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Data Integrity: A Regulator's Perspective

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2015 PDA Data Integrity Seminar

12th May 2015, The Hilton Hotel, Charlemont Place, Dublin 2

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Presentation Content

- What is Data Integrity
- Elements in inspection focus
- Sample deficiencies

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What is Data Integrity?

- Refers to maintaining and assuring the accuracy and consistency of data over its entire life-cycle and is a critical aspect to the design, implementation and usage of any system which stores, processes or retrieves data
- Data is recorded exactly as intended, and upon later retrieval, the data is the same as it was when it was originally recorded

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Data should be:

A – attributable to the person generating the data

L – legible and permanent

C – contemporaneous

O – original record or true copy

A – accurate

'Metadata' is the data about data and provides context and relationship to the primary data thus preserving the accuracy, completeness, content, and meaning.

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Inspection focus

- EU Regulatory Requirements – Part I Chapter 4 and Annex 11 and Part II
- Data integrity requirements applicable to:
  - API and FP manufacturers, including contract manufacturing
  - Testing units, including contract laboratories
  - Outsourced GMP activities such as equipment qualification and calibration

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Inspection focus - general

- Company understanding of computerised system capabilities and transfer of data between systems
- Up to date listing of all relevant systems and GMP functionality
- Control of networked & standalone instruments
- Policies and procedures detailing processing and control of data

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Inspection focus - qualification

- User Requirement Specification - should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact.
- Evidence of appropriate test methods and test scenarios for parameter limits, data limits and error handling
- Justification on the extent of validation and data integrity controls documented through risk assessment of the computerised system.

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Inspection focus – system administration

- Configuration of systems – GxP functions
- Security of the system and user access levels – appropriate segregation of duties
- Electronic signatures – use of individual and generic passwords

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Inspection focus - data

- Data processing and review
- Accuracy checks
- Potential for data manipulation and deletion
- Repeat testing / replicate data
- Date / time stamp manipulation
- Criteria used to invalidate data
- Data transfer to systems - Checks that data are not altered in value and/or meaning (primary and meta data). Level of checking should be statistically sound

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Inspection focus – storage of data

- Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.
- Archived data should be checked for accessibility, readability and integrity. If changes are to be made to the system, then the ability to retrieve the data should be ensured and tested

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Inspection focus

- Audit trails - Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions
- Vendors - Subject to Chapter 7 requirements, assessment of competency of contractor to deliver expectations.
- Change management - Changes to a part of the system may pose a risk due to interdependencies.

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Inspection focus

- Data Integrity included in risk assessments
- Data Integrity included in training programme
- Data Integrity included in self inspection programme - justify frequency of periodic evaluation based on system criticality and complexity

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Deficiencies - Computerised Systems

- A listing of GMP computerised systems was not maintained.
- The software utilised to control [equipment] had not been categorised.
- Not all critical GxP systems were present. For example the [Equipment] Program and Review software.
- While a statement of GxP or non-GxP was documented for Global Systems, there was no associated documentation justifying the statement.
- Computerised System Risk Assessments for critical systems were not in place.
- There was no system description/boundary despite the critical system being 'live'.

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Deficiencies - User Accounts

- It was possible for administrators to verify their own test result recording in ERP. There were no procedural restrictions around this and was hence considered to increase the overall risk of the associated testing processes.
- The 'system owner access level' was not described.
- The removal of test accounts had not been considered by the company prior to the system going 'live'.
- [ERP] access configurations for the job roles within the site was not adequately defined in that there was no documented correlation of roles to the user access elements defined by the Global [ERP] group.
- System authorization concepts were not always considered in that Users could be administrators with full system access and also have batch manufacturing responsibilities.

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Deficiencies - Audit Trails

- Audit trail comments on [the CDS] were not always sufficiently detailed. For example, a number of changes were observed to have been made to the integration method utilised on [a test] on [a date] and these had a comment of 'save' documented.
- Operating System User Accounts were utilised to access the <system>. There was no periodic review of Operating system audit trails (logs) as appropriate and this was not justified.

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Deficiencies - Qualification

- The qualification of the ERP system was considered deficient in that:
  - The independent code review was not available for review during the inspection.
  - The actual observed results were not always documented within the qualification records
  - The procedure for electronic signatures data transfer to the ERP system was not described in a procedure and was not qualified.
  - There was no assessment of ERP database integrity.
- The decision not to test requirement [Electronic Signatures] documented in [Rationale] was not considered to be justified in that the referenced documents disclaimer stated that the information should not be relied upon.

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Deficiencies - Qualification

- The Virtual Private Network software had not been subject to GxP assessment or qualification as appropriate.
- In relation to the back up and restoration of data
  - There was no process for logging of media used to back up the server systems.
  - The maximum number of uses for the magnetic tapes was not defined or the number of uses controlled.
  - All backup activities on the site were not procedurised. For example back up of the [Program] data from [Equipment] and back up of certain [Equipment] PLC code was performed on an ad-hoc basis using HDDs which were not stored in an appropriate location.

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Deficiencies - Periodic Evaluation

- The periodic assessment of computerised systems had not been completed for all equipment. For example, [computerised system] was installed [a long time ago] and at the time of the inspection had not been reassessed.
- Periodic review of global applications was not performed and there was no procedure in place for periodic review.
- The periodic system review of the <system> was <documented>. The review stated that there was no requirement for audit trail review as they were "displayed on the screen". This was not considered to justified. Further to this, there was no procedure in place for periodic audit trail review.

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Deficiencies - Change Management

- In relation to the testing associated with <IT Change Control System>, the evidence for the appropriate test scenario was not available for review. The system permitted only the most recent test scenario for the process to be viewed. There was no evidence that the system level risk assessment had been critically assessed prior to this change in order to determine the appropriate test scenarios. Further to this, the change to this production parameter had been assigned as a non regulatory change i.e. not subject to GxPs.
- Change logs for <ERP> user access sub-role profiles were maintained in an uncontrolled manner. E.g Z_XXX_XXX_XX_DATA, the associated text box change log had three entries post implementation of <IT Change Control System> whereas <IT Change Control System> listed four valid changes for this profile

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Deficiencies - Production

The following deficiencies were noted with regards to the blister packaging machine

- There was no controlled recipe in place to confirm that parameter settings on the machine were those approved.
- The time on the HMI was incorrect – the actual time (taken from the wall clock in the packaging area was recorded at 12:15, the machine time was displayed as 11:08.
- A generic operator password was in use
- Audit trails were not reviewed.
- The print out function was not enabled and there was no assessment to determine if stored data could be securely transferred or downloaded to storage media in an intelligible format for review
- Manufacturing data since 2003 from a previous manufacturer / owner was retained on machine.

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Deficiencies - Production

The qualification and data integrity controls for the filling machine were considered inadequate in that:

- There was no technical agreement with the vendor
- A single generic user name and password was used to access and operate the equipment.
- The time setting on the software control was inaccurate.
- The audit trail could not be generated at the time of inspection.
- The system and security for archiving of data was not known
- The User Requirement Specification did not specifically state all the requirements for the machine and was not linked to any critical process parameters / variables

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Deficiencies - Production

- The company is advised that manufacturing controls should be updated in line with technical progress (ref. Directive 2003/94/EC, Article 5 (2)). In particular fluid bed dryers should be equipped with chart recorders to facilitate monitoring and recording of the granulate drying process.
- The qualification / revalidation was deficient in that there was no consideration of the impact of updated requirements since the initial IOQ, specifically Annex 11.

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Deficiencies - Production

- In relation to Filter Integrity Testing:
  - There were no controls around the number of repeat FITs that could be performed in the event of a filter failure for either product or vent filters.
  - There was no requirement to reconcile the number of tests reported versus the number of tests performed on the Pall units.
  - Failed FIT runs were not recorded on form X although the form required a 'Pass/Test' result to be recorded.

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Deficiencies - QC data

- There was no justification for the test injections of samples including stability samples being run prior to system suitability.
- There was no explanation for why areas changed for test injections from test, test 1 and test 2, prior to running the sample set. It was noted that when the assay for test was calculated that this resulted in an OOS result, whereas the result for test 2 was within specification.
- The Empower list of users and user types did not reflect the highest level of access a user had.
- Analysts with System Administrator access had the ability to change custom fields including calculations and sample names.

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Deficiencies - QC data

- The company stated that sample injections were being run as there were problems with the systems, however; no evidence of this was presented.
- The results of a processed test injection had been deleted by an analyst with administrator access.
- There was no requirement to review raw data on electronic systems.
- There was no requirement to review audit trails.
- Projects were not locked and it was possible to reprocess results

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Deficiencies - QC data

- There was no date / time stamp of printing on analytical reports from 'system' (chromatograms, methods and sample set data) to facilitate traceability and ensure integrity of the data
- The procedure for test performance and review of documents did not make reference to review of the audit trail or review of soft copies of the chromatograms on the 'system' network
- A number of sample sets and their associated injections on the 'X system' in the stability laboratory, were not all appropriately identified and carried non descriptive titles, such as "trial"

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Deficiencies - QC data

- No deviations or explanations had been documented for a number of 'altered sample' incidences which were evident from 'X system' project audit trails
- There was no date / time stamp of printing on analytical reports from 'X system' (chromatograms, methods and sample set data) to facilitate traceability and ensure integrity of the data
- The procedure for test performance and review of documents did not make reference to review of the audit trail or review of soft copies of the chromatograms on the 'X system' network
- Alterations to runs were frequently performed to add an extra test or blank sample but there was no procedure in place for this and the reason for the changes was generally not recorded to a level of detail enabling the true reason for the change to be determined

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Deficiencies - QC data

- A number of sample sets and their associated injections on the 'X system' in the stability laboratory, were not all appropriately identified and carried non descriptive titles, such as "trial"
- Management of the 'X system' was considered deficient as a number of GxP functions were observed as not switched on (e.g. Allow lock channels after sign off, Disallow use of Annotation Tools etc). In addition, it was observed that a statement by 'X company' reflected below the GxP function window indicated that they recommended all GxP functions to be switched on
- The LC Solution system (version 'y.yyy') for the 'X' HPLC system was considered deficient in that all users could gain 'Administrator' access to the application system by using a common username 'Admin' and no password

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Deficiencies - QC data

- Raw data for HPLC/GC runs which had been invalidated due to failed system suitability criteria were stored separately to the QC raw data packages and were not included in the review process. The 'log for record of invalidated runs' was not incorporated under the quality management system and invalidated runs were not always evaluated and documented
- Original run sequences which had been amended during HPLC/GC runs were not printed and retained with the QC raw data packages
- Full Audit Trail did not appear to be available for the 'X' data acquisition system in that the different version numbers of the processing methods were not all visible in the audit trail (e.g. the current version of 'Y' method was 18 and only 7 lines were visible on the audit trail). In addition, there were no data audit trails available on this system

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Deficiencies - QC data

- For IT personnel with administrator rights it was possible to copy, rename or delete files (i.e. chromatograms and metafiles) in the system without it being tracked in an Audit Trail
- The process of review of HPLC analytical data packages by the QC checker does not require a formal review of the electronic raw data or a review of the audit trails for the processing method and instrument method associated with the analysis sequence. In the examples reviewed printouts of processing methods were not included with the QC raw data packages for review
- There was no requirement for electronic review of GC analytical data & relevant audit trails to be conducted during the review and approval of QC data. In addition, the QC/QA reviewers did not have access rights to the 'X' systems in order to conduct such reviews

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Deficiencies - QC records

- Entries made in training records, production logbooks and QC records were made by staff that the company biometric logging in record showed were not on site at the time that the entry was purported to have been made
- QC equipment records logged the use of a specific HPLC column for testing performed on site at a time when other records showed that the same column had been transferred to a contract testing laboratory
- Evidence of deleted TOC data files were noted. An analysis file from 'xxx' date was observed in the deleted files/recycle bin of the computer. A duplicate analysis file for the same samples on the same day was found within the file structure. There was no reference to the second file or any file deletion either in the test records or the system logbook and no explanation was offered during the inspection

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Deficiencies - QC equipment

- The control of un-networked equipment (UV and TOC) in the QC laboratory was deficient in that:
  - A number of data discrepancies were noted in the system file structure
  - Repeated and unlabelled testing data folders and test packages were observed
  - At the time of the inspection the company could not fully explain the discrepancies noted
  - Software had not been qualified or validated to demonstrate that the key functionality of the system functioned as required

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Deficiencies - stability

- Stability data had discrepancies including:
  - Initial records of secondary spots for TLC related substance tests were later re-annotated to indicate that no secondary spot had been identified
  - Data recorded in summary reports were not reflective of the raw data
  - Summary reports were presented to the inspector for which the supporting raw data could not be provided
  - Missing raw data and summary report for batch of 'X' Tablets where stability data had been used to support the risk assessment of product remaining on the market in the EU
  - Missing raw data and incorrect entries that were reviewed and authorised as correct
  - Some stability data presented to the inspector was from product packed in different packaging to that supplied to the market and therefore not relevant

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Deficiencies - stability

- Stability data had discrepancies including (cont'd):

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EudraGMDP – Statements of Non-compliance

- Issues identified which compromised the integrity of analytical data
  - Evidence seen of data falsification
  - Significant number of product stability data results reported in the Product Quality Reviews had been fabricated
  - Neither hard copy nor electronic records available
  - Issues seen with HPLC electronic data indicating unauthorised manipulation of data and incidents of unreported trial runs prior to reported analytical runs
  - Record integrity and veracity - some records made up or altered
  - Lack of mechanisms to ensure integrity of analytical data

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EudraGMDP – Statements of Non-compliance

- Critical deficiency cited with regards to testing of finished product and stability testing related to data integrity
  - Deleted electronic files with no explanation
  - The running of "trial testing" prior to performing system suitability and the formal testing
  - Loss of control of reconciliation of samples - those used for additional testing could not be traced
  - Manipulation and falsification of documents and data observed in different departments

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Summary

- You don't need to be an IT expert, but you need to know GMP requirements
- Understand the capability of your equipment, know if it stores electronic data, assess if parameters are changed what impact it will have.
- Integrity of data is not a 'new' regulatory requirement.

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References:

- EU Guidelines to GMP Part I and II
- EMA Questions and Answers: Good manufacturing practice
- MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015
- HPRA presentations
  - GMP information Day November 2014,
  - Trinity QP Forum 2014 and 2015,
  - ISPE GAMP Seminar April 2015