DATA INTEGRITY

ALICE REDMOND
VP FOR CAI EUROPE

SAAPI 04 OCT 2018

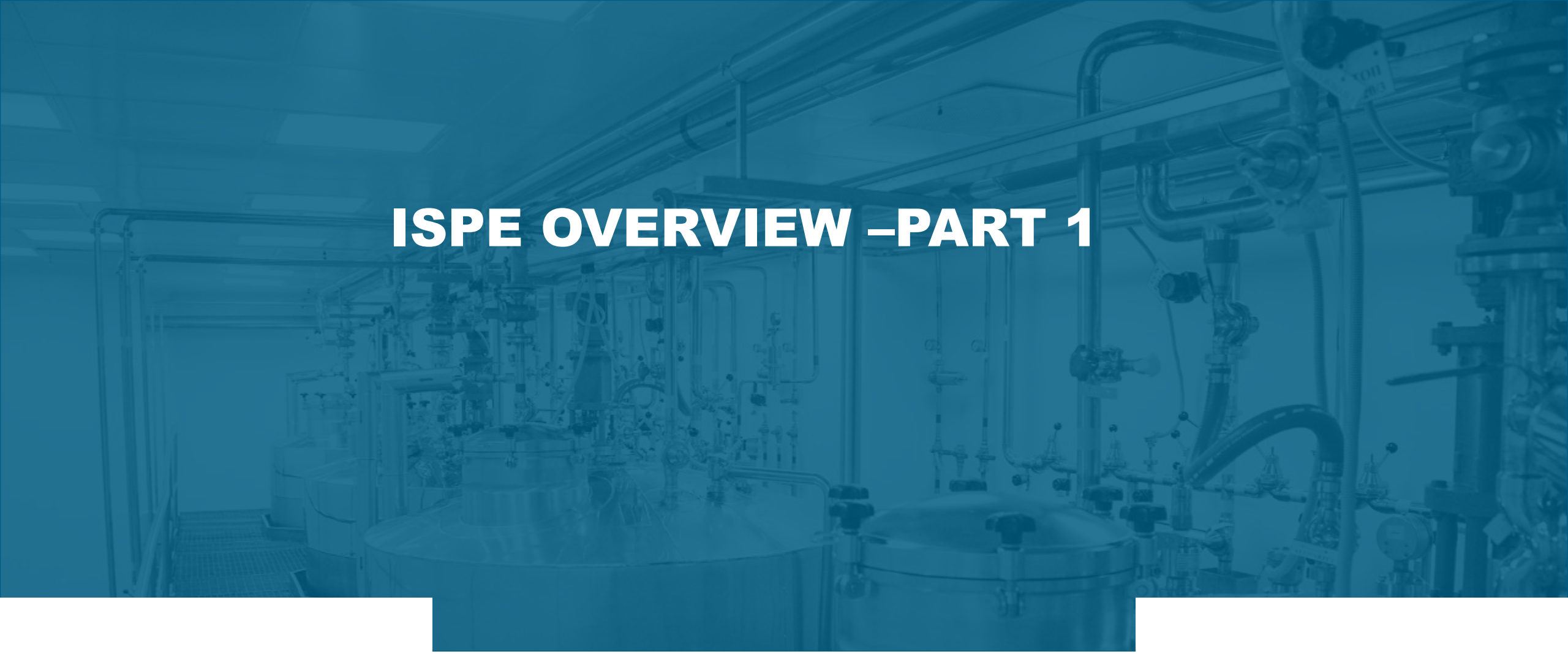
WHEN YOU NEED TO MEET A HIGHER STANDARD™

AGENDA

- Part 1- ISPE introduction
- Part 2- Introduction- Regulatory Basis Quality Data/Data integrity
- Part 3 -Data Integrity Overview
- Part 4 -The Holistic Approach- Implementation in Practice

Introductions

- B.Sc Biotechnology
- phD Cancer Research multiple drug resistance
- Masters in Project Management
- 9+ Years – Sandoz/Novartis
- 13* Years Professional Engineering and CQV services.
- 6+ Years VP for CAI.
- 2 Years on ISPE International Board of Directors
- 7 Years on the C&Q COP/Biotech/Disposables
- SME for CQV, Technology Transfer, QRM / Risk Based C&Q Topics



ISPE OVERVIEW –PART 1

WHEN YOU NEED TO MEET A HIGHER STANDARD™

ISPE Purpose Statement

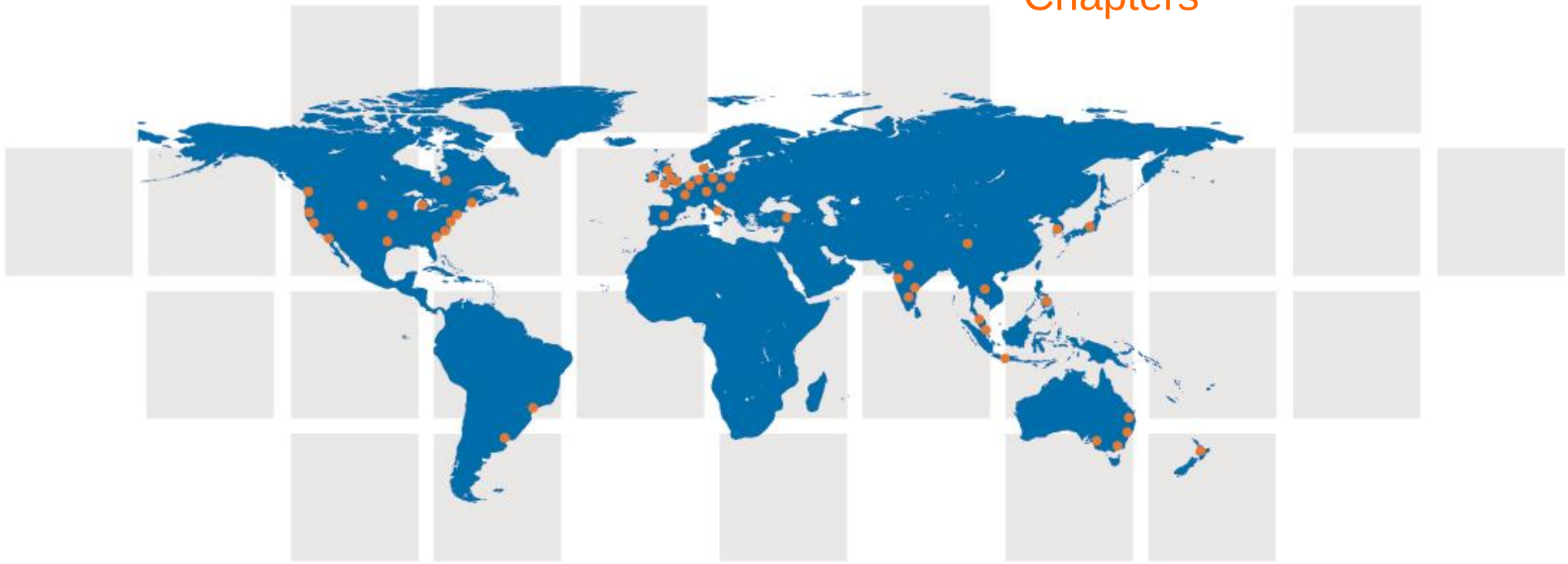
ISPE delivers technical
and operational solutions to support our
Members across the global pharmaceutical
and biopharmaceutical industry in the
manufacture of quality medicines for patients

ISPE Global Presence

18,500+ Members

90 Countries

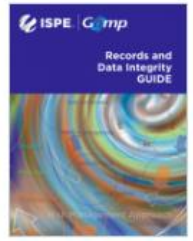
38 Affiliates and Chapters



GUIDANCE DOCUMENTS – BASELINE GUIDES

- Volume 1 – API
- Volume 2 – OSD
- Volume 3 – Sterile
- Volume 4 – Water and Steam Systems
- Volume 5 – C&Q
- Volume 6 – Biopharma
- Volume 7 – Risk Based Manufacture of Pharmaceutical Products (Risk-MAPP)
- GAMP 5 and associated guides

GAMP 5 Guide: Compliant GxP Computerized Systems



GAMP Guide: Records & Data Integrity

24 Good Practice Guides

Topics Include

- *Maintenance*
- *Process Gases*
- *Ozone Sanitization of Water systems*
- *Packaging and Labeling*
- *HVAC*
- *Good Engineering Practices*
- *Risk Based C&Q*

DATA INTEGRITY: PART 2

WHEN YOU NEED TO MEET A HIGHER STANDARD™

A BIT OF HUMOUR !

WHAT ARE PHARMA'S/MED TECH'S BIGGEST CHALLENGES?

1. **Focused on Compliance and not quality -Global harmonization slow**
2. **Data integrity is an issue**
3. **Silo and fragmentation of functions**
4. **Quality culture- is it inherent?**
5. **QRM is deployed in consistently**
6. **Lack of focus on the science and the *'voice of the product'***
7. **Knowledge management is limited or underdeveloped**
8. **Technology transfer is not optimized**

ARE THE DRUGS WE MAKE SAFER NOW ?

ICHQ8
ICHQ9
ICHQ10

FDA 21st century initiative

Draft ICHQ12

EMEA PV

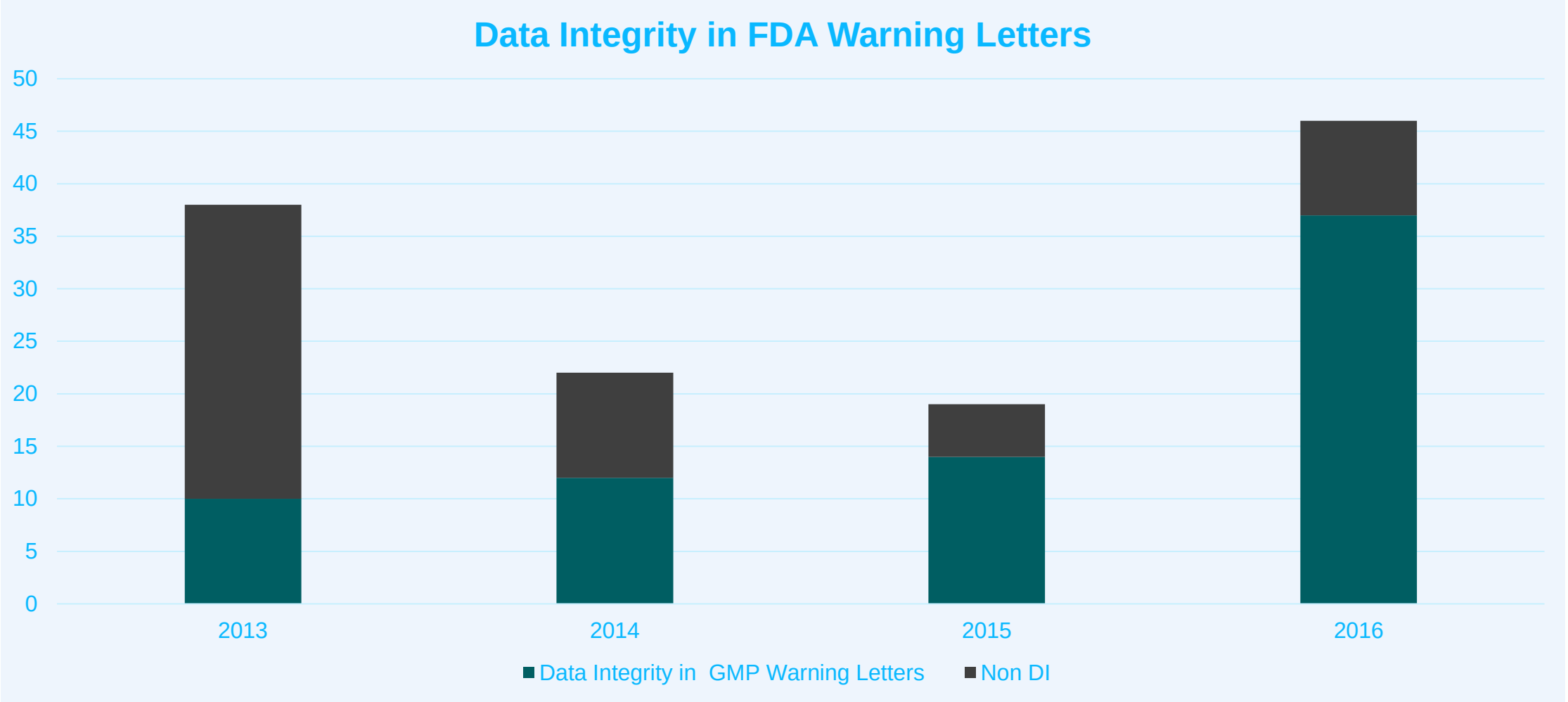
FDA PV Guide

FDA CITATIONS
2006 VS 2016

Center Name	483 issued
Foods	2452
Devices	887
Drugs	649
Incidental text	418
Biologics	299
Bioresearch monitoring	286
Parts 1240 and 1250	204
Veterinary medicine	202
Human tissue for transplantation	86
Special requirements	12
Radiological health	2
Sum Product Area 483s from System*	5497
Actual Total in system 483s**	4849

Center Name	483s Issued
Biologics	123
Bioresearch monitoring	283
Devices	1008
Drugs	678
Foods	2300
Human tissue for transplantation	81
Parts 1240 and 1250	66
Radiological health	17
Veterinary medicine	294
Sum Product Area 483s from Syst	**4850**
Actual Total in System 483s**	**4751**

DATA INTEGRITY WARNING LETTERS



DATA INTEGRITY OVERVIEW –PART 3

WHEN YOU NEED TO MEET A HIGHER STANDARD™

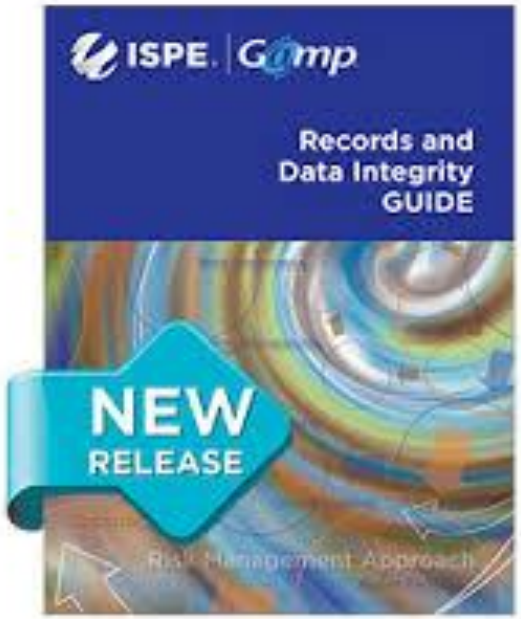
WHAT IS DATA INTEGRITY

The extent to which all data are complete, consistent and accurate throughout the data lifecycle

WHAT IS DATA INTEGRITY

- FDA Draft Guidance (April 2016)
  - *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)*
- World Heath Organization
  - *The degree to which a collection of data is complete, consistent and accurate throughout the data lifecycle.*
  - *The collected data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.*
- *MHRA*
  - *The extent to which all data are complete, consistent and accurate throughout the data lifecycle.*

GAMP RECORDS AND DATA INTEGRITY GUIDE- NEW….



\+ Gamp 5

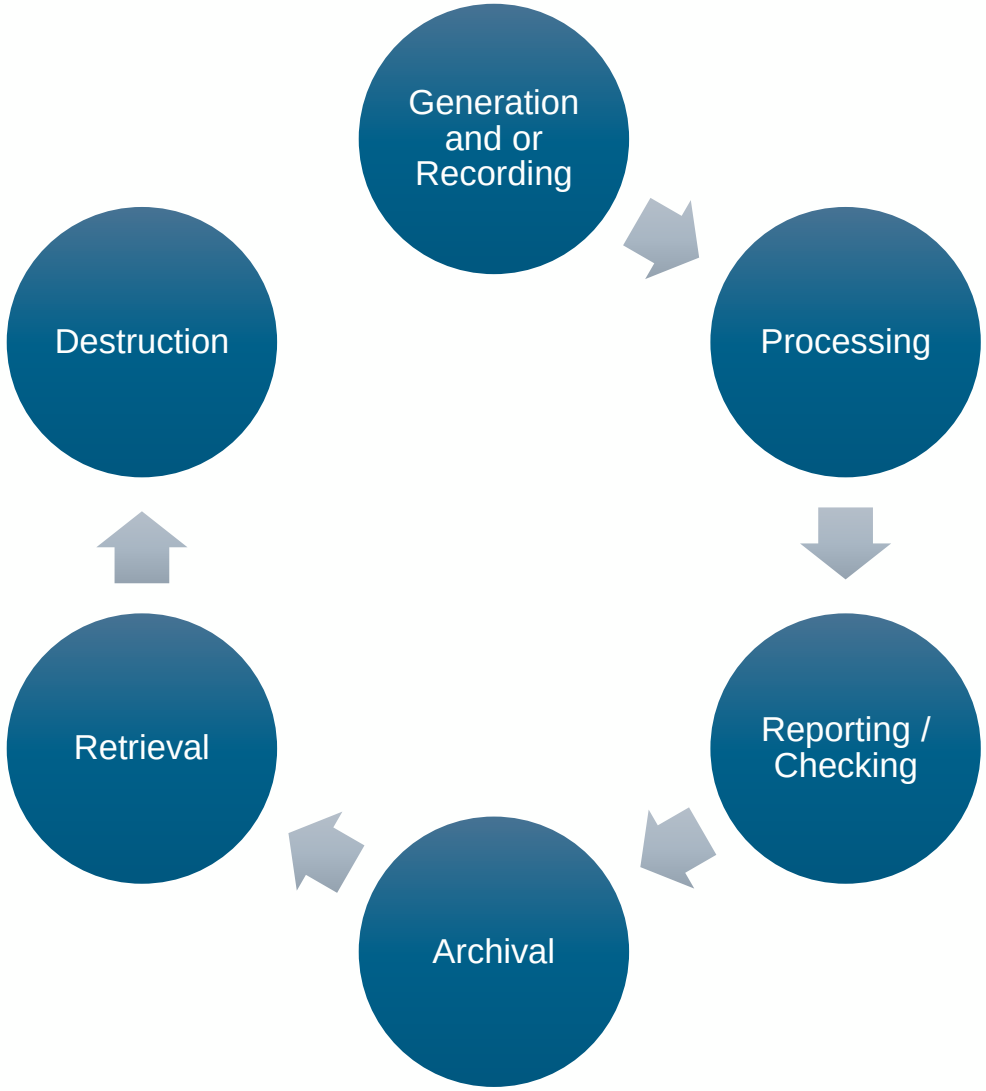
Mark Newton Associate Senior Quality Assurance Consultant, Eli Lilly and Company.

"Together, they provide a comprehensive overview of concepts necessary to create data with integrity and quality. The elucidation of the data life cycle, a maturity model "

GAMP DATA INTEGRITY GUIDE- APRIL 2017

- Governance and Management
- Procedure and technical controls
- Human Factors

DATA LIFECYCLE



EXPECTATIONS OF DATA

- Data should be:

Attributable

Legible

Contemporaneous

Original

Accurate

ATTRIBUTABLE

- Simply put, attributable means that the data should be linked to its source. It should be attributable to the individual who observed and recorded the data, as well as traceable to the source of the data itself.

LEGIBLE

- Data must be readable. It also implies that data must be recorded permanently in a durable medium. If changes are made, the changes must not obscure the original entry.
- For electronic records, legibility can be interpreted to mean “The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency” (21 CFR 11.10(b))

CONTEMPORANEOUSLY RECORDED

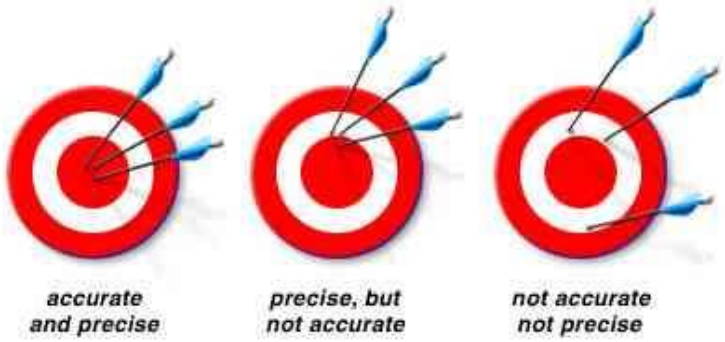
- Refers to the time the data is recorded with respect to the time that the observation is made. The data should be recorded at the time it is observed. There should be close proximity to occurrence.

ORIGINAL OR TRUE COPY

- Original data is generally considered to be the first or initial observation or recording of the data. It is therefore considered to be the most accurate and reliable representation of the data. The terms source data or raw data express this concept of first or initial observation or recording of the data.
- If the original data is not preserved, there must be a justification why it could not be preserved
- If the data is a copy, it must be a certified copy

ACCURATE

- Accurate means free from error or conforming exactly to truth or to a standard
- The data must correctly reflect the action taken or the observation made
- The data should be checked where necessary
- Corrections to the data must be documented where not self evident



DATA INTEGRITY: TWO BUCKETS

Intentional

Purposeful falsification or manipulation of data

- Failed requirements are made to appear acceptable during reporting
- Knowingly reporting incorrect information
- Deliberate deviation from procedure(s) combined with the plan to conceal the deviation

Unintentional

Bad business practices, mistakes, lack of understanding

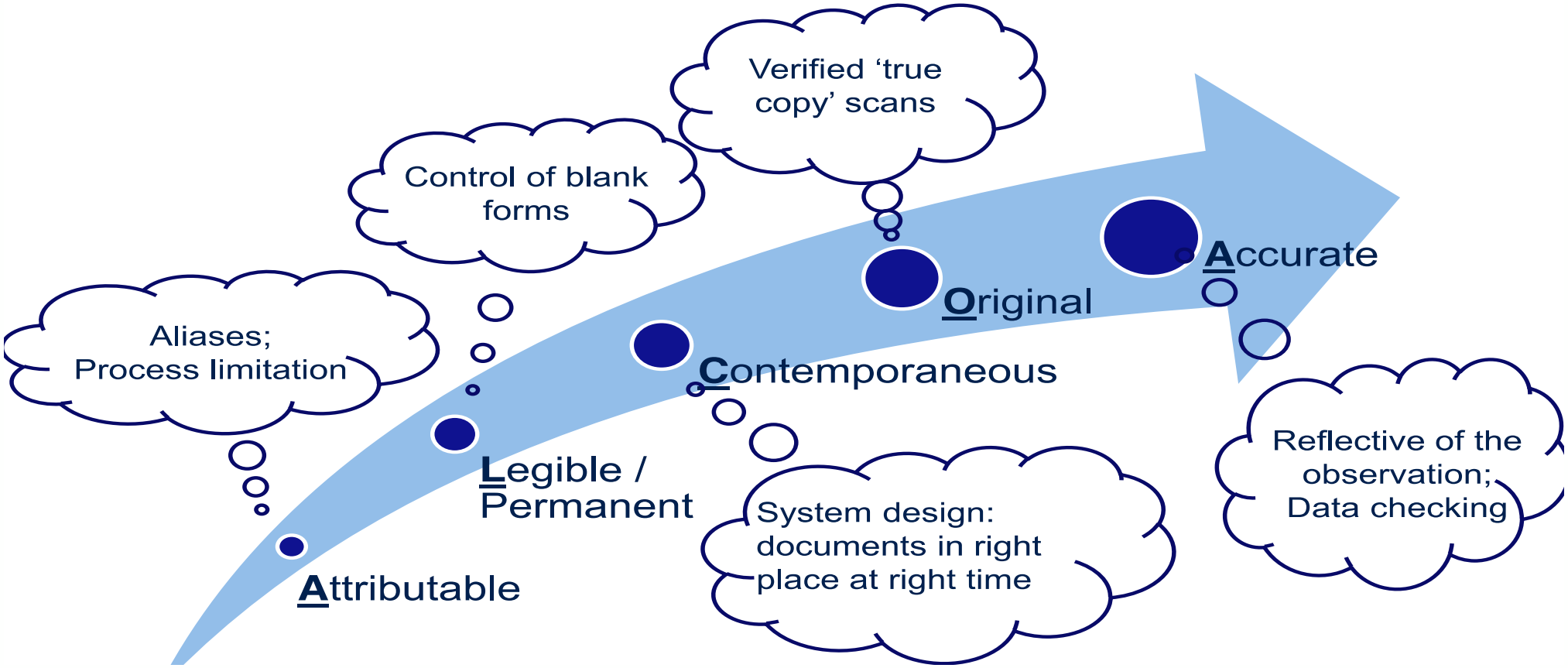
- Not recording all data (due to Systems and/or Procedures being inadequate or inadequate training)
- Discarding data or records believed to be no longer needed
- **Human errors during recording and/or data entry**

HOW DO WE ENSURE DATA INTEGRITY ?

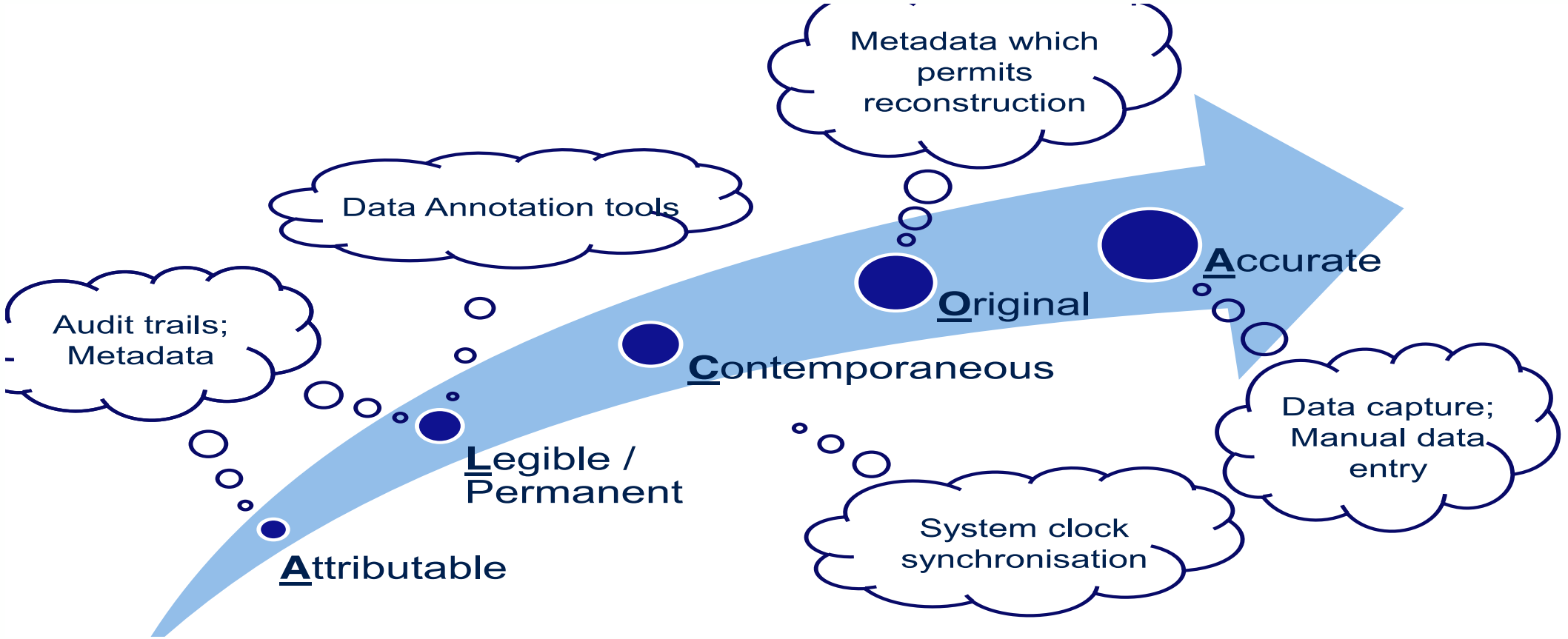
- Asses the Risk of Current Data available / used onsite:

Increased Risk Situations	Reduced Risk Situations
• Complex • Inconsistent • Open-ended • Subjective • Manual process or human interface • Stand-alone Computerized system* • Flat file*	• Simple • Consistent • Well defined • Objective • Automated • Networked Computerised system* • Relational database.*

DESIGNING COMPLIANT SYSTEM: PAPER



DESIGNING A COMPLIANT SYSTEM: ELECTRONIC



ALCOA +

- Complete, Consistent, Enduring, and Available.

- **ALCOA+ may be considered the data quality attributes that are focused on establishing and monitoring the support processes around data activities, continuous improvement and overall product quality.**

ALCOA +

- Complete, Consistent, Enduring, and Available.

Principle	Data Expectation
Complete	• All data, and relevant metadata, including any repeat or re-analysis performed
Consistent	• Application of good documentation practices throughout any process • The application of date and time stamps in the expected sequence
Enduring	• Recorded in a permanent, maintainable form for the retention period
Available	• Available and accessible for review, audit, or inspection throughout the retention period

EXAMPLES OF REGULATORY CITATIONS

FDA Example 1 – Wockhardt, Ltd. (India) – 23-Dec-2016

- Your firm failed to exercise appropriate controls over computer or related systems to assure that **only authorized personnel institute changes** in master production and control records, or other records (21 CFR 211.68(b)). → ***Accurate / Attributable***

FDA Example 2 – Sekisui Medical Co., Ltd. (Japan) – 08-Nov-2016

- Our investigator observed that your laboratory systems lacked controls to prevent **deletion of and alterations to electronic raw data**. → ***Accurate / Attributable***

EXAMPLES OF REGULATORY CITATIONS

- FDA Example 3 – Gopaldas Visram & Co. Ltd. (India) – 17-May-2017
- **Login details** for the QA Manager were shared with a delegate. → ***Attributable***
- Employees have **administrator rights** to GMP related software. → ***Accurate***

- EMA Example 4 – Chongqing Succeway Pharm. CO LTD (Ch) 17-Jul-2017
- Critical: **manipulation, backdating and falsification** of GMP documents such as batch manufacturing record, report of starting material manufacturer audit, GC and HPLC chromatograms. → ***Accurate, Complete***

MHRA TRENDS 2016 REPORT

Annex 11 - Deficiency examples

Deficiencies related to data backup:

- Following a software update, data was lost from an autoclave control system. The system backup was unable to recover lost data as the backup was only performed on a 3 monthly basis.
- The backup CD/DVD for the autoclave control system was not stored within a controlled environment to assure its integrity.
- Data from the integrity test was not backed up. The system was observed to overwrite previous data.
- Backups were required to be reviewed for accessibility annually for 5 years however this failed to ensure that data that is required to be stored for longer such as validation data, was accessible for its full retention period.
- Backups were permitted to be made on the same computer drive which failed to ensure that a separate copy was available following drive failure or corruption.

MHRA TRENDS 2016 REPORT

Annex 11 - Deficiency examples

Deficiencies related to inadequate control of computerised systems:

- Access to files and the system clock on the hard drive were available to all users.
- The lock screen used a shared password. If a user had logged into the software behind the lock screen and another user opened the computer, they could perform actions under the initial user's login.
- Users had more authorisation on the chromatography data system than was permitted according to the SOP.
- Access control systems were not considered GMP systems despite their intended purpose to control access to GMP areas.

MHRA TRENDS 2016 REPORT

Annex 11 - Deficiency examples

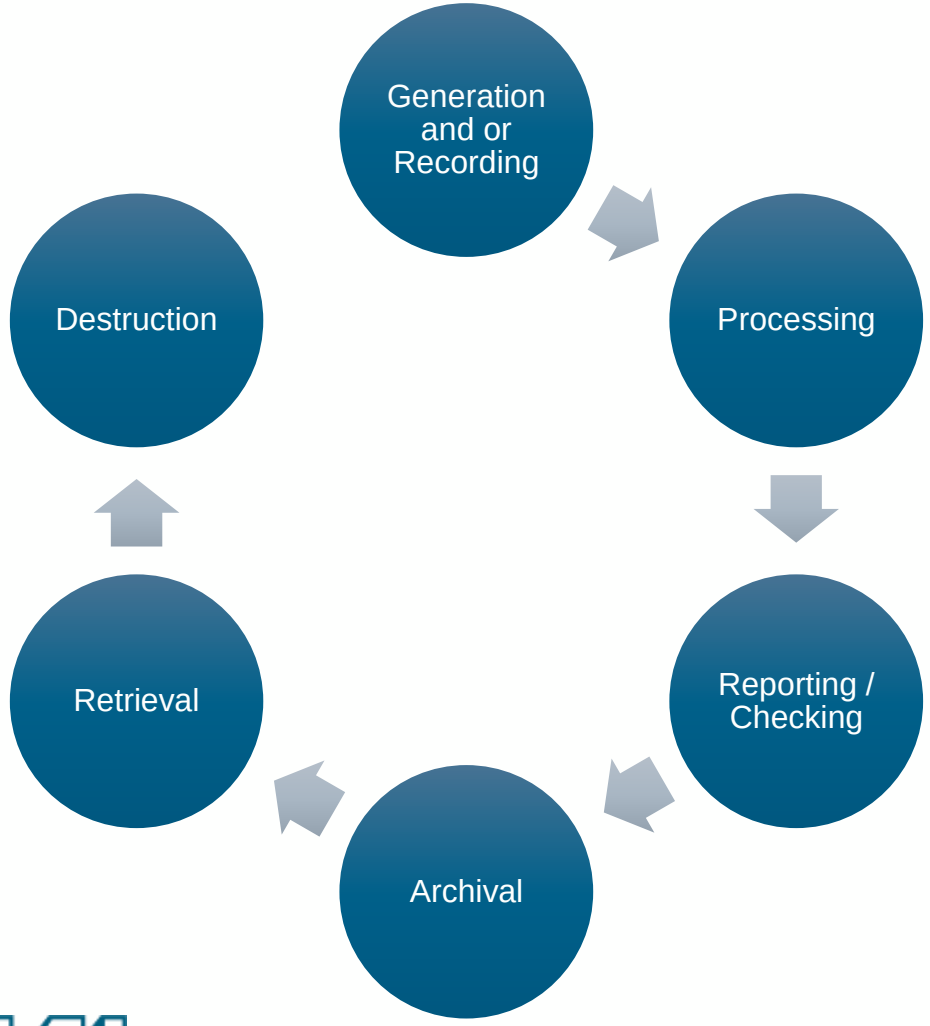
The HPLC software within the laboratory was not configured for GMP compliance:

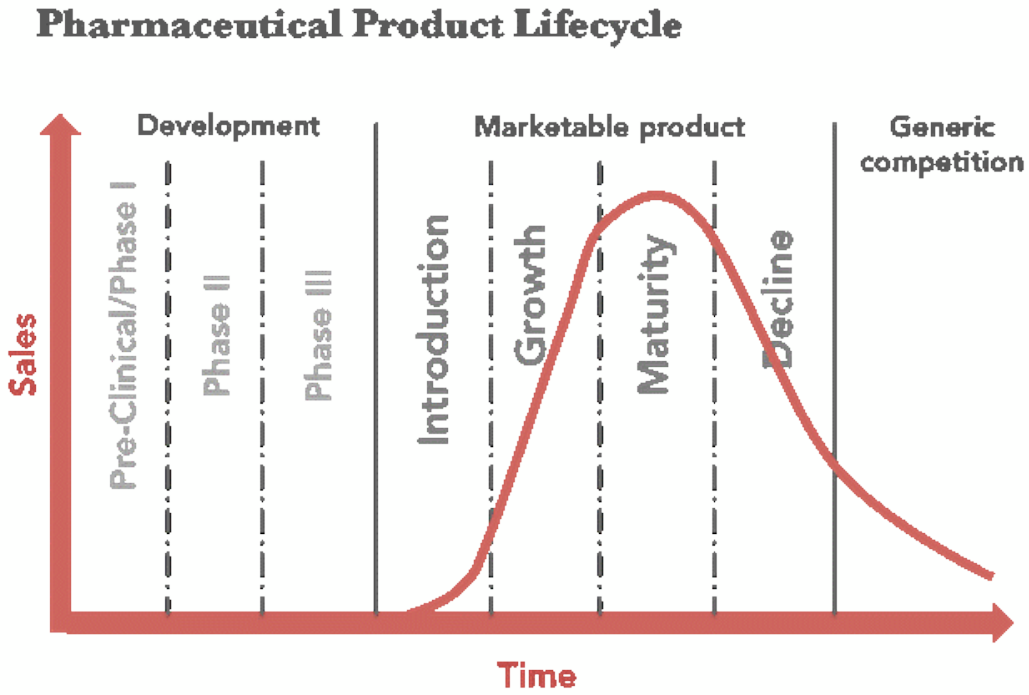
- Unique user passwords were not enforced.
- Users were permitted to change the default audit trail.
- Users were permitted to change the default “require user comments”.
- Users were permitted to copy non-related projects.
- Users were permitted to use annotation tools.

THE HOLISTIC APPROACH–PART 4A

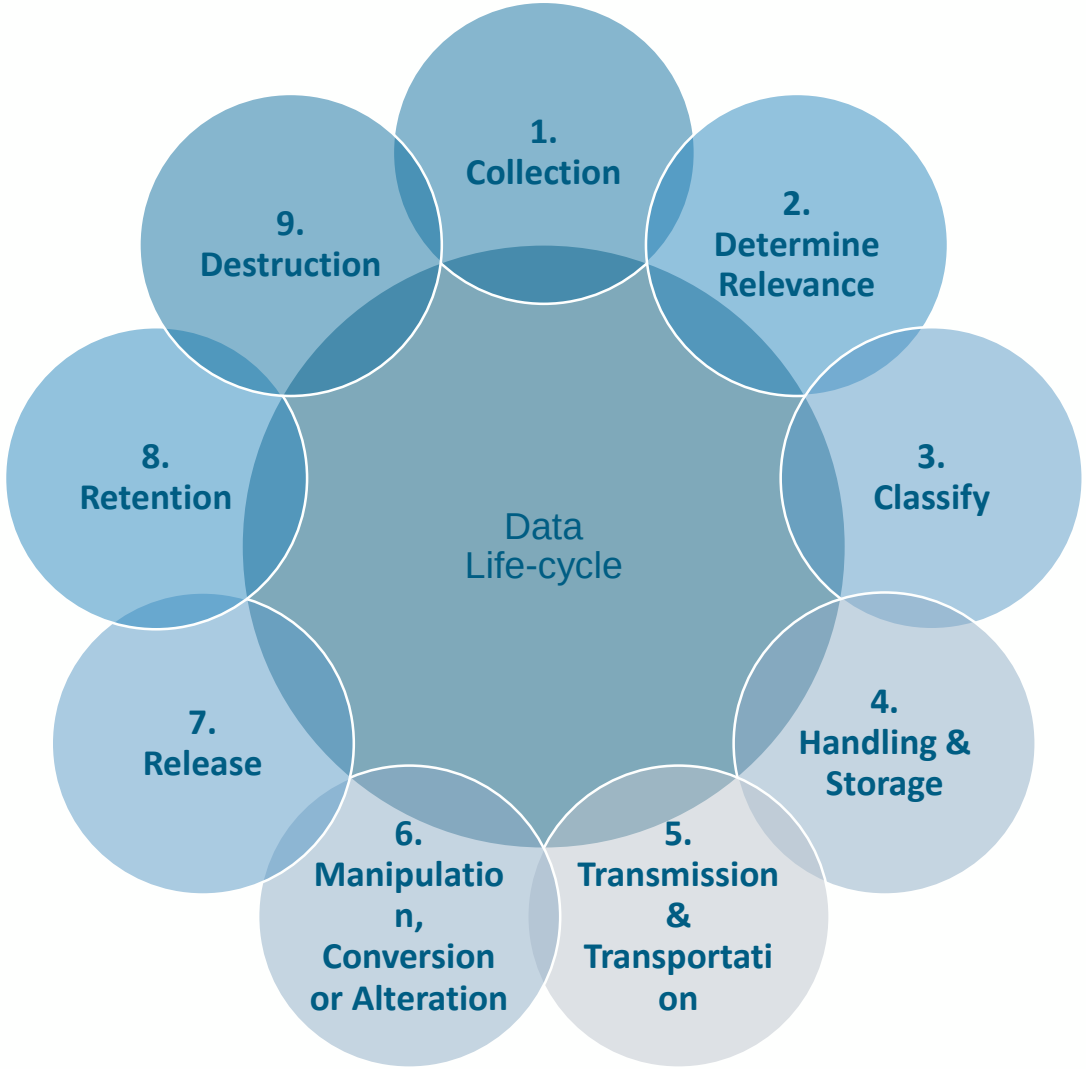
WHEN YOU NEED TO MEET A HIGHER STANDARD™

DATA LIFECYCLE—DRUG LIFECYCLE





DATA LIFE-CYCLE- MORE DETAIL



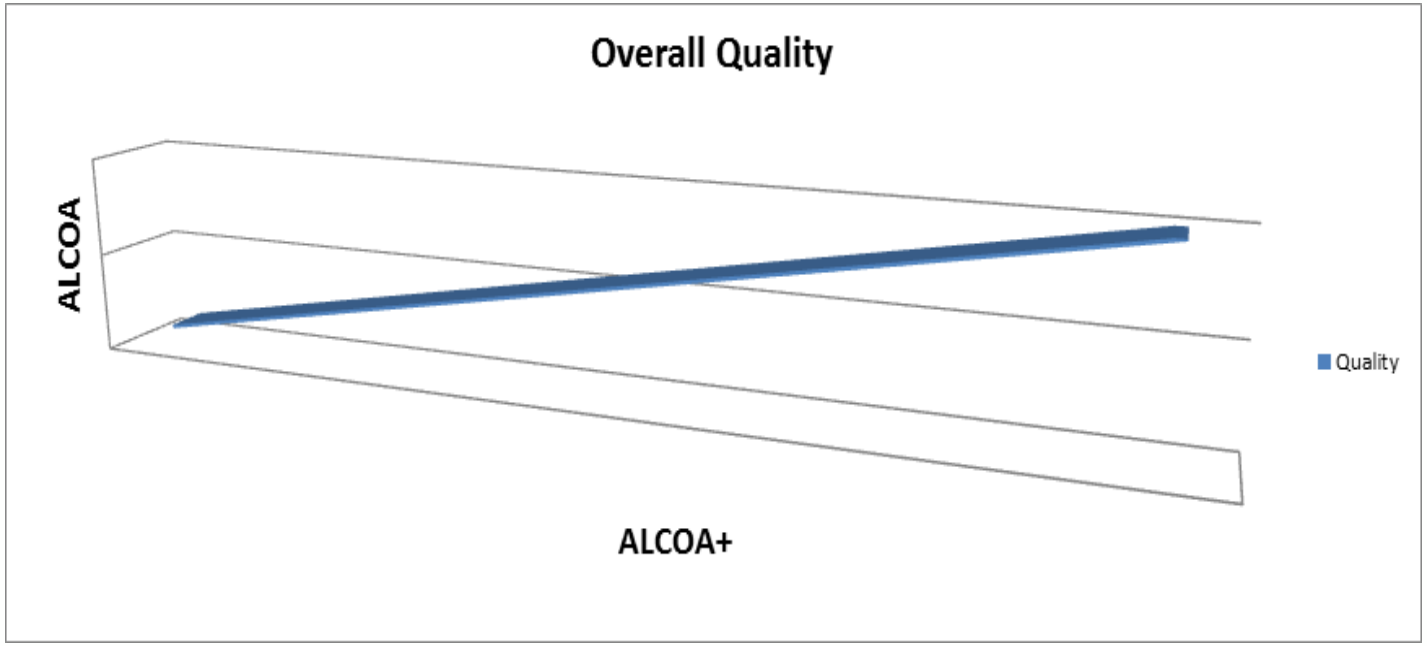
LETS PUT ALL OF THIS INTO CONTEXT !

So in order to achieve overall data quality and associated product quality, one must have both ALCOA and ALCOA+.

Product Quality is directly associated with Data Quality

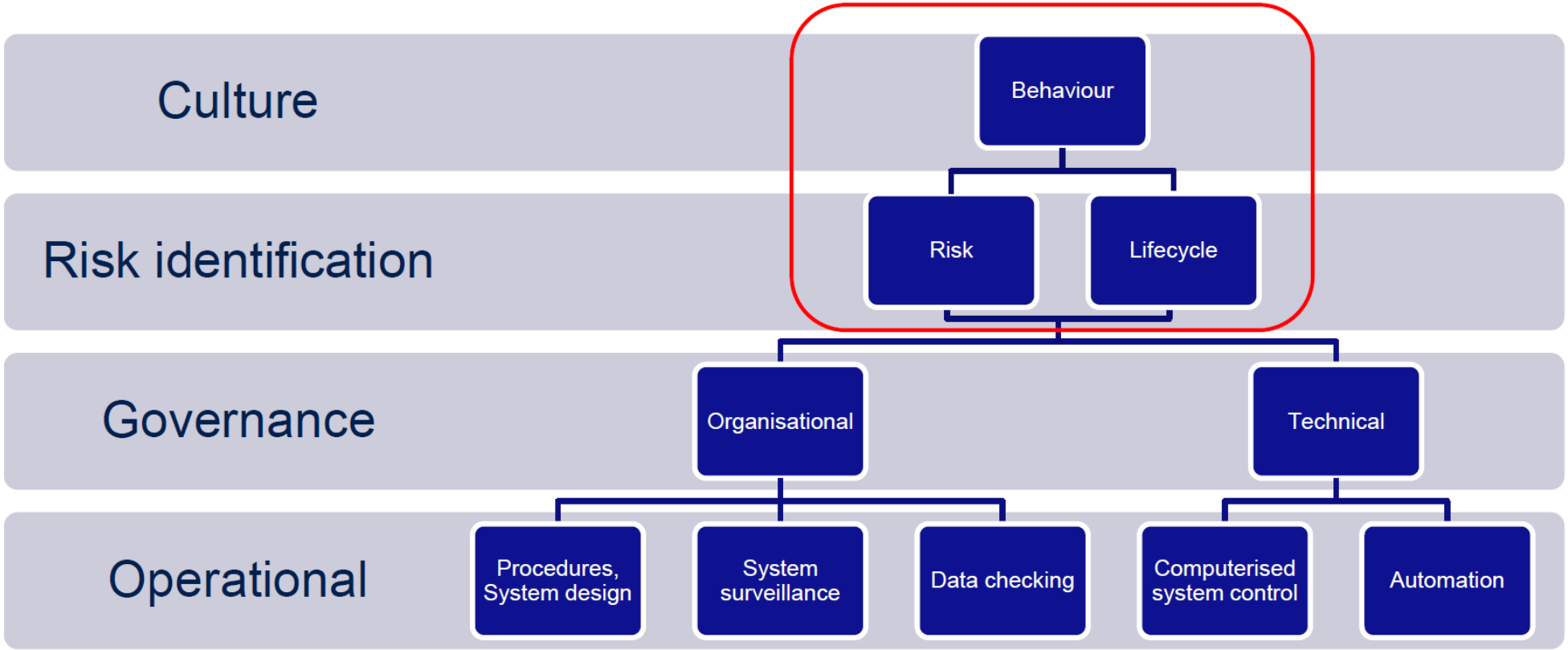
OVERALL QUALITY RELATIONSHIP

Attributable,
Legible,
Contemporaneous,
Original
Accurate

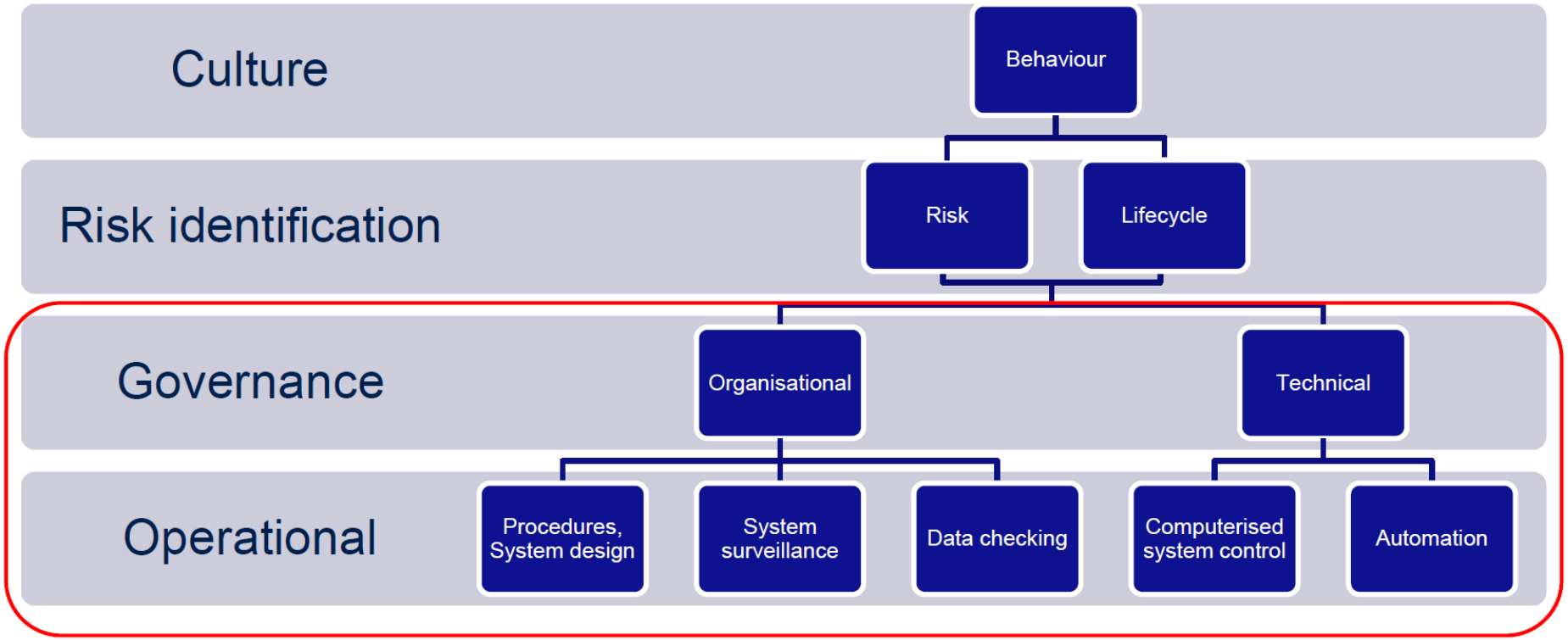


Lifecycle- Complete, Consistent, Enduring, and Available.

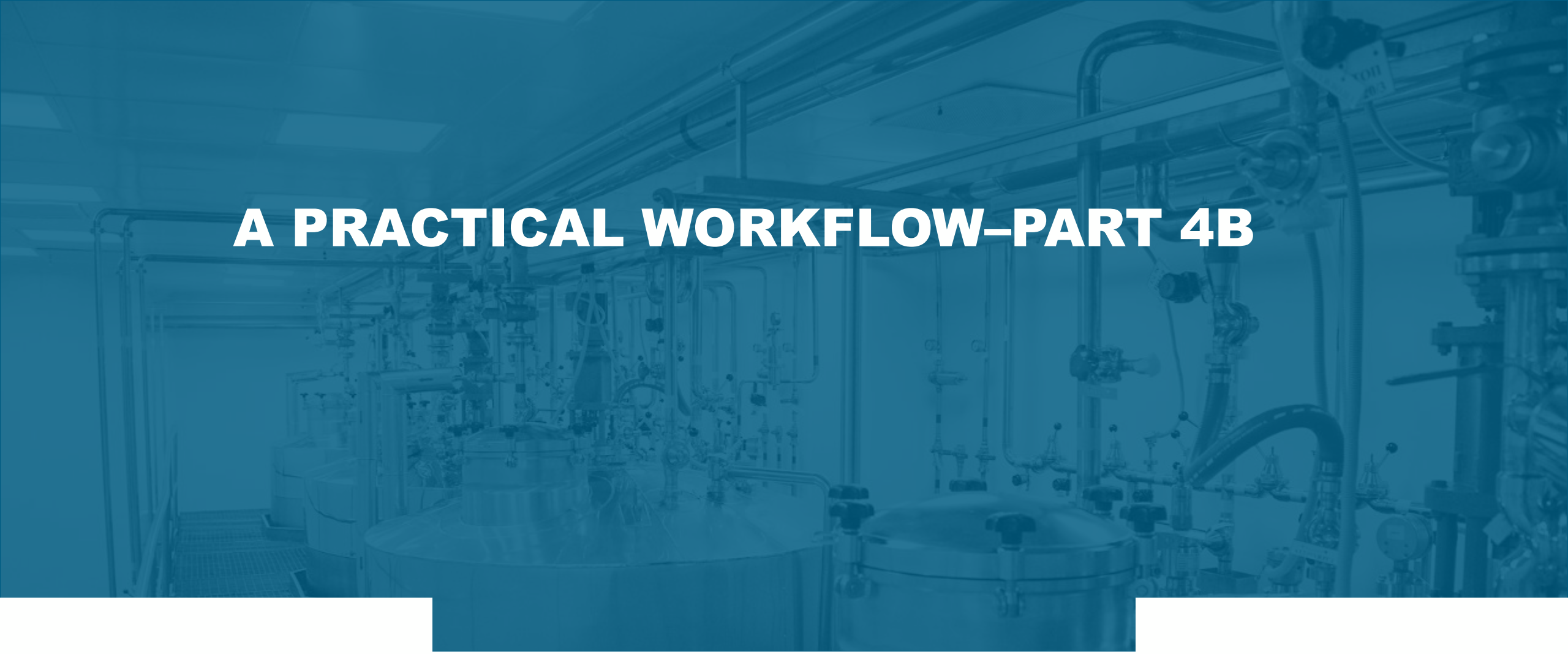
GOVERNANCE OVERSIGHT MODEL --THE HOLISTIC APPROACH



RISK REDUCING STRATEGIES



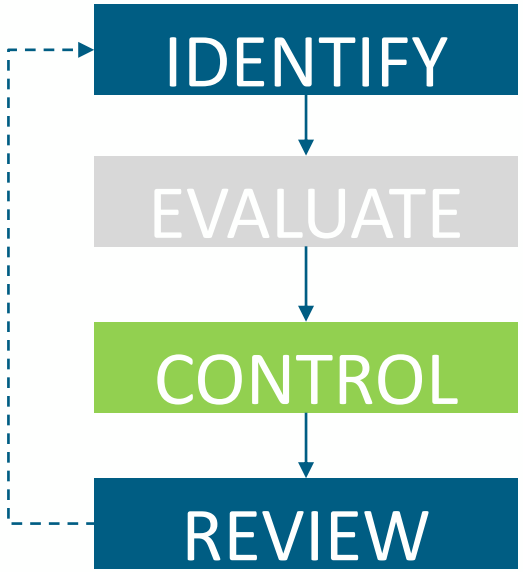
GMPs; Data Integrity Guidance documents



A PRACTICAL WORKFLOW–PART 4B

WHEN YOU NEED TO MEET A HIGHER STANDARD™

DI INVESTIGATIVE APPROACH



- Clarify scope & extent
- Severity & Root causes
- Deviation, Response & CAPA
- Vigilance, Governance & Management

DI INVESTIGATIVE STEPS

IDENTIFY

- **Identify Primary factors associated with DI issue**
  Environment, People, Process, System
- **Identify lifecycle stages associated with DI issue**
  Creation, Processing, Review, Reporting, Retention, Retrieval
- **Identify type of information associated with DI issue**
  Identification, Measurement, Activity-Event, Descriptive, Instruction- Methodology, Setup-Control, Meta data

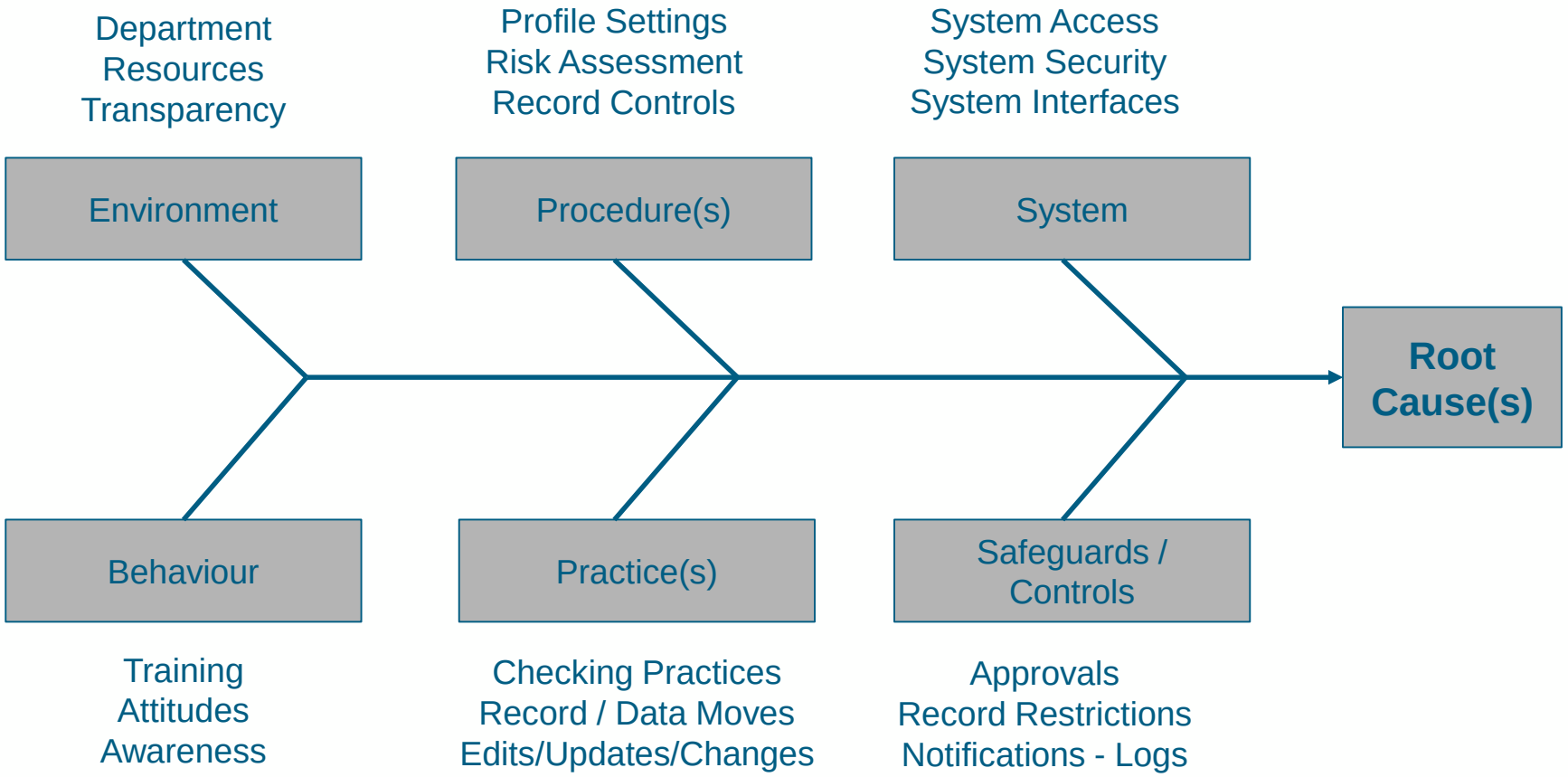
DI INVESTIGATIVE STEPS

EVALUATE

- Evaluate impact of DI issue
  (Direct-Product, Direct-Support, Indirect Support)
- Evaluate, Determine root cause of DI issue (System, Human)
- Evaluate DI Issue context - Non-intentional / Intention
- Evaluate, determine DI failing attributes
  (Attributable, Legible, Contemporaneous, Original, Accurate)

DI INVESTIGATIVE STEPS

EVALUATE



DI INVESTIGATIVE STEPS

CONTROL

- Controls approach for DI issue (Intervention, Control, Improvement)
- Controls escalation approach for DI issue
- Deviation and CAPA Management
- Control actions for DI issue (Environment & Behaviour) (Procedure & Practice) (Technical & Safeguards) (Oversight)

Improve
control
Intervention

Management level	Reporting measures
Department or function lead System / Data Owner	As part of quality management system and/or operational excellence (improvement)
Department or function lead Site quality function System / Data Owner	As part of quality management system and/or specific system action plan
Department or function lead Site quality function System / Data Owner	As part of quality management system and/or specific system action plan
Senior Management Department or function lead Site quality function System / Data Owner	As part of quality council review Specific system action plan As part of site risk 'profile'
Senior Management Department or function lead Site quality function System / Data Owner	As part of quality council review Specific system action plan As part of site risk 'profile'

DI Investigative Steps

REVIEW

Routine - Internal audit and progress review of activities

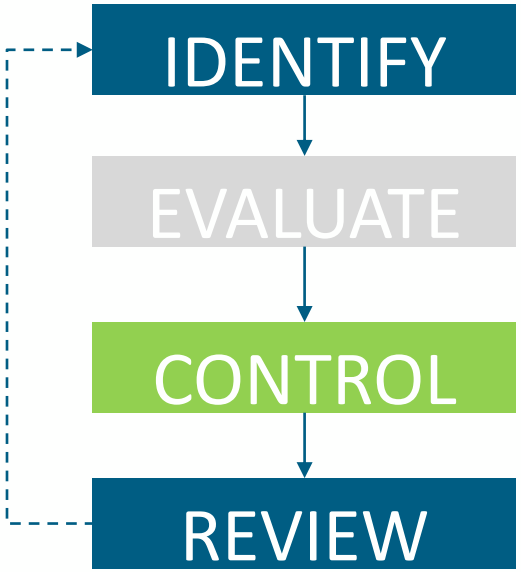
Routine - Internal audit and progress review of activities

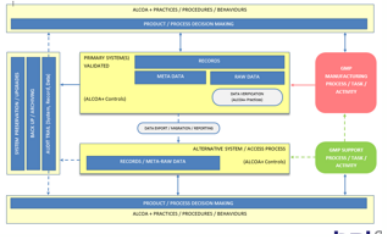
Escalated - Weekly review of action plan, assessment of use and processed product

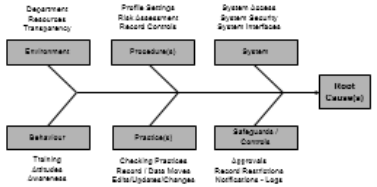
Escalated - Weekly review of action plan, daily assessment of use and processed product

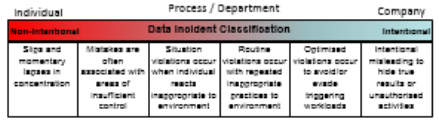
Highest escalation - Immediate actions relating to use and processed product

REVIEW PROCESS









Corrective Action(s) | Preventative Action(s)

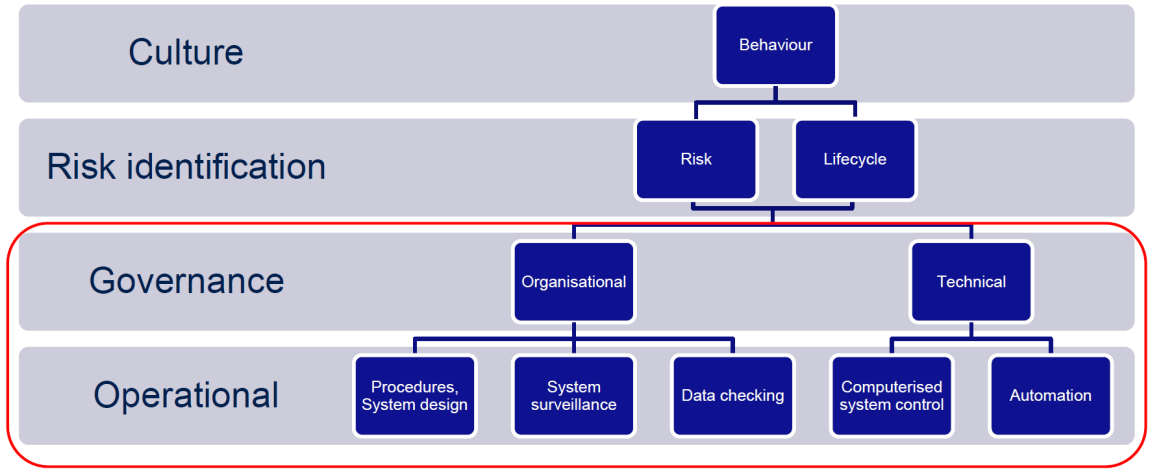
SUMMARY POINTS

- **DI is still a huge regulatory hot topic**
- **Build DI into each aspect of your PQS**
- Security, Audit Trails, Workflow are key considerations for DI
- Regulators have been clear on expectations
- An investigation process needs to be in place for DI
- Correct identification of System, Records, People, Lifecycle
- Root causes must be evaluated (Non-intentional / Intentional)
- Appropriate escalation and review relating to impact
- Lifecyle approach is key

SUMMARY

Technology in isolation, is not the answer

ALCOA+= *f {Culture, Risk, Governance, Ops}*



GMPs; Data Integrity Guidance documents

THANK YOU-QUESTIONS?

Alice Redmond

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