

DATA INTEGRITY, TRENDS, ISSUES AND CHALLENGES

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For PDA Israel Chapter, July 2017

DISCLAIMER

- KAREN GINSBURY IS A CONSULTANT
- Your company has a Quality System and Quality Unit
- Karen will make you think about things once again, but you MAY NOT change anything from approved SOPs because “Karen said so”
- Any changes must go through the change control / change management process and be discussed and agreed internally with your Quality Unit

Top universities accused of hiding rise in fake research

Rosemary Bennett,
Education Editor |
Oliver Moody,
Science Correspondent

March 28 2017, 12:01am,
The Times



- University of Birmingham
- University of Bristol
- University of Cambridge
- Cardiff University
- Durham University
- University of Edinburgh
- University of Exeter
- University of Glasgow
- Imperial College London
- King's College London
- University of Leeds
- University of Liverpool
- LSE (London School of Economics & Political Science)
- University of Manchester
- Newcastle University
- University of Nottingham
- University of Oxford
- Queen Mary University of London
- Queen's University Belfast
- University of Sheffield
- University of Southampton
- UCL (University College London)
- University of Warwick
- University of York

At least 300 allegations of plagiarism, fabrication and inaccuracy were reported at the Russell Group universities between 2011 and last year

PAUL ROGERS FOR THE TIMES

The Research Integrity Concordat = Code of Conduct for DI



[the-concordat-to-support-research-integrity.pdf](#)

Research is far from what we do?

24 March 2017
EMA/188204/2017

EMA recommends suspension of medicines due to unreliable studies from Micro Therapeutic Research Labs

Medicines where suitable alternative data are available can remain on market

The European Medicines Agency (EMA) has recommended suspending a number of nationally approved medicines for which bioequivalence studies were conducted by Micro Therapeutic Research Labs at two sites in India. Bioequivalence studies are usually the basis for approval of generic medicines. The list of medicines recommended for suspension can be found [here](#). The suspensions can be lifted once alternative data establishing bioequivalence are provided.

Alternative supporting data have already been provided for several of the medicines reviewed. Therefore, the CHMP recommended that these medicines can remain on the market. The list of medicines recommended to remain on the market is available [here](#).

The Agency also recommended that medicines not yet authorised but which are being evaluated on the basis of bioequivalence studies from these sites should not be authorised until bioequivalence is demonstrated using alternative data.

Micro Therapeutic Research Labs is a contract research organisation (CRO) which conducts the analytical and clinical parts of bioequivalence studies, some of which are used to support marketing authorisation applications of medicines in the EU.

Research is far from what we do?

The review of medicines studied by Micro Therapeutic Research Labs was started after inspections to check compliance with good clinical practice (GCP) by Austrian and Dutch authorities in February 2016. The inspections identified several concerns at the company's sites regarding misrepresentation of study data and deficiencies in documentation and data handling.

The review, by EMA's Committee for Medicinal Products for Human Use (CHMP), concluded that data from studies conducted at the sites between June 2012 and June 2016 are unreliable and cannot be accepted as a basis for marketing authorisation in the EU. However, there is no evidence of harm or lack of effectiveness of medicines authorised and being evaluated in the EU on the basis of studies at the sites.

Some of the medicines which have been recommended for suspension may be of critical importance (e.g. due to lack of available alternatives) in certain EU Member States. Therefore national authorities can temporarily postpone the suspension in the interest of patients. Member States should also decide whether recalls of the affected medicines are needed in their territories.

The Guidances – Harmonization?

TWO kinds: Culture / QS vs Q&A

The time for talking is past...

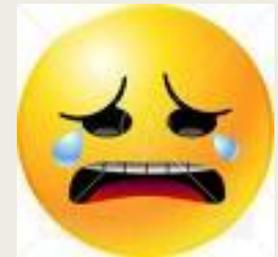
Date	Title	Content
11 Aug 2016	EMA: Good Manufacturing Guidance to Ensure the Integrity of Data	23 Q&A  EMA Data Integrity 110816.pdf
10 Aug 2016	PIC/s: Draft Guidance Good Practices For Data Management And Integrity In Regulated GMP/GDP Environments	41 pages  PIC/s 1 Draft 2 Guidance on Data Integrity.pdf
July 2016	MHRA: GXP Data Integrity Draft Guidance	14 pages  MHRA GxP data integrity draft 2016.pdf
April 2016	FDA: Draft Guidance: Data Integrity and Compliance with GMP Q&A	13 pages  FDA Data Integrity marked up.pdf
Sept 2015	WHO: Draft Guidance: Good Data and Record Management Practices	35 pages  WHO Good Data Management Practice.pdf
March 2015	MHRA: Data Integrity Definitions and Guidance for Industry	16 pages  MHRA Data integrity.pdf

Keywords List:

Objective

- Understand why Data Integrity is BURNING hot
- Issues and challenges
- Learn to BE objective

There is no place for emotions – put them aside



Metrics FDA is collecting

Tie in with: OOS, DI and Quality Culture

- **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance. LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe.
- **Product Quality Complaint Rate (PQCR)** as an indicator of patient or customer feedback. PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
- **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation of a laboratory. IOOSR = the number of OOS test results for lot release²⁷ and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe.^{28,29}

Shaming into compliance? Or Rewarding the good?

B. Quality Metric Reporters List

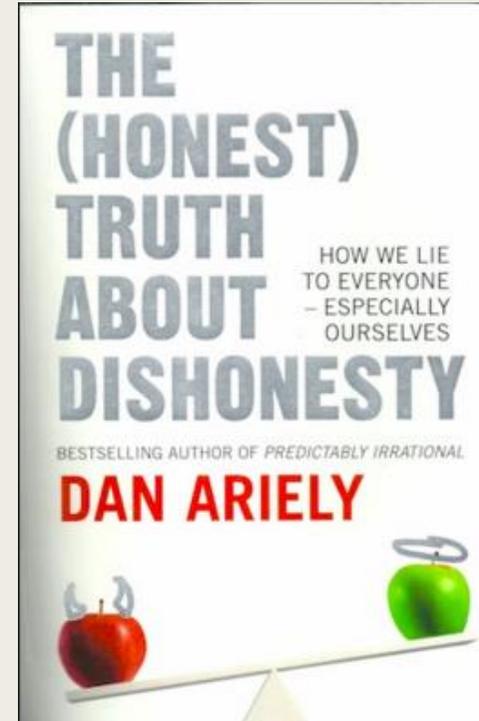
FDA intends to publish a list of the names of establishments that voluntarily report all or a subset of quality data as described in this guidance (i.e., product reporting establishments and site reporting establishments). We believe that there is a benefit to publicly sharing the names of establishments that voluntarily choose to submit these quality data to FDA because, through their participation, these establishments demonstrate a willingness to proactively engage with the Agency in pursuit of the goals described in this guidance. Participation in this voluntary reporting phase of the program also demonstrates a commitment to increasing transparency between industry and FDA and a contribution to improving quality monitoring throughout the industry.

This list may be useful to establishments within the pharmaceutical manufacturing industry when selecting contract manufacturers and component suppliers as one element of robust outsourcer or supplier selection (e.g., past inspection and regulatory authority history, audits of the facility and associated systems, and analytical testing). This list may also be useful for healthcare purchasing organizations, healthcare providers, patients, and consumers in sourcing drugs when used in conjunction with other information (e.g., inspection history). The list will provide information about *whether* an establishment voluntarily submitted quality metrics data to the Agency, and if

Integrity ...but I am HONEST



- We don't have data integrity issues here !!!



How many opportunities for cheating? ...but she is an HONEST person!



Karen Ginsbury, MSc, BPharm (~~MRPharms????~~)
CEO, PCI Pharmaceutical Consulting Israel Ltd

- Karen Ginsbury is a London, UK trained pharmacist with a second degree in Microbiology. With *close to 30 years'* experience in the pharmaceutical industry, Karen is a *quality practitioner* with a passion for doing things right and once only. She runs a *boutique quality systems consultancy* offering services to companies who want to set-up, maintain and constantly improve their quality management systems. Regularly lecturing in Israel and around the world, Karen also serves on international professional committees and *is co-chair of PDA's pharmacopoeial interest group*. In these and other capacities Karen benchmarks best practices around the globe in order to share them with her audiences. Double space or single space? Cherry picking???

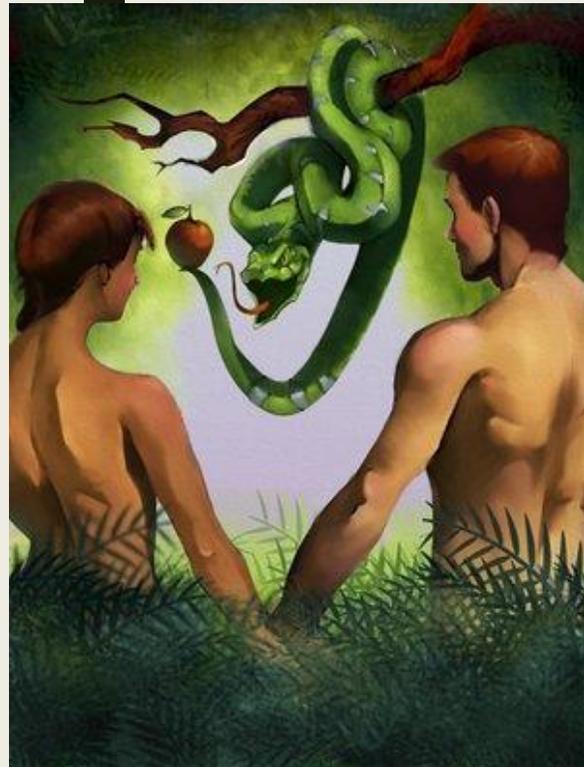
Any resemblance to the previous slide?



...but she is a “good” person

- Karen Ginsbury likes to do the right thing first time
- I have been working in the pharmaceutical industry since 1986 and remember the Barr court case
- I lecture and consult for different companies
I ask lots of questions and am asked a lot of questions
- I like to share best practices
- That’s what I am doing in San Diego
(other than mani/ pedi, shopping and walking on the beach)

Before... and After Truth / Lie Good/Bad



The Tree of Knowledge Obfuscation

The Ethical Skeptic

The obscuring of intended **meaning** in communication, making the message confusing, willfully ambiguous, or harder to understand.

Conclusion #1: Personal Integrity

- Is not enough
- We need PREVENTIVE measures and BARRIERS
- LONG TERM only **FULLY automated systems will PREVENT** data integrity issues

”ולפני עור לא תתן מכשול, ויראת מאלקד” (יט, ד)



- Assume people are intrinsically good
- Hierarchical and peer pressure, rush to get home, other psychological factors can cause them to make foolish decisions
- The purpose of the controls you put in place are to avoid making it easy
(putting a stumbling block before them)

It can't be left to chance - Data Governance

- The sum total of arrangements which provide assurance of data integrity
- ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used
 - *will ensure a complete, consistent and accurate record*
 - *throughout the data lifecycle*

Elements of a data governance plan

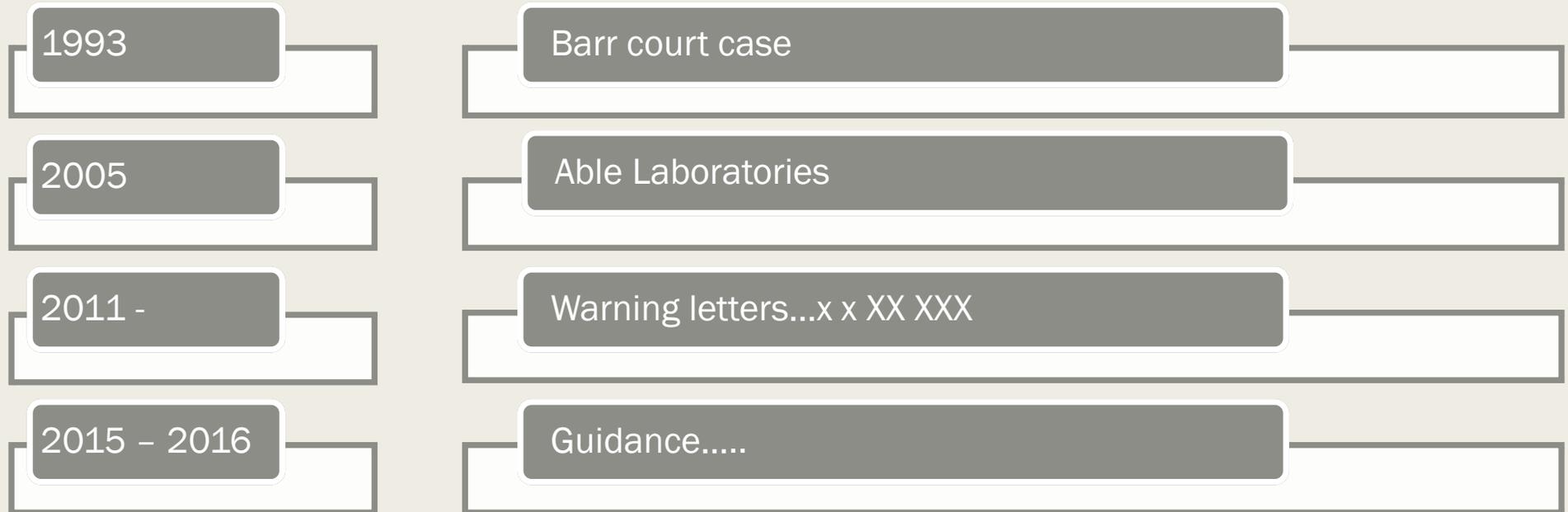
- Policy
- Educate
- Communicate
- Technology and IT
- Audit and CAPA

ALCOA+

- ✓ Accurate
- ✓ Legible
- ✓ Contemporaneous (real time)
- ✓ Original
- ✓ Attributable

- ✓ Accurate
- ✓ Complete
- ✓ Consistent
- ✓ Secure

OOS / Data Integrity timeline



1993 Barr

The New York Times

February 6, 1993

COMPANY NEWS; Judge Rules On Barr Labs

A generic drug manufacturer must recall batches of some of its medicines and stop distributing others until the company completes studies of its manufacturing process, a Federal judge ruled on Thursday. But United States District Judge Alfred M. Wolin refused a request by Federal pharmaceutical regulators to order a complete shutdown Saturday

Barr: What happened in court



The judge heard experts from FDA and Barr on retesting
FDA wanted retesting to be banned under all
circumstances

After a long hearing at which five industry experts, an
FDA investigator, and several company employees
testified, Judge Alfred M. Wolin, U.S. District Judge for
the District of New Jersey, issued a 79-page opinion

Barr: The outcome

Draft 1998; final 2006



- FDA OOS Guide
- OOS SOPs
- Later...OOT etc.



OOS.pdf

And along came Able...

17/08/2005 –

- Troubled generic drug manufacturer Able Laboratories has conceded defeat in its bid to get products back onto the market and elected to sell off the assets of the business

FDA Stops Them Manufacturing

- Able was forced to cease manufacturing and recall all of its products in May after serious questions were raised about **quality control** data used to obtain approval for products made at its manufacturing facility in New Jersey
- Able proposed FDA allow them to re-validate product development data from the ANDA under new management and with data verification by an independent outside consultant

FDA refuse

- FDA declined the proposal which is against its policy in situations involving questions of data integrity
- Able's only route back to market was to resubmit ANDAs with new data for review. This could take 18 months for each case a delay that was too long and costly and bankrupt the company
- *Able has determined that the best course of action would be to immediately reduce overhead and expenses as much as possible and to initiate the process of selling the company's business and assets*

Able happened 11 years ago

WAKE UP INDUSTRY

The Quality Unit failed to:

- Review computer audit trails in the Waters Empower Data Acquisition System
- Provide adequate training to analytical chemists

These practices led to:

- The QU releasing batches failing in-process, finished product and stability specifications
- Submission of erroneous data in Annual Reports and Prior Approval Supplements
- Ceasing manufacture, distribution and recall of all products as of 13 May 2005 and withdrawal of at least 5 ANDAs

Able: Resample, Re-injection, Reprocessing

Samples of drug products were routinely resampled, and re-injected or reprocessed in the Waters, Empower Data Acquisition System during testing in the QC Laboratory when out of specification (OOS) results were obtained. There were no Laboratory Investigations into OOS results or notebook documentation available to explain the re-injection or retesting of in-process, finished product and stability samples which did not meet specifications. The OOS results were not reported and within specification results from reprocessed or re-injected samples were reported on: In-Process Specification, Product Specification and Stability Study Specification Release Reports

Able 483 findings

OOS substituted with passing results

- The substitution of data was performed by:
 - *cutting and pasting chromatograms*
 - *substituting vials*
 - *changing sample weights*
 - *changing processing methods*
 - *OOS results found in electronic data files not documented in lab records*

2011 Warning Letter – Turbo 483

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed, and you failed to extend the investigation to other batches of the same drug product that may have been associated with the specific failure or discrepancy [21 CFR. § 211.192]

2011 Warning letter continued...

Your firm did not thoroughly investigate lot #1129BX014, when it failed to meet the established specification for both the single largest impurity and for total impurities amount.

- Specifically, the laboratory test results had a single impurity at RRT **0.8** minutes of **0.34** (specification limit NMT **0.3%** and total impurity result of **1.05%** (specification limit **NMT 1.0 %**)
- Your firm subsequently invalidated these results although your investigation was unable to confirm a root cause of the failure
- Your firm *selectively used passing results from a different analysis to approve the lot*

Altering time and date stamps



routine inspections of computerized systems may reveal gaps in security controls that inadvertently allow personnel to access and potentially alter time/date stamps. These findings help raise awareness to management of need to allocate resources to improve computerized systems validation controls;

WHO guidance

Independent IT personnel as administrators?



reduce data integrity risks. For example, identifying and addressing technical difficulties of equipment used to perform multiple GxP operations may greatly improve the reliability of data for all of these operations; identifying security conflicts and allocating independent information technology (IT) personnel to perform system administration for computerized systems, including managing security, backup and archival, reduces potential conflicts of interest and may greatly streamline and improve data management efficiencies.

WHO guidance

QU evaluate configuration settings data annotation tools...



In addition, key personnel, including managers, supervisors and quality unit personnel, should be trained in measures to prevent and detect data issues. This may require specific training in evaluating the configuration settings and reviewing electronic data and metadata, such as audit trails, for individual computerized systems used in the generation, processing and reporting of data. For example, the quality unit should learn how to evaluate configuration settings that may intentionally or unintentionally allow data to be overwritten or obscured through the use of hidden fields or data annotation tools; supervisors responsible for reviewing electronic data should learn which audit trails in the system track significant data changes and how these might be most efficiently accessed as part of their review.

WHO guidance

Rename, copy, delete local files on stand alone system?



- If users of stand-alone computerized systems are provided with full administrator rights to the workstation operating systems on which the original electronic records are stored, this may inappropriately grant permissions to users to rename, copy, delete files stored on the local system and to change the time/date stamp. For this reason validation of the stand-alone computerized system should ensure proper security restrictions to protect time/date settings and ensure data integrity in all computing environments, including the workstation operating system, the software application and any other applicable network environments.*

WHO guidance

Q#1 What is an OOS

Q#2 and is it a problem?

Q#3 is data integrity only in the lab?

- Hint: Stability testing and COA
- Hint 2: Analytical methods validation
- Hint 3: DI and regulatory submissions?

What is an OOS

- What is a specification? A document that lists all the results and the limits that you are supposed to get when testing a product or material or a component
- A specification is a list of Critical Quality Attributes of a material, component, product that must meet a limit, range or specified value in order for the item to perform its function as intended
- A result which does meet the specification meaning that the item deviations / does not meet the requirements: ONE OR MORE OF THE CRITICAL QUALITY ATTRIBUTES is NOT met which means the item will not / cannot function as intended and IS LIKELY to cause HARM

IF I have several OOS / OOT's for a product over time

- I can't and won't know if the problem is in the test method or the process
- So I have to look at the validation file and at PQR – product quality reviews annual product review as well and trends – has the process or the method moved? / changed
- And I open the validation of the analytical method and the process what should I look for?
- Extremes – where do I get extremes, ranges, variations, reproducibility or lack of it

Q#3 What is an OOT?

- Q#4 And is it a problem?
- Q#5 Do we *ALWAYS* have to respond to an OOT

What is an OOT: Out of Trend

- Results that are close to the upper or lower limit
- Results that are different from what we are used to getting
- Stability results that are out of the usual trend
- Needs to be statistically based
- The average and the limits are statistical

A RESULT CAN ONLY BE OUT OF TREND, IF I HAVE A WRITTEN METHOD FOR COLLECTING AND STATISTICALLY ANALYZING TRENDS

OOT in stability

- Different to QC release or in process or starting material test?
- What is your POLICY?
- Do analysts UNDERSTAND
- What about new hires?
- What about SUPERVISORS and approvers
- What about OUTSIDE the lab?s

Q#6: What is an Unusual, Questionable, “Atypical” Result

- Q#7 Is it a problem?

What is an Unusual, Questionable, “Atypical” Result

- It is a result which the analyst “doesn’t like”
- Can you retest? Should you retest?

Warning Letter 19 October, 2016 China

Unstable baseline; cleaning hard drive

2. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

Our investigators observed systemic data manipulation across your facility. They documented unexplained deletions of laboratory test results. They discovered that you repeated tests until you obtained acceptable results and that you failed to investigate out-of-specification or otherwise undesirable test results. Your firm relied on these falsified and manipulated test results to support batch release and stability data. Your firm routinely re-tested high performance liquid chromatography (HPLC) samples and deleted previous chromatograms without justification. Your management acknowledged that employees in your quality control laboratory have access, authority, and the ability to delete and repeat HPLC injections when undesirable results were encountered prior to reporting final results.

Your response states repeated testing was due to quality control operators continuously injecting solvents until a stable baseline was achieved. The response also states the results of repeated tests were deleted to decrease the number of saved chromatograms on your hard drives. Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes. In order to exclude data from the release criteria decision-making process, you must have valid, documented, scientific justification for its exclusion.

Reducing the number of records on your hard drives is not a sufficient justification for excluding data. Your response is inadequate because you have not shown how you will correct the data manipulation and falsification practices discussed above, nor have you demonstrated how you will ensure that all CGMP test results are retained and considered by your quality unit as a part of batch release.

You do NOT want to go there...

DI Remediation

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

You do NOT want to go there...

Investigators are out of patience

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

GIGO: ALCOA+

nothing lost, changed or manipulated

Data → Information → Knowledge



Performed by....
Defined in an SOP

- To perform the action
- 100% responsible for the action and all activities associated with its performance and documenting its performance (may be electronic documentation)

Verified by... Defined in an SOP

- To verify that the action was performed according to the current, written approved instructions
- 100% responsible for verifying that the action was performed correctly including all activities associated with its performance and the documentation of these
- MUST BE PRESENT THROUGHOUT AND WITNESS, THE PERFORMANCE OF THE ACTION AND ITS DOCUMENTATION before signing as verifier

The reviewer or approver Defined in an SOP

- Approves data and analysis of the data –
IS NOT PRESENT when the work is
performed
- Should be provided with sufficient raw
data and analysis to enable a complete
and accurate review

Have you ever...

- Back dated a document
- Filled in missing data
- Replaced a page in a controlled document to correct a typo without changing the version number...
BECAUSE YOU CAN and not because you are a wicked person – unconscious...or conscious incompetence?

WHO Guide pages 16 – 20
take a look

- Risk based approach outlining the particular risks for each aspect of ALCOA+

PIC/s Guidance

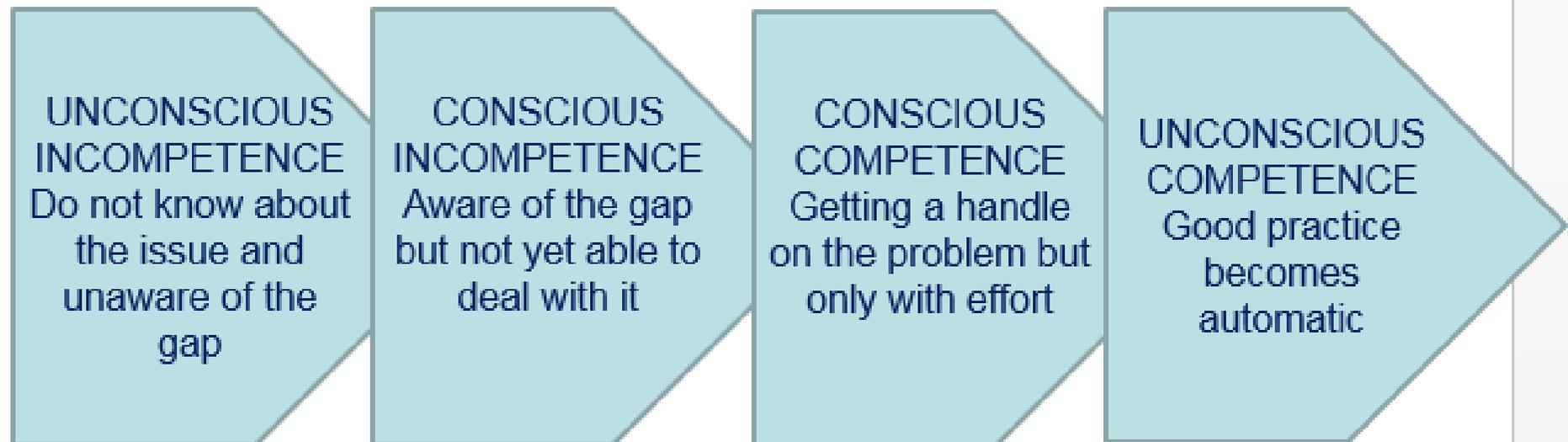
Does have limited mention of PLCs

The number of tests should be guided by a risk assessment but the critical functionalities should be at least identified and tested, e.g., certain PLCs and systems based on basic algorithms or logic sets, the functional testing may provide adequate assurance of reliability of the computerised system. For critical and/or more complex systems, detailed verification testing is required during IQ, OQ & PQ stages.

Restricting access to PLC nodules (sic probably modules) , e.g. by locking access panels.

PI 041-1 (Draft 2) 29 of 41 10 August 2016

Data Integrity



Warning Letter: Lack of Basic Controls

- c) A “File Note” dated February 10, 2014, signed by the QC Head, established that the printed data used for batch disposition decisions from the Metrohm Titrando Instrument MLG/QC/12/048 hard drive was not necessarily the complete data for a batch. Our inspection found that data on the instrument was selected for use and was not protected from change and deletion. Notably, the audit trail capability of this QC “commercial” laboratory instrument was not enabled, even after creation of the “File Note.”

Backdating

- Our investigators found backdated batch production records dated February 10 to February 25, 2014, signed by your Production Manager and Technical Director in the “Batch Manufacturing Record Reviewed by” section.
- The Technical Director stated that he was not in the facility on these dates and was “countersigning” for another person who allegedly performed these review activities. However, these records did not contain signatures (contemporaneous or otherwise) of the alternate reviewer who purportedly conducted the review.
- Furthermore, the Technical Director backdated his own signature to the date the quality unit (QU) reviewed and released your drug product. You released these batches before the Technical Director returned to the facility and backdated his signatures.

Failure to record activities at the time they are performed and destruction of original records

- Specifically, your employees completed batch production records entries days after operations had ended, released lots before the proper approvals, and failed to maintain original manufacturing data for critical steps in the batch production records. For example, Our investigators found that some of your operators used “rough notes” (unbound, uncontrolled loose paper) to capture critical manufacturing data and then destroyed these original records after transcription into the batch production records
- For example, the (b)(4) chemist recorded original manufacturing data as rough notes and left these rough notes for the (b)(4) chemist to transcribe into the batch production records. The next morning, the chemist signed the batch production records and destroyed the original rough notes. We interviewed employees during the inspection who confirmed your firm’s practice of transcribing data to batch records and destroying original records.

Shared Passwords

- 6. Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b))
- You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters. Access to production equipment used in parenteral manufacturing and solid dosage forms used a password shared by four or five individuals to gain access to each individual piece of equipment and access level.
- During our inspection, your Executive Production and QA manager confirmed that the password was shared. During our inspection, firm officials also confirmed that you had not established or documented a control program to describe the roles and responsibilities of production equipment system administrators. There was also no record documenting the individuals who have access to the production equipment or the manner in which individual personnel access production equipment.

Data Integrity: Paper / hybrid / Electronic

- Data is precisely recorded. On retrieval, the data is the same as when originally recorded, complete, consistent, accurate, attributable throughout the lifecycle (archiving, retrieval)
- The accuracy and consistency of stored data, indicated by an absence of any alteration in data between two updates of a data record. Data integrity is imposed on a system at its design stage through standard rules and procedures, and maintained through error checking and validation routines.
- Critical aspect in the design, implementation and usage of any system which stores, processes or retrieves data

Data integrity issues:

- Deletion – raw data
- Change – raw data
- Incomplete – raw data
- Unofficial or trial testing
- AA spectro – over 400 analyses – only 38 data files
- Audit trails deleted
- SOPs don't include instructions for retention of raw data
- Date of second signature – what does SOP say?
- Disabled audit trail function
- Unauthorized file folders e.g. for column wash data

MetaData

- is data that describe the attributes of other data, and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual.

MHRA, Data Integrity Definitions and Expectations and Guidance for Industry, January 2015

MetaData

Example: data (bold text)

3.5

and metadata, giving context and meaning, (italic text) are:

sodium chloride batch 1234, 3.5mg J Smith 01/07/14

Metadata forms an integral part of the original record.
Without metadata, the data has no meaning.

MHRA, Data Integrity Definitions and Expectations and Guidance for Industry, January 2015

Original record vs True copy

- **Original record:** Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerised system
- **True Copy:** An exact copy of an original record, which may be retained in the same or different format in which it was originally generated, e.g. a paper copy of a paper record, an electronic scan of a paper record, or a paper record of electronically generated data

MHRA, Data Integrity Definitions and Expectations
and Guidance for Industry, January 2015

Original record vs True copy

- Raw data generated by electronic means *may be* retained in a paper or pdf format. The data retention process must be shown to include verified copies of all raw data, metadata, relevant audit trail and result files, software / system configuration settings specific to each analytical run*, and all data processing runs (including methods and audit trails) necessary for reconstruction of a given raw data set. It would also require a documented means to verify that the printed records were an accurate representation. This approach is likely to be onerous in its administration to enable a GMP compliant record.
- * computerised system configuration settings should be defined, tested and 'locked' as part of computer system validation. Only those variable settings which relate to an analytical run would be considered as electronic raw data.

STRATEGY - DEFINE

Have you defined (in an SOP)...
Educated and communicated...
Verified understanding of...

- Data
- Raw Data
- Meta Data
- Derived Data
- Original Record
- Primary Record
- True Copy
- Certified Copy

Some risks

- Paper based: missing signatures, details
- Excel spreadsheets
- Stand alone software
- Log on / log off
- Printouts vs unintegrated data

Risk Mitigation

Might be better to move to VALIDATED electronic records where QA review electronic record and cut out several paper based risks:

Electronic data – printout – reduce size – paste in notebook – QA review and sign notebook

Or one step?

What are the Stumbling Blocks?

Credit to: Madlene Dole, Novartis

- Performance and business pressure
- Lack of awareness or capability
- DI not (fully) integrated into our culture
- Inadequate processes and technology

KG: there is no excuse for a balance without a printout
KG: after meeting with client x – it is not good enough!!

Login



GUEST



1234

Remember me

[Forgot your password?](#)

LOGIN

STRATEGY – PLAN, DEFINE, IMPLEMENT, MAINTAIN, AUDIT

Audit trail and controls at two levels:

System Life Cycle

- Planning and Specifications
- Development
- Verification and acceptance
- Operation and Maintenance
- Retirement

Data Life Cycle

- Data Creation
- Data Processing
- Data Review
- Data Reporting
- Data Retention

STRATEGY – SEGREGATE DUTIES TO MAXIMIZE OBJECTIVITY

Minimize threats to DI by:

- Segregation of Duties (SOD)
- Configuration of systems
- Backing up data regularly
- Controlling access to data via security mechanisms
- Designing user interfaces that prevent the input of invalid data
- Using error detection and correction software when transmitting data
- Audit trail Review

Segregation of duties

Roles and Responsibilities allowing a conflict of interest that would allow alteration of data.

For example, the QC Lab Manager acting as system administrator for Empower would violate segregation of duties

Data Governance Policy

- Values:
The Officers of this company expect every employee to provide accurate, complete and contemporaneous (real-time) records of activities and to perform all tasks with integrity especially when no one is looking
- Tools:
Managers are expected to provide staff with the means to allow them to perform their tasks with integrity, to collect, analyze and report data accurately, completely and on real-time including but not limited to:

Data Governance

- Senior management is responsible for the implementation of systems and procedures to minimise the potential risk to data integrity, and for identifying the residual risk
- Contract Givers should perform a similar review as part of their vendor assurance program

Data Integrity Code of Conduct

- Annual signature of all employees that they are aware of it and followed it...what about MOST senior management / officers of the company???
- Culture?

Warning letters

a. The inspection documented that HPLC processing methods (including integration parameters) and re-integrations are executed without a pre-defined, scientifically valid procedure. Your analytical methods are not locked to ensure that the same integration parameters are used on each analysis. A QC operator interviewed during the inspection stated that integrations are **performed and re-performed until the chromatographic peaks are “good”**, but was unable to provide an explanation for the manner in which integration is performed. Moreover, your firm does not have a procedure for the saving of processing methods used for integration.

Your response did not include a description of the method by which chromatograph integrations are to be performed (e.g., what constitutes a chromatographic peak, how shoulder peaks are to be handled, etc.). **In addition, your response did not include an audit of past chromatographic data to determine whether data used to support release and stability studies originated from appropriately integrated chromatograms.**

Warning letters

- the use of the Excel® spreadsheets in analytical calculations are neither controlled nor protected from modifications or deletion. The investigator noticed that the calculation for residual solvent uses an Excel spreadsheet that has not been qualified. We are concerned about the data generated by your QC laboratory from non-qualified and uncontrolled Excel spreadsheets.

In response to this letter, provide a retrospective evaluation of the analytical values reported where such Excel spreadsheets have been used.

CAN'T WE DO BETTER THAN EXCEL?

Computerized Spreadsheets

- Error in / incorrect formula
- Spreadsheet not protected or locked
- Data loss through inadvertent or intentional deletion, errors, computer issues
- Omitted, added or altered information
- Entry / transcription errors

Data integrity audits

- Educate
- Show others what is unacceptable
- Show them how to correct bad practices
- **Integrate automated methods for data integrity which are difficult to bypass**
- AUDIT, CORRECT, AUDIT, CORRECT, involve management and measure – metrics – are the number and seriousness of the findings decreasing?

In Conclusion: Strive for Truth

- Know the basic concepts of Data Integrity
- Keep a close eye on OOS and EDUCATE everyone – up and down in the organization
- Understand the use of audits
 - *Formal: internal audit program*
 - *On-the-spot: sometimes and whenever a problem is suspected*
- Recognize that the opportunity with data integrity is to **DESIGN** controls **INTO** the computerized system
- People based systems are stumbling blocks and will ultimately fail

In Conclusion: Strive for Truth

- Traceability
- Transparency – document, date and sign with reason for ANY amendment recorded

Links to guides

- EMA Data Integrity Guidance Q&A
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp#section17
- PIC/s Data Integrity Guidance
https://www.picscheme.org/useruploads/documents/PI_041_1_Draft_2_Guidance_on_Data_Integrity_2.pdf
- MHRA: GxP Data Integrity Definitions and Guidance
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/538871/MHRA_GxP_data_integrity_consultation.pdf
- WHO: guidance on good data and record keeping
http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15-624_16092015.pdf
- FDA Data Integrity and Compliance with cGMP
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf>
- MHRA: GMP Data Integrity Definitions and Guidance
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf

THANK YOU FOR PARTICIPATING

Questions ???

Find me

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Keywords – List...

- ALCOA+
- Compliance
- Notification
- Trust
- Patient safety
- Dollar signs – silly stuff

OOS Keywords

- OOS
- OOT
- Questionable / unusual / atypical result
- Reportable result
- Retest
- New test
- Invalid test
- Aborted test
- New test
- Resample
- Data Integrity
- Batch release
- Investigation
- Laboratory error
- Production error
- Sampling error
- Data integrity
- Data quality
- Averaging
- Training, qualification, education
- COA
- Reporting Results