REDICA Systems

Data Integrity and Quality Culture
Enabling far more than “just” compliance

Presented by:

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Associate Partner and Service Lead Data Integrity, GXP-CC

GxP-CC
The way forward through compliance challenges

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8264 7998

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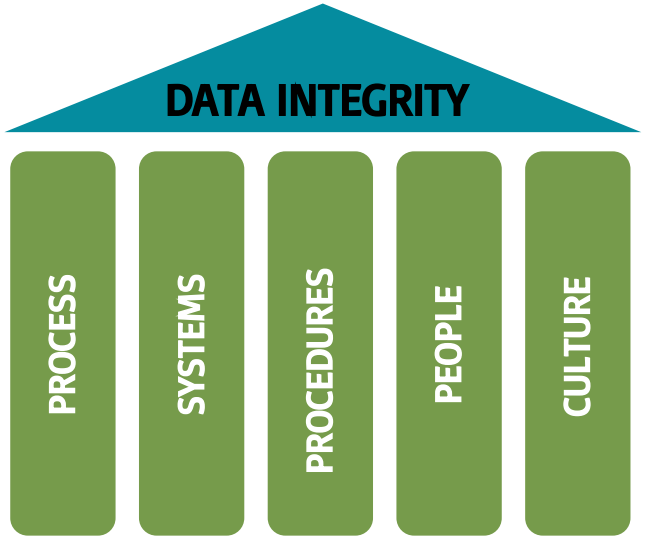
Introduction Data Integrity

- **Data integrity** is the **backbone** of life sciences and health care industries
  - Prevents harm to customers and patients.
  - Provides objective evidence for quality and business decisions.
  - Helps your company respond to regulatory bodies (inspection).



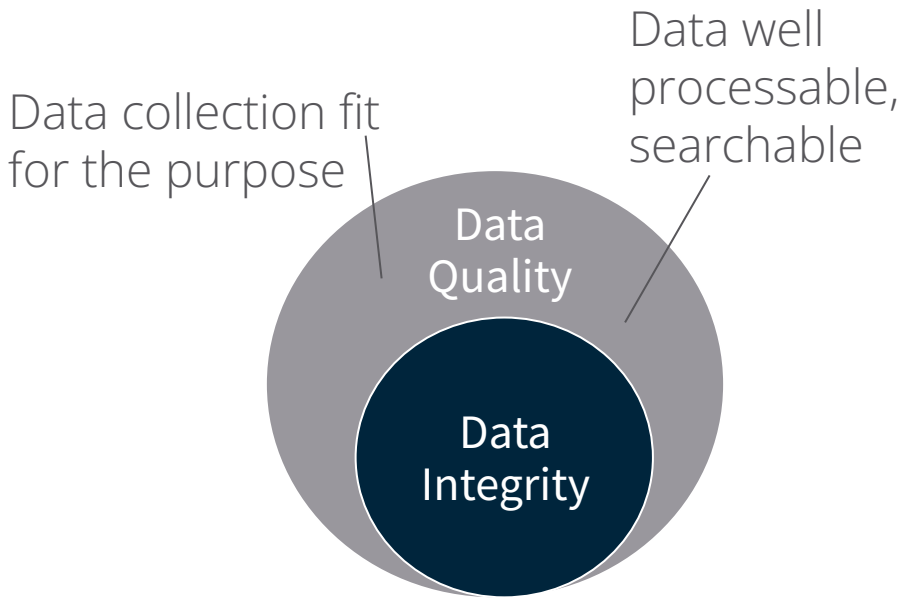
Data Integrity:
Complete, consistent, and accurate data should be **a**ttributable, **l**egible, **c**ontemporaneously recorded, **o**riginal or a true copy, and **a**ccurate (**ALCOA**).

(FDA's Q&A Guidance Data Integrity, 2018)

Introduction Data Integrity

Data integrity refers to the **completeness**, **consistency**, and **accuracy** of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (**ALCOA**).[1]

ALCOA	Measures
A - Attributable	Access Control
L - Legible	Retention
C - Contemporaneous	Time Stamps
O - Original (or true copy)	Retention, Audit Trail
A - Accurate	Validation, Audit Trail

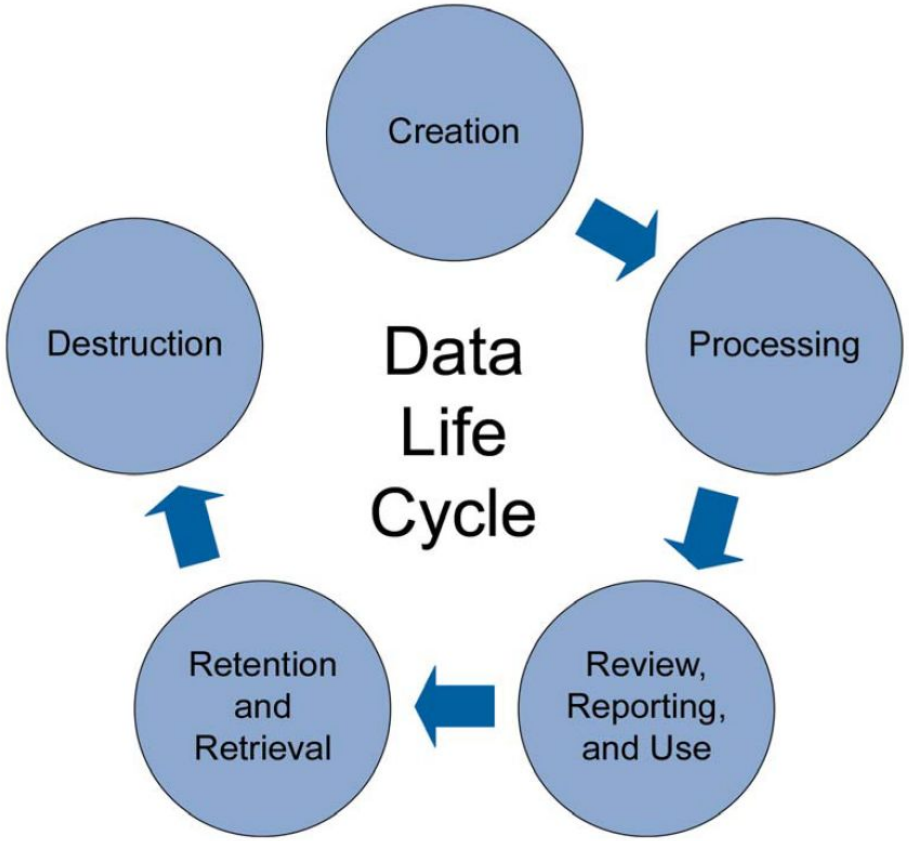


Be aware that you need both: Data Integrity and Data Quality

[1]Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry; 2018

Introduction Data Integrity

- Data Integrity is a **Life-Cycle** task

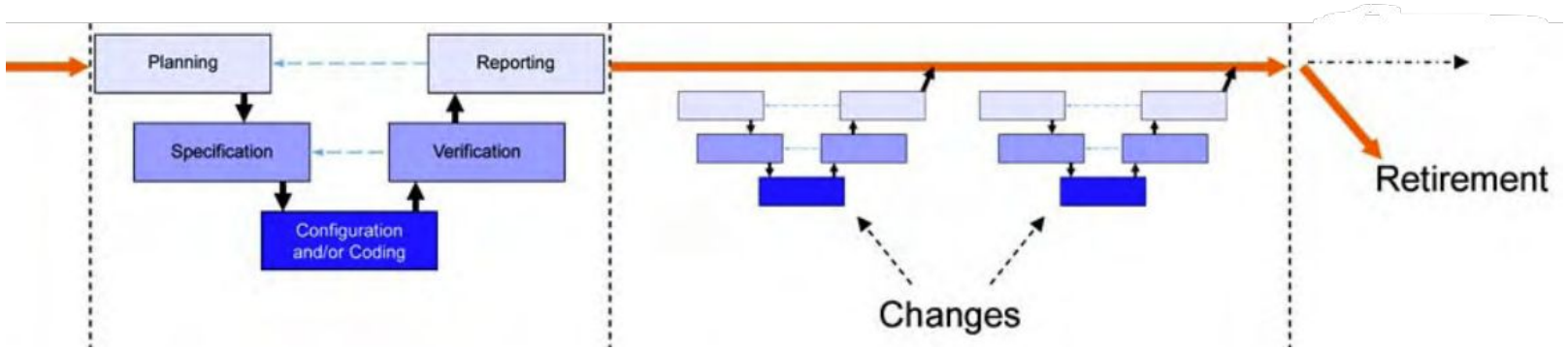


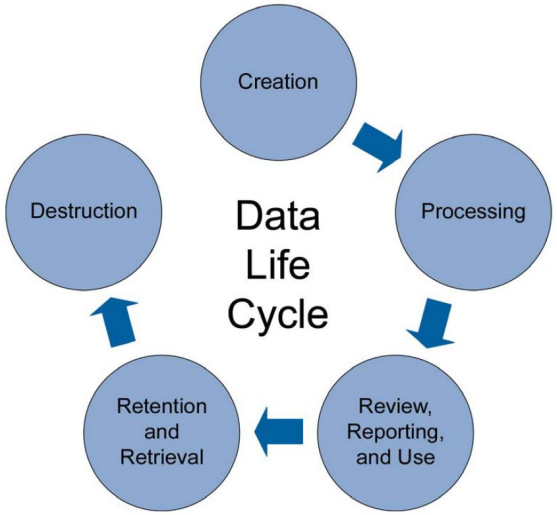
ISPE Good Practice Guide; Data Integrity by Design; 2020

- **Risks** relevant in **each phase** of the Data Life-Cycle should be considered during the **design** phase
- **“Data Integrity by Design”**

Introduction Data Integrity

- Data Integrity is a **Life-Cycle** task
  - **System** Life Cycle





- **Data** Life Cycle

- **Product** Life Cycle

Introduction Data Integrity

5.5.5 Critical thinking skills should be used by inspectors to determine whether control and review procedures effectively achieve their desired outcomes. An indicator of data governance maturity is an organisational understanding and acceptance of residual risk, which prioritises actions. An organisation which believes that there is 'no risk' of data integrity failure is unlikely to have made an adequate assessment of inherent risks in the data lifecycle.

Critical Thinking

- No "one size fits it all" solution
  - No "Checklist Solutions"; analytical, logical, knowledge
- What does "compliance" mean? Is there a 100% compliant solution?
  - No unlimited resources! Effort vs. benefit?
  - Prioritize
- Regulators are aware of this concept

PIC/S: GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS; 2021

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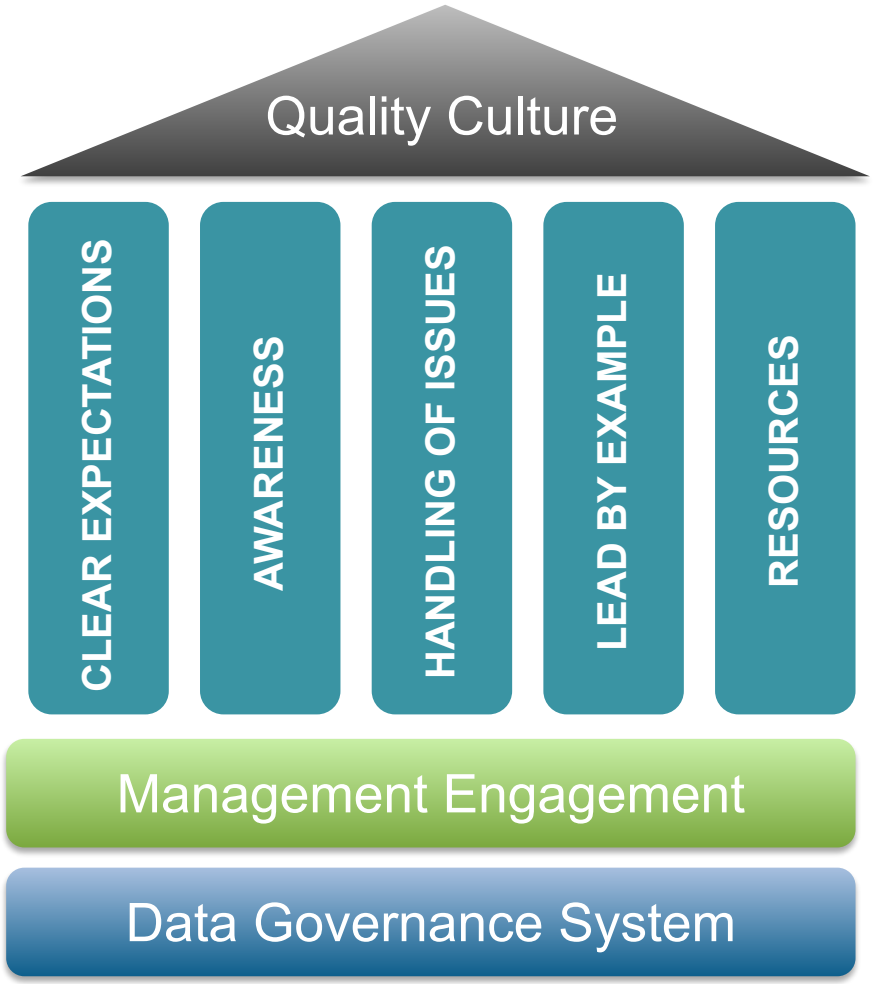
Quality Culture (PIC/S Guideline)



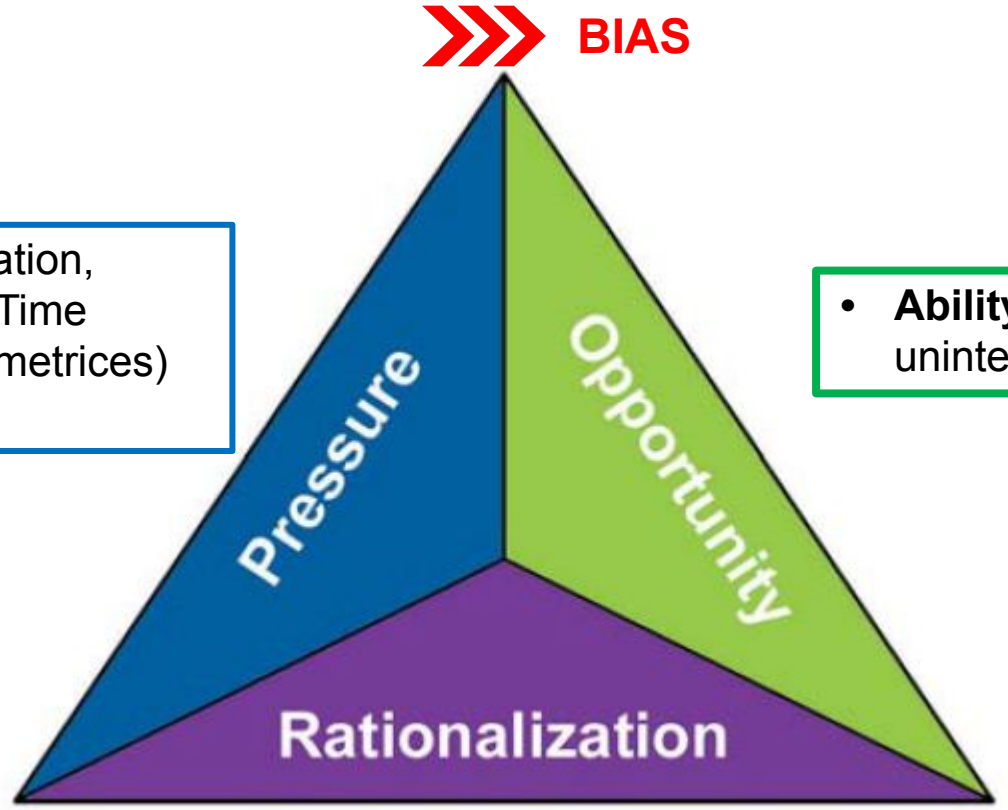
- **Set, communicate and train expectations** for ethics and behavior concerning data handling
  - Defined unacceptable practices
  - clear **consequences**

- Quality culture = **responsibility of the management**
  - Keep learning
  - Metrics and reviews
  - Enable the quality unit

PIC/S: GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS; 2021

Quality Culture: The Fraud Triangle

- **External factors** can lead to alteration, deletion or omission of data. (e.g. Time allocated for the task, inadequate metrices)



- **Ability** to impact the data in an intended or unintended way which is **not detected**

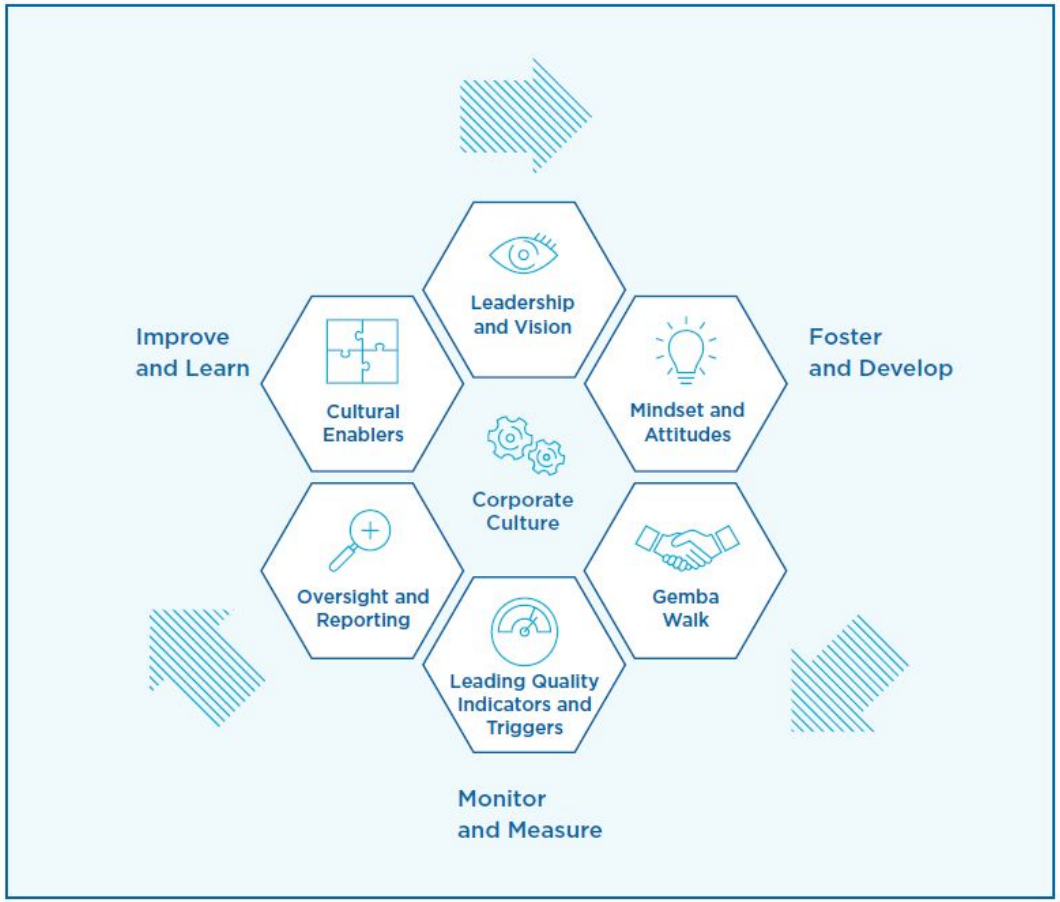
- Impacting data in an unallowed manner is **rationalized** (e.g. not following an SOP; not raising a deviation)?

[1] ISPE Good Practice Guide Data Integrity - GUIDE

Considering Human Factors in Assessing Risk: The Impact

Data Integrity: Quality Culture

Figure 1: Six dimensions of cultural excellence framework



- **Leaders** establish and engender the **vision**
- Leaders and Management have to provide ressources

- **Mindset and attitudes** play a **key role** in driving cultural performance
- They can be difficult to define, observe, and measure.

- **Gemba walks**: **Management and QA engagement** on the **floor** is powerful!
- **Empower „front-line“** employees by **involving** them!

- **Monitoring** and **surveillance** of key triggers

- Support healthy quality culture, they demonstrate **transparency**, facilitate **dialogue**, bring attention to …

… **issues**, so that they can be **addressed**
… **best practices**, so they can be replicated

Warning Letter Trends FDA – Quality Culture

In response to this letter, provide:

• A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.

o Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

[1] (Sep 2021)

Management Engagement

[1]: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/marcus-research-laboratory-inc-615153-09302021

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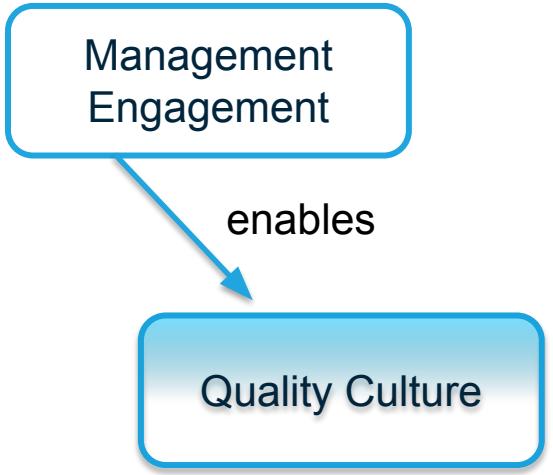
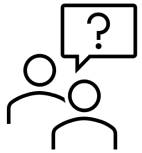


It is the role of management with executive responsibility to create a quality culture where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance.



[2] FDA's QnA Guidance on Data Integrity (Dec 2018)

[1]: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/marcus-research-laboratory-inc-615153-09302021

Quality Management Maturity (QMM)

Demonstrate Maturity through Meaningful Metrics!

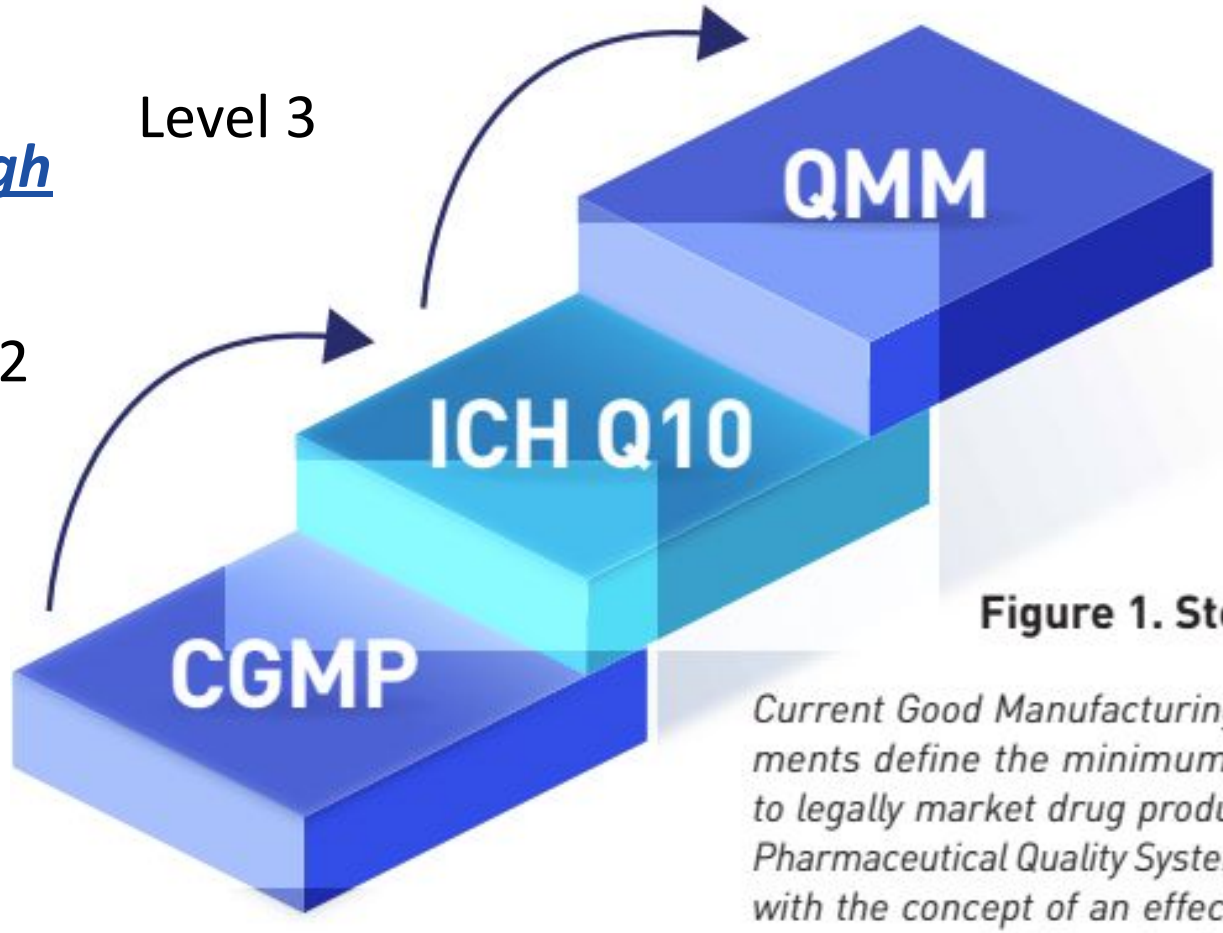


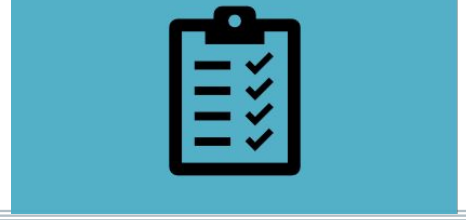
Figure 1. Steps to QMM

Current Good Manufacturing Practice (CGMP) requirements define the minimum manufacturing standards to legally market drug products in the US. The ICH Q10 Pharmaceutical Quality System guidance augments CGMP with the concept of an effective pharmaceutical quality system over the lifecycle of a product. QMM requires, in part, thoroughly implementing the concepts of ICH Q10 to promote continual improvement.

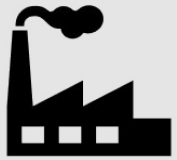
FDA's QMM: *The good news; Peter Baker; PDA Data Integrity Workshop 2022; Washington DC*

Quality Management Maturity (QMM)

Performance Areas Identified for the QM Reporting Program



- **Manufacturing Process Performance**
  - Process Capability/Performance indices (Cpk/Ppk)
  - Right-First-Time Rate
  - Lot Release Cycle Time
- **Pharmaceutical Quality System (PQS) Effectiveness**
  - CAPA effectiveness
  - Repeat Deviation Rate
  - Change Control Effectiveness
  - Equipment Effectiveness & Unplanned Maintenance
- **Laboratory Performance**
  - Adhere to Lead Time
  - Right-First-Time Rate
  - Calibration Timeliness
- **Supply Chain Robustness**
  - On-Time In-Full (OTIF)
  - Fill Rate
  - Days of Inventory On-Hand
  - Disposition On Time



T. Hui, CDER US-FDA , Journey of FDA's Quality Metrics Program, PDA Data Integrity Workshop 2022; Washington D.C.

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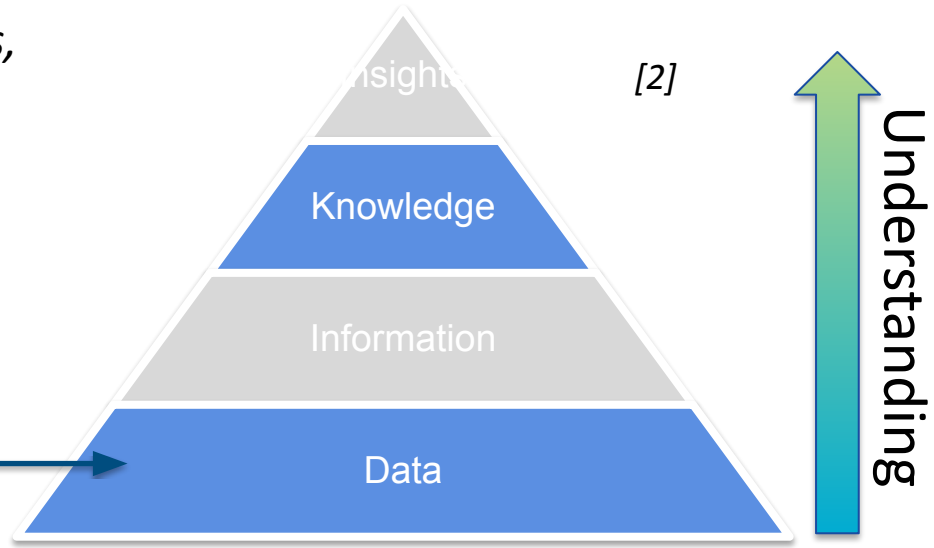
From Knowledge Management to Quality Intelligence

Evidence-Based Decision Making

*"While **subjectivity cannot be completely eliminated** from QRM activities, it may be controlled by addressing bias, the proper use of QRM tools and **maximising the use of relevant data** and sources of knowledge."* [1]



[2]

Decisions based on **Data**

ICH Q8 (R2) Pharmaceutical Development

ICH Q9 (R1) Quality Risk Management

ICH Q10 Pharmaceutical Quality System

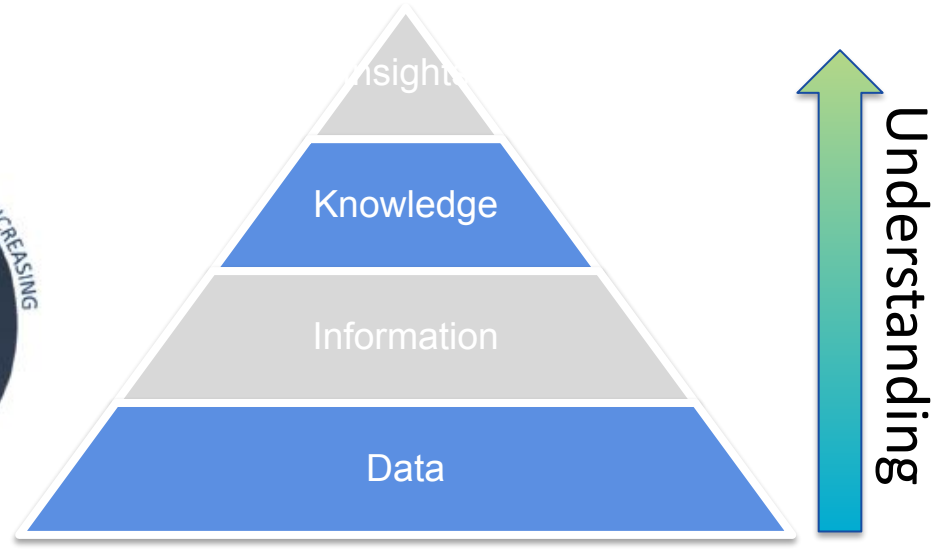
[1]https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Step_2_Presentation_2021_1126.pdf

[2] Adopted from: Melanie J. Adams et al., From Data to Knowledge Management: What to Consider, Pharmaceutical Engineering, 2022

From Knowledge Management to Quality Intelligence

- Knowledge Management is an enabler for Quality Risk Management (ICHQ9, R1) and Pharmaceutical QMS (ICHQ10)

[3]



[3] ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry, 2021

From Knowledge Management to Quality Intelligence

- This does not work with paper, outdated systems and data silos!

Unsilo your data!

Data needs to be accessible for future technologies:

- Artificial Intelligence (e.g., predictive maintenance)
- Digital Twins (e.g., batch planning)
- Real Time Statistics (e.g., continuous manufacturing; “golden batch”)

Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

What is the **c** in **c**GMP?

Data Governance + Quality Culture = Data Culture

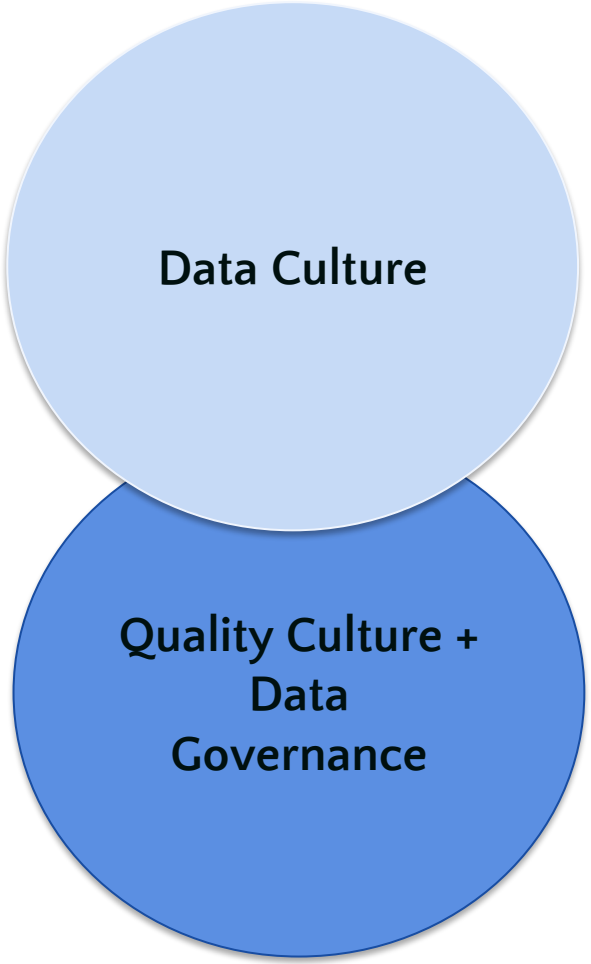
Kir Henrici: Data Governance + Quality Culture: The Whole is Greater than the Sum of its Parts PDA Data Integrity Workshop 2022, Washington DC

Data Governance + Quality Culture = Data Culture

Quality Management Maturity (QMM)

Quality culture must be foundational for mature quality management. Quality culture is an environment in which those who have responsibility for oversight and control over manufacturing taking ownership for quality. Quality culture is demonstrated by organizations in which the objectives drive quality.

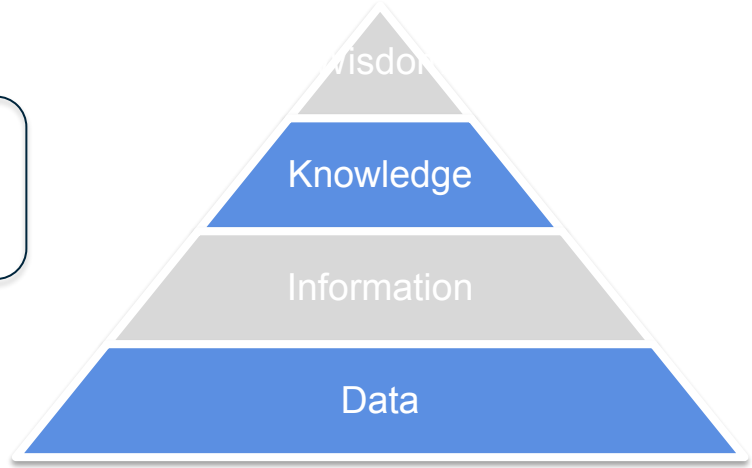
- CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
An Office of Pharmaceutical Quality (OPQ) White Paper
Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals



In these organizations, there are not separate business and quality objectives; they are linked together!

3.3 Data Integrity Trends: Knowledge Management

„Data as an Asset“
Data Culture



ICH Q9 Update R1 (2022):
KM introduced

New Inspection Protocol Program (**NIPP**) exploits inspection data to gather knowledge

(Dec 2020)

In response to this letter provide the following:

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/clientele-inc-607476-12032020

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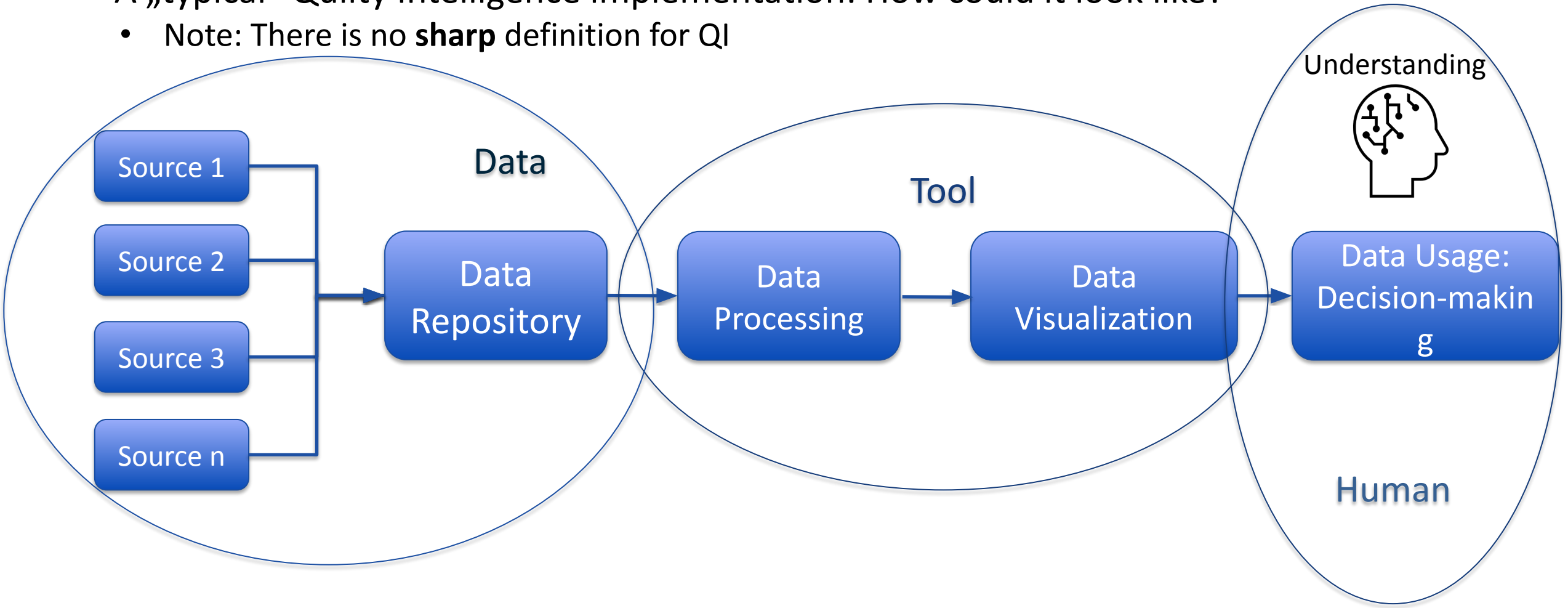
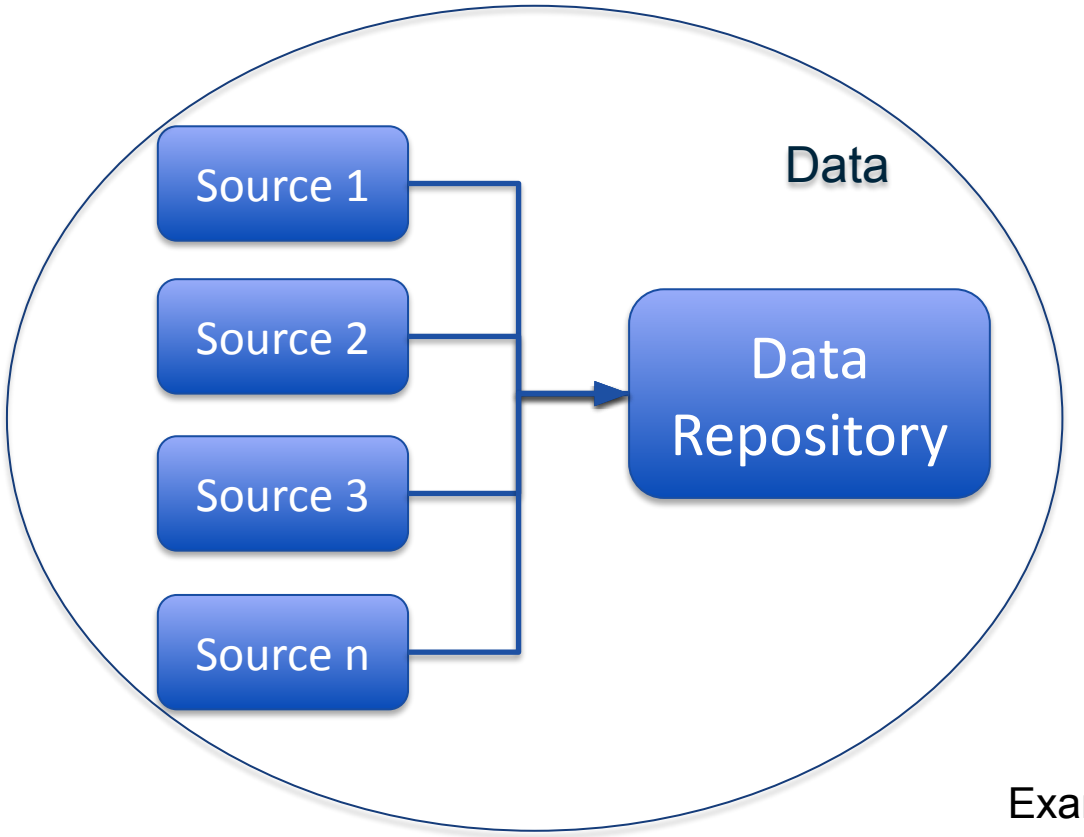
Quality Intelligence: An overview - Technical Considerations

A „typical“ Qulity Intelligence implementation: How could it look like?

- Note: There is no **sharp** definition for QI



Example 1: Golden Batch



- What if we could…

… aggregate process data and **response** data.

  - Not wait for the results but act in **real-time**
  - **Predictive instead of reactive**

- Data Sources to be aggregated “live” are
  - SCADAs (process batch)
  - Batch conditions and environment
  - LIMS (response data)

- The **Data Historian** serves as Data Repository

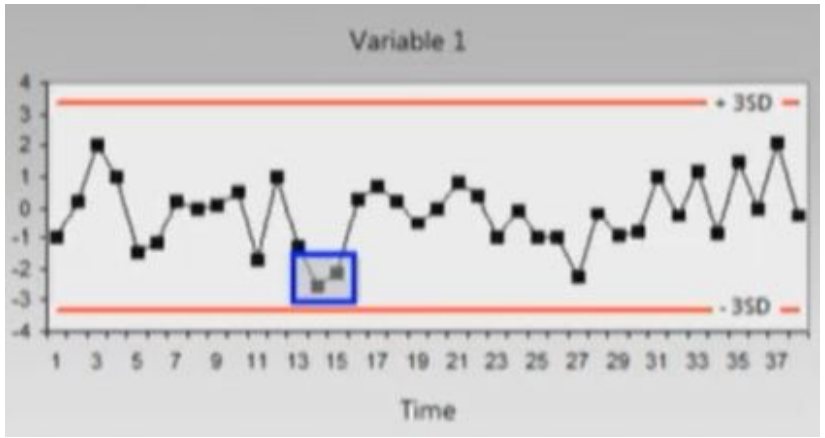
Example extracted from:
https://www.osisoft.de/customer-stories/boehringer-ingelheim-golden-batch

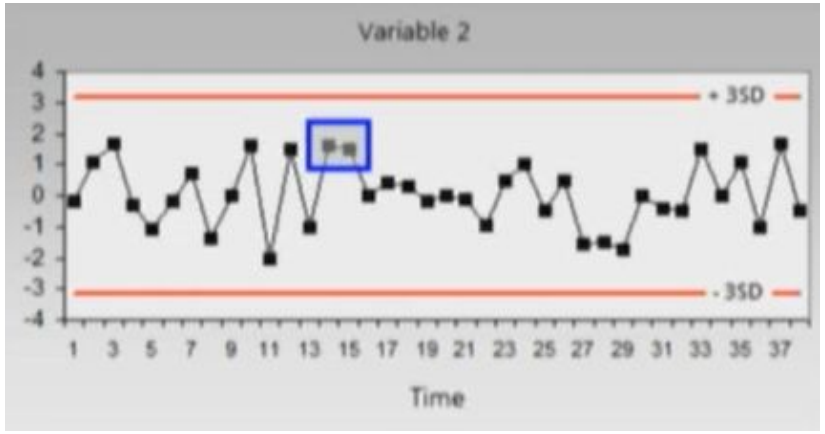
Example 1: Golden Batch

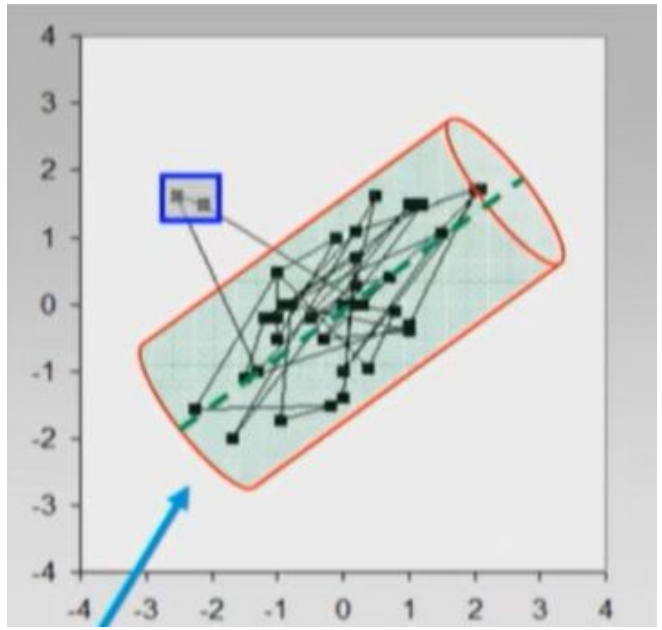
- This enables real-time **multivariate** process control

$$\sigma^2_{total} = \sigma^2_1 + \sigma^2_2 + \cdots + \sigma^2_n$$

Univariate charts are in control spec.



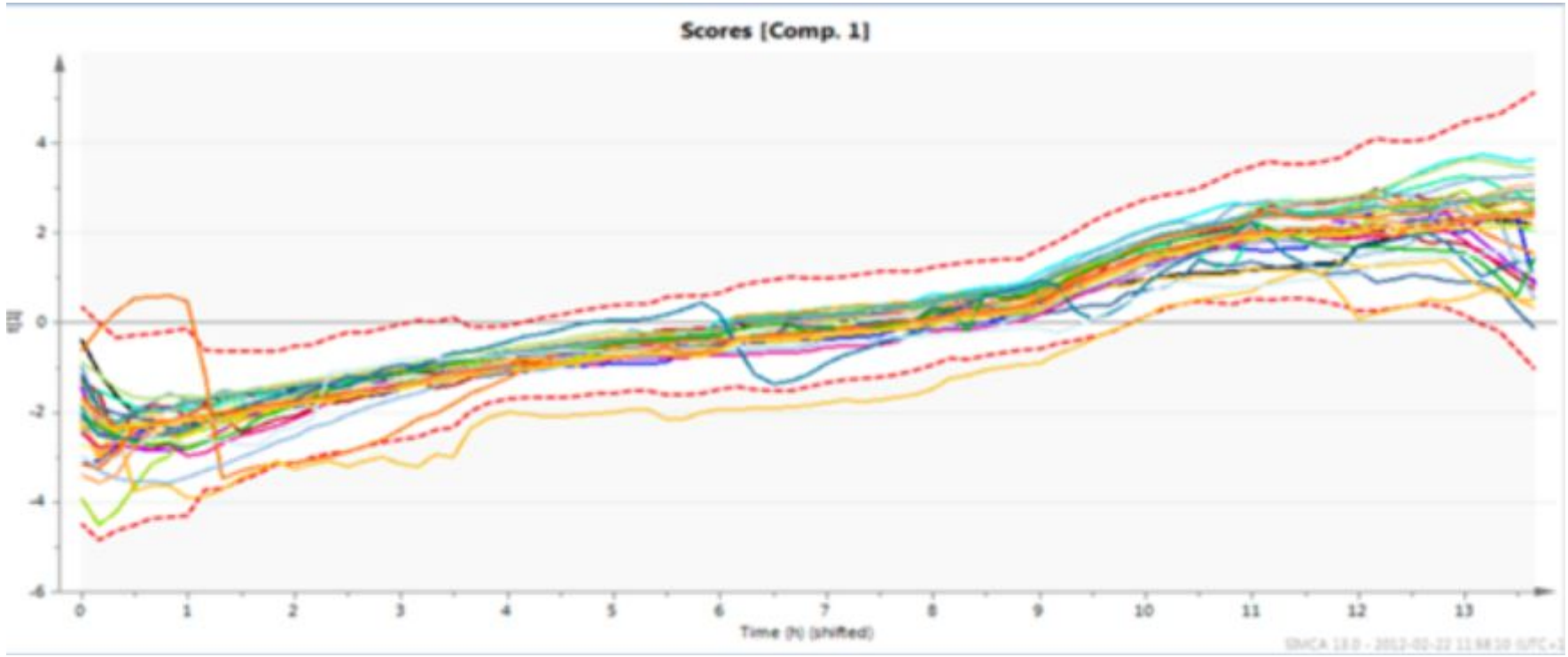




Multivariate Control limits detect an unusual point here

Example extracted from: https://www.osisoft.de/customer-stories/boehringer-ingelheim-golden-batch

Example 1: Golden Batch

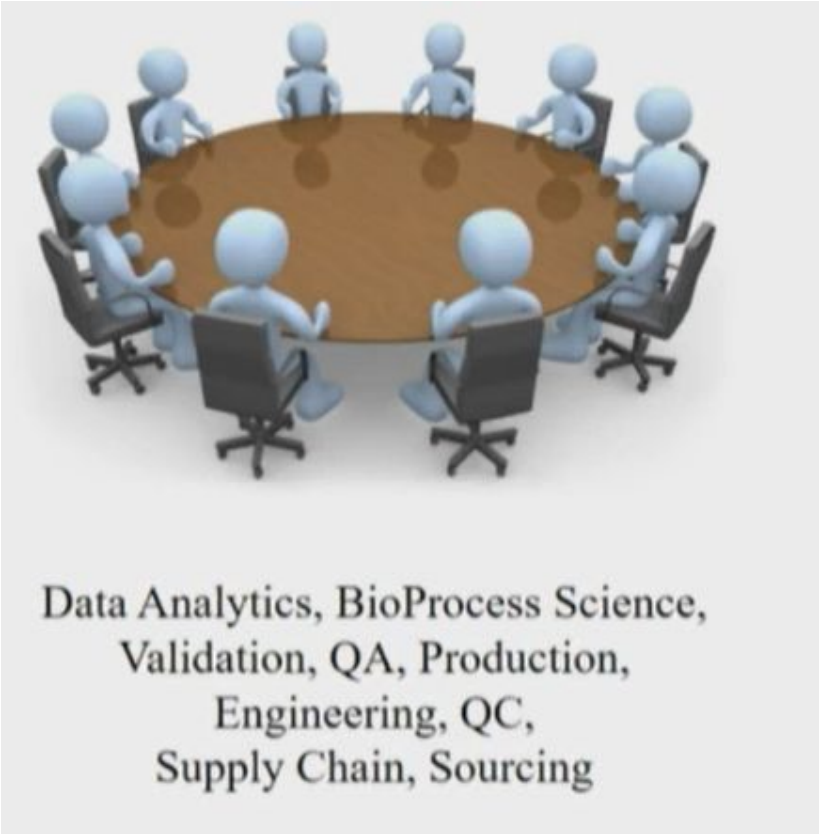


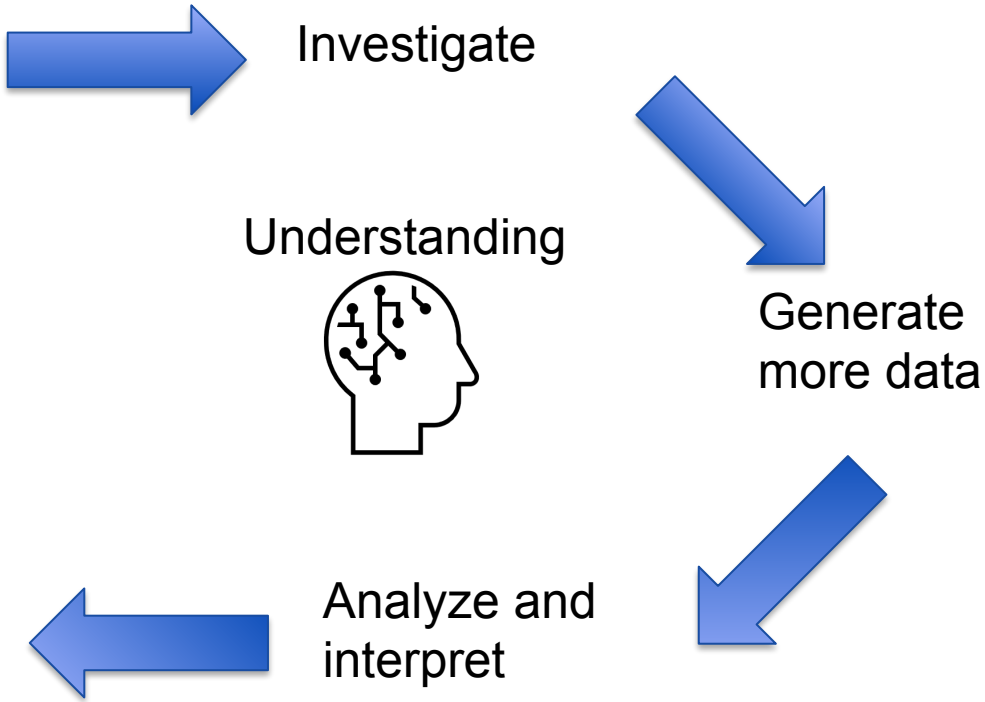
- Events can be seen as they ocur
  - Issues can often be indirectly be detected (e.g., contamination) even without measurement
  - Parameters can **proactively** be adjusted.

Example extracted from: https://www.osisoft.de/customer-stories/boehringer-ingelheim-golden-batch

Example 1: Golden Batch

- The outcome needs to be interpreted by human and actions defined
  - **Data Culture**





See:

Example 1: Golden Batch

- This is applied **Data Culture**!

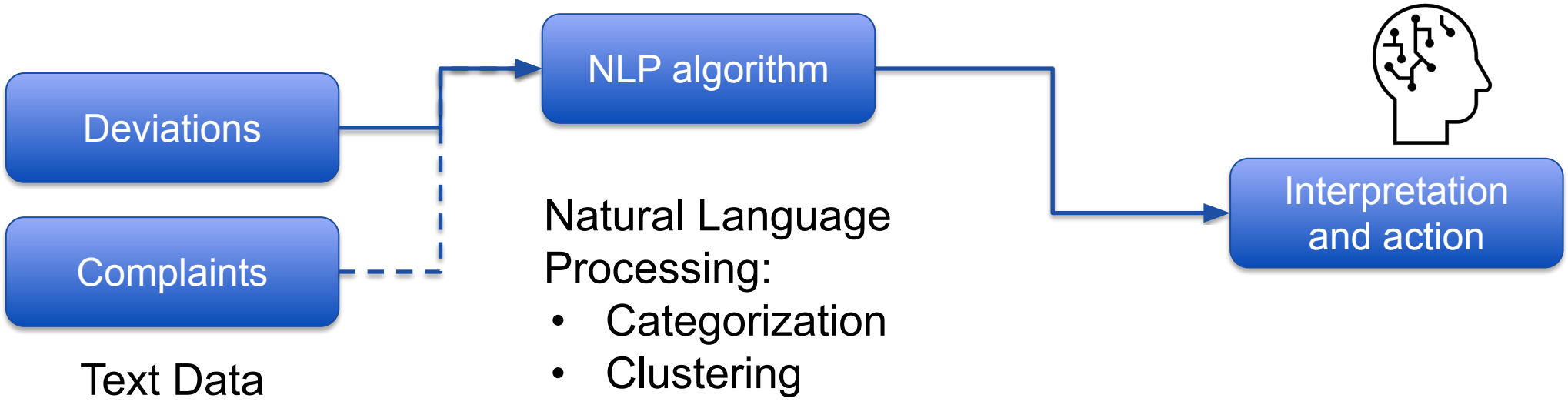
In response to this letter provide the following: (Dec 2020)

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/clientele-inc-607476-12032020

Example 2: NLP algorithm (simplified)

This case study is an **imaginary** case study, it is based on [1] and on interviews with Mark DiMartino (former AMGEN).



[1] How AMGEN uses AI Tools To Improve Manufacturing Deviations Investigations, J.Chapman, 2018

Example 2: NLP algorithm (simplified)

NLP algorithm

"Today, one of the **most popular tasks** in **Data Science** is processing **information** presented in the **text** form. Exactly this is text representation in the form of mathematical equations, formulas, paradigms, patterns in order to **understand** the text semantics (content) for its further processing: **classification**, **fragmentation**, etc. The general area which solves the described problems is called **Natural Language Processing** (NLP)" [2]

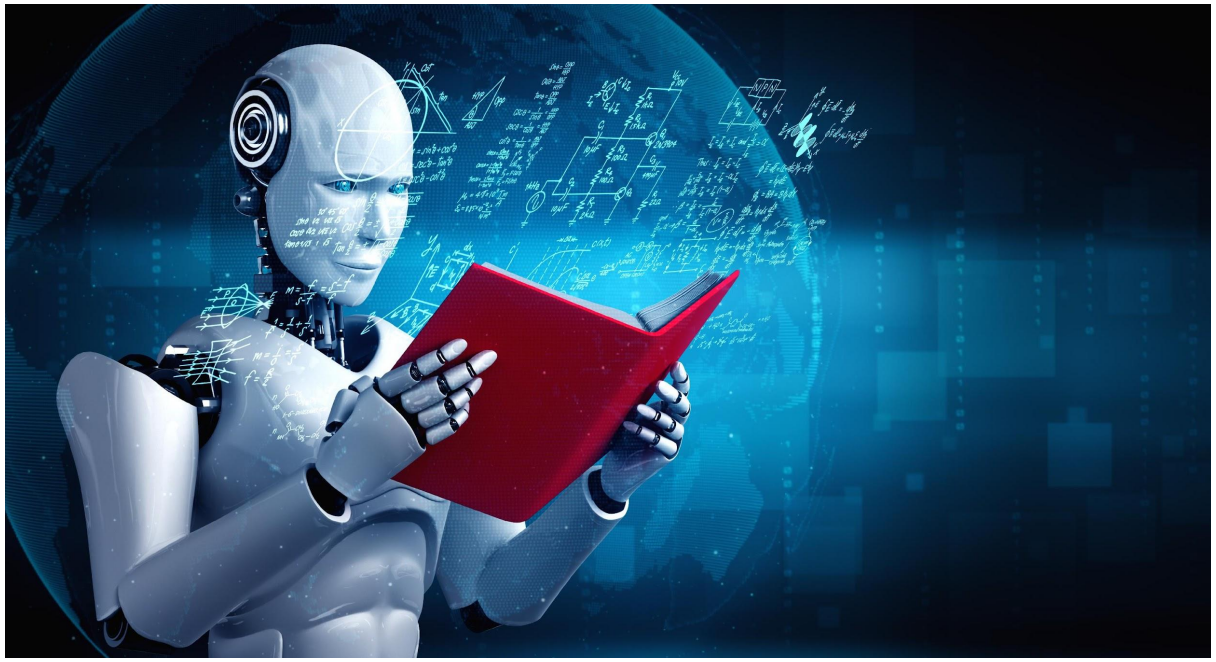
- NLP is an AI technology, the NLP algorithm keeps learning (with human input)
  - Since quality departments handle a lot of text information applying NLP has a lot of potential
- Mature NLP algorithms and tools are open available for free
  - They are widely commercially used (google, amazon etc.)
  - **But how does it actually work?**

[2] https://www.datasciencecentral.com/top-nlp-algorithms-amp-concepts/

Example 2: NLP algorithm (simplified)

- Text is **not a friend of computers**, since it works with binaries (=numbers)
- The pattern to be searched has to be reflected by **scores**

- One example for this are **Word Counting** and the **Cosine Similarity**



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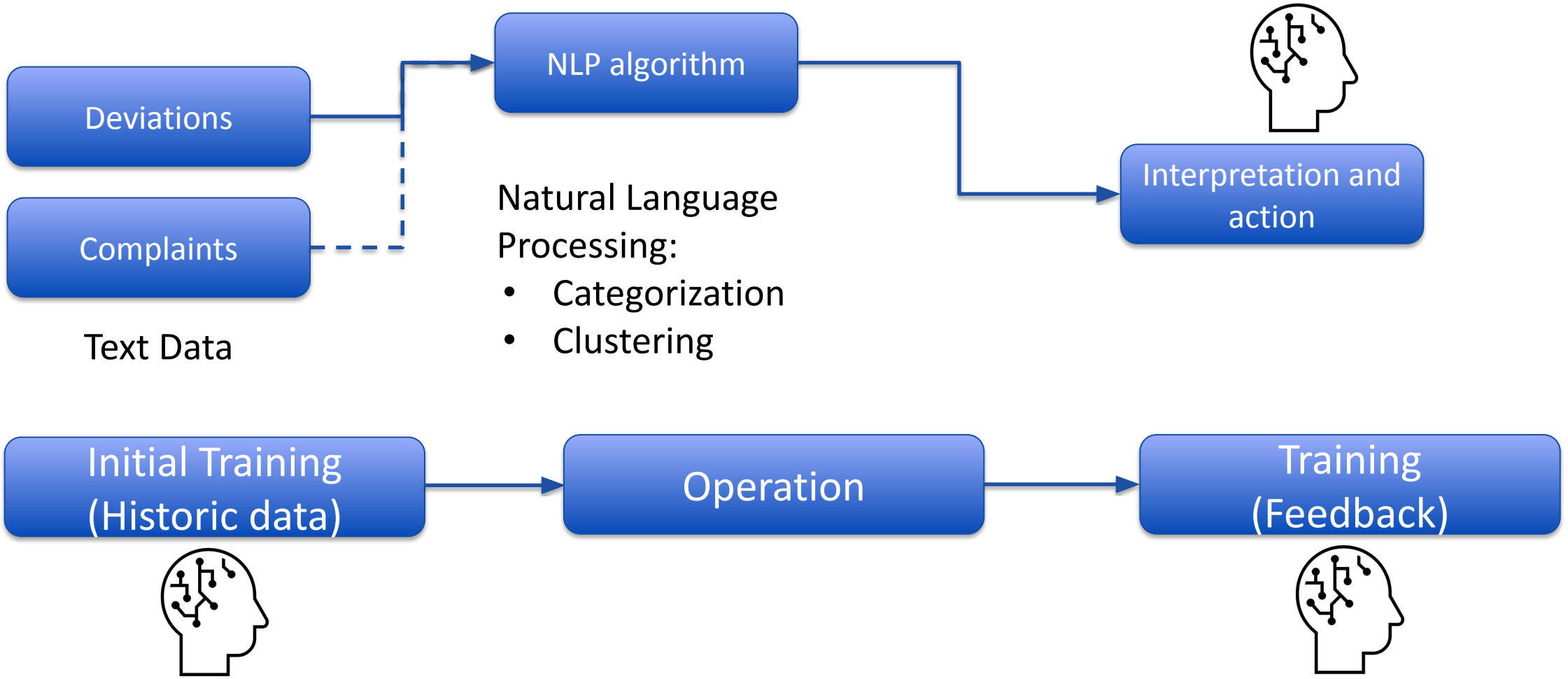
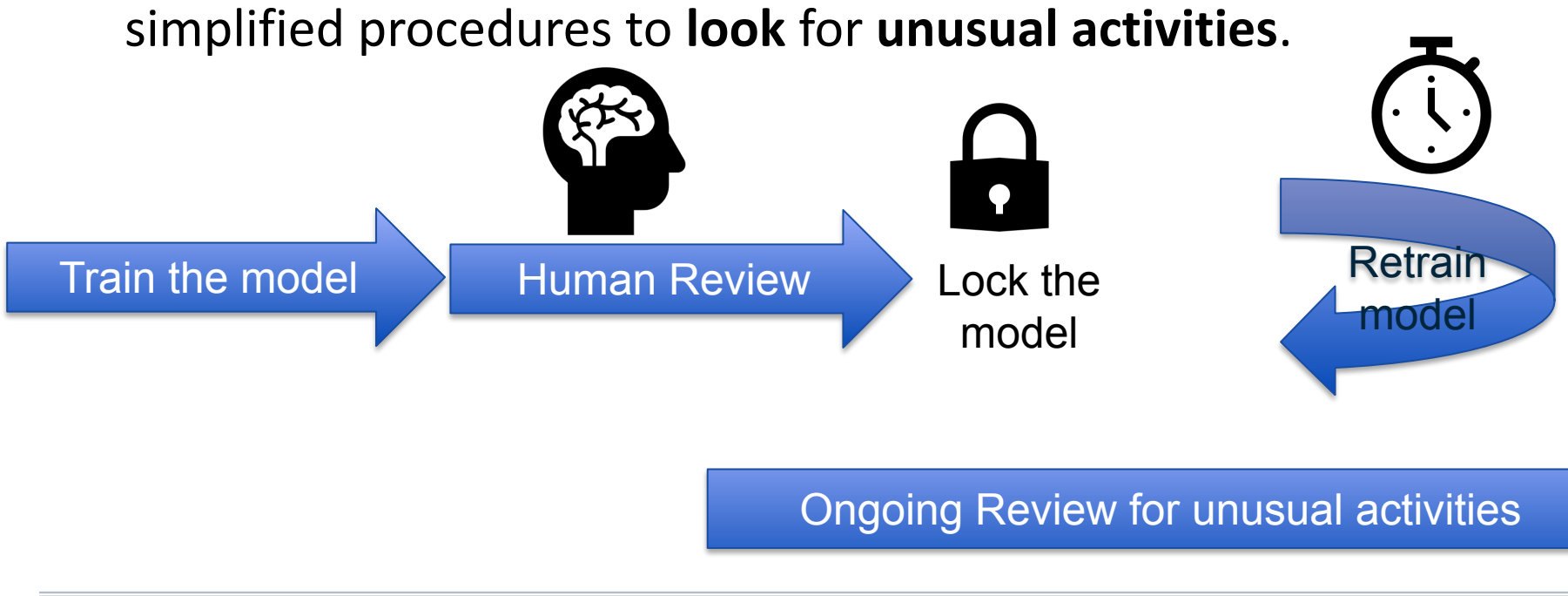


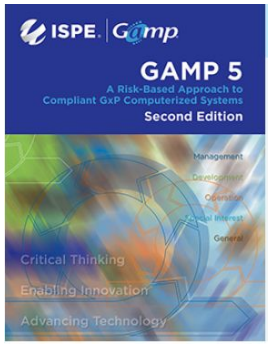
Example 2: NLP algorithm (simplified)

How could the validation strategy for the NLP algorithm look like?

Interview Mark DiMartino;

- "For the "AI" algorithm, we would **train the model, do the human review and then lock it.** We put in a procedure to **retrain the model at a set frequency** and developed simplified procedures to **look** for **unusual activities**.





Example 2: NLP algorithm (simplified)

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Pharmaceuticals

Annex 11: Computerised Systems

Principle

This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfill certain functionalities.

The application should be validated; IT infrastructure should be qualified.

Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.

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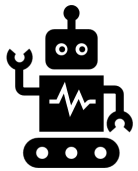
Conclusion

- Data must be reliable and trustworthy; this is the basis!

- The *Human Factor* and *Quality Culture* have a huge impact on Data Integrity
  - Senior Management is ultimately responsible for Quality Culture

- Data should be exploited to gather explicit Knowledge
  - See ICH Q9 and Q10
  - This will not work with paper records and/or data silos.



- Data as an asset opens the way for a data-driven future
  - Business and Quality Unit are on the same page here!

Thank you for attending!

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Does anyone have any questions?

Please provide your feedback

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