Advanced GMP Workshops 2018,

Organized by the Indian Pharmaceutical Alliance (IPA)

12-20 November 2018, Goa, Hyderabad & Ahmedabad, India

Good Data and Record Management Practices-

WHO PQ's expectations and experiences

PREQUALIFICATION OF MEDICINES PROGRAMME

A UNITED NATIONS PROGRAMME MANAGED BY WHO

World Health Organization

PQP

QUALITY MEDICINES FOR EVERYONE

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

ALCOA	Meaning	Explanation	Comments
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

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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

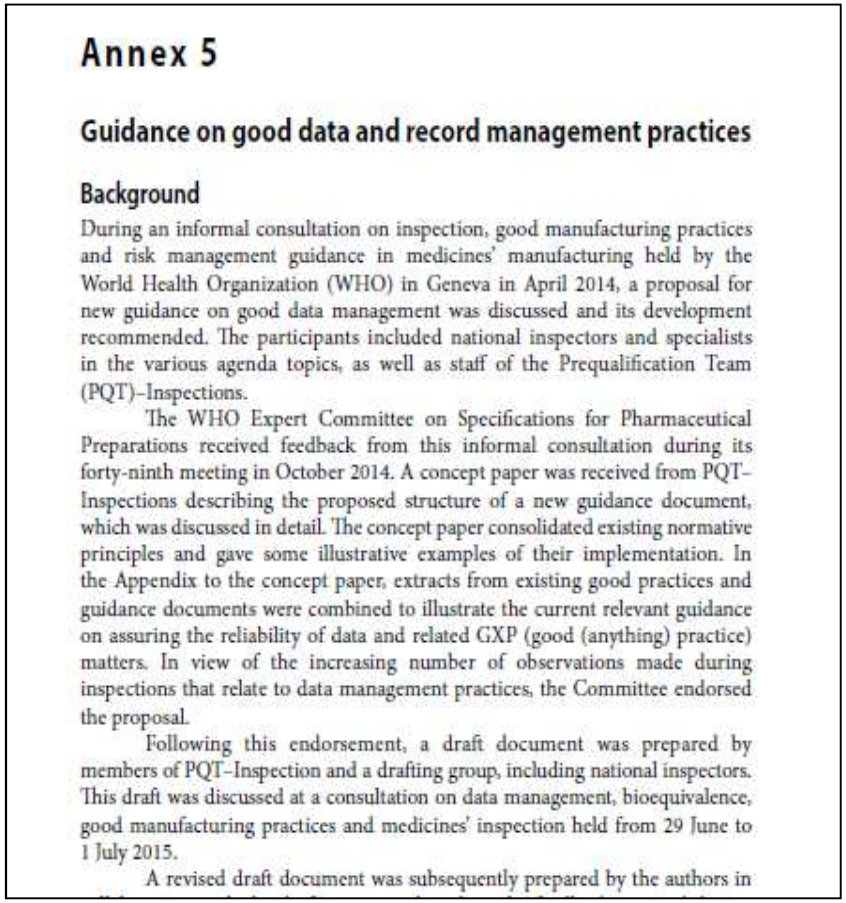
To national and international programmes, concerned NMRA and their assessors and inspectors?

- 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
- US CFR regulation 21 CFR Part 11, and associated guidance
- 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

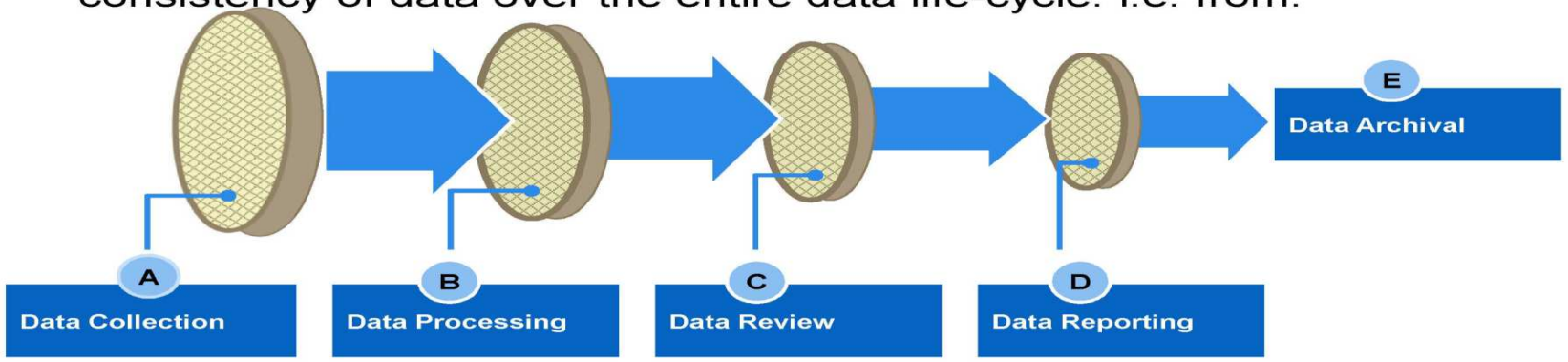
In addition, code of conduct by PDA, ISPE GAMP Guide: Records and Data Integrity, European Compliance Academy Guidance Document & may be more

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^{+}.

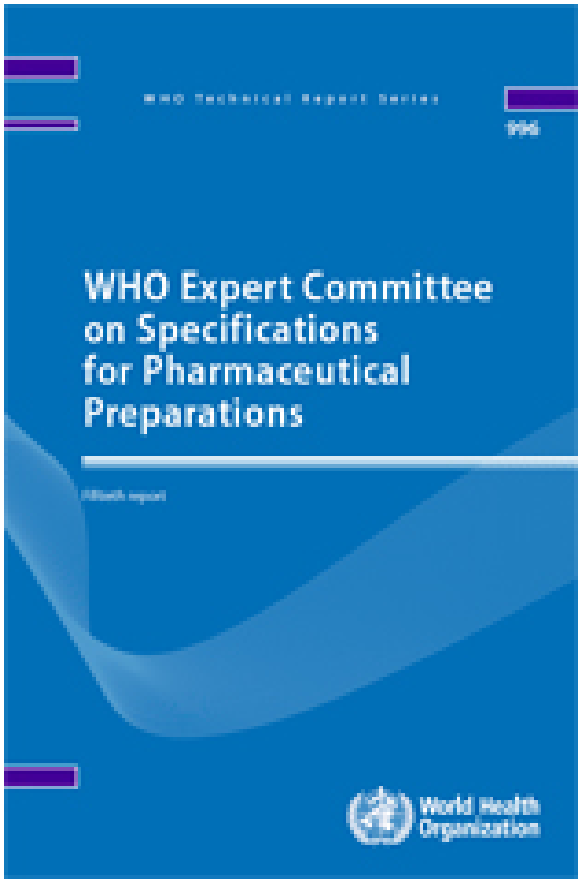
Data Integrity – A Lifecycle Approach

- The degree to which a collection of data is complete, consistent and accurate.
- Compliance to data integrity starts from:
  Development → Manufacturing → Packing → Distribution
- Data integrity refers to maintaining and assuring the accuracy and consistency of data over the entire data life-cycle. i.e. from:



"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".

Content and format



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

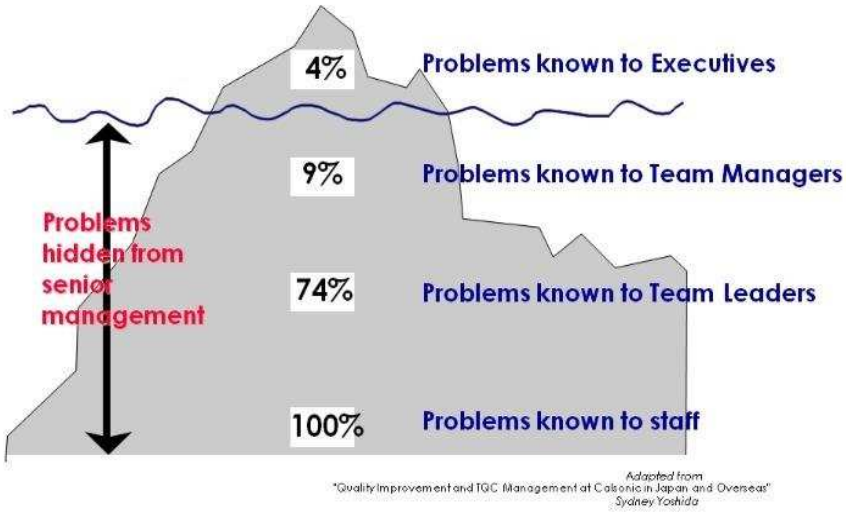
6. Management governance and quality audits

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.

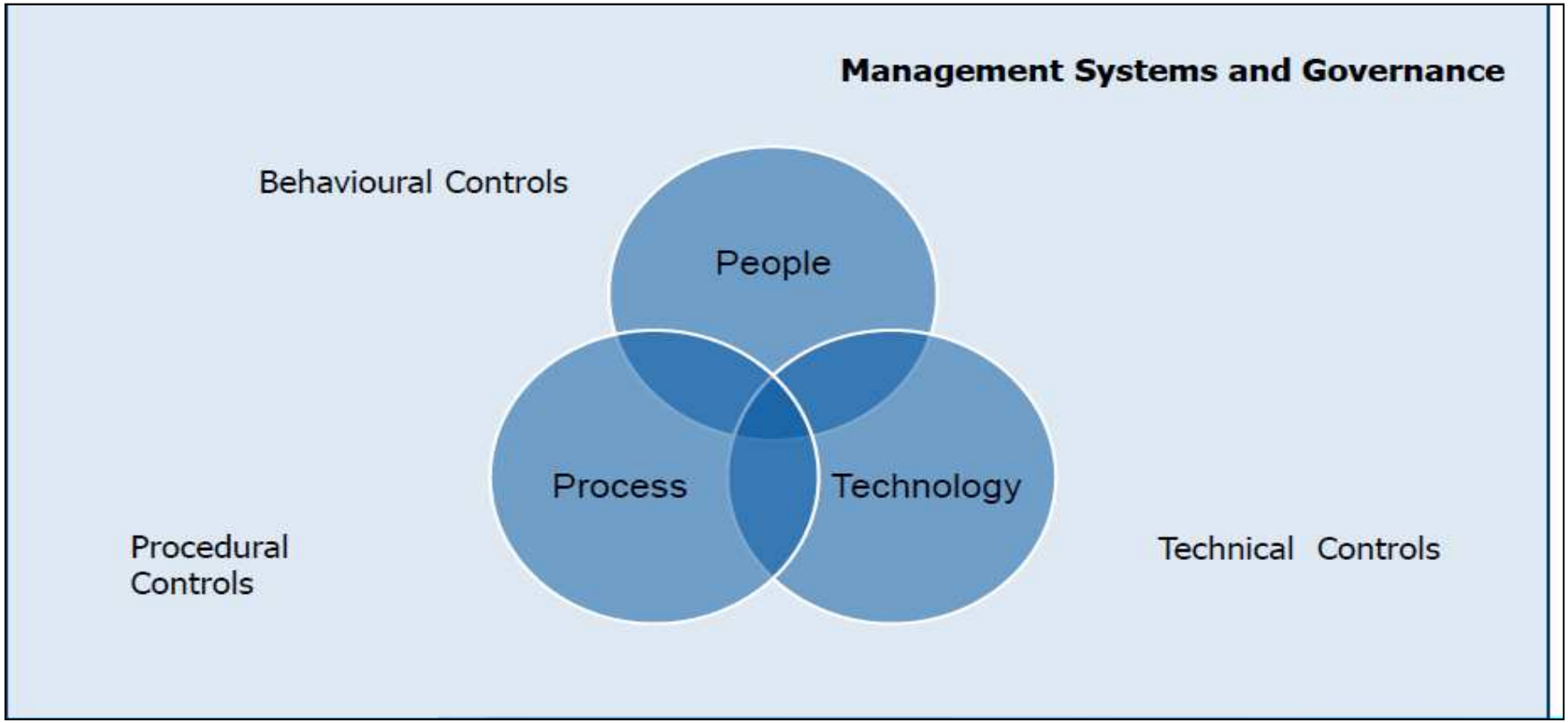
Management Oversight (Governance) and Empowerment

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?



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' 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.

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.

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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 out side 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.

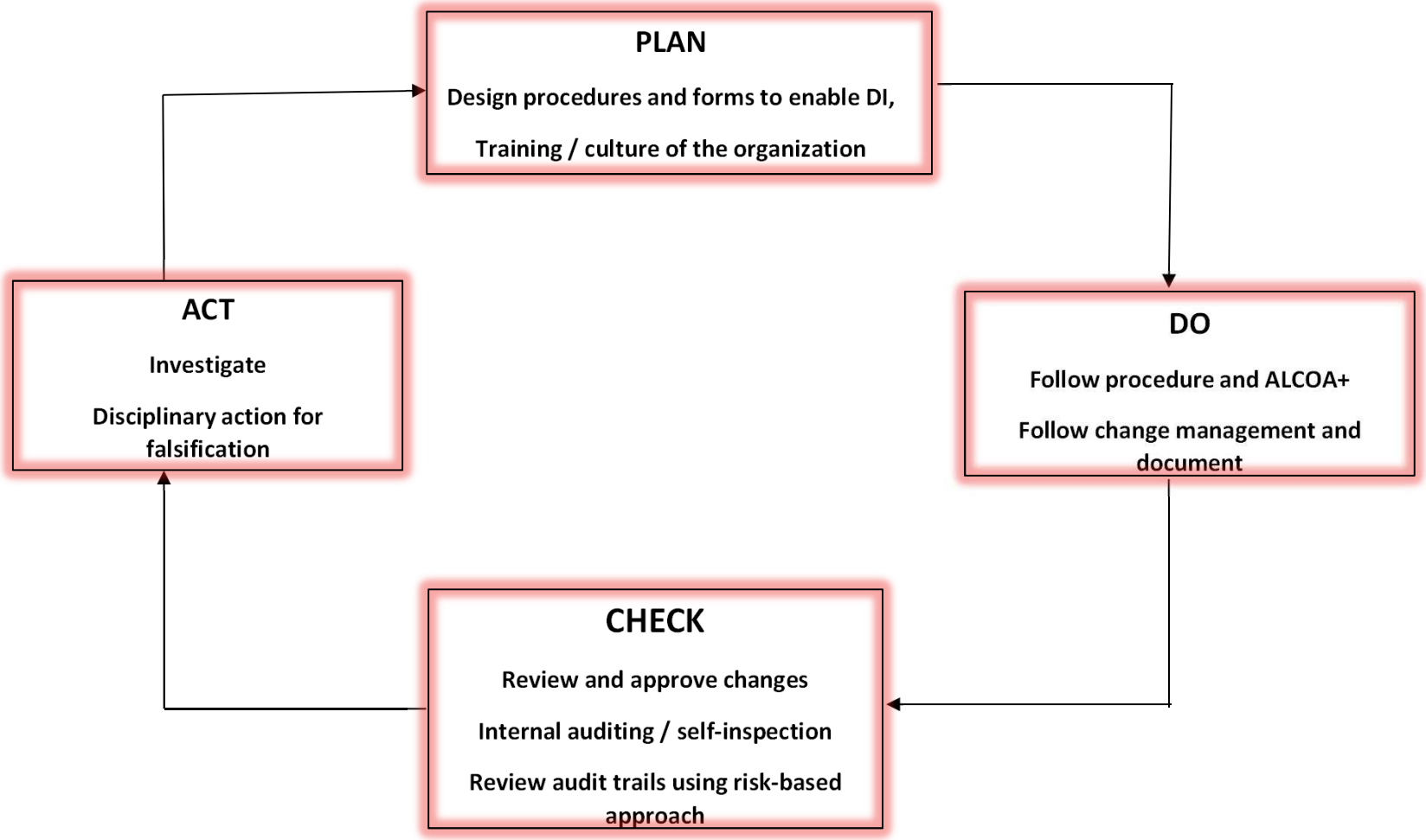
Red flags during inspections

- 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



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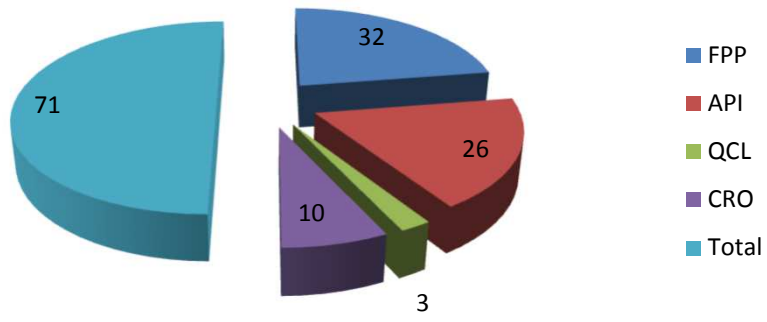
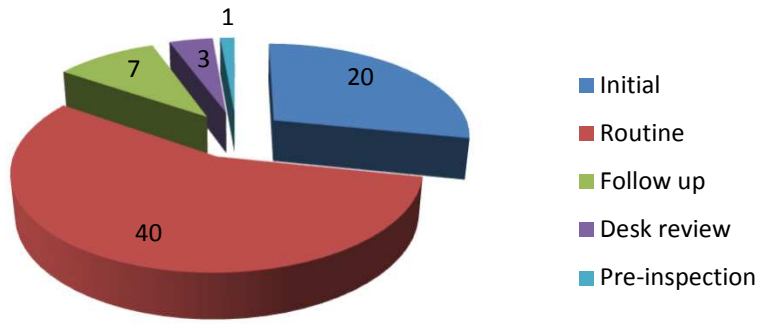
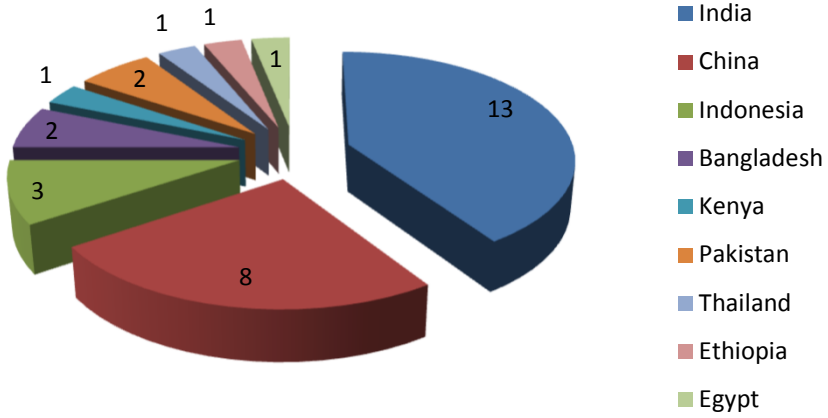
All inspections 2017



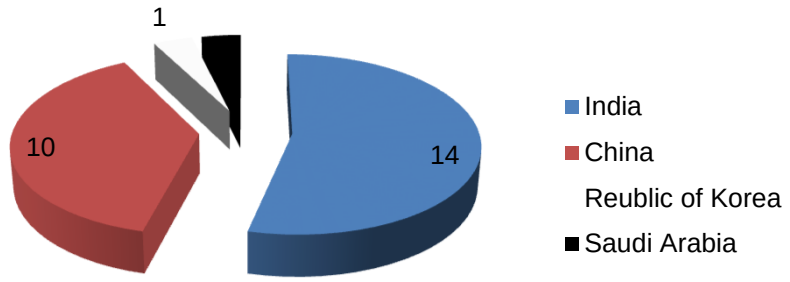
Inspections 2017



FPP inspections per country 2017



API inspection per country 2017



Oral Solid Dosage (OSD) Initial Major Deficiencies 2017

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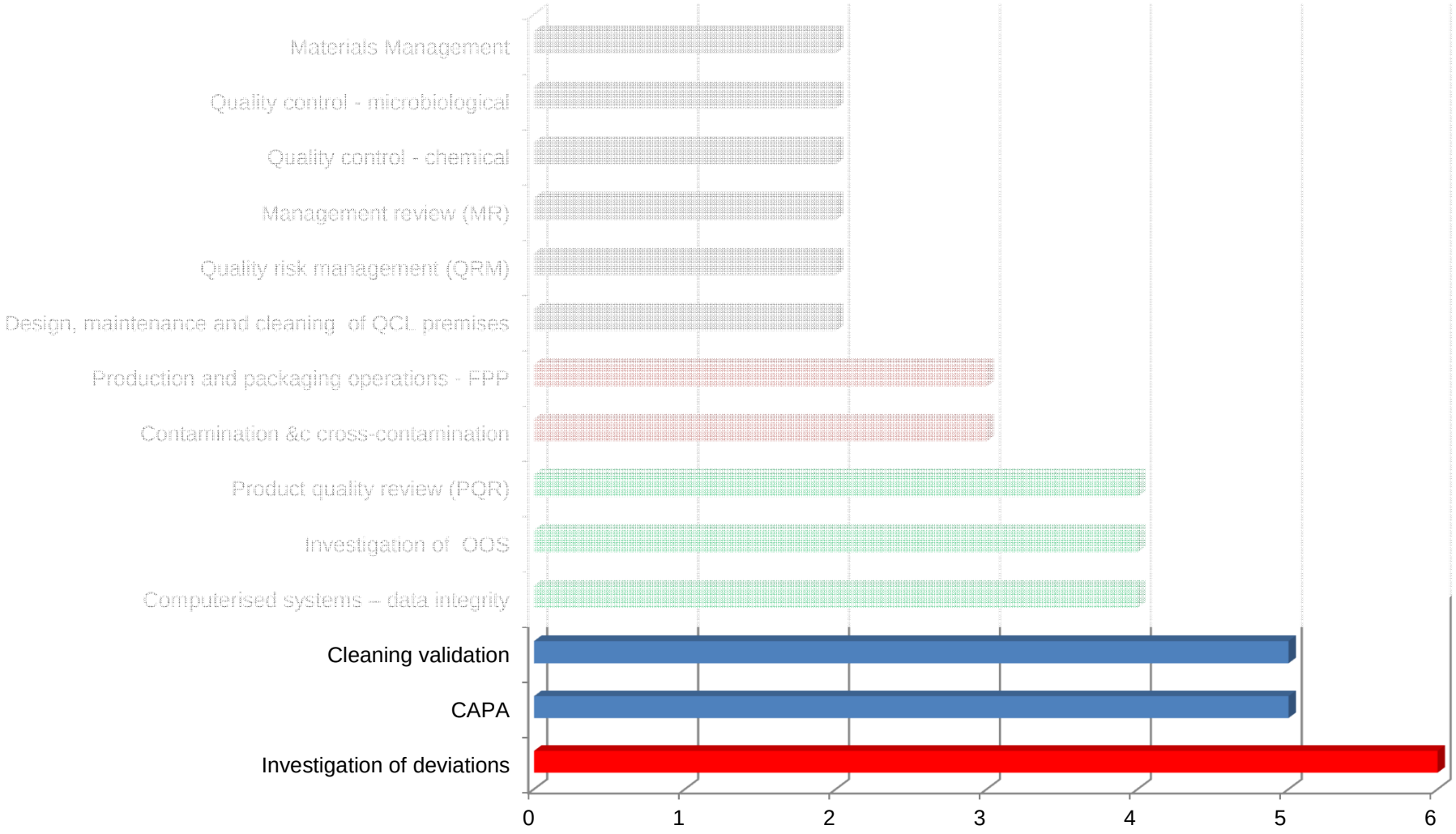
OSD Routine Major Deficiencies 2017



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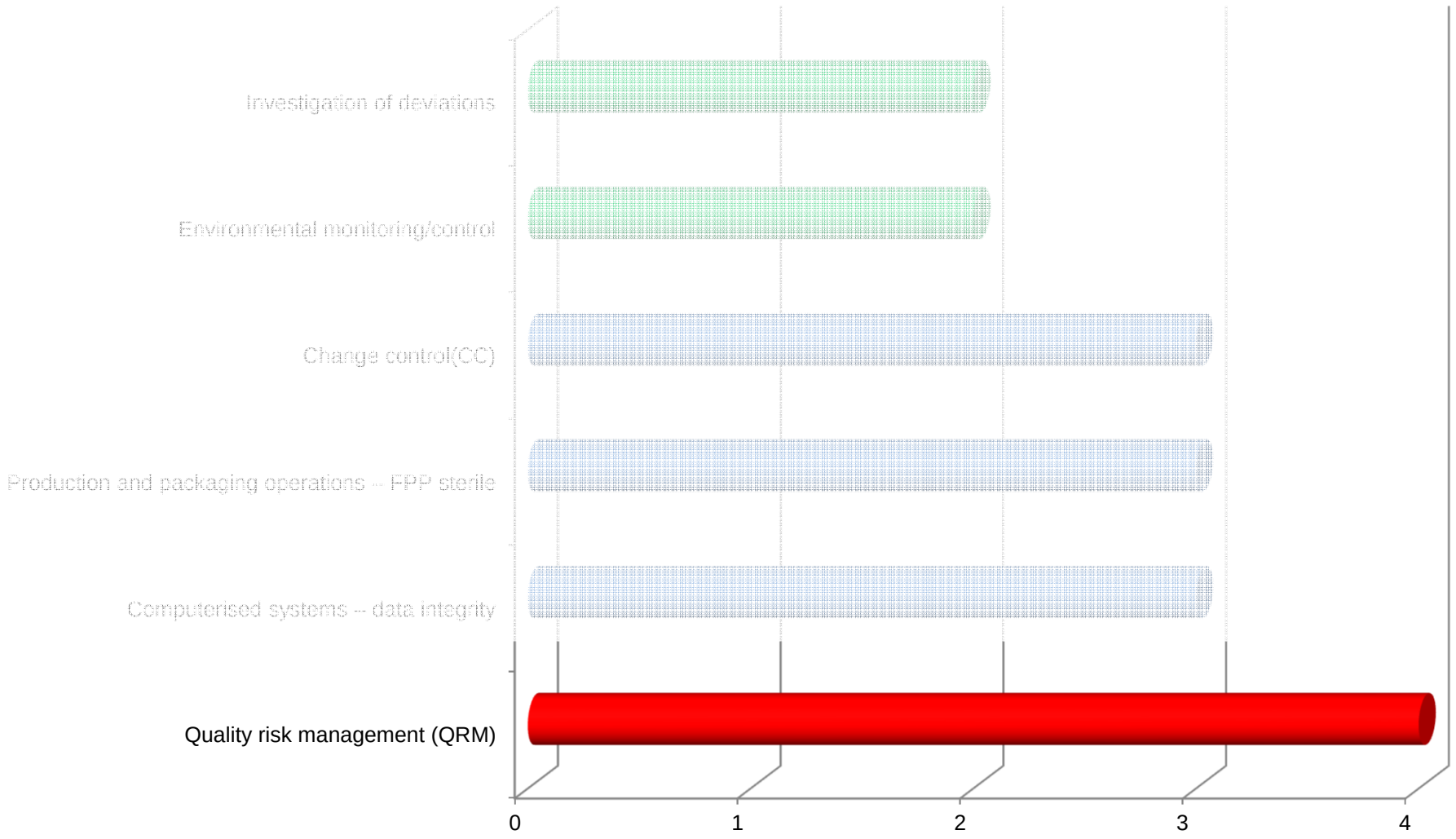
Sterile FPP Initial Major deficiencies 2017



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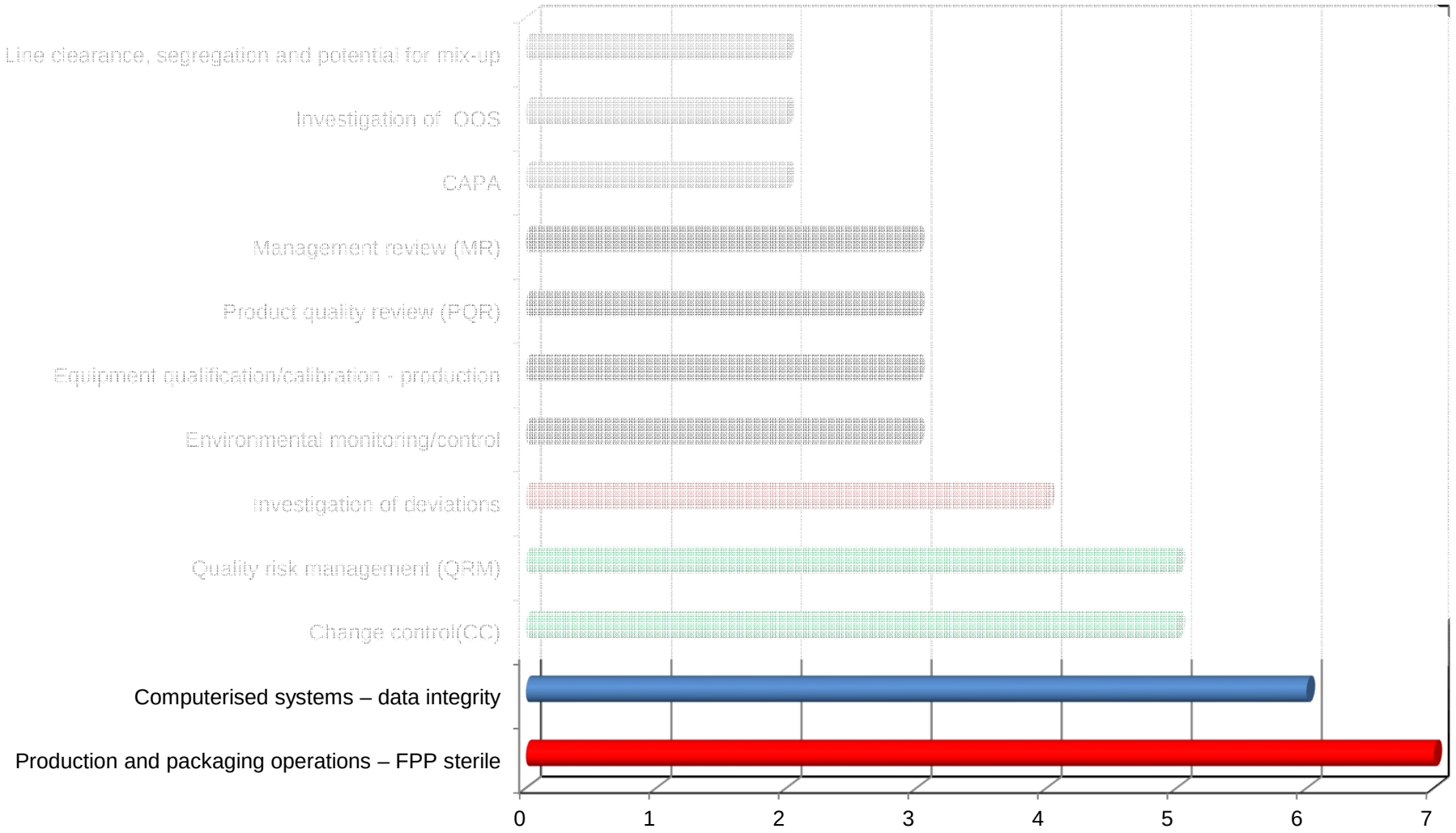
Sterile FPP Routine Major deficiencies 2017



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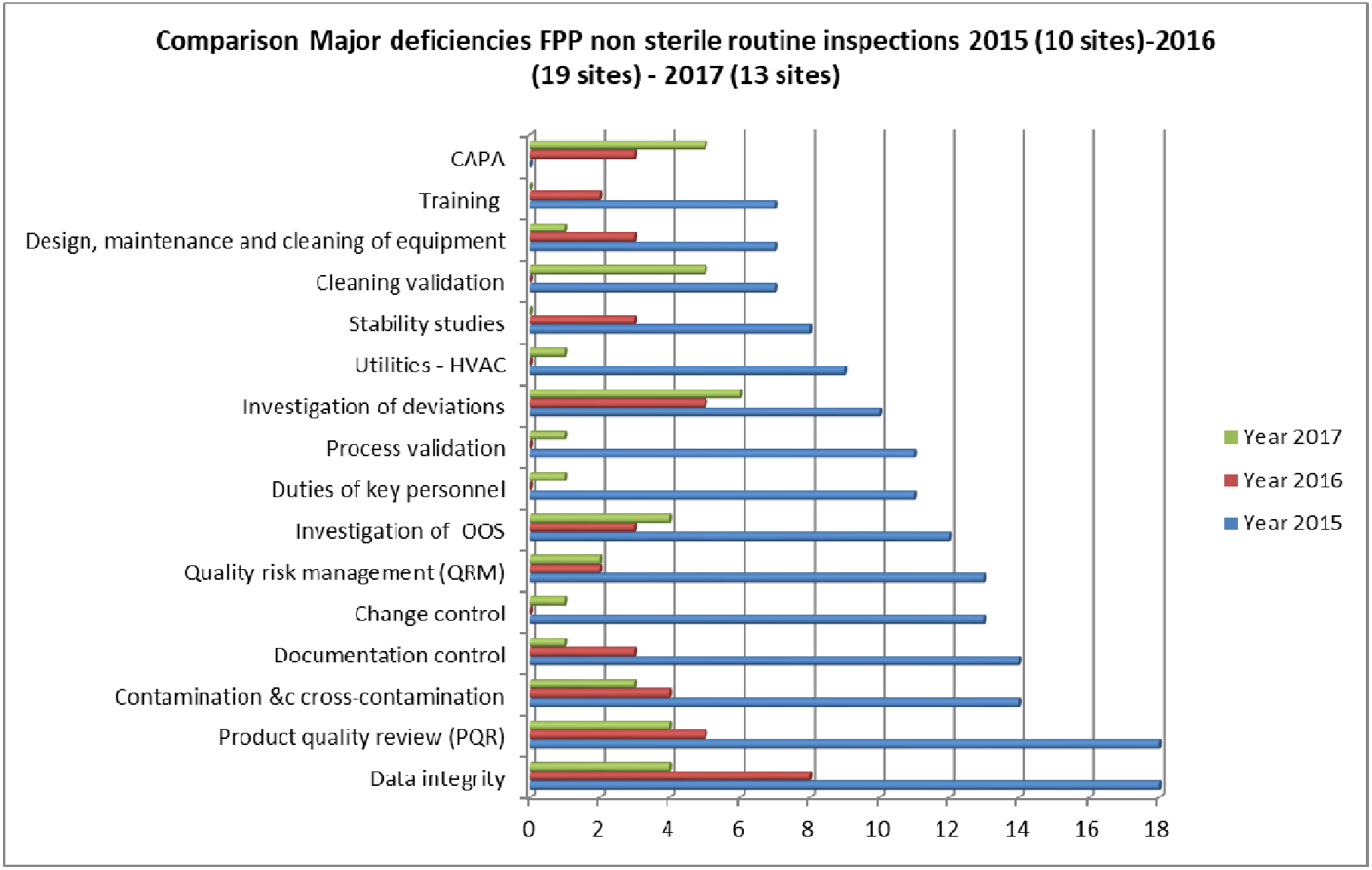


Examples of data integrity issues-1

- 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-2

- 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.

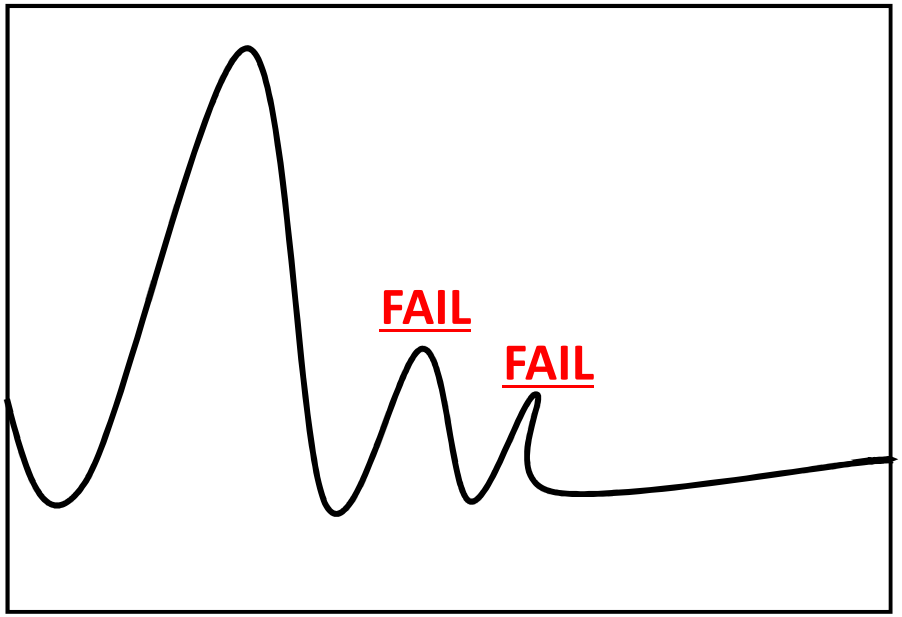
Examples of data integrity issues-3

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.

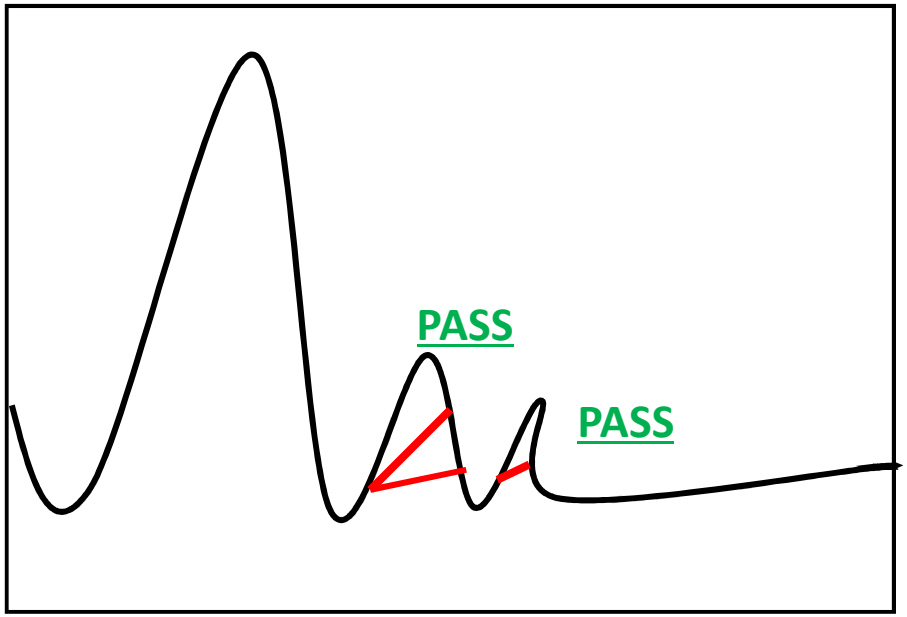
Examples of data integrity issues-4

Original Chromatogram



Available as Electronic Record of CDS/HPLC

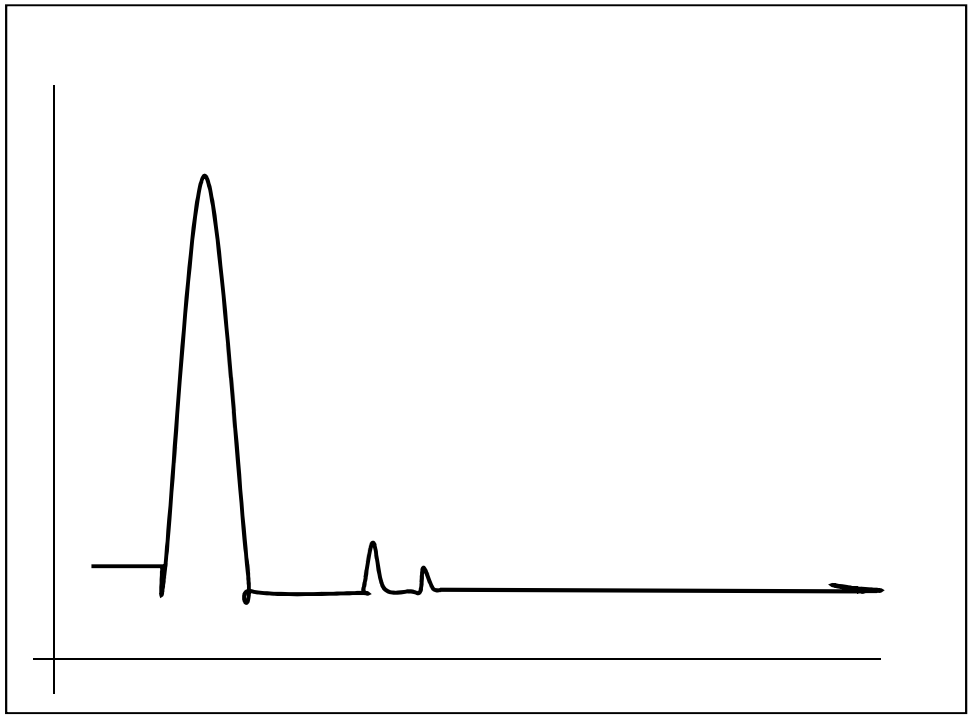
Manual Integration (Tweaking) of Peaks by Analyst



Review of Meta Data by Inspector

Examples of data integrity issues-5

Chromatogram Reviewed by QC Supervisor/Manager



<u>Printout</u> of Chromatogram in Analytical Report/CoA

Examples of data integrity issues- 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

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-

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.

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"

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

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!

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Further information

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