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GaBI Educational Workshops

1st ASEAN Overview Workshop on
GMP for BIOLOGICALS/BIOSIMILARS

5 August 2018, Furama Resort Da Nang, Vietnam

Data Integrity from an inspector's point of view

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5 August 2018

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1st ASEAN Overview Workshop on GMP for Biologicals/Biosimilars

Da Nang, Vietnam, 5 August 2018

Data Integrity From An Inspector's Point of View

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OVERVIEW AND OBJECTIVES

- ❑ What is data integrity?
- ❑ Why does data integrity matter?
- ❑ Where can you find the WHO guidance?
- ❑ What does WHO Data Integrity and Good Data and Record Management expect?
- ❑ Misconceptions & misunderstandings concerning data requirements?
- ❑ Examples of types of data integrity issues from PQ and other inspections
- ❑ Some concluding thoughts

WHAT IS DATA INTEGRITY?

- Ensuring data is recorded as intended
- Ensuring data is the same in content and meaning as it was when it was originally recorded – throughout the retention period
- Preventing unintentional or unauthorized changes to data

In a nutshell, data integrity is the degree to which a collection of data is ALCOA.

WHAT IS THE RELEVANCE OF DATA INTEGRITY TO WHO STAKEHOLDERS?

UNRELIABLE DATA = UNRELIABLE DECISIONS = POTENTIAL FOR HARM

To the physician and his/her patient?

The quality and completeness of data of clinical and scientific data (and implicitly that data's reliability) is the basis of all important programmatic and daily risk/benefit decisions regarding the selection and use of Healthcare Products

"To practice and prescribe to the best of my ability for the good of my patients, and to try to avoid harming them." (Hippocratic Oath, 4th c. BCE)

WHAT IS THE RELEVANCE OF DATA INTEGRITY TO WHO STAKEHOLDERS? UNRELIABLE DATA = UNRELIABLE DECISIONS = POTENTIAL FOR HARM

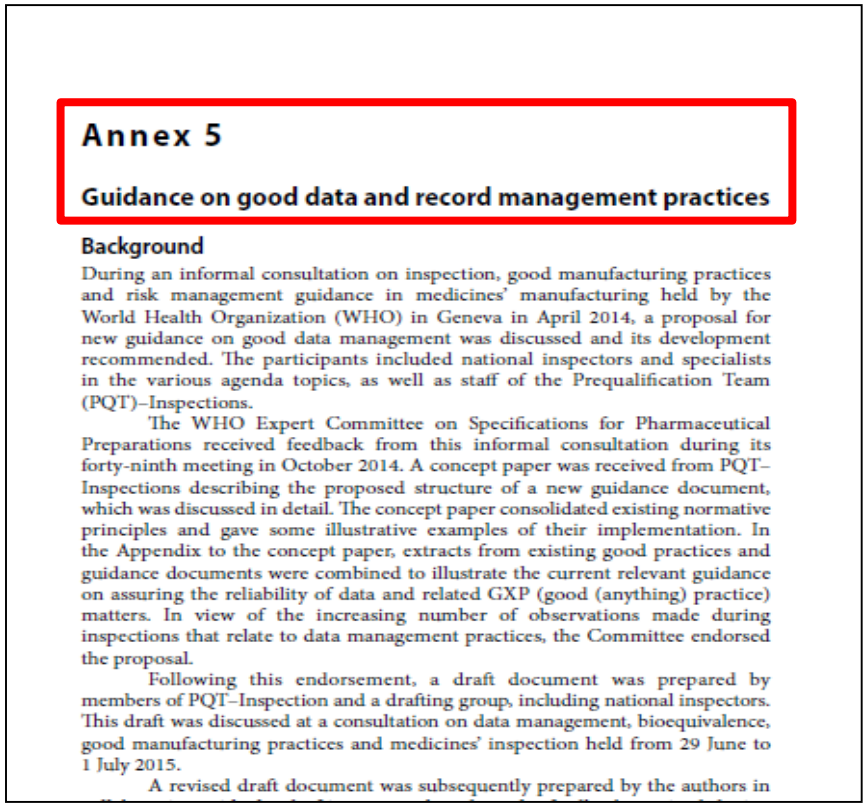
To national and international programmes, concerned NMRA and their assessors and Inspectors?

- Regulatory systems worldwide have always depended upon the knowledge of organizations that develop, manufacture and package, test, distribute and monitor pharmaceutical and biologics products.
- Implicit in the assessment and review process is a trust between the regulator and the regulated that the information submitted in dossiers and used in day-to-day decision-making is comprehensive, complete and reliable.
- DIRECT HARM TO PATIENTS
- LOSS IN TRUST IN THE EFFECTIVENESS OF PRODUCTS
- LOSS IN TRUST IN THOSE THAT RECOMMEND THEM
- ……. AND THOSE THAT SUPPLY THEM

WHERE CAN I FIND WHO EXPECTATIONS ON GOOD DATA AND RECORD MANAGEMENT PRACTICES?

"Good data and record management are critical elements of the pharmaceutical quality system and a systematic approach should be implemented to provide a high level of assurance that across the product life cycle all GxP records and data are accurate, consistent, trustworthy and reliable.

The data governance programme should include policies and governance procedures that address the general principles listed below for a good data management program."



Annex 5

Guidance on good data and record management practices

Background

During an informal consultation on inspection, good manufacturing practices and risk management guidance in medicines' manufacturing held by the World Health Organization (WHO) in Geneva in April 2014, a proposal for new guidance on good data management was discussed and its development recommended. The participants included national inspectors and specialists in the various agenda topics, as well as staff of the Prequalification Team (PQT)–Inspections.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations received feedback from this informal consultation during its forty-ninth meeting in October 2014. A concept paper was received from PQT–Inspections describing the proposed structure of a new guidance document, which was discussed in detail. The concept paper consolidated existing normative principles and gave some illustrative examples of their implementation. In the Appendix to the concept paper, extracts from existing good practices and guidance documents were combined to illustrate the current relevant guidance on assuring the reliability of data and related GXP (good (anything) practice) matters. In view of the increasing number of observations made during inspections that relate to data management practices, the Committee endorsed the proposal.

Following this endorsement, a draft document was prepared by members of PQT–Inspection and a drafting group, including national inspectors. This draft was discussed at a consultation on data management, bioequivalence, good manufacturing practices and medicines' inspection held from 29 June to 1 July 2015.

A revised draft document was subsequently prepared by the authors in

WHERE CAN I FIND MORE EXPECTATIONS ON GOOD DATA AND RECORD MANAGEMENT PRACTICES?

- US Codes of Federal Regulations (CFRs) covering GCP, GLP, GMP, and medical devices
- US CFR regulation 21 CFR Part 11, and associated guidance
- Relevant sections of EU GMPs including Chapter 4 and Annex 11
- MHRA GMP Data Integrity Definitions and Guidance for Industry, Revision 1.1 March 2015
- MHRA GxP Data Integrity Definitions and Guidance for Industry, Draft version for consultation July 2016
- FDA -Data Integrity and Compliance With CGMP -Draft Guidance for Industry
- PIC/S Guidance –Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, Draft Published August 2016
- PDA (code of conduct for data integrity)

WHAT DOES WHO DATA INTEGRITY AND GOOD DATA AND RECORD MANAGEMENT EXPECT?

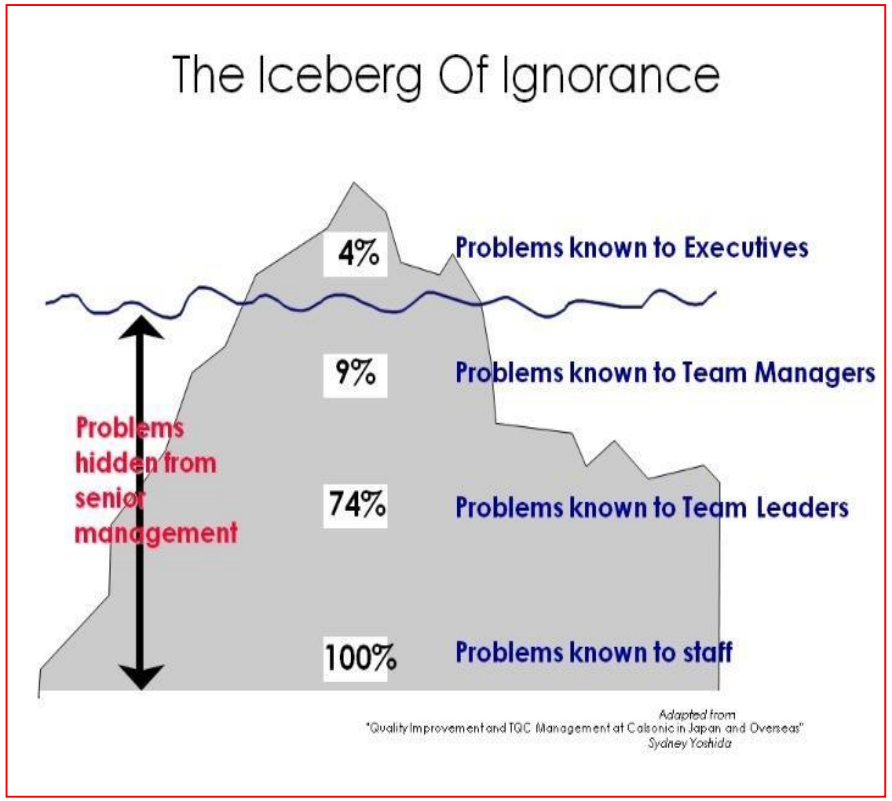
"Data integrity "is the degree to which a collection of data is complete, consistent, and accurate throughout the data lifecycle. The collected data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Assuring data Achieving data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices."

*"**Data Lifecycle**: **A planned approach** to assessing and managing risks to data in a manner commensurate with potential impact on patient safety, product quality, and/or the reliability of the decisions made throughout **all phases of the process** **by which data is created, processed, reviewed, analysed and reported, transferred, stored and retrieved, and continuously monitored until retired**".*

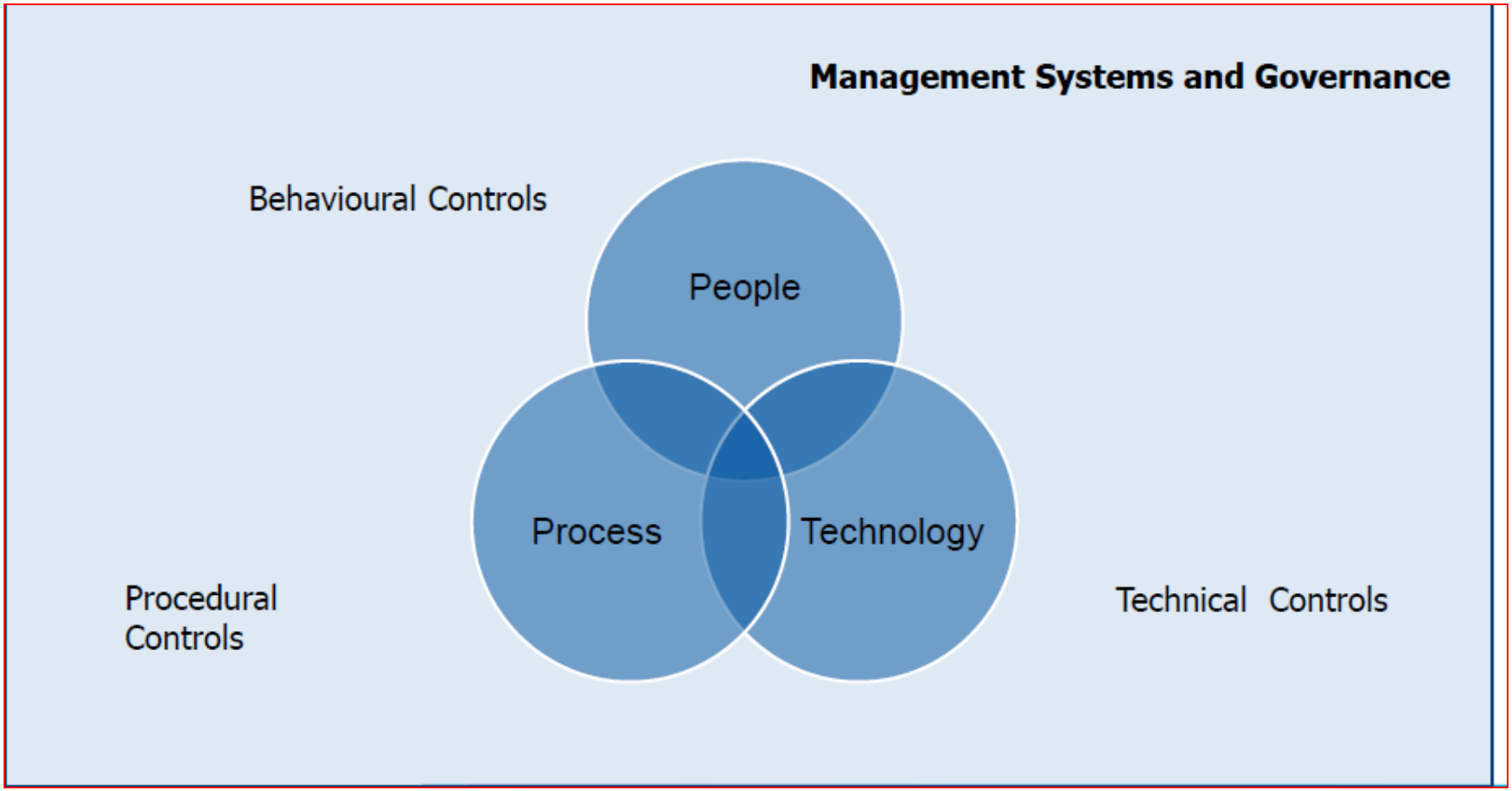
MANAGEMENT OVERSIGHT (GOVERNANCE) AND EMPOWERMENT

6.2 The building blocks of behaviors, procedural/policy considerations and basic technical controls together form the foundation of good data governance, upon which future revisions can be built.

- Management Oversight (Governance)
  - Provides philosophical and financial support to address risks
  - This often includes provision of funding to accomplish permanent fixes to problems
- Two Key Aspects
  1. Management Review (See *ICH Q10*)
  2. Escalation
  - When are problems escalated?
  - What is senior management's response when the problems are escalated?



MANAGEMENT OVERSIGHT (GOVERNANCE) AND EMPOWERMENT



APPENDIX - ALCOA PRINCIPLES AND WHAT THEY MEAN FOR ALL RECORDS AND DATA?

Appendix 1

Expectations and examples of special risk management considerations for the implementation of ALCOA (-plus) principles in paper-based and electronic systems

Organizations should follow good documentation practices (GDocP) in order to assure the accuracy, completeness, consistency and reliability of the records and data throughout their entire period of usefulness – that is, throughout the data life cycle. The principles require that documentation should have the characteristics of being attributable, legible, contemporaneously recorded, original and accurate (sometimes referred to as ALCOA).

The tables in this appendix provide further guidance on the implementation of the general ALCOA requirements for both paper and electronic records and systems. In addition, examples of special risk management considerations as well as several illustrative examples are provided of how these measures are typically implemented.

These illustrative examples are provided to aid understanding of the concepts and of how successful risk-based implementation might be achieved. These examples should not be taken as setting new normative requirements.

Attributable. Attributable means information is captured in the record so that it is uniquely identified as having been executed by the originator of the data (e.g. a person or computer system).

Attributable	
Expectations for paper records	**Expectations for electronic records**
Attribution of actions in paper records should occur, as appropriate, through the use of: • initials; • full handwritten signature; • personal seal; • date and, when necessary, time.	Attribution of actions in electronic records should occur, as appropriate, through the use of: • unique user logons that link the user to actions that create, modify or delete data; • unique electronic signatures (can be either biometric or non-biometric); • an audit trail that should capture user identification (ID) and date and time stamps; • signatures, which must be securely and permanently linked to the record being signed.

Special risk management considerations for controls to ensure that actions and records are attributed to a unique individual

- For legally-binding signatures, there should be a verifiable, secure link between the unique, identifiable (actual) person signing and the signature event. Signatures should be permanently linked to the record being signed. Systems which use one application for signing a document and another to store the document being signed should ensure that the two remain linked to ensure that the attribution is not broken.
- Signatures and personal seals should be executed at the time of review or performance of the event or action being recorded.
- Use of a personal seal to sign documents requires additional risk management controls, such as handwritten dates and procedures that require storage of the seal in a secure location with access limited only to the assigned individual, or equipped with other means of preventing potential misuse.
- Use of stored digital images of a person's handwritten signature to sign a document is not acceptable. This practice compromises confidence in the authenticity of these signatures when these stored images are not maintained in a secure location, access to which is limited only to the assigned individual, or equipped with other means of preventing potential misuse, and instead are placed in documents and emails where they can be easily copied and reused by others. Legally binding, handwritten signatures should be dated at the time of signing and electronic signatures should include the time/date stamp of signing to record the contemporaneous nature of the signing event.

APPENDIX - ALCOA PRINCIPLES AND WHAT THEY MEAN FOR ALL RECORDS AND DATA?

Contemporaneous

Contemporaneous data are data recorded at the time they are generated or observed.

Contemporaneous	
Expectations for paper records	**Expectations for electronic records**
Contemporaneous recording of actions in paper records should occur, as appropriate, through use of: • written procedures, and training and review and audit and self-inspection controls that ensure personnel record data entries and information *at the time of the activity directly in official controlled documents* (e.g. laboratory notebooks, batch records, case report forms); • procedures requiring that activities be recorded in paper records with the date of the activity (and time as well, if it is a time-sensitive activity); • good document design, which encourages good practice: documents should be appropriately designed and the availability of blank forms/ documents in which the activities are recorded should be ensured; • recording of the date and time of activities using synchronized time sources (facility and computerized system clocks) which cannot be changed by unauthorized personnel. Where possible, data and time recording of manual activities (e.g. weighing) should be done automatically.	Contemporaneous recording of actions in electronic records should occur, as appropriate, through use of: • configuration settings, SOPs and controls that ensure that data recorded in temporary memory are committed to durable media upon completion of the step or event and before proceeding to the next step or event in order to ensure the permanent recording of the step or event at the time it is conducted; • secure system time/date stamps that cannot be altered by personnel; • procedures and maintenance programmes that ensure time/date stamps are synchronized across the GXP operations; • controls that allow for the determination of the timing of one activity relative to another (e.g. time zone controls); • availability of the system to the user at the time of the activity.

EXAMPLES OF DATA INTEGRITY ISSUES-1

Microbiological trend results for filling line from January to April 2018 were presented. All the test results presented were within the specification including for grade A under RABS and aseptic room.

- At the request of the inspectors during the tour, the counting/reading of the environmental monitoring plates and media was conducted and cfu (s) were found for location under Grade A within the RABS.
- The inspectors requested to call back the plates and media that were discarded for incineration after being counted/read and to review these plates.
- As per spot check, the inspectors and the company representatives took out from the plastic bag some plates for counting/reading and cross checking with the recorded data. The recovered plates from the plastic bag located within filling line RABS of grade A were presenting cfu (s) however these positive counts were not reported.
- The company destroyed the raw data sheet records of environmental monitoring of the manufacturing areas whereas data were printed from excel sheet.

EXAMPLES OF DATA INTEGRITY ISSUES-2

The company failed to record and report reliable and accurate data for the environmental monitoring results. The critical data integrity issues in form of fraudulent data were witnessed during the inspection

- False results were recorded on the QC records and reports. It was witnessed that the plates recorded and reported as negative by QC personnel were in fact positive for contaminations.
- Contaminations (cfu counts) in grade A were recorded and reported as nil but in fact were positive. Contaminations of grade B were recorded and reported as nil or as within the specification of established alert limit but in fact they were positive and above the specified limit. Contaminations (cfu counts) for operators gown in grade B were reported as nil but in fact they were positive.

EXAMPLES OF DATA INTEGRITY ISSUES-3

- Company representative reported that no failure of integrity test was recorded during filter integrity test. Logbook of integrity tester confirmed there were no failures of integrity test. When inspectors switched on integrity tester and access to history file, several failures were recorded as shown in photo taken and shared with company;
- No deviation was raised for failure of integrity test of sterilizing filters of material and products including finished products;
- No investigation on the quality impact analysis on material and products including finished products was performed.

EXAMPLES OF DATA INTEGRITY ISSUE – LATEST CASE

Viral post inflames anger in China over vaccine safety

Outrage over alleged shady dealings at major drug firm shatters tenuous trust in regulators

BEIJING • China's newest product

While there have been no known reports of people being harmed by the vaccine, Chinese regulators ordered Changsheng to halt production and recall the product.

President Xi Jinping – on a trip to Africa – on Monday called the vaccine company's actions "vile and shocking" and said the authorities should deal with the matter swiftly.

Many parents are sceptical about the government's response. As of Monday evening, a hashtag referring to the scandal had received tens of millions of views on Weibo, a popular social media platform.

One image circulating online shows a screenshot of a news item touting a promise from Premier Li Keqiang on Sunday to "resolutely crack down on all illegal and criminal acts that endanger the safety of people's lives".

Next to it is a similar statement Mr Li made after a 2016 vaccine scandal, suggesting the government has done nothing to address the problem.

Hong Kong clinics said they have seen a surge in demand for chil-

China Food and Drug Administration officials checking rabies vaccines at the Disease Control and Prevention Centre in Anhui province yesterday. The Chinese authorities are scrambling to defuse public outrage over a safety scandal involving vaccines. PHOTO: AGENCE FRANCE-PRESSE

23 July 2018 : Data Integrity Scandal reported at Changsheng Biotechnology, CHINA

- Company Chairman detained by police for investigation;
- President Xi Jingping of China called the company's action "vile and shocking"

NUMBER OF DATA INTEGRITY ASSOCIATED WARNING LETTERS BY COUNTRY CY 2008-2017

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	TOTAL
China	1	1	3	1			2	2	14	19	43
USA	1	2	1	1	1			0	7	15	28
India	1	1		2		6	7	10	9	12	48
Europe		1					1	2	6	3	13
Brazil								0	3		3
Japan	1							0	2	1	4
Thailand								1			1
Canada			1		1					2	4
Mexico					2					1	3
UAE					1						1
Jamaica					1						1
South Korea										2	2
Singapore										1	1
TOTAL	4	5	5	4	6	6	10	15	41	56	152

This is not limited to the GMP area but now includes good clinical practice (GCP), with the most impactful cases at sites that perform bioavailability and bioequivalence studies. For these firms, the data for hundreds of products is impacted. Most recently, this has included failures identified at GVK and Semler Research. Consequences at Semler included a three-page Form 483, untitled letter, WHO notice of concern, and EMA recommendation of suspension.

Source: https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-warning-letters-on-data-integrity-0003

ROOT CAUSES

People	Method/System	Hardware
• Inadvertent errors • Ignorance • Work arounds • Lack of Training • Time Pressure • Culture • Personality • Resources • Organisational friction IT/QA/QC • Lack of understanding of DI vulnerabilities	• Lack of Policies • Lack of QMS • No internal Audit/ Oversight • Database manipulation practices • Cross-functional DBM accountabilities poor • Company management information systems review and monitoring	• Lack of CSV • Lack of IT policies • Inadequate IQ • Lack of security, backup, authorities • Lifecycle management • Obsolescence • IT system "not up to the task"

CONCLUSION

- Data integrity issues are increasing off late. It was not customary to caption every deficiency in relation to data integrity as such.
- Taking a look at inspections and inspection results by regulatory agencies, it can frequently be seen that in inspections of third countries, the deficiencies relating to data integrity especially were the ones leading to GMP and GCP non-compliance. It might be through deliberate or undeliberate procedures at the company in question.
- Important to note that data integrity is not only an IT topic; it includes all areas of the documentation.
- The requirement that every change to a document has to be initialed and dated and that the original information has to stay legible despite all changes, is of essential importance for paper documentation as well as electronic documentation.
- For electronic documents, this should basically be implemented through validated audit trail functionality.
- Data integrity issues are corrosive to science and trust, once lost, trust cannot be overnight restored as there are no CAPAs to fix the trust.