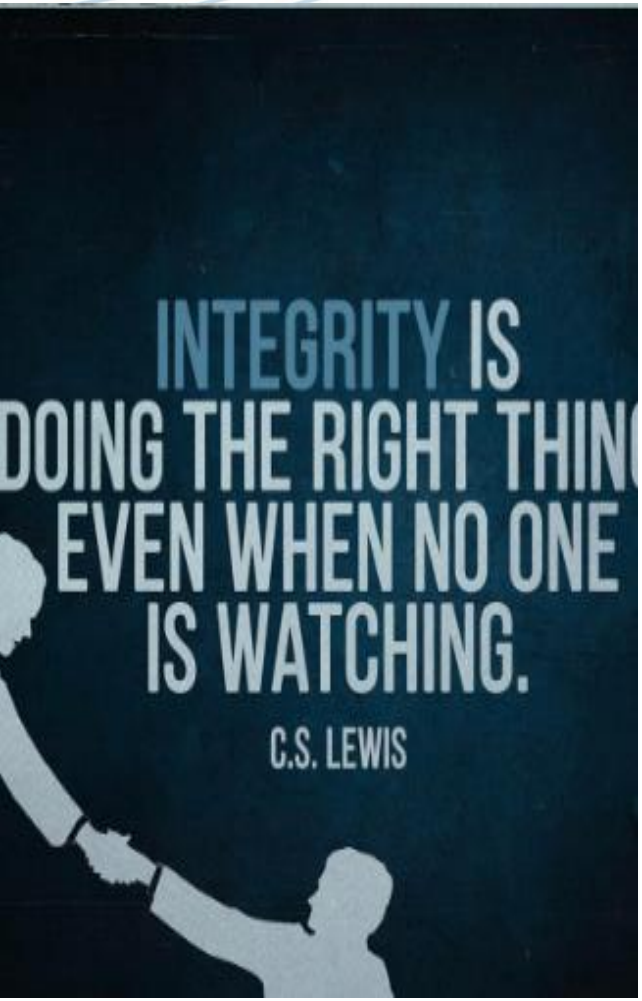
2. ***Training*** - Proactively refresh personnel on the requirement on Good Documentation practices:
   - SOP - Good Documentation Practices
   - Instructor or Web-Based Training - Good Documentation Practices for Operations

3. ***Operations oversight*** - Include Data Integrity as part of the Quality Oversight or GEMBA walks
   - Focus on Learning not punishment

4. ***Internal audits*** – ensure are DI is part of the internal audit
   - Prepare your team by conducting mock inspections of the topic

5. ***Take action***– take all the input and create a comprehensive plan.
   - Get Management buy-in.

What else you can do?



Quality Month

Quality Week

Targeted Information Sharing

Critical Steps Hypercare

Staff Development Program

Improved Feedback Loop

Encourage the Devil Advocate Role

Suppliers

What are potential signals?

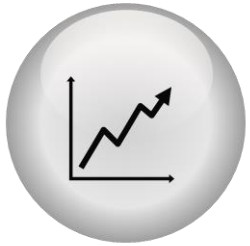
Frequent discrepancies between the CoA information and your internal QC testing

Frequent communications of changing on critical components not notified before the change

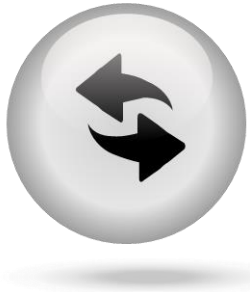
Long investigations lead times with no reasonable explanations

Quality as a cornerstone of your partnerships

Early Signal Detection



Enhance Process Robustness – Critical attributes



Integrate Your Quality Systems

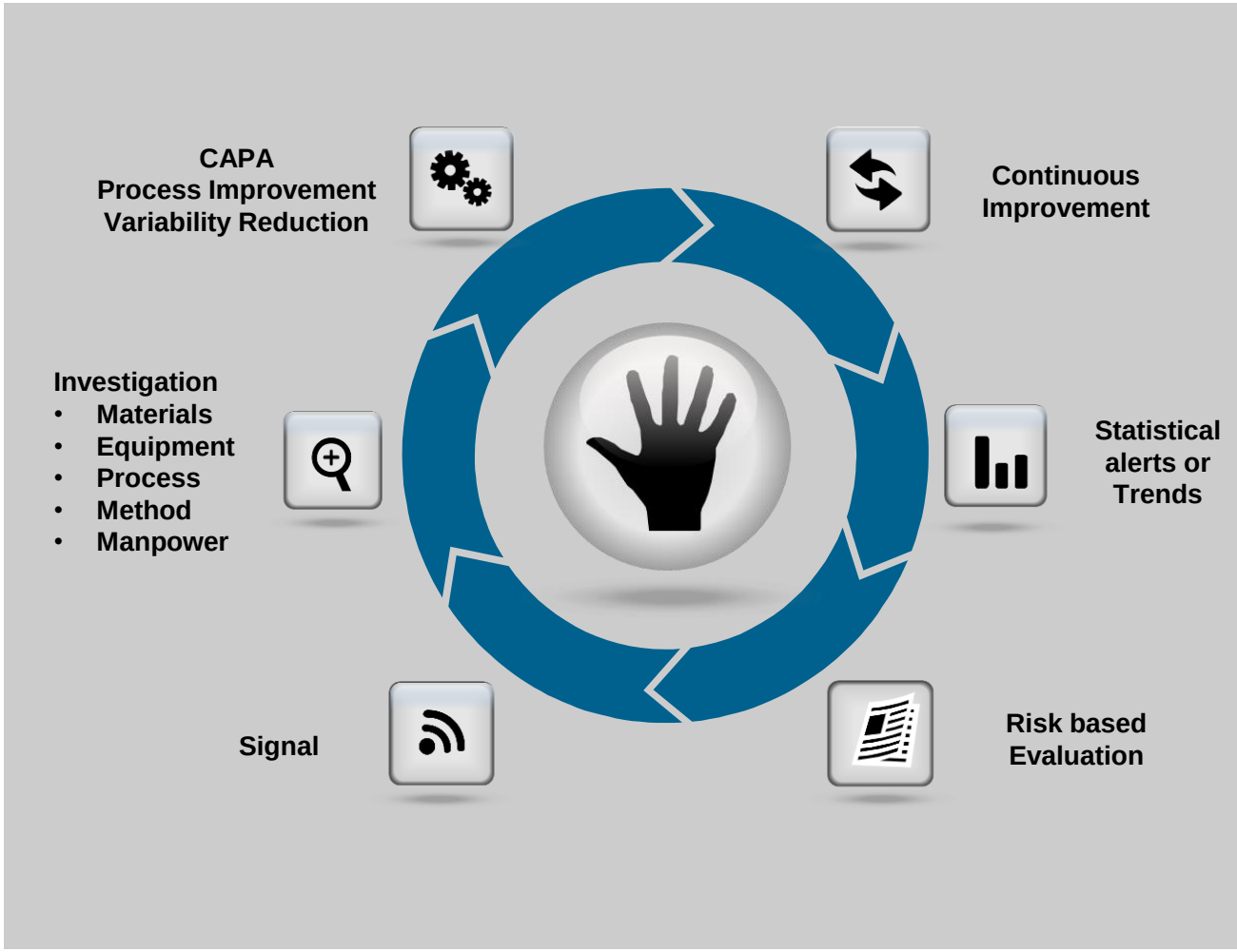
Develop their Quality Culture

Suppliers are key to part of our success!

Early Signal detection

Objectives:

- **Early detection & action**
- **Reduce Variability**
- **Improve robustness**



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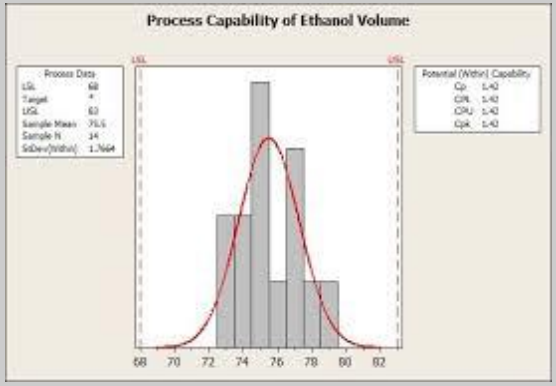
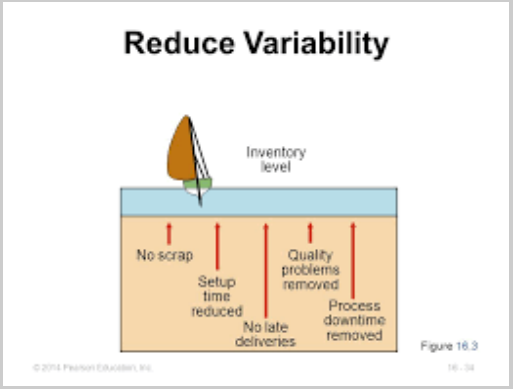
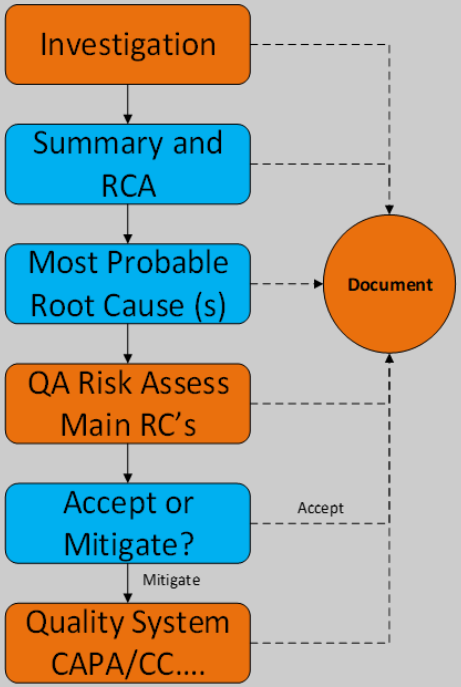




1. **Control Critical Quality attributes**
2. **Use Statistical analysis to improve processes**
3. **Identify activities to improve Cpk's**
4. **Reduce variability**

Integrate Quality systems



- **Investigation process should include a Root Cause Analysis (RCA)**
- **RCA should identify Most Probable Root Cause(s)**
- **Application of a risk assessment should lead to a decision point of acceptance or mitigation of the risks**
  - **If risk accepted → proceed to document decision**
  - **If decided to mitigate → proceed to use of quality system**

Advance their culture of quality

Mature Quality Attributes = Positive Behaviors

Leadership Commitment

Commitment to Quality
- Accountability and Quality Planning

Enabling Capable Resources
- Safety Program
- Rewards and Recognition
- Feedback & Staff Development

Continuous Improvement

CAPA robustness
- Root Cause
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Communication & Collaboration

Quality Communications
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Management Review and Metrics
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Internal Stakeholder Feedback
- Internal Stakeholder Feedback
- Quality Culture Survey

Collaboration with Assessors (*optional*)
- Operations Readiness & Knowledge

Employee Ownership and Engagement

Understanding Quality Goals
- Impact on Product Quality
- Patient Impact

Staff Empowerment and Engagement
- Process Ownership & Engagement
- QMS Processes

Technical Excellence

Utilization of New Technologies
- Manufacturing Technologies

Maturity of Systems
- Training
- Business Conduct
- Quality Risk Management

Source: 2019 PDA/FDA Regulatory Conference | September 16-18 | Washington, DC

Conclusion

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- Data Integrity = a complete, consistent, and accurate data to assure patient safety and product quality.
- Key issues of a wrong Data integrity/Quality Cultures are:
  - ***Lack of integrity*** undermines the assurance and confidence in a drug's Safety, Efficacy and Quality
  - Data integrity problems ***break trust***
  - Data integrity problems can ***severely impact*** your **business**
- Quality Culture is a ***Journey*** and the PDA tool can help you to identify the right path with a structured approach
- ***Take action***– take all the input and create a comprehensive plan.
  - ***Get Management buy-in***.

Data Integrity – Sources & links

FDA position on Data integrity (2017)

- https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/missouri-valley/data-integrity-issues-concerns.pdf?sfvrsn=406c808e_4
- PDA Technical report 80 – Data Integrity Management system for Pharmaceutical Laboratories
    - Section 3.0 Regulatory trends for data integrity in Pharmaceutical Laboratories
- FDA CAPT Sharon K. Pederson (Thoma), PharmD - Data Integrity Issues & Concerns - PDA Meeting Kansas City, MO August 21, 2017
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