Advanced GMP Workshops 2018,
Organized by the Indian Pharmaceutical Alliance (IPA)
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Good Data and Record Management Practices -
WHO PQ’s expectations and experiences
Presentation Outline

- What is data integrity?
- History of development of guideline
- WHO Guidance on GDRMP
- Misconceptions and misunderstandings
- Red flags during inspection
- PQ inspection experience and findings
- Concluding messages
WHAT IS DATA INTEGRITY?

- Ensuring data is recorded as intended
- Upon later retrieval, ensuring the data is the same in content and meaning as it was when it was originally recorded – through the retention period
- Preventing unintentional or unauthorized changes to data

“Data is the most valuable commodity in the economy we live in, giving enormous power to companies which have access to it.”
- Economist Magazine, 2017
“Data Integrity” is the Degree to which a Collection of Data is **ALCOA**

<table>
<thead>
<tr>
<th>ALCOA</th>
<th>Meaning</th>
<th>Explanation</th>
<th>Comments</th>
</tr>
</thead>
</table>
| A     | Attributable| Who performed an action and when? If a record is changed, who did it and why?| **Who did it? Source data**  
  e.g. Handwritten signature, personal seal, login ID & password, biometric E-signature (Iris, Finger-print) & electronic date/time stamp |
| L     | Legible     | Data must be recorded in a permanent durable medium and be readable | **Can you read it? Needs to be permanent**  
  e.g. Use of permanent, indelible ink, single line cross-outs with date and signature, use of bound paginated books, No correction fluid, No pencil |
| C     | Contemporaneous | Data must be recorded when it was performed followed by date and time | **Was it done in real time?**  
  e.g. As evident from date/time stamping system that cannot be altered by staff, computer system with enforced saving of electronic data, including Meta Data at time of activity, No “Temporary Folder” which Permit Saving of Data at a Later Period |
| O     | Original    | Is the information on original data or a certified true copy of the original data? | **Is it original or true copy?**  
  Data has not been “Tampered” during Retention (Life-Cycle) |
| A     | Accurate    | No errors or editing performed without documented amendments | **Is it accurate?**  
  Data has to be correct, complete & reliable  
  Accuracy is assured through: Qualification & Validation of Computerized Systems, Regular Calibration & Maintenance Programs, Investigation of Process Deviations, Investigation of OOS (Failure Investigation), etc. |

The acronym ALCOA has been widely associated with Data integrity of WHO and other agencies
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HISTORY OF DEVELOPMENT OF THE GUIDELINE (WHO – GDRMP)

- WHO Expert Committee on Specifications for Pharmaceutical Preparations received feedback from ad hoc meeting of inspectors during informal consultation in April 2014. During its forty-ninth meeting in October 2014, formally adopted a concept paper, a core writing/editing group established consisting of experts from USA, UK and WHO PQ.
- Draft guidance prepared for June 2015 informal consultation with international experts in Geneva
- Public consultation concluded on the revised guidance in November 2015
- Finalized draft post consultation adopted by Expert Committee in February 2016
- Published in TRS 996 as annex 5 in 1st week of June 2016
What is data integrity?
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Concluding messages
WHO Guidance on Good Data & Record Management Practices

Objectives

- Consolidates existing principles on Good Documentation Practice & Data Integrity in current GXP Standards
- Clarifies existing principles in GXP Standards & what should be implemented in practice to demonstrate compliance
- Provides illustrations/examples to link principles with current business models & technologies employed by industry
- Gives detailed explanation on how a lack of data management can undermine data reliability, completeness & overall integrity
- Elimination misunderstanding & misconceptions about data management

WHO Guidance is evolutionary, illustrative & subject to periodic review based on experience of NMRAs, industry and stakeholders
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?

- Medicines regulatory systems worldwide have always depended upon the knowledge of organizations that develop, manufacture and package, test, distribute and monitor pharmaceutical products.
- Implicit in the assessment and review process is a trust between the regulator and the industry 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 more WHO expectations on good data and record practices and what do they mean in practice and implementation?

“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 in Annex 5 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 practices and what do they mean in practice and implementation?

- US Code of Federal Regulations (CFRs) covering GCP, GLP, GMP, and medical devices
- FDA - Data Integrity and Compliance With CGMP - Draft Guidance for Industry April 2016
- MHRA ‘GxP’ Data Integrity Guidance and Definitions, March 2018
- Relevant sections of EU GMPs including Chapter 4 and Annex 11
- EMA Q&A on Data Integrity
- PIC/S Guidance – Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments, Draft Published August 2016

In addition, code of conduct by PDA, ISPE GAMP Guide: Records and Data Integrity, European Compliance Academy Guidance Document & may be more
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 (ALCOA).
- Achieving data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.”
- In addition to ALCOA requirements, it is implicit that records are complete, consistent, enduring and available i.e. ALCOA+. 
“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, reported, transferred, stored, retrieved, and continuously monitored until retired.”
1. Introduction
2. Aims and objectives of this guidance
3. Glossary
4. Principles
5. Quality risk management to ensure good data management
6. Management governance and quality audits
7. Contracted organizations, suppliers and service providers
8. Training in good data and record management
9. Good documentation practices
10. Designing and validation of systems to assure data quality and reliability
11. Managing data and records throughout the data life cycle
12. Addressing data reliability issues

References and further reading

Appendix 1
Expectations and examples of special risk management considerations during the implementation of ALCOA (plus) principles for paper-based and electronic systems

http://www.who.int/medicines/publications/pharmprep/trs_996/en/

5.3 QRM is an essential component of an effective data and record validity programme. The effort and resources assigned to data and record management should be commensurate with the risk to product quality.
Management Oversight (Governance) and Empowerment

6. Management governance and quality audits

6.1 Assuring robust data integrity begins with management, which has the overall responsibility for the technical operations and provision of resources to ensure the required quality of GXP operations. Senior management has the ultimate responsibility for ensuring that an effective quality system is in place to achieve the quality objectives, and that staff roles, responsibilities and authorities, including those required for effective data governance programmes, are defined, communicated and implemented throughout the organization. Leadership is essential to establish and maintain a company-wide commitment to data reliability as an essential element of the quality system.
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?

![The Iceberg Of Ignorance](image-url)
Management Oversight (Governance) and Empowerment
Appendix 1 - ALCOA Principles and what they mean for ALL records and data?

- Use of stored digital images of a person’s signature not acceptable
- Use of hybrid systems is discouraged, where legacy systems are awaiting replacement, mitigating controls should be in place.
- Hybrid approach might exceptionally be used to sign electronic records when system lacks features of electronic signatures, provided adequate security can be maintained.
- Use of a scribe to record an activity on behalf of another operator should be considered only on an exceptional basis e.g. documenting line interventions by aseptic area operators, due to language limitation where an activity performed by an operator but witnessed and recorded by a supervisor. Supervisory recording should be contemporaneous.

### 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.

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

**Data Integrity issues are a new problem? Data Integrity is all about testing and particularly chromatography systems?**

- Issues with data integrity have always been a feature of inspections and this is certainly true of WHO PQT.
- Some of the most serious early issues date to manipulation of bioequivalence studies identified e.g. manipulation of chest x-rays and ECGs, submission of stability study data without performing testing
- It is however correct that failings with data integrity of analytical data is today more frequent than in the past and is primarily due to the focus and the inspector's better training in this area and experience in this type of inspection
- The world is also a smaller place and news travels faster and has wider impact than ever

**Data Integrity couldn’t happen in my company?**

- Is senior management aware and on top of this issue.
- Does your organization have policies and transparency and have you ever performed an audit by those with the training to discover such issues?
- All are under ever intense cost and capacity pressures.
Clearing misconceptions and misunderstandings concerning data requirements?

R&D Labs are outside of GXP inspection!
- Development labs need to comply with GXP when they perform GXP investigations. Key studies forming part of the dossier submissions may be inspected in pre-approval inspections.
- There are examples of the transfer of lab equipment to hide its existence.

Data Integrity is a generics industry problem!
- Examples in recent months include two of the biggest international innovator companies. So even the biggest pharma company and the most sophisticated company needs to be thinking hard about this and doing deep-dive audits.
Organisations need to demonstrably have systems that answer the following questions:

**Have we read and understood the relevant guidance?**
- WHO Recommendations on Good Data and Record Management

**Do we have all our data?**
- Design of data collection: protocol, process, method
- Is the context of my data collection maintained?
- Data life cycle controls for data (including metadata for e-data)

**Has our data been objectively processed?**
- Controls to prevent & detect testing toward outcome

**Are we reviewing all our relevant data?**
- Printouts versus source electronic records
- Review of Audit Trails
- Are we reporting all our data?
  - Controls to prevent & detect selective reporting

**Has senior management of our organization established a quality culture?**
- That encourages personnel to be transparent in failures/errors so that Management has an accurate understanding of risks and can then provide the necessary resources to achieve expectations and data quality standards.
Organisations need to demonstrably have robust and sustainable Management Governance Systems in place

Elements of effective management governance should include:

- Application of modern quality risk management principles and good data management principles to the current quality management system to integrate those elements that assure the validity, completeness and reliability of data.
  - E.g., monitoring of risks and application of appropriate quality metrics can help Management gain the awareness necessary for good decision-making to reduce data integrity risks.

- Management should ensure personnel are not subject to commercial, political, financial and other organizational pressures or incentives that may adversely affect the quality and integrity of their work.

- Management should allocate adequate human and technical resources such that the work load, work hours, and pressures on those responsible for data generation and record keeping do not increase errors.

- Management should also make staff aware of the importance of their role in ensuring data integrity and the relationship of these activities to assuring product quality and protecting patient safety.
What verification activity has been the WHO PQ inspectional practice in the past and now and what have been our experiences?

PQ inspections routinely involve several aspects of data and record verification:

- That information submitted in dossiers is accurate and complete – So called “application integrity checks”
- That routine data used in every day decision making e.g. confirmation of batch manufacturing & packaging records, validation reports, study protocol, informed consent forms, case report forms, laboratory reports, and many more is complete and conforms to the ALCOA norms.
- Differentiation between poor practices and weak systems versus intentional manipulation when issues do arise.
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Red flags during inspections

Examples of what inspectors look out for: signs of data manipulation

- Data that is "too good to be true".
- Discrepancies between electronic data and paper raw data.
- Dates which do not match (e.g. dates of chromatograms do not match those being claimed for the analysis)
- Integration parameters that are not traceable or retrievable.

→ Laboratories should be able to demonstrate that same results can be obtained when integration parameters are re-entered / re-integration.
Red flags during inspections

- Electronic data that is not retrievable or destroyed.
- Integration parameters being different for standard vs. the samples of the same run or between samples injections in the same run.
- Audit trails not turned on and lack of periodic review
- Injection sequences that are not clearly documented (Repeat of analyses and picking of best results).
- Raw electronic data not containing unique identifiers and the absence of clear guidelines for the saving of analytical data.
Red flags during inspections

- Lack of basic **access control** and security measures allowing unauthorized changes
- Shared **user logins**, missing or disabled audit trails
- Lack of **contemporaneous** recording of activities
- Failure to investigate data **discrepancies**
- Testing into compliance e.g. ‘interim analysis and trial run’
- Incomplete collection, retention, and review of data for quality decisions
- Overwriting or deletion or original data.
PDCA for Data Integrity

**PLAN**
- Design procedures and forms to enable DI,
- Training / culture of the organization

**DO**
- Follow procedure and ALCOA+
- Follow change management and document

**CHECK**
- Review and approve changes
- Internal auditing / self-inspection
- Review audit trails using risk-based approach

**ACT**
- Investigate
- Disciplinary action for falsification
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- What is data integrity?
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All inspections 2017

<table>
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<tr>
<th>Country</th>
<th>FPP</th>
<th>API</th>
<th>QCL</th>
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<td>Ethiopia</td>
<td>20</td>
<td>10</td>
<td>7</td>
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Inspections 2017

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<tr>
<th>Type</th>
<th>Initial</th>
<th>Routine</th>
<th>Follow up</th>
<th>Pre-inspection</th>
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<tr>
<td>FPP</td>
<td>7</td>
<td>20</td>
<td>3</td>
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<tr>
<td>API</td>
<td>1</td>
<td>40</td>
<td>7</td>
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</tbody>
</table>

FPP inspections per country 2017

- **India**: 13 inspections
- **China**: 8 inspections
- **Indonesia**: 2 inspections
- **Bangladesh**: 3 inspections
- **Kenya**: 10 inspections
- **Pakistan**: 14 inspections
- **Thailand**: 14 inspections
- **Ethiopia**: 11 inspections
- **Egypt**: 8 inspections

API inspection per country 2017

- **India**: 10 inspections
- **China**: 14 inspections
- **Republic of Korea**: 1 inspection
- **Saudi Arabia**: 1 inspection
<table>
<thead>
<tr>
<th>Category</th>
<th>Initial Major Deficiencies 2017</th>
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<tbody>
<tr>
<td>Materials Management</td>
<td></td>
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<tr>
<td>Handling and control of starting materials</td>
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<tr>
<td>Documentation – batch processing records</td>
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<tr>
<td>Contamination &amp; cross contamination – chemical/physical</td>
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<td>Pharmaceutical Quality System</td>
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<td>Change control (CC)</td>
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<td>Quality risk management (QRM)</td>
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<td>Product quality review (PQR)</td>
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<td>Investigation of deviations</td>
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<tr>
<td>Computerised systems – data integrity</td>
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Oral Solid Dosage (OSD) Initial Major Deficiencies 2017
**OSD Routine Major Deficiencies 2017**

- Materials Management
- Quality control - microbiological
- Quality control - chemical
- Management review (MR)
- Quality risk management (QRM)
- Design, maintenance and cleaning of QCL premises
- Production and packaging operations - FPP
- Contamination & cross-contamination
- Product quality review (PQR)
- Investigation of OOS
- Computerised systems - data integrity
- Cleaning validation
- CAPA
- Investigation of deviations

0 1 2 3 4 5 6
Sterile FPP **Initial** Major deficiencies 2017

- Investigation of deviations
- Environmental monitoring/control
- Change control (CC)
- Production and packaging operations – FPP sterile
- Computerised systems – data integrity
- Quality risk management (QRM)
Sterile FPP Routine Major deficiencies 2017

- Computerised systems – data integrity
- Production and packaging operations – FPP sterile
- Change control (CC)
- Quality risk management (QRM)
- Investigation of deviations
- Environmental monitoring/control
- Equipment qualification/calibration - production
- Product quality review (PQR)
- Management review (MR)
- CAPA
- Investigation of OOS
- Line clearance, segregation and potential for mix-up
- Major deficiencies 2017
Comparison Major deficiencies FPP non sterile routine inspections 2015 (10 sites)-2016 (19 sites) - 2017 (13 sites)

- CAPA
- Training
- Design, maintenance and cleaning of equipment
- Cleaning validation
- Stability studies
- Utilities - HVAC
- Investigation of deviations
- Process validation
- Duties of key personnel
- Investigation of CQOs
- Quality risk management (QRM)
- Change control
- Documentation control
- Contamination & cross-contamination
- Product quality review (PQ)
- Data integrity

Year 2015
Year 2016
Year 2017
Examples of data integrity issues-¹

- Inspectors were able to verify, in front of company IT that the audit trails for Analyst 1.4.2 and 1.4.1 could be bypassed. This test was done on several systems. The integrity of the data cannot be demonstrated by the company due to the ability to backdate and delete data without such operations being captured in an audit trail.
- There was no audit trail of any kind for the computer systems, which therefore could not prevent back handed modifications of the stored data.
- The administrator did not login under his own name, but using a generic “Administrator” username which does not provide any traceability as to whether passwords were being shared with staff members that were not entitled to such roles. Furthermore, there were 3 different generic administrator usernames visible in the systems.
- Analysts had the access rights to delete, rename, copy, cut and paste chromatographic data files.
Examples of data integrity issues-

- HPLC Agilent 1200 M64 was a stand-alone equipment and two levels of access rights were established according to the procedure. Although date and time had been removed from the windows toolbar it was possible to access them and amend them through the control panel. Similarly projects or data folders were not locked and could be copied and transferred to other folders.

- Assurance of data integrity in the QC laboratory was deficient in that:
  
  a. Procedure on operation of Empower 3 chromatography software did not define the process for granting access rights
  
  b. According to procedure the System Administrator had the following rights:
     - i. Remove project archives
     - ii. Delete/alter projects
     - iii. Delete libraries
     - iv. Alter date/time in server
  
  c. Control of the QC IR instrument was inadequate. The latest version of the calibration spectrum (recorded on 12/04/18) could not be displayed.
Examples of data integrity issues-³

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

Original Chromatogram

Manual Integration (Tweaking) of Peaks by Analyst

Available as Electronic Record of CDS/HPLC

Review of Meta Data by Inspector
Examples of data integrity issues\(^5\)

Chromatogram Reviewed by QC Supervisor/Manager

Printout of Chromatogram in Analytical Report/CoA
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”
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Concluding messages

- **Data lifecycle**: creation, processing, review, reporting and review, retention and retrieval and destruction

- **Risk management approach**: the efforts and resource assigned to data governance should be **commensurate with the risk** to product quality, safety and efficacy

- **Paper and electronic record** and signature components can coexist (i.e. hybrid situation) as long as wider GXP requirements are met and the content and meaning of those records are preserved, **hybrid situation should be avoided**.

- **Audit trail review** should be part of the routine data review / approval process before final approval of the record. **Risk based approach** for review of audit trails.
Concluding messages

- Examples of approaches that may enhance data reliability are given as recommendations, other approaches may be justified and shown to be equally effective in achieving satisfactory control of risk.

- Senior management is responsible for the quality of the pharmaceutical products but its realization is a collective responsibility.

- Data integrity is not something to be fearful of but it requires robust implementation.

- Data integrity issues are corrosive to science and trust, once lost, trust cannot be restored overnight as there are no CAPAs to fix the trust.

- Culture is the Cornerstone of Quality.
Thank you very much for your attention!

Vimal Sachdeva,
Senior inspector (Technical officer),
Prequalification Team (PQT),
World Health Organization
Geneva, Switzerland
sachdevav@who.int
Further information

Website:  [https://extranet.who.int/prequal/](https://extranet.who.int/prequal/)
Email:  prequal@who.int