Data Integrity & Governance

글로벌 DI 규제 대응 전략 세미나

- Data Integrity
- Regulation
- Automation
- AI

2026년 5월 26일 (화) 09:30 - 17:30

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LIVE OAK

QUALITY ASSURANCE

Data Integrity

PETER BAKER

FDA official says data integrity issues are the main reason for ANDA delays

Regulatory News | 10 April 2025 | Joanne S. Eglovitch

BETHESDA, MD – Data integrity issues were the primary reason for the US Food and Drug Administration's (FDA) delay in approving abbreviated new drug applications (ANDAs) past their review goal date, according to Darby Kozak, deputy director of the Office Generic Drugs (OGD) at the Center for Drug Evaluation and Research (CDER).

Kozak made these remarks during the agency's Generic Drug Forum (GDF) on 9 April, and said the information was gleaned from the results of a recent transparency pilot.

His presentation addressed three key aspects of the generic drug program: the current status of generic drug approvals, some notable approvals, and new strategies the agency is using to expedite the development of generic drugs. Prior to his presentation, FDA officials said they would not discuss the recent layoffs at the agency during the meeting.

Darby Kozak spoke at FDA's Generic Drugs Forum on 9 April 2025. (credit: Joanne S.

- FDA is unlikely to move away from a focus on DI in the coming years
  - Both from an inspection & review standpoint

https://www.raps.org/news-and-articles/news-articles/2025/4/fda-official-says-data-integrity-issues-are-the-ma

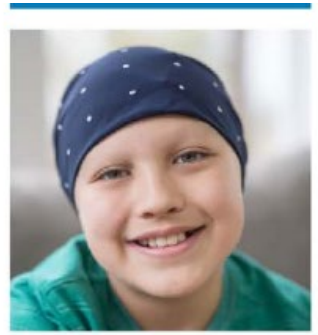
Examining Inspection Readiness in 2025/6: *FDA's Two Driving Factors (**GXP**)*

1. Drug Shortages

Drug Shortages:

Root Causes and Potential Solutions

2019



2. Patient Safety

More than 80 people in the U.S. tested positive for eye infections from the rare bacterial strain, according to the **most recent update** from the Centers for Disease Control and Prevention. Among them, 14 people suffered vision loss, four had to have an eye removed and four died, the CDC said.

“Simple adherence to CGMP standards…”

FDA inspects manufacturing facilities and takes regulatory action, if needed, to enforce CGMP regulations. The Agency’s investigators look for deficiencies in meeting CGMPs, but these assessments of CGMP compliance do not measure how far the facility is above the CGMP requirements in its quality management systems. Simple adherence to CGMP standards does not indicate that a firm is investing in improvements or planning or deploying statistical process control techniques that could better enable it to prevent supply disruptions.

Drug Shortages:
Root Causes and Potential Solutions
2019

https://www.fda.gov/media/131130/download

FDA's Response & Reaction

- ***Vigilant oversight*** has become a major regulatory focal point
  - Not a front-line responsibility to identify unexpected adulteration, but rather a **cultural expectation**

"In God we trust, everyone else has to bring us data"

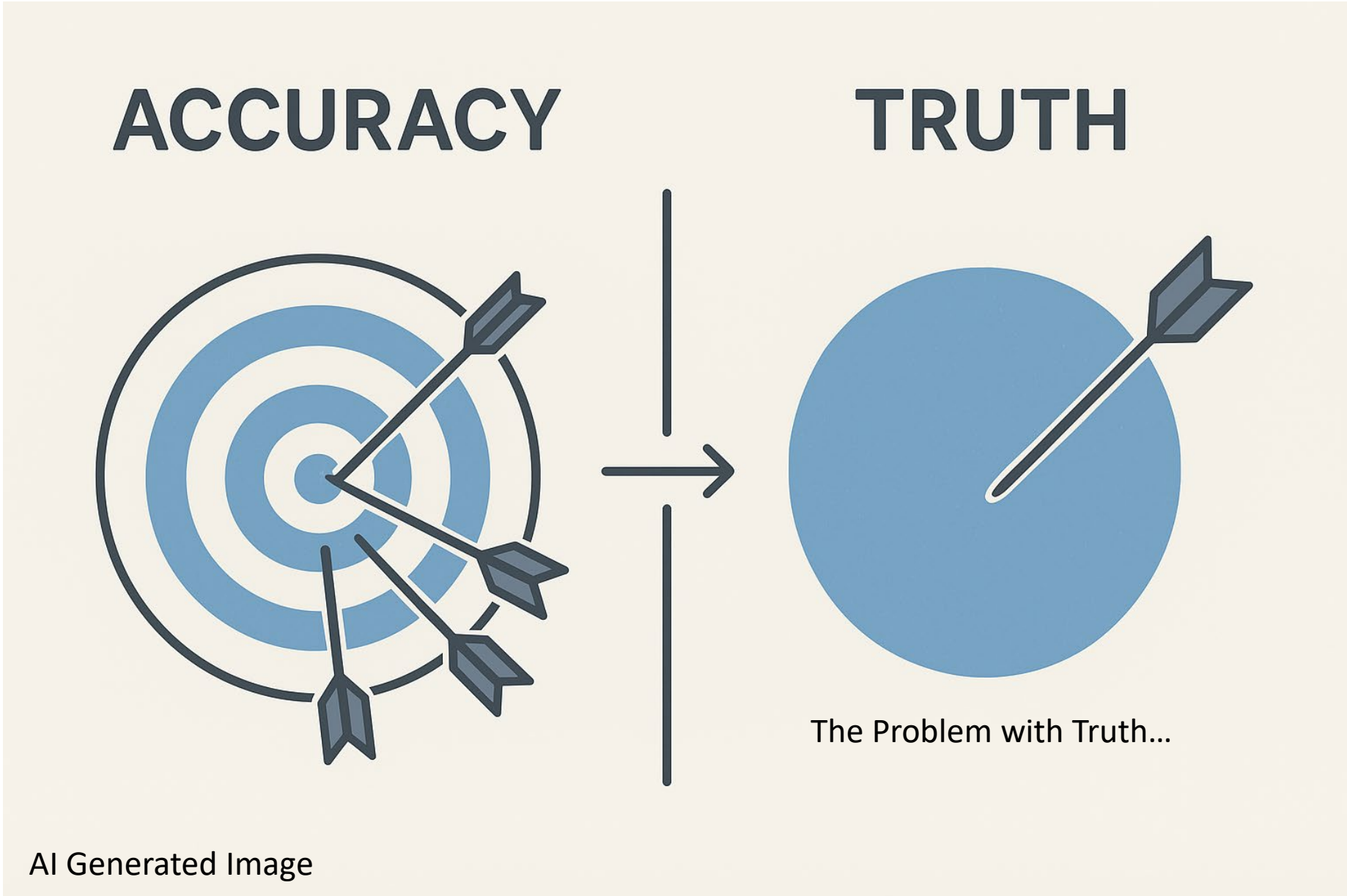
— *Dr. Janet Woodcock*

Featured in *Bloomberg Businessweek*, Sept. 16, 2019. Subscribe now. *Photo illustration: Justin Metz for Bloomberg Businessweek; Photo: Getty Images*

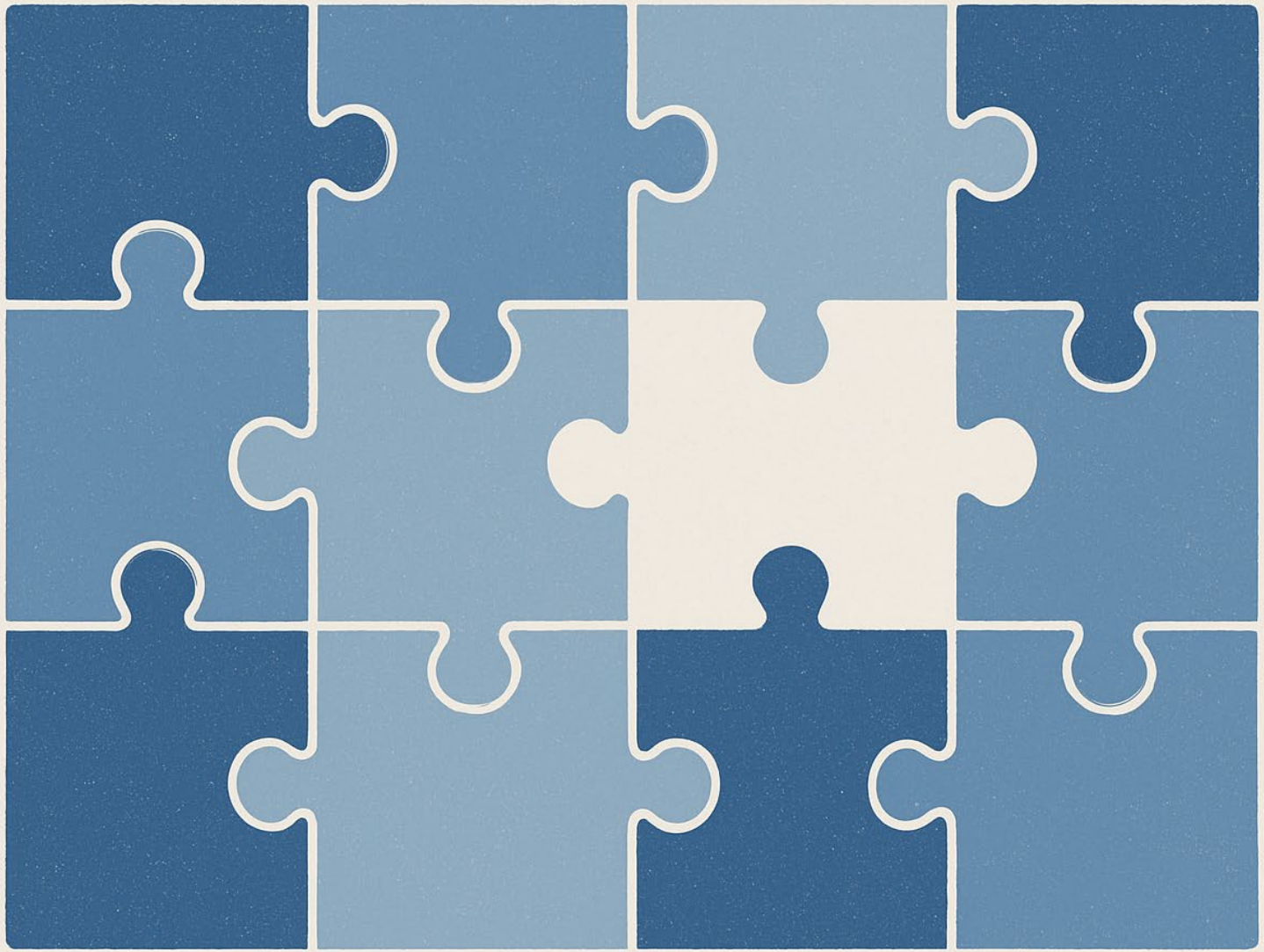
Why Data Integrity Matters

"…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."

Food and Drug Administration Safety and Innovation Act, Sec. 711
Enhancing the Safety and Quality of the Drug Supply



AI Generated Image



AI Generated Image

Data Must Be: ***Accurate & Complete***

Achieved via a ***validated workflow***

Several cases of sepsis — three of which ended in patients deaths — were traced to a Fresenius Kabi manufacturing plant in a new report from the U.S. Centers for Disease Control and Prevention. And the findings were released a year after the U.S. Food and Drug Administration cited the company for contamination problems and other quality control issues at the same facility.

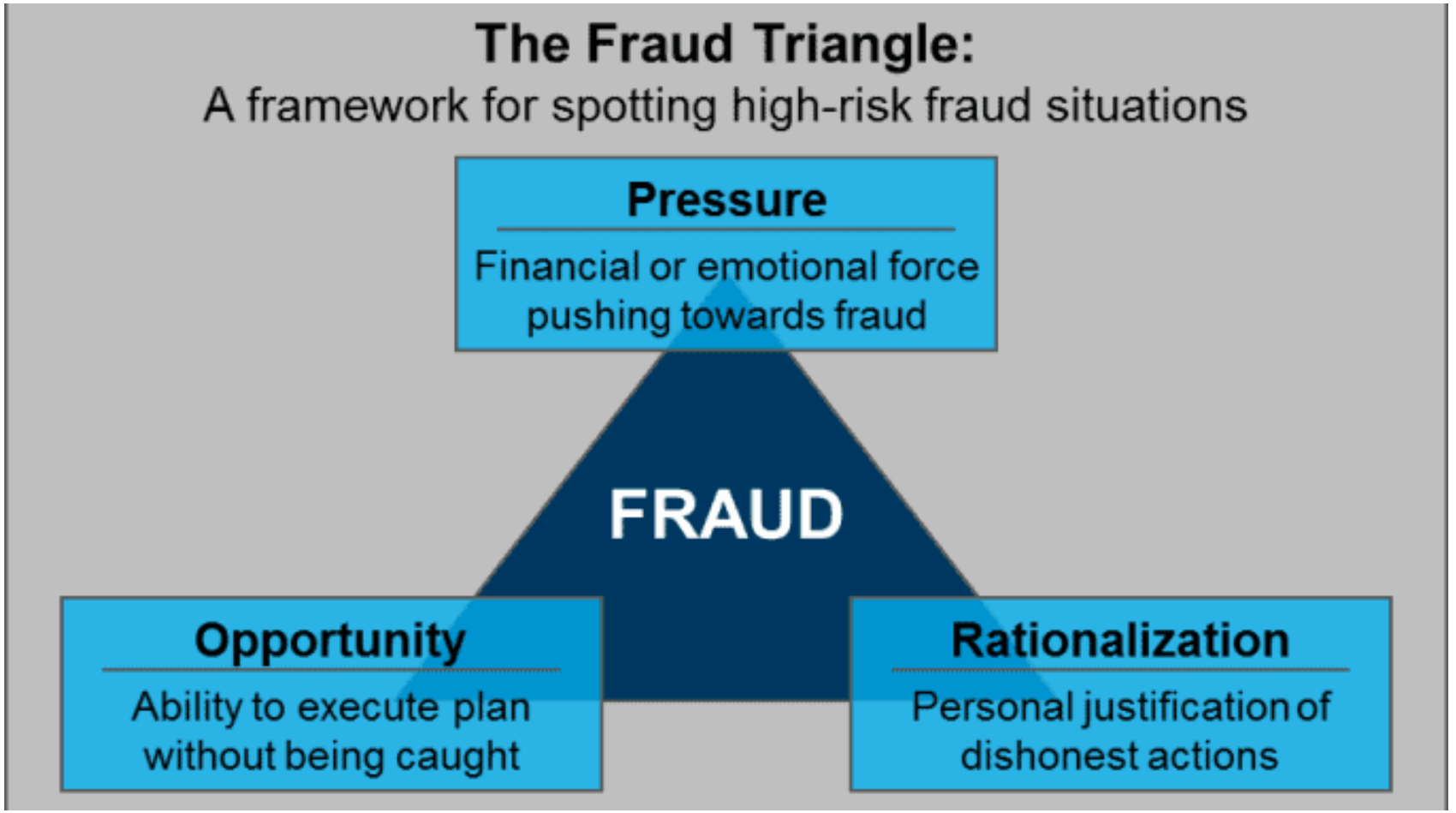
STAT Reporting from the frontiers of health and medicine

https://www.statnews.com/pharmalot/2023/10/04/fresenius-fenwal-fda-cdc-sepsis-bacteria-contamination-mold/

To Prevent Such Tragedies, the regulators are focused on identifying uncertainties

- How certain are you that your products are safe and effective, considering the number of variables involved in drug manufacturing?

Perfect Storm Scenario



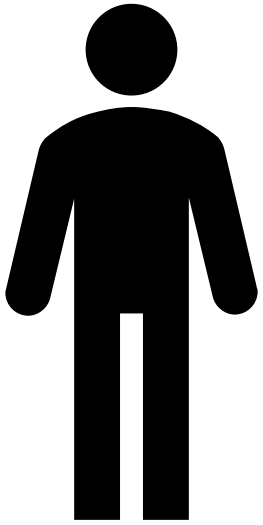
https://www.brumellgroup.com/news/the-fraud-triangle-theory/

Protecting the Patient: *the ledge analogy*

DEFINITION OF DEFICIENCIES
TO BE USED IN PIC/S INSPECTION REPORT

1. **CRITICAL DEFICIENCY**

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.



Worst-Case Scenario

SCIENTIFICALLY VALID EVIDENCE

RELIABILITY

https://picscheme.org/docview/3461

CASE STUDY!

Records are not completed contemporaneously.

WFI

Specifically, during my inspection of your microbiology laboratory on 08/08/17, I observed your microbiologist preparing to load the purified water and (b) (4) plates into the incubator for samples collected and prepared earlier that day. However, the sample preparation worksheets for these samples were either partially completed or blank.

Sampling Details

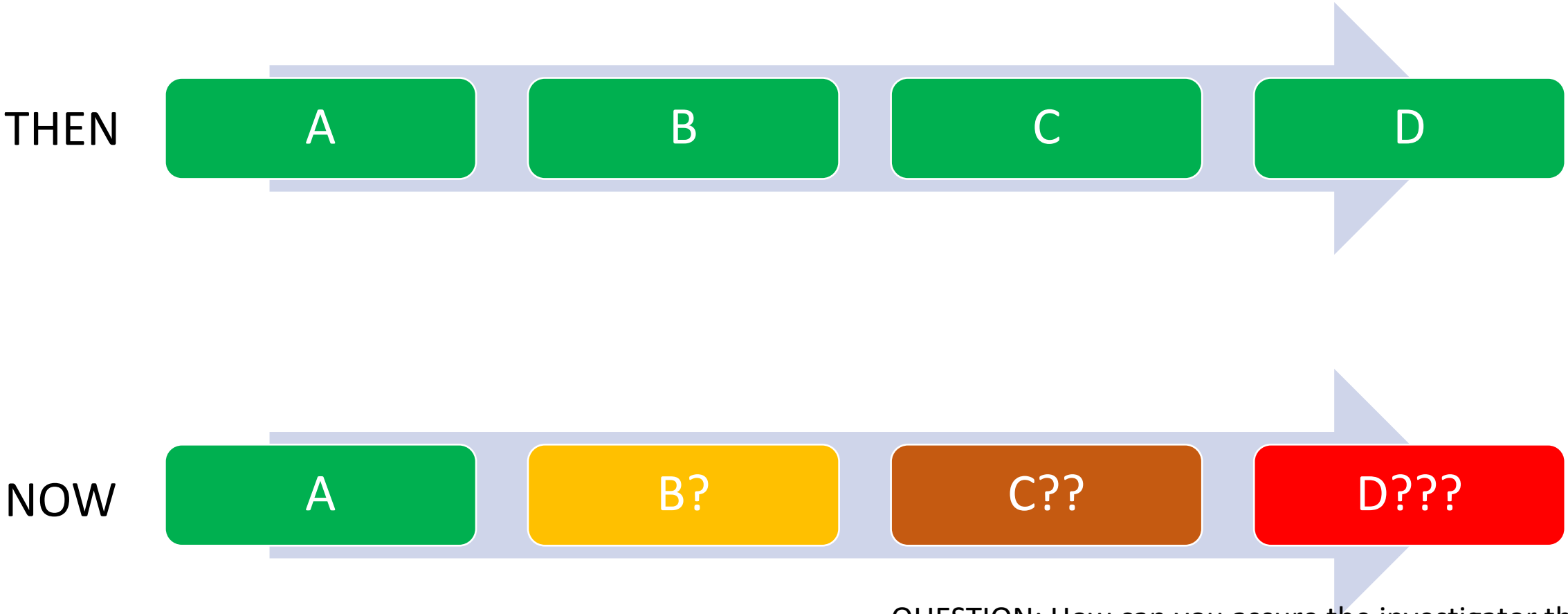
1. Date/Time
2. Sampling Point & SOP
3. Signature/Date

Sample Preparation

1. Filtration Details
   - Dilution (PW only)
   - Filter details
   - Washing

Loading

Compliance: Then & Now

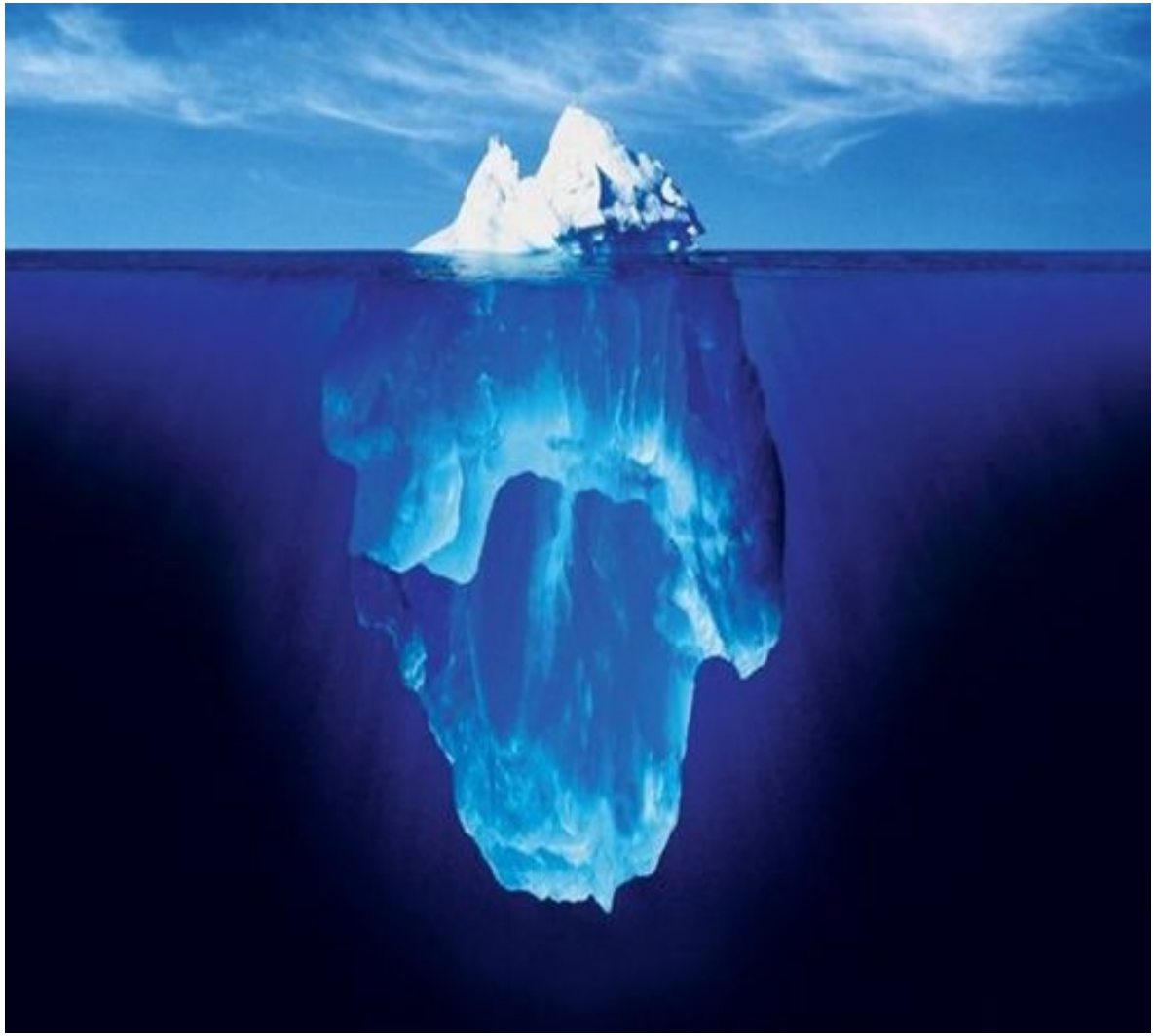


QUESTION: How can you assure the investigator the decision (D) is: 1) accurate, and 2) complete?

DI from a Regulator's Perspective

What they find

Reality



Hence: regulatory focus on the process!

How can we ensure continuous *Inspection Readiness*

5 DATA GOVERNANCE SYSTEM

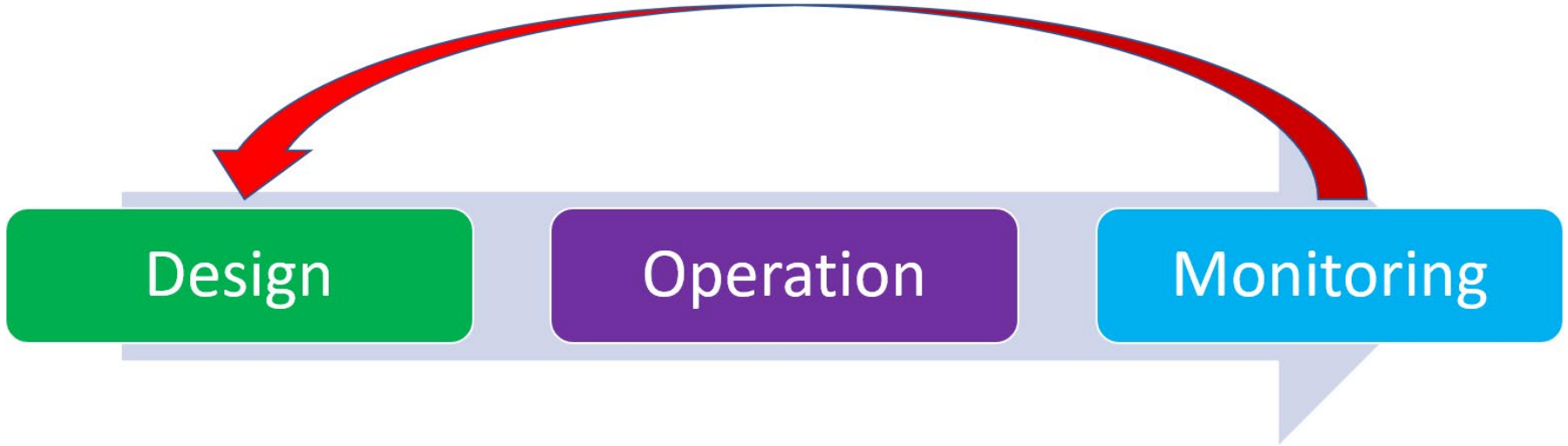
5.1 What is data governance?

5.1.1 Data governance is the sum total of arrangements which provide assurance of data integrity. These arrangements ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used will ensure an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available record throughout the data lifecycle. While there may be no

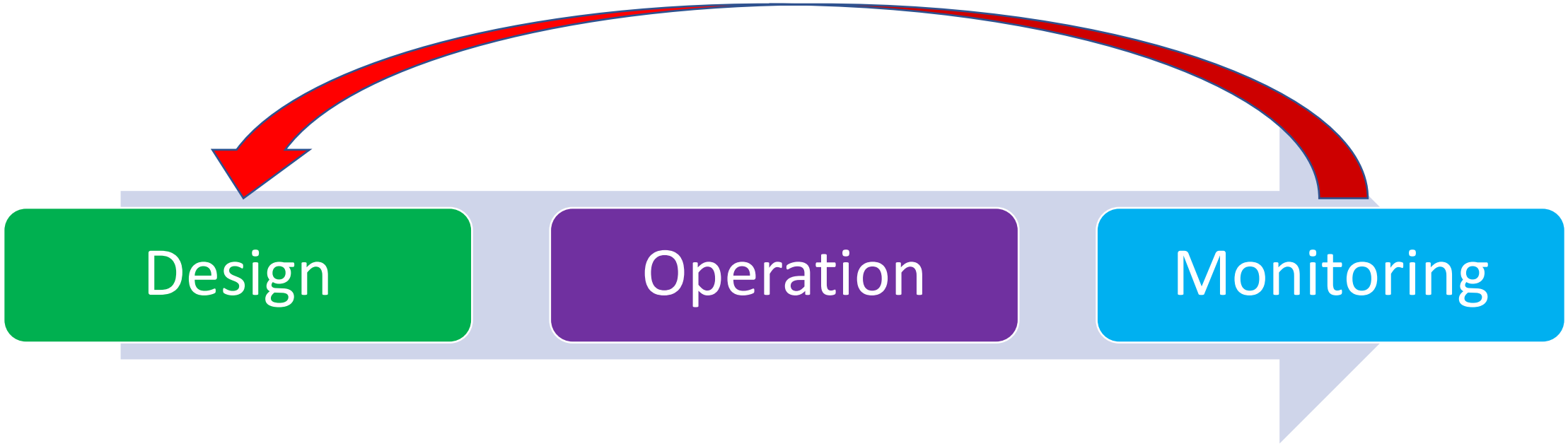
- Understanding all factors that contribute to variability, such that our decisions are based on science; thereby ensuring patient safety

Lifecycle Approach to Data Integrity

- "Meaningful and effective strategies should consider the **design, operation, and monitoring** of systems and controls based on risk to patient, process, and product."
  - "Controls that are appropriately designed to validate a system for its intended use address **software, hardware, personnel, and documentation**."



https://www.fda.gov/media/119267/download



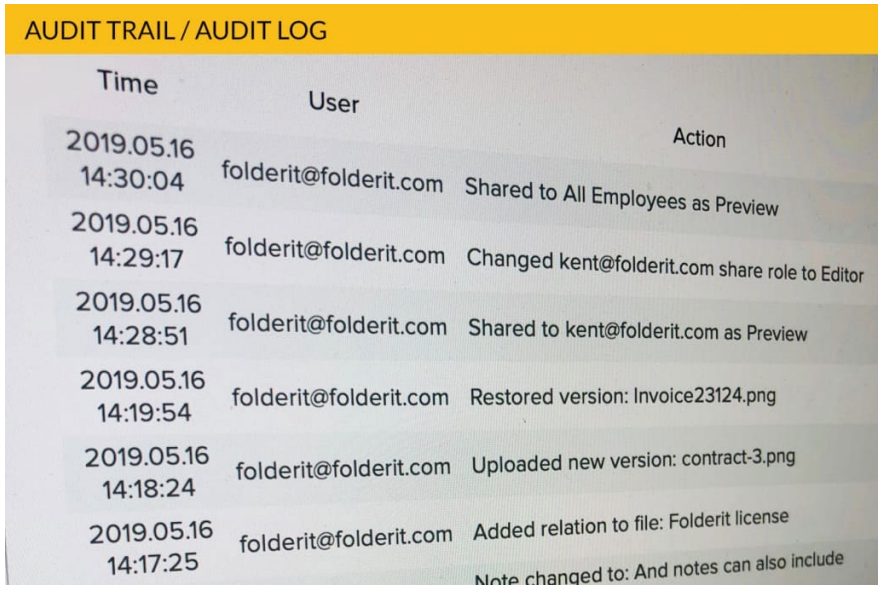
1. Data & Process Mapping
2. Risk Assessment
3. Qualification/CSV

1. SOPs
2. Training

1. QA/External Auditing
2. Quality System Feedback
3. CPV
4. Management Review
5. Periodic Review

One New Key Addition to the Guidance

- Data Ownership:
  - “The allocation of responsibilities for control of data to a specific process owner. Companies should implement systems to ensure that responsibilities for systems and their data are appropriately allocated and responsibilities undertaken.”


AUDIT TRAIL / AUDIT LOG

Time	User	Action
2019.05.16 14:30:04	folderit@folderit.com	Shared to All Employees as Preview
2019.05.16 14:29:17	folderit@folderit.com	Changed kent@folderit.com share role to Editor
2019.05.16 14:28:51	folderit@folderit.com	Shared to kent@folderit.com as Preview
2019.05.16 14:19:54	folderit@folderit.com	Restored version: Invoice23124.png
2019.05.16 14:18:24	folderit@folderit.com	Uploaded new version: contract-3.png
2019.05.16 14:17:25	folderit@folderit.com	Added relation to file: Folderit license
		Note changed to: And notes can also include

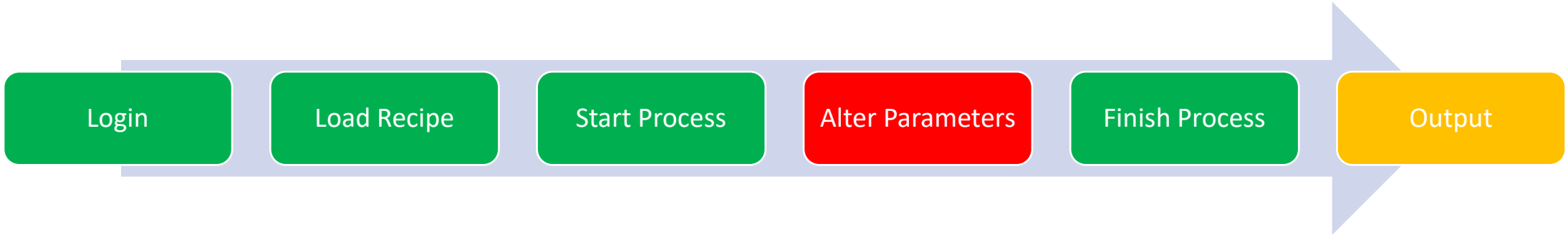
https://www.folderit.com/blog/audit-trail/

Annex 11 – Key message

- “Computerised systems should be qualified and validated in accordance with the principles of quality risk management. Decisions on the scope and extent of qualification and validation of specific functionality and entire systems should be based on a justified and documented risk assessment of individual requirements and, where relevant, functional specifications, considering the risk for product quality, patient safety and data integrity.”

Q3: Does each CGMP ***workflow*** on a computer system need to be validated?

"Yes, a CGMP **workflow**, such as creation of an electronic master production and control record (MPCR), is an intended use of a computer system to be checked through validation… The extent of validation studies should be commensurate with the risk posed by the automated system."



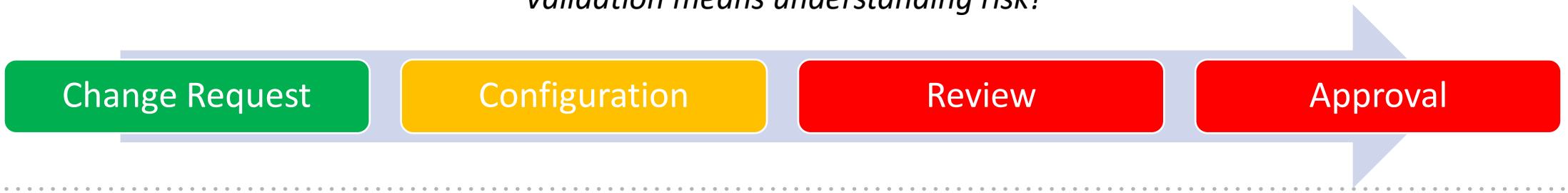
https://www.fda.gov/media/119267/download

“If you validate the computer system but you do not validate it for its intended use, you cannot know if your workflow runs correctly”

Here we see a break from traditional ways of demonstrating ***compliance*** – to a focus on demonstrating assurance of patient safety (aka Quality Assurance)

“For example, qualifying the Manufacturing Execution System (MES) platform, a computer system, ensures that it meets its relevant requirements and specifications; however, it does not demonstrate that a given MPCR generated by the MES contains the correct calculations.”

Validation means understanding risk!



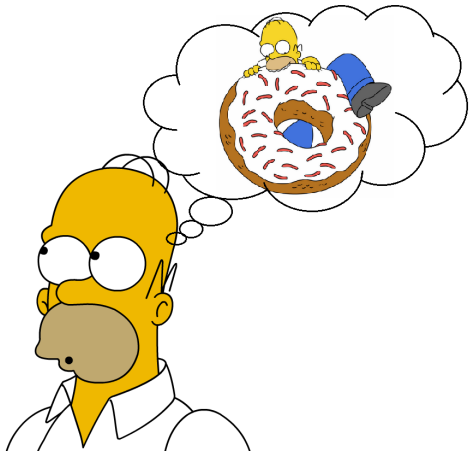
https://www.fda.gov/media/119267/download

Key Points to Consider: Evaluating Risk

"In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output."

Q: For Data Integrity Control Strategies – what makes up our data set?

Q: How can we demonstrate our data set during inspection?



The QRM process normally consists of several steps including:

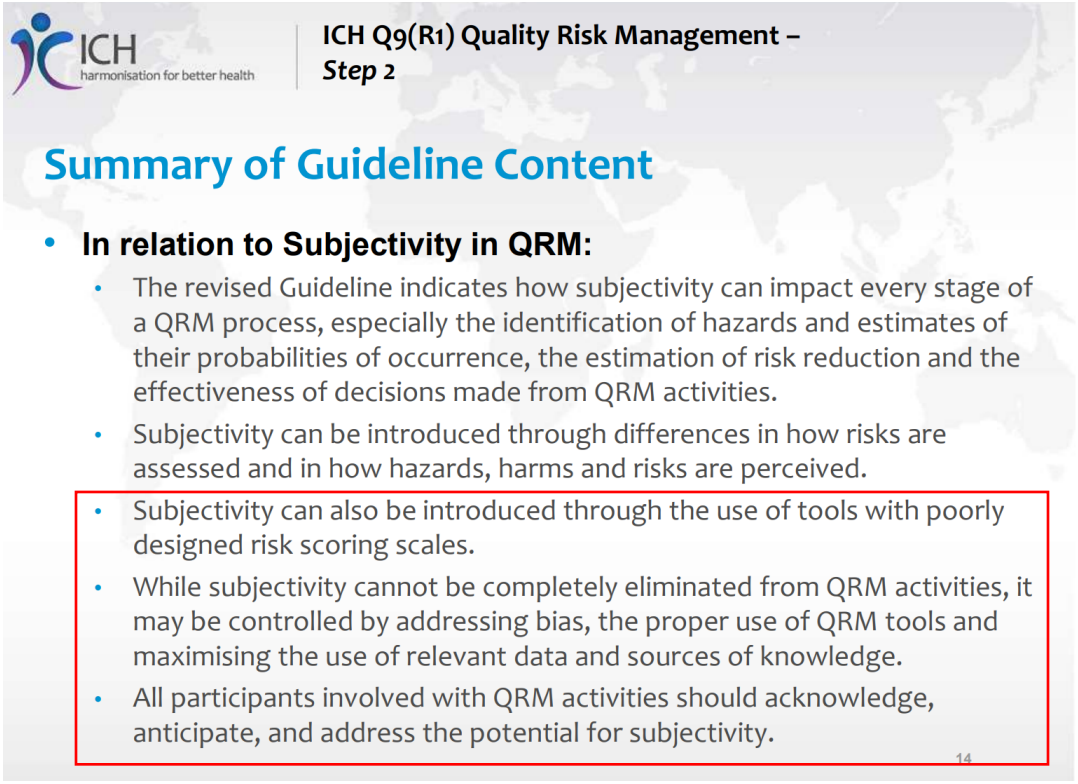
- Process mapping identifying all inputs, outputs and existing control measures;
- Risk Assessment (incl. risk- identification, risk-analysis and evaluation);
- Risk Control (including risk reduction and risk Acceptance);
- Communication (i.e. the residual risk should be communicated to the regulators and customers);
- Regular Review of the risks.

There is a risk that **inappropriate conclusions** may be drawn should assessments be based upon:

- Unjustified assumptions;
- Incomplete identification of risk(s) or inadequate information;
- Lack of relevant experience of the process being assessed and/or inappropriate use of the risk assessment tools.

ICH Q9 and FDA Guidance allow for “Flexible” Strategies… *Industry struggles with this*

As a result, ICH Q9 has been revised (draft) to address industries reluctance to fully embrace risk-based strategies



ICH harmonisation for better health

ICH Q9(R1) Quality Risk Management – *Step 2*

Summary of Guideline Content

- **In relation to Subjectivity in QRM:**
  - The revised Guideline indicates how subjectivity can impact every stage of a QRM process, especially the identification of hazards and estimates of their probabilities of occurrence, the estimation of risk reduction and the effectiveness of decisions made from QRM activities.
  - Subjectivity can be introduced through differences in how risks are assessed and in how hazards, harms and risks are perceived.
  - Subjectivity can also be introduced through the use of tools with poorly designed risk scoring scales.
  - 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.
  - All participants involved with QRM activities should acknowledge, anticipate, and address the potential for subjectivity.

14

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

Summary of Guideline Content

- **In relation to Formality in QRM:**
  - The revised Guideline addresses what constitutes formality in QRM and it outlines how varying degrees of formality may be applied during QRM activities, including when making risk-based decisions. In this way, formality can be considered a continuum (or spectrum), ranging from low to high.
  - It addresses the factors that may be considered when determining how much formality to apply to a given QRM activity.
  - It provides guidance on the characteristics of higher and lower levels of formality.
  - It indicates that there is flexibility in how much formality may be applied in relation to QRM activities, emphasising that the robust management of risk should always be the overarching goal of QRM.

Summary of Guideline Content

- **In relation to Risk-based Decision Making:**
  - The revised Guideline provides clarity on what effective risk-based decision making is, and it indicates that approaches to risk-based decision-making are beneficial, because they address uncertainty through the use of knowledge. This facilitates informed decisions in a multitude of areas, including when allocating resources.
  - The revised Guideline provides guidance on how there are different processes that may be used to make risk-based decisions, and how these are directly related to the level of formality that is applied during the QRM process.
  - It addresses how there can be varying degrees of structure with regard to approaches for risk-based decision making, and guidance on such approaches is provided.

YES!

EU GMP Chapter 4 (draft): Documentation

Data Risk Assessment	The process of evaluating the risks associated with the regulated user's data. It ensures an efficient and effective approach to data integrity by considering the vulnerability of data to involuntary or deliberate alteration resulting in risk-based control measures.

- Most ***objective*** pathway to assessment of DI risks

Statistical (Critical) Thinking

- Probability vs. Statistics

Probability

Statistics

Case Study: working from the bottom up.

Statistical (Critical) Thinking

- **Probability** (lower level of uncertainty): We know what is in the bag (large sample size), and can therefore make inferences to what is in the hand (small sample size)
  - Example = Las Vegas Casino
  - GXP Example = Based on historical evidence, 1 in 100 entries could result in contamination if gowning is not perfect.
- **Statistics** (higher level of uncertainty): We can measure what we have in our hand (small sample size), and then make inferences to what is in the bag (large sample size)
  - Example = surveys/polls
  - GXP Example = Retain Sample Analysis (put in context to make inferences) shows there is XX% confidence that… (confidence intervals)

Data/Metadata does not reflect the true value or history of events

OBSERVATION 3
Your examination and testing of samples did not assure that the drug product and in-process material conformed to specifications.

Specifically,

Your SOP MX-IVT-CMP003 "Working Visual Instruction for (b) (4) mL Solution Bag", used for visual inspection of (b) (4) solution, USP, Section 1- Bag Manufacturing states your operator will visually inspect for approximately (b) (4) On 11/28/18, during manufacturing of (b) (4) mL bag lot (b) (4) I observed the operators were inspecting the bag completely in approximately (b) (4) Similarly, (b) (4) Injection (b) (4) %, USP , (b) (4) bags for (b) (4) were also being verified in less than (b) (4)

In addition, operators observed performing visual inspections of both (b) (4) solution, USP (lot (b) (4) and (b) (4) Injection (b) (4) %, USP (lot (b) (4) were not documenting defects they observed during pack out. A second operator was observed completing the batch record for visual defects.

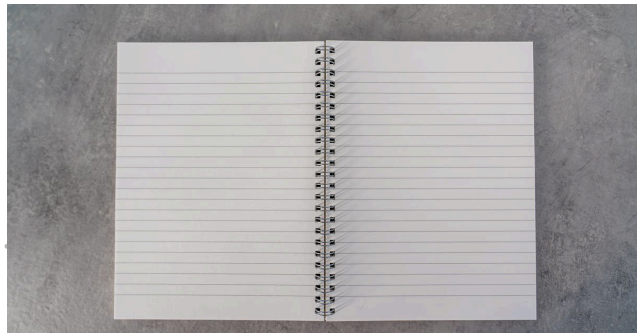
- Rapid visual inspection of solution bags: is the data accurate?

https://platform.redica.com/documents/100122949

Downstream consequences of bad data governance design

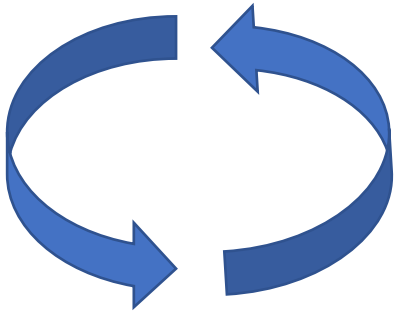
Some manufacturing data was recorded on secondary, uncontrolled notebooks or on loose sheets of scratch paper. We observed an uncontrolled notebook in Manufacturing Room **(b)(4)** that contained tares, raw material release labels, and remaining amounts of raw materials. We also observed a slip of loose paper with production information. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

- Any thoughts on potential root causes for this behavior?



https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/andapharm-llc-566492-02282019

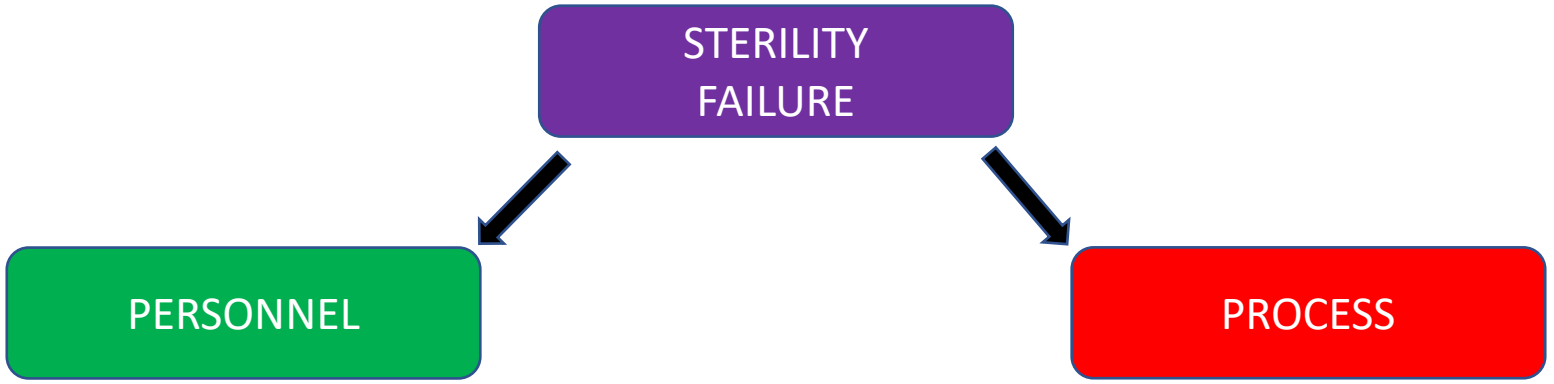
Pitfalls - Closed Loop Thinking



- Bloodletting
  - Survived as a legitimate treatment until the early 1800's (~1,700 years)
- Failure does not lead to progress
  - Opposite behavior is "open loop" = Transparent in failure
- Deviations Trending – *Human Error*
  - No matter what happens, the process is never questioned
  - *But we cannot stop with a simple observation related to inadequate investigations!*

Closed Loop Thinking – Enforcement Actions

- WL - 8/2/2019 : “According to your sterility failure investigations, the most probable root cause for both events (sterility failures) was laboratory error. Your firm’s investigations substantially addressed the potential for microbial contamination during sterility testing, but *deemphasized* potential manufacturing causes.”



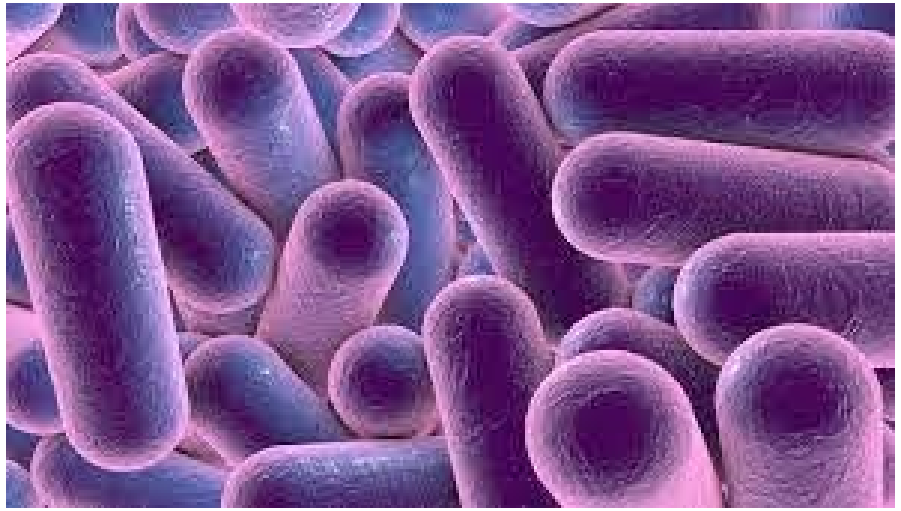
What did the data say?

“while the organisms isolated during the failing sterility tests had been recovered in the laboratory in the past, the same microorganisms were also recovered in the production area in a six-month timeframe prior to the sterility failures.”

STERILITY FAILURE

PERSONNEL

PROCESS



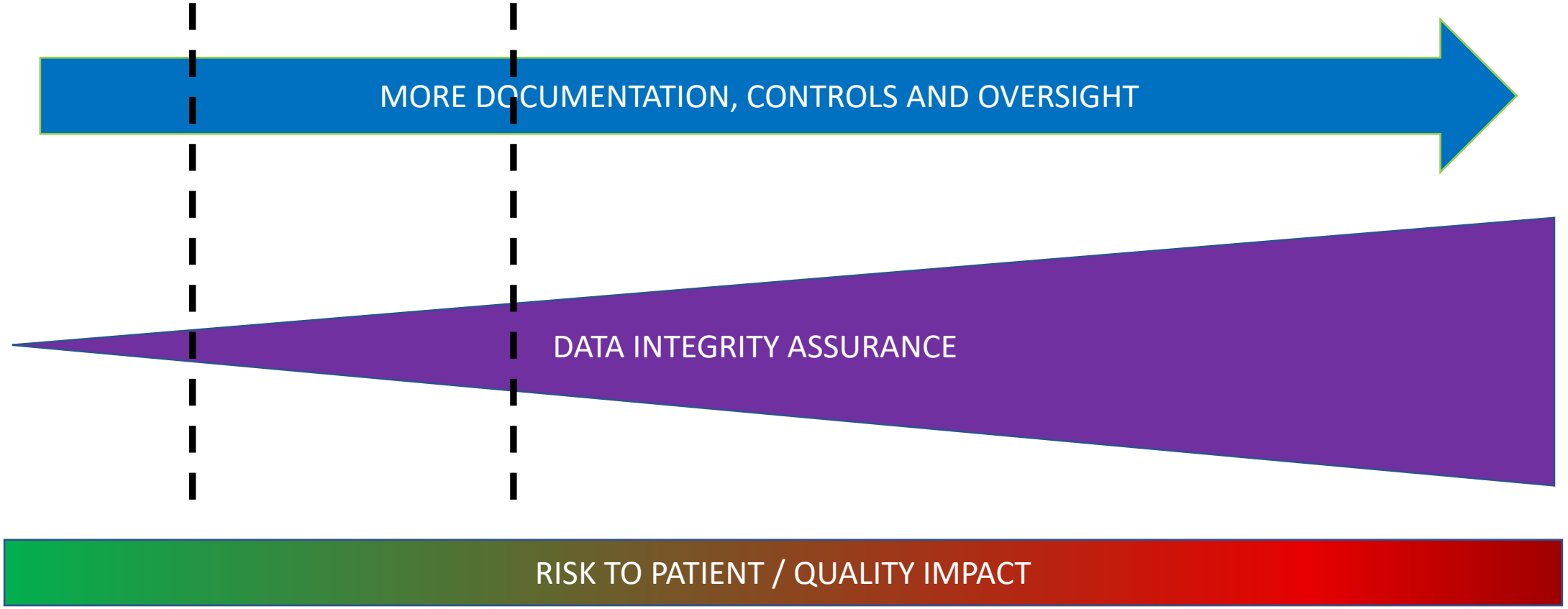
Quality Risk Management will not work properly without ***Risk Acceptance***

Firm's currently scramble to conclude there is "no risk" in their processes & procedures

Risk acceptance is a decision to accept risk. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

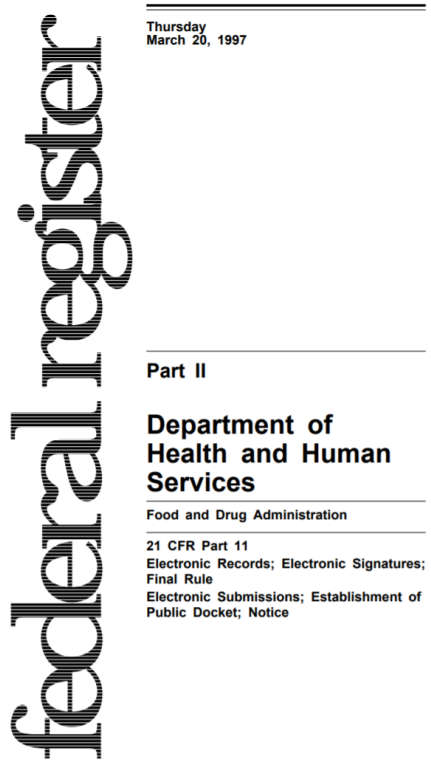
So are we all OK with accepting some level of residual risk in our operations and processes?

Controls = “Commensurate with the Risk”!



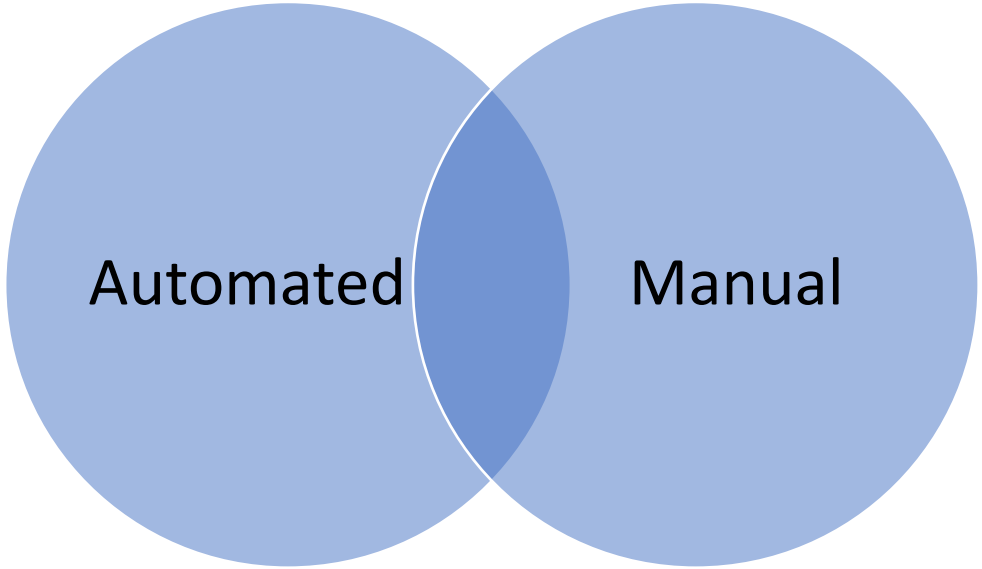
When determining a risk-based strategy, we consider falsification by “ordinary means”

Let’s go back in time to understand Part 11 in the context of Data Integrity



Managing “Hybrid Systems”

“Hybrid systems **require specific and additional controls** in reflection of their complexity and potential increased vulnerability to manipulation of data. For this reason, the use of hybrid systems is **discouraged** and such systems should be replaced *whenever possible*.”



When minimum automated functions are not available, manual controls can be considered to reduce risk:

- Logbooks
- “4 eyes principle” (witnessing)

An update to the 2003 guidance
…still tricky – companies can justify bad data governance

10. Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

A paper printout or static record may satisfy retention requirements if it is the original record or a true copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). During data acquisition, for example, pH meters and balances may create a paper printout or static record as the original record. In this case, the paper printout or static record, or a true copy, must be retained (§ 211.180).

Applies to legacy equipment
This guidance lacks a clear definition of "original record"
Vast majority of "simple" instruments used in 2020 create an electronic "original record"
ASSUMES sites understand the need to use QRM to justify each data governance strategy.

Is the data accurate and complete?

A) Laboratory data may be documented on forms that are not controlled. At the time of inspection your firm maintained a database where over 100 electronic forms (eForms) and logbooks used in microbiological supplemental testing, and for quipment monitoring and usage, could be accessed and printed by any laboratory personnel. Forms are not uniquely numbered or identified when printed and there is no accountability for the number of sheets printed and used. For example, on 05/30/23 we observed an analyst print two copies of Form F14A-142.17 for microbiological isolate morphology testing. The analyst stated that two copies were printed in error and one copy would be thrown away. The copies of Form F14A-142.17 were not issued in a traceable manner or effectively controlled to maintain their integrity.

EMPLOYEE(S) SIGNATURE		DATE ISSUED
Jolanna A Norton, Investigator Matthew R Clabeaux, Investigator	X Jolanna A Norton Investigator Signed By: Jolanna A. Norton -S Date Signed: 06-01-2023 15:17:40	6/1/2023

https://platform.redica.com/documents/100163260

THANK YOU