Centre for Biopharmaceutical Excellence

Data Integrity In the Global Pharmaceutical Industry

Module Topics

- What is Data and Data Integrity?
- Global Regulatory Agency Perspectives
- **Root Causes and Examples**
- Solutions-Governance Systems

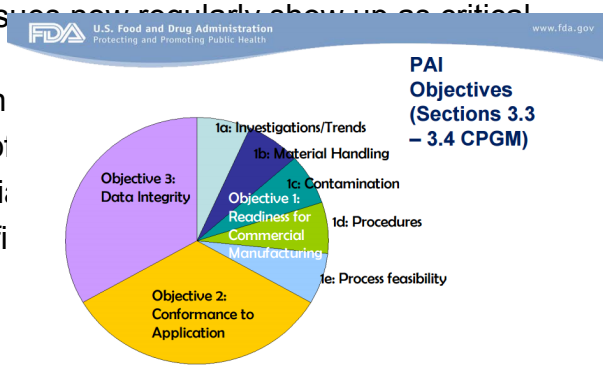
What do you think?

Example occurring in same facility:

1. Raw materials specifications set up by IT within MRP system "writes" to a word document in QC and printed out. (Nothing validated, not in QMS)
2. QC uses specification and performs HPLC assay and other tests. No printouts from balances/ autotitrator, HPLC raw data deleted after 1 month after Chromatograms printed out.
3. All QC testing results calculations recorded on note paper, sticky notes and thrown away after a final "neat" report is typed in MS Word for release.
4. All QC testing records are therefore "perfect"?

Current Status

- Data integrity iss observations in:
- FDA 483 Warnin
- WHO "Notices o
- EU Non-Compli
- FDA now Specifi



ISPE ANNUAL MEETING
TARA GOOEN, Team Leader CDER/OC

Who Does It Apply To?

Extract from PDA Points to Consider Elements of a Code of Conduct for Data Integrity:

- Manufacturers of finished drug products for clinical trials, bioequivalence studies, and commercial distribution
- Companies that conduct clinical trials in support of new drug applications including, but not limited to: Investigational New Drug (IND), Clinical Trial Application (CTA), Investigational Medicinal Product Dossier (IMPD), Biologics License Application (BLA), Marketing Authorization Application (MAA), New Drug Application (NDA), and Abbreviated New Drug Application (ANDA)
- Laboratories that develop methods or formulations intended to support new drug applications or laboratories that analyze samples generated from clinical trials
- Manufacturers of excipients, intermediates, or active pharmaceutical ingredients (APIs)
- Contract manufacturing organizations (CMOs)
- Contract research organizations (CROs)
- Contract testing laboratories
- Contractors, consultants, suppliers and vendors that provide services and data that support the production and control of APIs, drug or biological products

What is Data?

The IT definition is that ***DATA*** are the ***RAW FACTs*** that describe the characteristic of and event.

Information is ***DATA*** converted into meaningful and useful context.

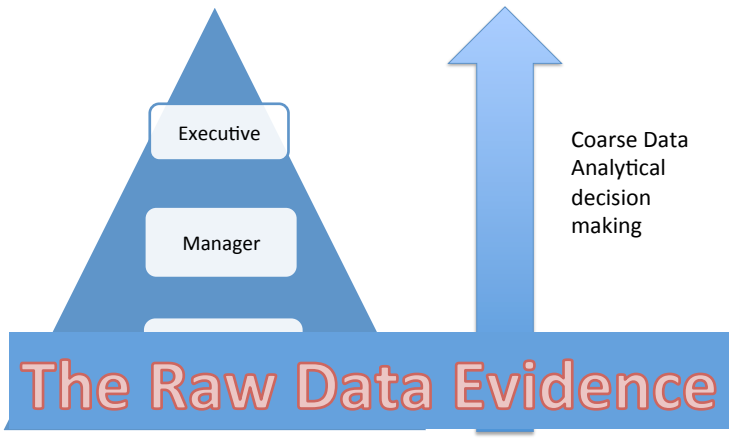
Wisdom (or fact based decision making ability) is what we have then, when we have both.

It follows that if you do not have the ***DATA*** how do you prove your decisions were not simply based upon opinion and not fact based drivers?

Definition of Raw Data in Our Industry ?
(FDA CFR 58 - GLPs)

- *Raw data* means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study.
- In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data.
- *Raw data* may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

Information Systems



We will come back to this in the context of problem areas later….

What is Data Integrity?

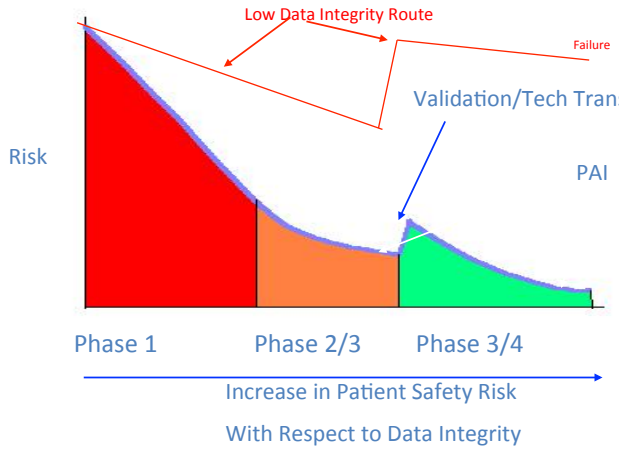
MHRA Inspectorate Blog[1]-

- *The extent to which all data are complete, consistent, and accurate throughout the data lifecycle*.*

- From initial data generation and recording through processing (including transformation or migration), use, retention, archiving, retrieval and destruction.

(**Note the lifecycle approach is consistent with the principles of ICH Q10 Pharmaceutical Quality Systems*)

Lifecycle Approach



So Data integrity covers the whole drug development to launch lifecycle- clinical trials data through to final release for sale Certificate of Analysis.

Global Regulatory Views

CFR 211 indirectly addresses Data for example:

1. Any Calculations must be verified 211.68(b)
2. Methods must be documented and approved 211.160 (a)
3. Data generated and transformed must meet criteria of scientific soundness 211.160(a)

But more specifically under **211.194 Laboratory Controls**

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

- (1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.
- (2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested…….. The suitability of all testing methods used shall be verified under actual conditions of use.
- (3) A statement of the weight or measure of sample used for each test, where appropriate.
- (4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.
- (5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
- (6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

AND SO ON
AND SO ON

WHO

WHO Expert Committee on Specifications for Pharmaceutical Preparations Forty-eighth report:

"*15.9 Data (and records for storage) may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulae and detailed SOPs relating to the system in use should be available and the accuracy of the records should be checked.*

If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer system, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available."

- Also mentioned in 15.1 and 17.3d

WHO NOC 2014 Summary

- 5 HPLC's running with audit trail function in software disabled.
- Although audit trail was enabled on some HPLC there was no explanation or audit trail between actual integration and manual method that was used for final result.
- On the same systems the time and date function had been unlocked allowing for editing.
- All analysts within the same lab used a shared password therefore no specific analyst in audit trail.
- Analysts could access and make change to files and HPLC run file where found in "recycle bin".

Global Regulatory Views

CFR 211 Part 11 Electronic Records and Signatures.

PIC/S GUIDANCE PI 011-3 25 Sept 2007 Good Practices for Computerised Systems in Regulated "GXP" Environments.

Both cover in detail the requirements for computerised systems- but this is not the topic of this presentation.

A more important document is the FDA's Compliance Program Guidance Manual 7346.832 NDA- Pre Approval Inspections

Global Regulatory Views

Compliance Program Guidance CPG 7345.832 has specific directive to FDA PAI inspectors regarding auditing of Data Integrity:

"*There are three primary inspectional objectives of this PAI program, all of which require an informed strategy and careful on-site evaluation. These objectives are:*

Objective 1: Readiness for Commercial Manufacturing
Objective 2: Conformance to Application
Objective 3: "Data Integrity Audit"

Global Regulatory Views

Objective 3: Data Integrity Audit

"Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate."

"The inspection strategy may select key data sets or randomly select data…….. Generally, data on finished product stability, dissolution, content uniformity, and API impurity are good candidates for this audit."

" ***During the inspection, compare raw data, hardcopy or electronic, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section***"

"Raw data files should support a conclusion that the data/information……"

Global Regulatory Views

Objective 3: Data Integrity Audit

"Examples of a lack of contextual integrity include the failure by the applicant to scientifically justify non-submission of relevant data, such as aberrant test results or absences in a submitted chromatographic sequence, suggesting that the application does not fully or accurately represent the components, process, and finished product."

Remember DATA-→INFORMATION→ WISDOM (decisions, justifications, rationales..)

Inspectors are expected now to sit at the computer terminal and have you "replay" the raw data, and so basically if you no longer have the actual original raw data when an audit inspector says "SHOW ME" they will consider all decisions made downstream are suspect and possibly fraudulent/fake.

Root Causes

1. Ignorance
2. Lack of, or ineffectual training
3. Basic company IT ignorance on data base management
4. Organisational culture
5. Awareness of the risks
6. Human error/mistakes
7. Wilful falsification
8. Manipulation post acquisition
9. Leadership (walk the talk)
10. Lack of understanding of information systems
11. Actual hardware issues, data transmission.
12. Software errors, lack of change control
13. Obsolescence of hardware/recording media
14. Poor controls over database management systems DBMS
15. Technophobia of key staff

Causation By Category

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

Short Industry Examples

Company	Observation	P/S/H?
A	QC Laboratory data acquisition software was not validated to ensure the re-writing, and deletion of data was prohibited	
B	QC records did not show who performed the analysis; raw data was not recorded contemporaneously (real time) nor by the performing analyst. Failed in injections of QC standards deleted from the sequence without explanation	
C	Batch records found falsified after discarding original ones to provide "clean records"	
D	Within the QC laboratory there was evidence of non-contemporaneous recording of lab data, using scrap papers, yellow sticky notes. Some of this raw data was also found in waste bins.	
E	Unofficial "trial" testing of samples for production "management information only"	

Short Industry Examples

Company	Observation	P/S/H?
F	OOS results found within records of QC data acquisition system not investigated. Retesting carried out and not justified.	
G	QC staff routinely collected raw data on scrap paper and collated with printed off chromatograms to write a "clean report" in MS Word to present to the head of QA. A review of reports so prepared showed zero errors or natural errors normally expected within a busy QC environment- original raw data, weighing's, observations not kept. In some cases the equipment log was used to capture raw data.	
H	The Data acquisition systems of the HPLC and GC systems was not backup up nor part of any company back up policy or program. After Chromatograms had been printed out raw data was deleted on a monthly basis due to hard disk constraints. There was no way to re-verify results from release or stability testing. There were no QC procedure regarding management of electronic data, backup, security or strict access levels. Data and methods could be accessed by QC staff sharing passwords.	

Key Expected Attributes-ALCOA

Attributable	Legible	Contemporaneous	Original	Accurate
• Who actually acquired the data or performed the actions and when? • Signed and dated	• The data must be legible. • The record should be permanent. • The record should not be obsolete and not readable i.e. microfilm. • Corrections should be made in line with GDP signed and dated. • No Company shorthand • The record should be enduring and on proven storage media (beware thermoprinters)	• Data must be recorded in real time as and when it occurred. • Any practical workarounds due to clean room environments must be according to written procedure. • Should be carried out in close proximity to it occurrence (see second point).	• Data must be preserved in its unaltered state according to written procedures and in agreement with record retention requirements. • If raw data is not kept there must be solid documented justification. • The records should not have been tampered with.	• Data must correctly reflect the actual measurement or observation made. • There should be no editing or errors without documenting and approval of the amendments.

Short Industry Examples

Company	Observation	ALCOA?
I	Production records revealed that the dispensary records had not been filled out contemporaneously and nor had they been checked but completed with the theoretical amounts after the event.	
J	The paperless chart recorder monitoring the Purified water plant recorded the data from inline conductivity and TOC on an SD card. There was no policy or procedure for downloading this data nor any means to "replay/review" it offline should it be required; the SD card was simply formatted as and when full of data indicated by and alarm.	
K	The NIR used to conduct raw material ID by QC within the inwards goods store regularly recorded "fail" results or outliers of the approved data set. The investigation routinely cited "passes compendial testing" added to data set. There was no explanation or procedure for routine expansion of data sets or how such results are not investigated using the OOS procedure.	
L	Inspection of the HPLC data acquisition system logs and sequences revealed that several blocks of data or analysis could not be matched with product release testing records (paper) that is the batch in question had more than one data set. Both data sets passed but only one was used without explanation.	

Risk Analysis

As part of introduction of any new hardware or software including Human Machine Interface there should be an impact assessment which should be part of CSV Master Plan.

An outcome of the IA may lead to a more complex RA as part of overall validation program justifications.

It is good practice to have such IA as a mandatory part of capital expenditure forms so as to predict the actual cost of implementation/validation i.e. LIMS, ERP

Risk Analysis

FRM-SOP-VAL-XXX
Equipment Impact Assessment Checklist

Item Name:	Equipment #:
Part of Process Line:	Location/Room:
GxPs taken into account: ☐ GMP ☐ GDP ☐ G(QC)LP ☐ GAMP ☐ Other	
Description of the main functions:	

Impact Assessment Checklist

	Complete the checklist questions below by ticking each line. If the answer is Yes but only related to a component of the item tick Yes and the Component box.	Component	Yes	No
1	Is the item, or components in direct contact with the product or auxiliary solutions during production or during "monitoring?	☐	☐	☐
2	Item provides an excipient or process ingredient?	☐	☐	☐
3	Does the item (or a component) produce data which impacts in process or final product release?	☐	☐	☐
4	Does the item wholly or partly independently decide on the further processing of products?	☐	☐	☐
5	Does the item (or a component) monitor a CPP or WPP control system with no independent verification?	☐	☐	☐
6	Item preserves product quality e.g. vent filter, HVAC, Gas etc.?	☐	☐	☐
7	Failure or alarm has direct effect on product quality or impacts a CPP/WPP?	☐	☐	☐
8	Does the item directly or indirectly control/monitor prescribed environmental conditions of products?	☐	☐	☐
9	Is the item involved in the generation / processing of analysis values?	☐	☐	☐
10	Does the item permanently save "critical" data?	☐	☐	☐
11	Does the item use electronic records / electronic signatures?	☐	☐	☐
12	Does the time contain data that describes the product or product quality?	☐	☐	☐
13	Does the item contain data (paper, files) that are used for registration with agencies?	☐	☐	☐
14	Is the item used as a primary or supporting source for batch tracing?	☐	☐	☐
15	Does the item directly or indirectly control/monitor the storage of products in regard to packaging, temperature, RH% or storage duration?	☐	☐	☐
16	Does the item automatically provide medically relevant information?	☐	☐	☐
17	Are products labeled with the item?	☐	☐	☐
18	Is item used for cleaning/sanitation or product contact equipment or sterilization?	☐	☐	☐

Opinion of a Subject Matter Expert (if in doubt)

	Sign
	Date

Classification

☐	**DIRECT IMPACT**	If the answer to any one of the above is Yes then the item is **Direct impact**.
☐	**INDIRECT IMPACT**	If the answer to any one of the above is Yes but relates to a component only then the item is **indirect Impact**.
☐	**NO IMPACT**	If the answer to all of the above is No then the item is has **no (GxP) impact**. This conclusion does not imply that it does not have GEP significance.

Complexity Assessment

Classify the item as:

☐	**COMPLEX**	**Complex** equates to novel or multi-module equipment where there is a need for integrated components to work synchronously e.g. a freeze dryer or filling machine
☐	**NOVEL**	A novel item is one that is custom built for the process step – it may be either complex or simple, but is generally classified as complex.
☐	**SIMPLE**	**Simple** equates to equipment that has only one module or unit e.g. a filter press, a mixing tank or an incubation room. These items are often purchased "off the shelf" are stand alone and not integrated

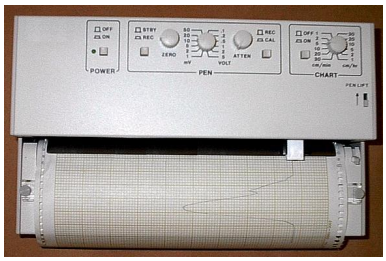
Conclusion:

Provide a concise justification for the classification of the item addressing both criticality and complexity.

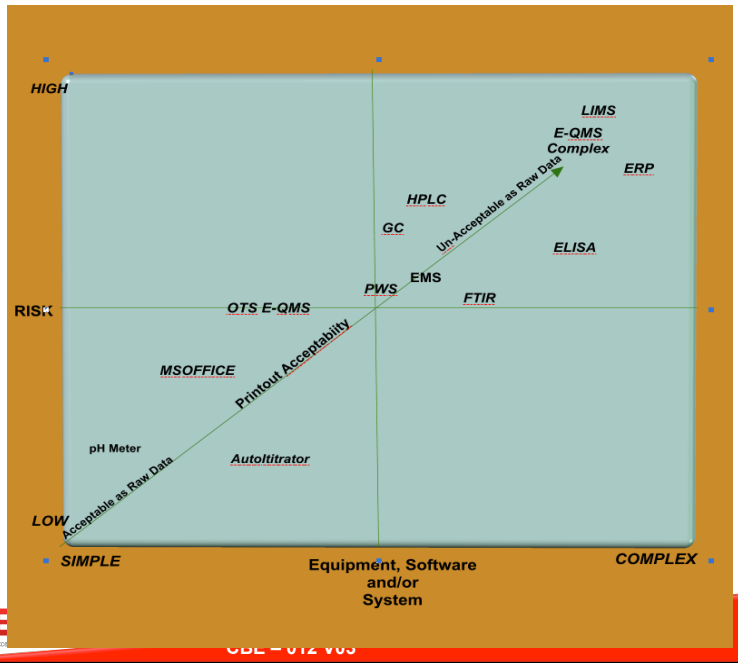
Approval of Report:

Name/Title	Signature	Date
Engineering		
Production		
Quality Assurance		

Things Have Moved On…☹



Risk Profiles



Risk Profiles

1. Laboratory Equipment-Automation/Data Processing/ LIMS
2. Facilities-Equipment-Automation/Data Processing
3. Production- Equipment-Automation/Data Processing
4. Quality Assurance –*E QMS*
5. Business-ERP/MRP/GDP

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Solutions?

- The IT group needs GMP training in respect of CSV and Data integrity (Finance usually already get audited).
- Data integrity needs to be built into the Quality Management System at a Policy “Level”.
- Data integrity need become a specific focus of regular internal audit programs.
- The PDA “Points to Consider Elements of a Code of Conduct for Data Integrity” provides a good basis for a Data Integrity Policy with its scope covering:
  - • Good Manufacturing Practice (GMP)
  - • Good Clinical Practice (GCP)
  - • Good Pharmacovigilance Practice (GVP)
  - • Good Laboratory Practice (GLP)
  - • Good Distribution Practices (GDP)
  - • Good Tissue Practice (GTP)

References

1. https://mhrainspectorate.blog.gov.uk/2015/06/25/good-manufacturing-practice-gmp-data-integrity-a-new-look-at-an-old-topic-part-1/
2. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf
3. PDA Code of Conduct
4. FDA CPG M7346832S508a

Global Regulatory Views

The same basic principles can also be found in the PIC/S and ISO guidelines:

- PIC/S Guide PE009-8:
  - CH4
  - Annex 11
- ISO 13485
  - Sections 4.2.3, 4.2.4

Pin Tail on Donkey

Coarse Data
Analytical
decision
making

Fine Data
Transactional
Processing

We will come back to this in the context of problem areas later….