Data Integrity - A Perspective from the WHO Prequalification Team

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From the WHO PQT Perspective

• Some definitions
• Why does data integrity matter?
• Where can you find guidance?
• What are the ALCOA Principles and what do they mean for records and data?
• Misconceptions & misunderstandings concerning data requirements?
• What should organizations be doing now?
• Examples of types of data integrity issues from inspections
• What should a company be doing should data integrity issues be uncovered in its own, or a contractor audit
• If critical data integrity issues are uncovered during a WHO-PQT or NMRA inspection - what does the organization need to do?
• Some concluding thoughts
What does WHO PQ mean by Data Integrity and Good Data and Record Management?

• “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”.

Joint UNICEF, UNFPA & WHO MEETING with manufacturers and suppliers
What is the relevance of data Integrity to PQ 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 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 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

Joint UNICEF, UNFPA & WHO MEETING with manufacturers and suppliers
Where can I find more about good data and record practices, ALCOA principles 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 below for a good data management program.”
What are the ALCOA Principles and what do they mean for ALL records and data?

<table>
<thead>
<tr>
<th>Attributable</th>
<th>Expectations for paper</th>
<th>Expectations for electronic</th>
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<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, or</td>
<td></td>
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<tr>
<td>• Full handwritten signature, or</td>
<td>• Electronic signatures, (either biometric or non-biometric).</td>
<td></td>
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<tr>
<td>• Personal seal.</td>
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**Special risk management considerations for controls to attribute actions to a unique individual**

- For legally binding signatures, there should be a verifiable, secure link between unique identifiable, (actual) person signing and the signature event.
- Signatures should be executed at the time of signing, with the exception of personal seals that are properly maintained.
- Use of a personal seal to sign documents requires additional risk management controls such as procedures that require storage of the seal in a secure location with access limited only to the assigned individual, or other means of preventing potential misuse.
- Use of stored digital images of a person’s hand-written signature to sign a document is generally not acceptable. This practice compromises the confidence in the authenticity of these signatures when these stored images are not maintained in a secure location with access limited only to the assigned individual or other means of preventing potential misuse, and instead are placed in documents and emails where they can be easily copied and re-used by other persons.
Clearing misconceptions and misunderstandings concerning data requirements?

- **Data Integrity issues are a new problem? Data Integrity is all about chromatography systems?**
  - Issues with data integrity have always being 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 in inspections in 1994.
  - It is however correct that failings with data integrity of analytical data is today more frequent than in the past and is most likely due to the inspector's better training 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 GMP inspection!**
  - Development labs need to comply with GMP when they perform GMP investigations. Key studies forming part of the dossier submissions may be inspected in pre-approval inspections.

• **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 organisation 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.
If the concepts are not new why do companies not already have robust systems in place?

Contributing factors may include:

- failure by organizations to apply robust systems that:
  - inhibit data risks,
  - improve the detection of situations where data reliability may be compromised,
  - robustly investigate and address root causes when failures do arise.
- Adequately control cumbersome hybrid systems
- These observations highlight the need for industry to modernize historical control strategies and apply modern quality risk management and sound scientific principles to current business models (such as out-sourcing and globalization) as well as the current technologies in use (such as computerized systems)
What verification activity has been the WHO PQT inspectional practice in the past and now and what have been our experiences?

- **PQT 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 process performed in BMRs, analytical test work is complete and conforms to the ALCOA norms.
  - Differentiation between poor practices and weak systems versus intentional manipulation when issues do arise
What verification activity has been the WHO PQT inspectional practice in the past and now and what have been our experiences?

Example findings:

- Back dated, late entry and otherwise non-contemporaneous records
  e.g. Back dated training records or certificates to correct omissions or lost records
- Ineffective or vulnerable archival and back up procedures
  e.g. Organisations frequent do not understand the differences
- Open systems that do not record the “context” of a record or data and any changes
  e.g. audit trails not switched on or secured, shared log-ons
- Manipulation of Chromatography Data in CDS
  e.g. Unjustified/uncontrolled changes to integration parameters
- Missing data or omitted data
  e.g. incomplete injection sequences, selective reporting, trial injections, OOS procedures not followed – investigations not performed
What verification activity has been the WHO PQT inspectional practice in the past and now and what have been our experiences?

Example findings:

• Numerous **failing runs** in validation declared as “instrument failure” no indicative of poorly performing method. Method unreliably detected analyte and led to faulty conclusions.

• **Ghost testing and ghost laboratories**
  
  e.g. not all EM plates placed or read in sterile area monitoring, Cleaning validation not occurring between manufacturing runs, but records fabricated to indicate it had occurred

• **Lack of systematic record keeping** leading to erroneous conclusion
  
  e.g. Adverse events documented in multiple, disparate systems were not compiled to fully-reflect actual signal of AEs.

• Incidents of contamination were discounted as sporadic and inconsequential. e.g. **No investigation and no detection of true impact.**
What verification activity has been the WHO PQT inspectional practice in the past and now and what have been our experiences?

- **Failure to adequately control contractors**
  - Simple acceptance of outsourced lab data
- **Ghost patients and volunteers in clinical trials**
  - e.g. reanalysis/renaming/switching of samples with a different identity
- **Manufacturing records prepared separately from production**
  - e.g. Re-written records to complete fabrication.
- **Undeclared suppliers**
  - e.g. API from unapproved suppliers – sometimes due to poor systems and at other times apparently by intent
- **Shadow or Ghost facilities**
  - e.g. Some (or all) product not made at declared (inspected sites)
The Data Manipulation Triangle

**Incentive / Pressure**
Incentives or pressures on management or other employees to materially mis-state or mis-represent the truth

**Opportunity**
Circumstances that provide an opportunity to carry out a material misstatement

**Attitude / Rationalization**
An attitude, character or set of ethical values that allows one or more individuals to knowingly and intentionally commit a dishonest act, or a situation in which individuals are able to rationalize committing a dishonest act (e.g., the environment imposes sufficient pressure on them to meet certain goals or targets).

*After: “The Fraud Triangle” Occupational Fraud and Abuse, by Joseph T. Wells, 1997*
The Data Manipulation Triangle – Chromatography systems

**Incentive / Pressure**
- OOS are frowned upon and always blamed on the analyst
- We don’t have enough licences for the software because they are expensive
- We don’t have enough instruments / columns
- Columns are expensive so we do not replace in time

**Attitude / Rationalization**
- My source data is my paper record no one will know
- Re-integration is routine and fine, no authorisation necessary
- It’s only just out of specification – it will not affect the patient
- OOS takes too long to perform and is just paperwork for the regulator
- We are all under pressure and I must complete my allocation otherwise I’ll not look good to my peers and supervisor and not get my overtime.
- The method has been validated so it must be me.
- My family depends on me
- The whole industry works this way!

**Opportunity**
- No system or method audit trials
- No individual user log on and profiles – all have Administrator rights
- Archival of data is minimal
- Methods are not locked down
- Supervisor only reviews paper print outs

*After: “The Fraud Triangle” Occupational Fraud and Abuse, by Joseph T. Wells, 1997*
What should a company be doing should data integrity issues be uncovered by itself?

• **Do not throw away trust** by not being proactive and communicate with relevant stakeholders
• Ensure the scale and scope of its problems are really understood
• The pressures, opportunities and the factors that allowed the organisation to rationalise the practices that allowed the data integrity issues to arise must be well understood.
• Identify root causes and set about a realistic plan to resolve the issues
• Their effect on marketed product safety needs to be determined. This is essential in building a credible remediation plan.
• Investment in equipment, personnel **BUT most importantly management governance and operational surveillance systems are key**. At the very least a culture change will be necessary and recognition that may mean some new staff in key management positions.
Questions asked by WHO PQT inspectors when data integrity issues are found during inspections? Critically review the hard evidence of the data integrity failure and ask the following questions:

- Was their actual manipulation or simply potential for issues?
- What is the criticality of the data that is subject to the data integrity problem?
- If there are recording or data loss issues is there other evidence that the actions actually happened?
- Was it inappropriate action but appropriately documented?
- Was there management collusion or management ignorance?
- What products might be affected? Are any of these products not only medically necessary BUT in short supply?
- Does there appear to be simply isolated instances or is there evidence that suggests a more systematic problem – what is the evidence for and against this hypothesis?
- Did weak systems allow data integrity issues to arise? Or were there systems that failed or were bypassed for some reason?
- How does the company respond both immediately and in its CAPA
If critical data integrity issues are uncovered during a PQ or NMRA Audit what does the company need to do?

- **Trust and reputation take years to build and can be lost in an instant.**
- When data integrity issues have been discovered the company will already have lost the confidence and trust of the regulator (or PQT). Regaining some trust is a key factor in any remediation plan.
- The company may be in a state of shock, disbelief and worst of all denial. Until the denial phase is passed there can be no substantive progress.
- The extent of the issues and their effect on marketed product safety needs to be determined. This is essential in building a credible remediation plan.
- The pressures, opportunities and the factors that allowed the organisation to rationalise the practices that allowed the data integrity issues to arise must be well understood.
- Investment in equipment, personnel and most importantly management governance systems. At the very least a culture change will be necessary and recognition that may mean some new staff in key positions.
If critical data integrity issues are uncovered during a PQ or NMRA Audit what does the company need to do in its CAPA?

• The problem will almost certainly be one of senior management governance of data integrity and lack of effective policy and/or its implementation. Denial of this factor in the source of the problem and its eventual resolution is likely only to protract its remediation.

• Most likely current staff will not be totally transparent and open as they will fear for their positions. Almost certainly outside review by auditor/consultants will need to be part of the remediation project. These outside consultants are likely to be in high demand and relatively few in number. They will need to be highly experienced not just in data management and integrity but also the management of the change of organisational behaviours.

• The company needs to be transparent to both the regulators and to itself about its programme and be realistic about the time to implementation – this could be a 24 month job!!!
Take away messages

• Detection of data integrity is increasing and is increasingly being shared – organisations need to be well prepared, understand their gaps and be taking positive and credible measures to bridge their gaps.
• Senior management leadership and commitment is essential in setting the policies and corporate cultures that inhibit, detect and remedy data issues.
• Currently there are few international norms concerning data integrity – WHO with its international partners is bridging the gaps with recently published draft guidance.
• No company is immune and WHO PQT understands that companies may be at different points in their lifecycles of mediation.
• Automation is useful but will never be the complete answer. It is the human systems that usually fail.
Take away messages

• Data Integrity emphasizes quality control and testing ........ Quality should be designed in!
• Data integrity is more difficult to address than other more technical deficiencies because it is partially about honesty, openness, trust and being believed – ethics are in question and so emotions will naturally run high on both sides of the inspection table
• When problems occur it is best if these can be proactively discussed in a positive way with PQT and the relevant NMRAs – Our ears are open to listening
• NMRA need to be open to such approaches and need to be well prepared and understand how they might manage risk, including that of product shortages when establishing policies and handling individual cases.
• Action is never just national but always has an international context – think big and not just look to your own immediate constituency important though that is.