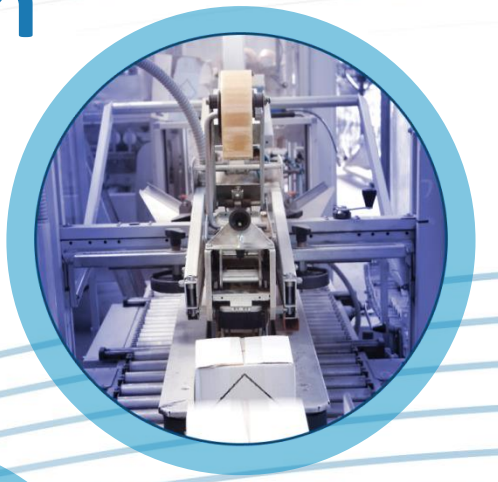
Connecting People, Science and Regulation®

Data Integrity and Quality Culture Virtual Symposium
21st May 2020

Data Integrity – Focus on Microbiological Testing Challenges



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Data Integrity

Challenges in Microbiological Testing

- Are DI issues happening more frequently?
  - No, we are more aware
- Are they always intentional acts?
  - Not always; a lot are due to poor GMP practices (Improper Practice). 80/20 rule applies (probably!)
- Is the impact on integrity of data different?
  - Whether inaccuracies are intentional or unintentional, the impact on the data is the same.
- Why focus on DI in Microbiological Testing?
  - They are mainly manual, qualitative processes

Data Integrity – First Principles

Definitions – Data Integrity

- **The extent to which all data are complete, consistent and accurate throughout the data lifecycle. This means:**
  - Data integrity arrangements must ensure that the accuracy, completeness, content and meaning of data is retained throughout the data lifecycle.
- *Ref MHRA Data Integrity Definitions and Guidance March 2018*
- Most recent (Nov 2018) PIC/S Guidance "Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments" matches the MHRA definition
- FDA defines DI as
  - **"data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).**

Data Integrity

Definitions – Data Integrity

ALCOA+

- Complete
- Consistent
- Enduring
- Available

Data Integrity

Definitions – Data Integrity

- **Complete**
  - All data from an analysis, from the start of analysis to the end and any repeated or reanalysis performed on the sample.
  - For electronic systems, the paper output must be linked to the underlying electronic records used to produce it.
- **Consistent**
  - All elements of the analysis, such as the sequence of events, follow on and data files are date (all processes) and time (when using electronic systems) stamped in the expected order
- **Enduring**
  - Recorded on authorised media e.g. laboratory notebooks, numbered worksheets, for which there is accountability or electronic media
- **Available**
  - The complete collection of records can be accessed or retrieved for review over the lifetime of the record.

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Definitions – Improper Practice

A scientifically unsound or technically unjustified omission, manipulation, or alteration of procedures or data that bypasses the required quality control parameters, making the results appear acceptable.

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Definitions – Laboratory Fraud

The deliberate falsification of analytical or quality assurance results, where failed method requirements are made to appear acceptable during reporting.

- The intentional recording or reporting of incorrect information
- An intentional deviation from method specified analytical practices, combined with the intent to conceal the deviation.

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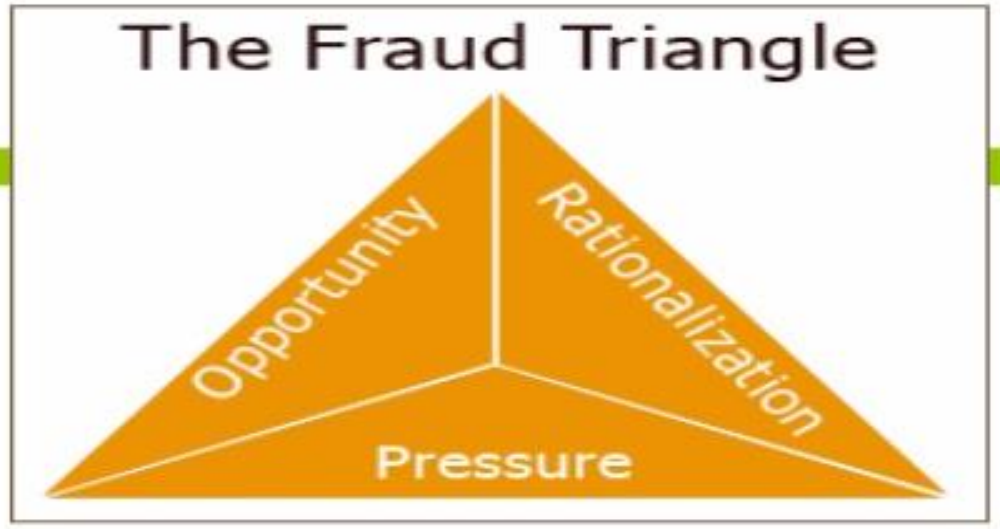
What is the Difference Between Fraud and an Improper Practice?

- **Improper practice** could be a DI issue linked to system/ process design, training, method incorrect
- **HOWEVER,**
- **Fraud** is purposeful and intentional
- Fraud is not a mistake.
- Fraud is an intentional misrepresentation of lab data to **hide known** or potential problems.
- Fraud makes data look better than it really is, **with the intent to deceive**.
- Sometimes the perceived difference between fraud, improper practice and honest mistake is inadequate documentation.
- **However, FDA in their 2016 DI Guide do not differentiate!**

Data Integrity - Fraud

Cressey Fraud Triangle



- Generally employees commit fraud because there is
- "Opportunity", "Pressure", and they "Rationalize" their conduct
- **We need to break the triangle: First step is to remove or minimize "Opportunity"**

Source: Dysfunctional anti fraud compliance - Kamudoni Nyasulu Director at United Nations Sep 2015

Data Integrity – why focus on Microbiological Testing?

Data must comply with all of the ALCOA+ Principles

This is easier said than done especially for Microbiology Laboratories

WHY?

They are mainly manual processes

Less automation than Chemistry Laboratories

There has been less Regulatory Guidance for the microbiologists

OPPORTUNITY

exists for both intentional and non intentional Fraud

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Microbiological techniques - Facts

- **Microbiological techniques rely on:**
  - Personal Integrity of the microbiologist
  - Experience
  - Training
  - Ability of the peer review to detect poor data integrity and to speak up (Culture of the company)

- **Many microbiological techniques also have a subjective and variable interpretation and documentation of test results in not standardised**

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Key tests

- **What tests get most scrutiny?**
  - Test for Sterility
  - Endotoxin testing (gel clot)
  - Environmental Monitoring
  - Product Enumeration tests including Bioburden and utility test samples

- **They all rely on one individual to do the testing and maybe the same person to read the samples and record the results**
- **Applying ALCOA+ principles to every aspect is difficult**

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Key Message from Regulators – Quality Culture

"Management should aim to create a work environment that is transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes, including potential data reliability issues so that corrective and preventive actions can be taken."

Source: PIC/S Guidance - Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments PI-041-1 (Draft) 30Nov2018

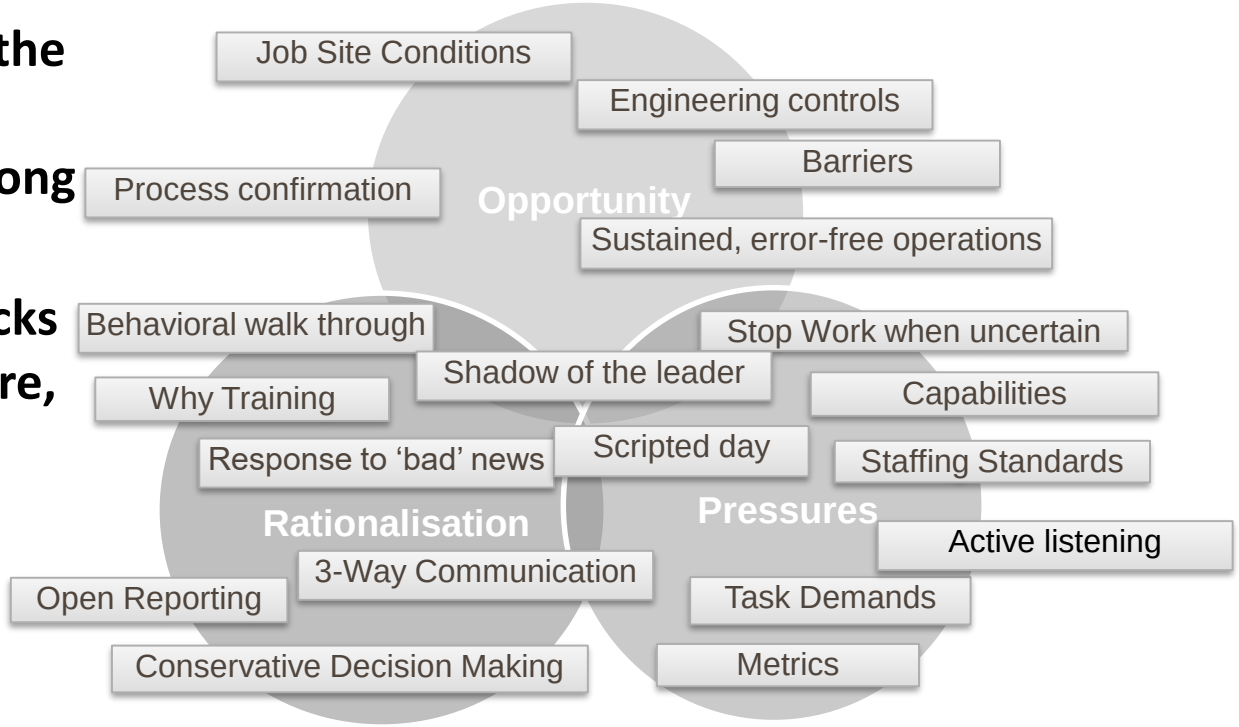
What can happen when Data Integrity Issues are not addressed?

- **When Data Integrity issues are not addressed, we can become blind to them, and they become systemic.**
- **When a lower standard is accepted, the lower standard can lead to a drift into failure.**
- **What we permit and promote on a daily basis becomes the unwritten standard.**

How do we avoid DI Incidents?

Cressey Fraud Triangle

- **Make it easier to do the right thing, more difficult to do the wrong thing. (Opportunity)**
- **Remove the roadblocks to following procedure, put safeguards and detection in place to taking shortcuts (Pressure)**
- **Hold the system to account not just the people (Rationalization)**
- **Address the 3 enablers of fraud (Cressey):**



It is human nature to try to meet goals and to do a good job

- **People will do reasonable things given their perception of:**
  - Goals
  - Knowledge
  - Focus of Attention

- **They do what makes sense at the time (sometimes contrary to their Training).**

- **This is known as the Local Rationality Principle.**
- **In order to investigate, we must understand what the conditions were at the time of the event**
- **In order to prevent data integrity issues involving human error, we must influence the conditions around people to help them to succeed.**

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How to evaluate DI risk

- Evaluate each high risk technique
- Solutions should not introduce more errors or add risks to the process
- Process map each step of the task
- Use Risk analysis techniques – do not just use FMEA
- Apply ALCOA+ principles and ask how you can make it easy to do the task at each step
- Then determine the risk to the data
- Remember - Prevention is first task, detection is second (but both important)
- Reduce the opportunity (**intentional and unintentional**) to get it wrong, calculate how long each step takes to reduce testing pressures

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Attributable example

- Traceable to a UNIQUE person
- **You should be able to tell who created, modified, or deleted a record. AND, you can judge if that person was appropriately authorised to do it!**
- Environmental monitoring plates:
  - Who accepted the plates into laboratory - confirmation of number of plates expected / received (Sample custody / traceability)
  - Use of Bar codes to reduce transcription errors and to record actual times and dates, locations
  - Put in the incubator – time; date; who by?
  - Plate reading – single person, or a team?
  - Paper records or electronic records?
  - Do we need a second person verification – e.g. de plates; over alert or action limits?

The Second Person Check (1)

PIC/S Guidance Nov 2018 – Selected Extracts

- "A - Records of critical process steps, e.g. **critical steps within batch records**, should be:
- - reviewed/witnessed by designated personnel (e.g.: production supervisor) **at the time of operations occurring**; and
- - reviewed by an authorized person within the production department before sending them to the Quality Assurance unit ; and
- - reviewed and approved by the Quality Assurance Unit (e.g. Authorized Person / Qualified Person) before release or distribution of the batch produced.

- C- **Laboratory records for testing steps** should also be reviewed by designated personnel (e.g.: second analysts) **following completion of testing**. Reviewers are expected to check all entries, critical calculations, and undertake appropriate assessment of the veracity of test results in accordance with data-integrity principles."

The Second Person Check (2)

Implications

- Does this mean doubling the size of the QC department?!
- No – PIC/S also states:
  - "The need for, and extent of a secondary check should be based on quality risk management principles, based on the criticality of the data generated."

- So the key is the criticality of data, also whether there are any other means of verification of data available (based on risk management principles). i.e. if quantitative data from the test is captured using an automated system (Remove/reduce "opportunity" for fraud)
- However, many microbiological tests only produce qualitative data, where an element of interpretation is required i.e. Consider 2nd person check (contemporaneous)

Data Integrity – Reminder of how ALCOA applies to Microbiological Testing

Legible examples

- Readable, Traceable Changes, Permanent
- **You should be able to read all the entries on the paper record. If a change was made, the original value was crossed out with a single line, and the change was dated and initialled.**
- **You should be able to see in an electronic files data changes and deletions. Is it clear what the original value was? When it was created and who created it?**
- Environmental plates:
  - How is the data being recorded – paper or directly electronically
  - If electronic can you see any amendments; is it immediately recorded or is it only when save is pressed?
  - Is there enough space to record the data
  - Is there enough space for a second person verification when required. Consider traceable photograph of critical plate results.
  - Is the paperwork at the right place to document the work

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Contemporaneous

- Record the activity at the time it occurred
- **For a paper record the creation, modification, and deletion of data happens at the right time in the process.**
- **For an electronic record when it was created in a process, the audit trail should confirm the time of test.**
  - This topic seen to be difficult by some authors of papers e.g. PIC/S
  - You cannot stop an aseptic operation to record an activity
  - As part of process mapping, what activities can be 'batched' together with a time started and finished with the sign & date criteria
  - Be pragmatic – make it easy to get it right
  - This happens in manufacturing & it can be the same in Microbiology Laboratory; put it in the procedure and the templates
  - 2nd person to record?

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Original

The first record made by appropriate person (Could be a 2nd person)

If not original, it should be exact (or "true") copy - Original records and true copies must preserve the integrity (accuracy, completeness, content and meaning) of the record. Exact (true) copies of original records may be retained in place of the original record (e.g. scan of a paper record), provided that a documented system is in place to verify and record the integrity of the copy.

You must be able to reconstruct the activity from the original or true copy data

- **How do you ensure the record is an original record; because often in industry there is a tendancy to use loose leaf forms (lab (e)notebook is better)**
  - Are they pre numbered ?
  - Are they reconciled?
  - Are they formally issued to the microbiologist?
  - Is there a segregation of duties?

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Accurate

- **Accurate, consistent and real representation of facts.**
- **No editing without documented amendments /audit trail entries by authorised personnel**
  - Make sure of the information that you are recording is correct, honest and transparent
  - Record the data directly into the controlled unique blank record/bound book/electronic programme
  - Where possible use automatic data capture
  - Are the electronic records the same as the paper records
- Sometimes in Industry we do pre-reads of tests such as sterility tests. Do our records reflect interim reads and the last result (Complete data)
- Is it Subjective data (opinion?)
- Second person verification may be needed for the final reading; or to confirm suspected positive

Data Integrity – Microbiological Testing Issues (examples)

How can we Detect……

- Caramelised media
- Delays between preparation of media and sterilisation
- Disinfectant residues on glassware
- Agar temperatures during pour plate analysis
- Depth of poured plates
- Errors/insufficient presumptive identification – use of incorrect card type
- Over decolourisation of gram stain
- Interpretation of automated system result
- Aged culture affecting identification profile
- Sample Custody- are you assured of the location of your EM plates that are now under test?

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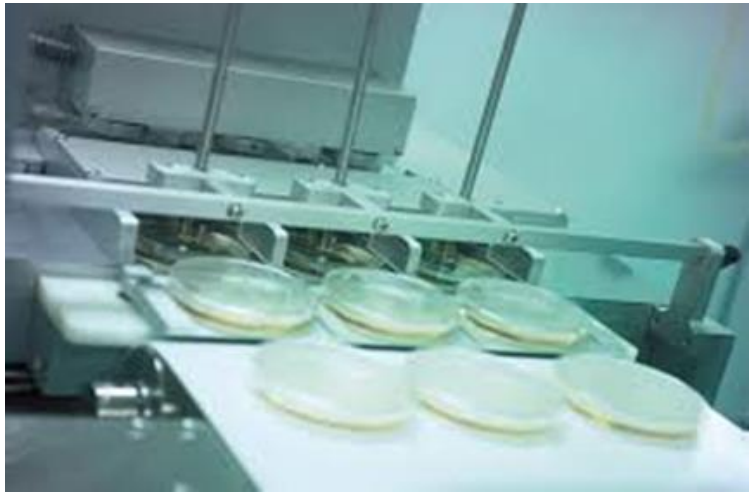
How can we Prevent……

- Caramelised media – **use automatic validated media makers or buy in**
- Delays between preparation of media and sterilisation – **appropriate contemporaneous recording**
- Disinfectant residues on glassware – **use validated automatic glass washing equipment**
- Agar temperatures during pour plate analysis – **water baths with temperature records**



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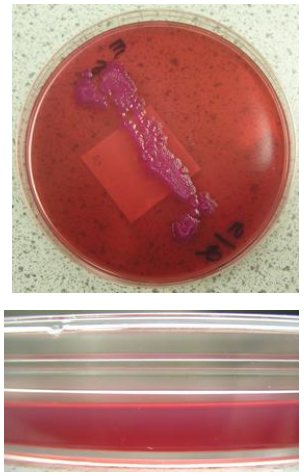
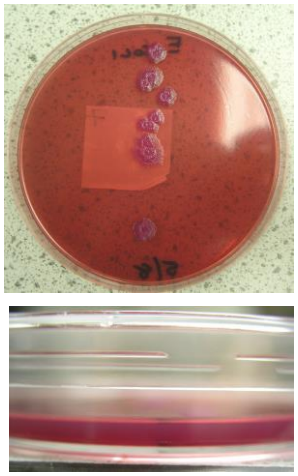
How can we Prevent……

- Depth of poured plates – **spot checks**
- Over decolourisation of gram stain – **use a Gram positive control on every slide and record the result; use photographs**
- Interpretation of automated system result – **have a minimum acceptance criteria; check morphology of original colony with the system result**
- Errors/insufficient presumptive identification – use of incorrect card type
- Aged culture affects identification profile



Thick 'n' thin

(effects on microbial recovery)



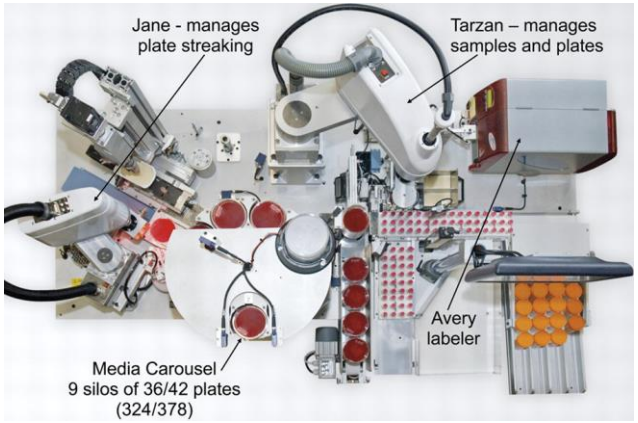
DI– We need more automation!

Rapid Microbiological Methods

- New equipment and methods are being developed all the time.
- Data Integrity requirements have to be built into the URS
- Have to follow the same principles as a Chemical Analysis
- They have their issues too:
  - ensuring that the methods are “Suitable for Intended Purpose”
  - **They have to follow the basic requirements of ICH Q2(R1) guidance and USP chapter <1223>**
  - **The equipment used has to follow EU GMP Annex 11 and Annex 15 requirements**

Manual

Automated



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Conclusion

- **Microbiological Laboratories have manual testing and recording of data**

- bringing "Opportunity" for 'falsification' or 'incorrect method'

- **First task – Risk Assess the data you are gathering**
- **Not easy to put in detection methods**
  - Need to embrace more rapid microbiological methods (more automation)
  - Remember to build in detection methods as part of the URS
- **Traditional methods to detect DI issues:**
  - Look at trends – if too good to be true ……..
  - Look for data patterns
  - Perform spot checks – including Self Inspection, Indeper Audit, *ad hoc* GEMBA
  - Introduce second person verification for critical parts of a test

- **Make it easy to get it right (reduce space of fraud triangle)**
- **Speak up if something needs to be changed (corporate culture)**

Reminder on “Data” – Why so crucial?!

W Edwards Deming