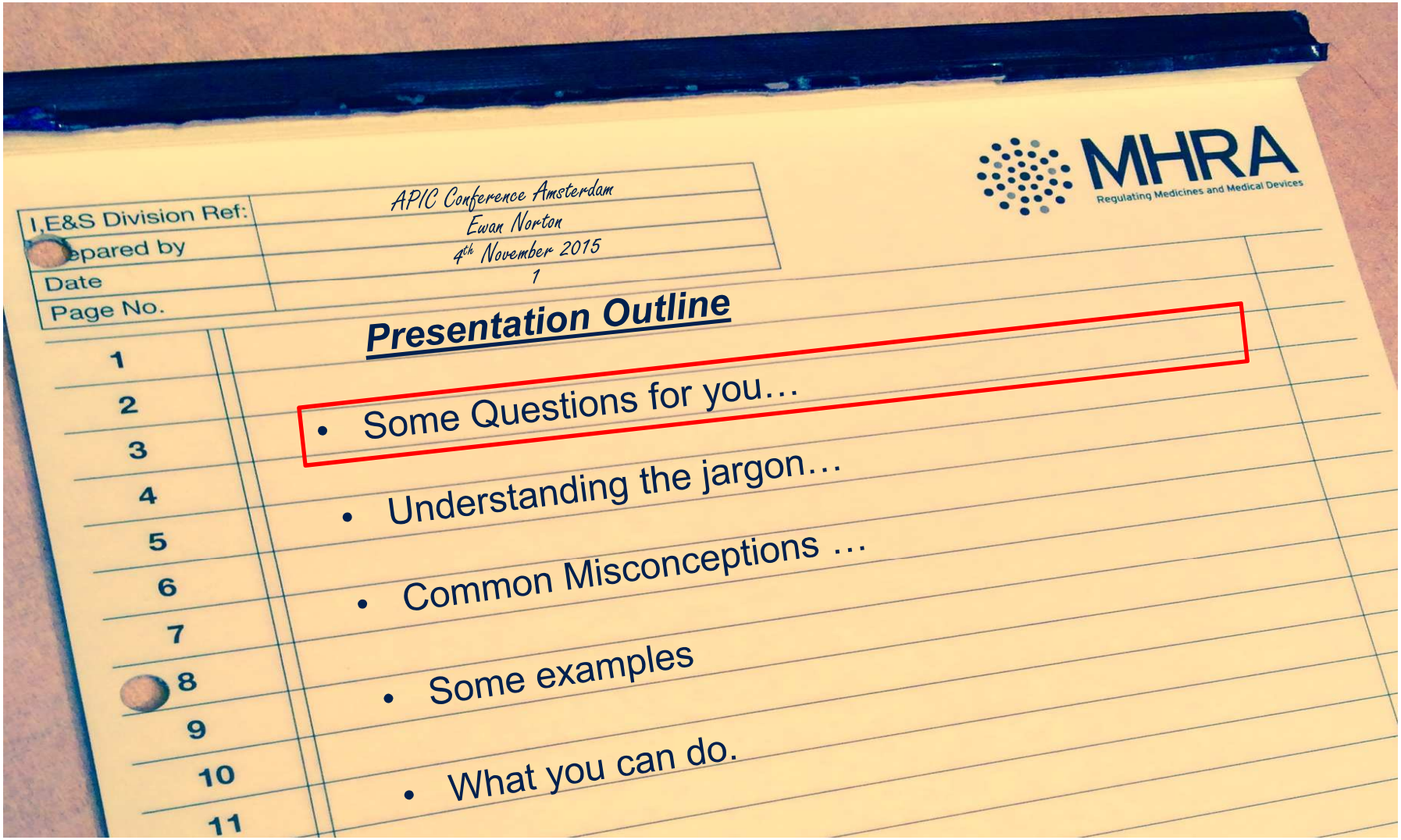
Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Data Integrity

Ewan Norton MHRA GMDP Inspector

APIC Conference Amsterdam November 2015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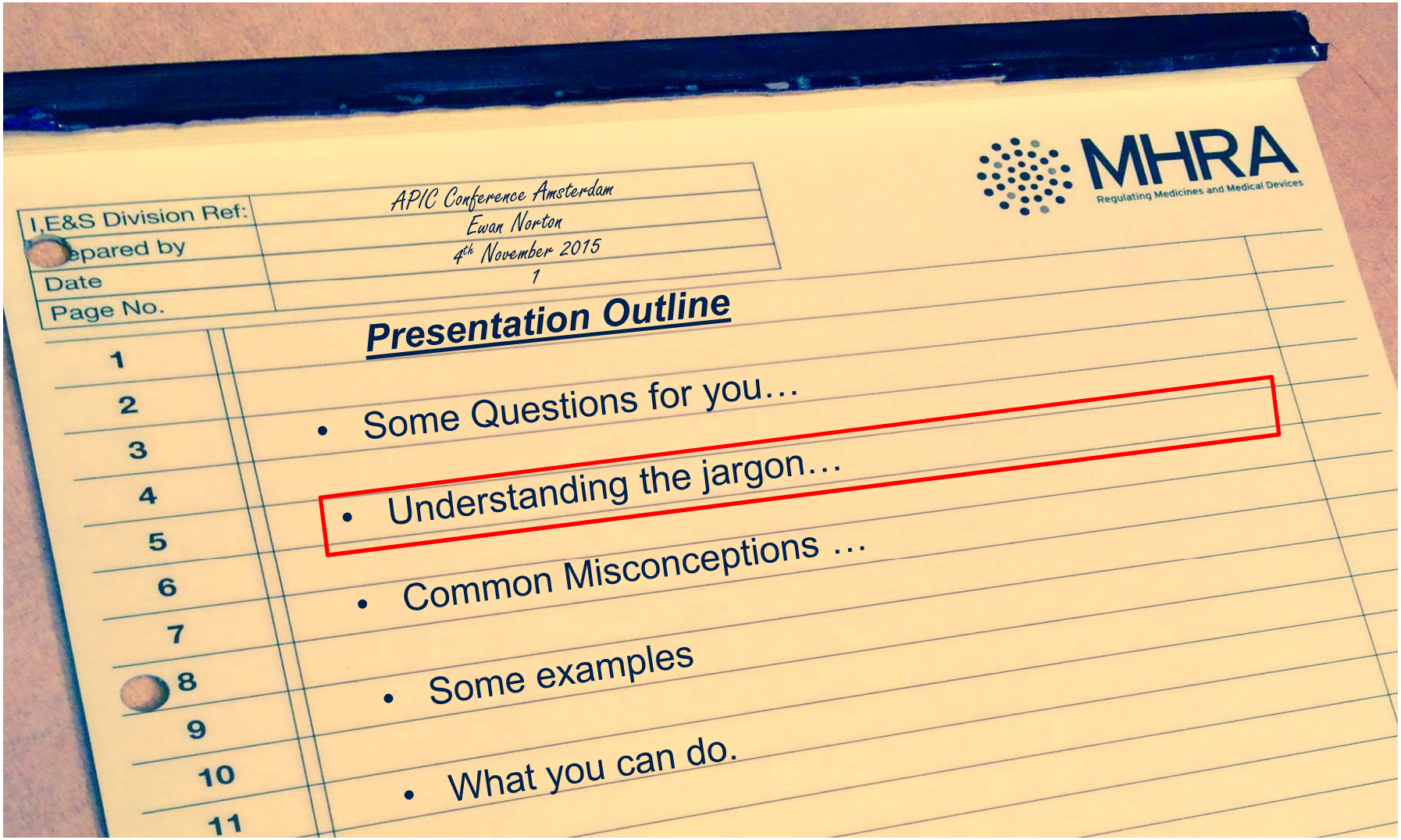
Presentation Outline
Some Questions for you…
Understanding the jargon…
Common Misconceptions …
Some examples
What you can do.

Some Questions for you…

- Do you think Data Integrity Issues are common ?
- Would you be surprised if someone found data integrity issues at your site ?
- Is it easy to find Data Integrity issues ?
- Are all Data Integrity Issues deliberate ?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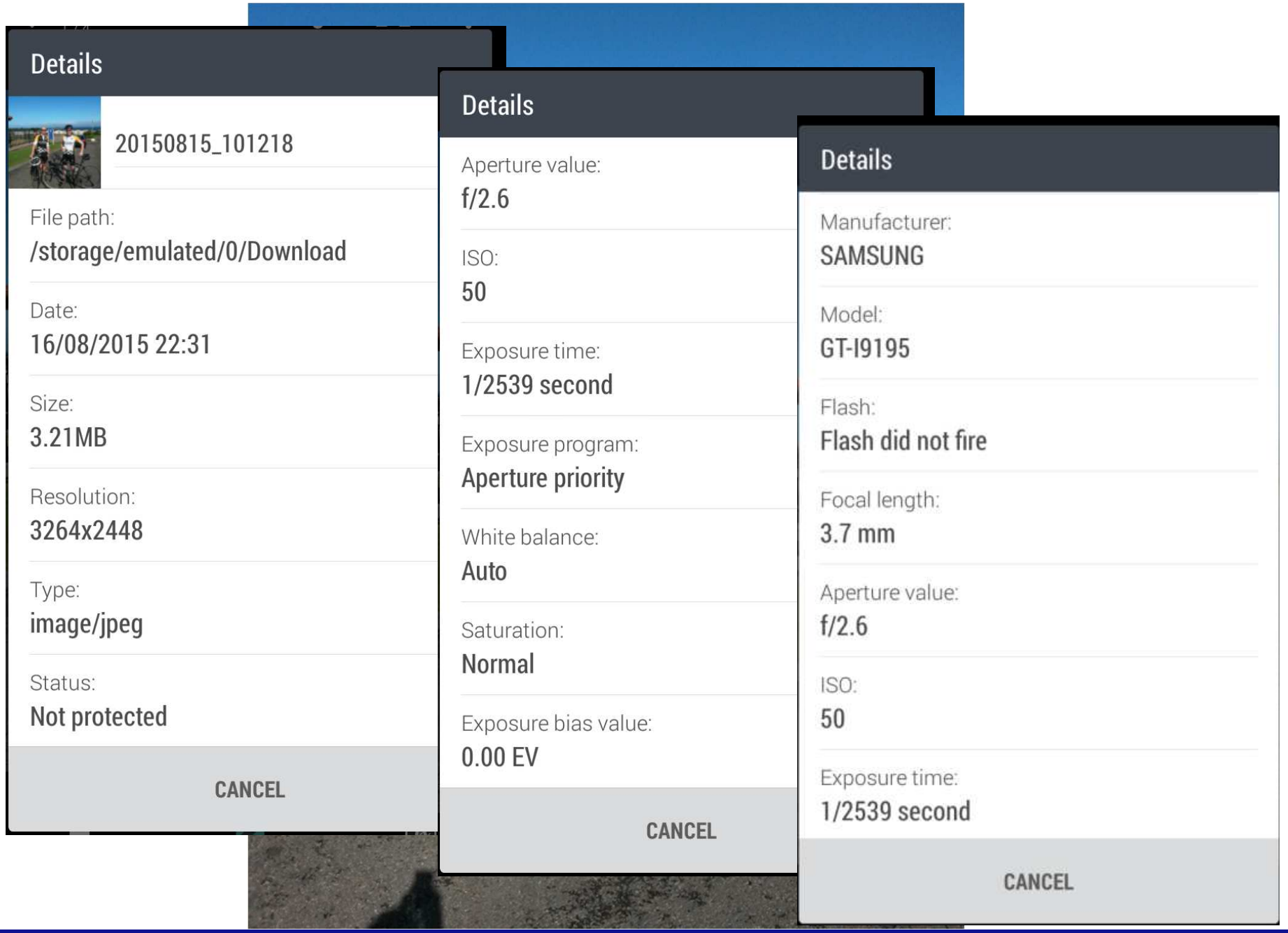
Understanding the jargon…

- Data Integrity
- Data Lifecycle
- Audit Trail
- A L C O A
  - Accountable, Legible, Contemporaneous, Original, Accurate
- Meta Data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ISO:
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Exposure program:
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White balance:
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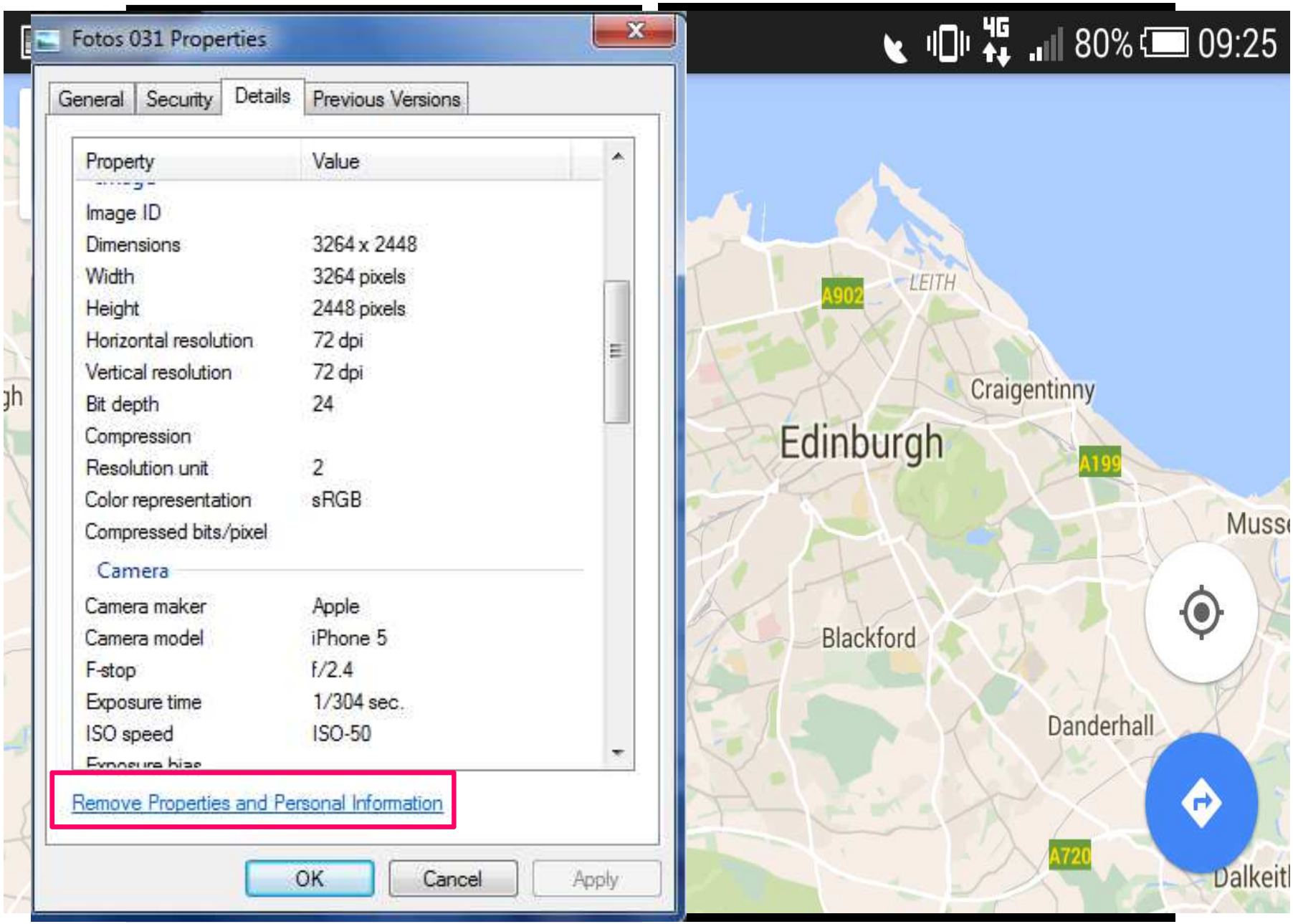
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Security
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Previous Versions
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Height 2448 pixels
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Vertical resolution 72 dpi
Bit depth 24
Compression
Resolution unit 2
Color representation sRGB
Compressed bits/pixel
Camera
Camera maker Apple
Camera model iPhone 5
F-stop f/2.4
Exposure time 1/304 sec.
ISO speed ISO-50
Remove Properties and Personal Information
OK
Cancel
Apply
80%
09:25
A902
LEITH
Craigentinny
Edinburgh
A199
Blackford
Danderhall
A720

Meta Data…

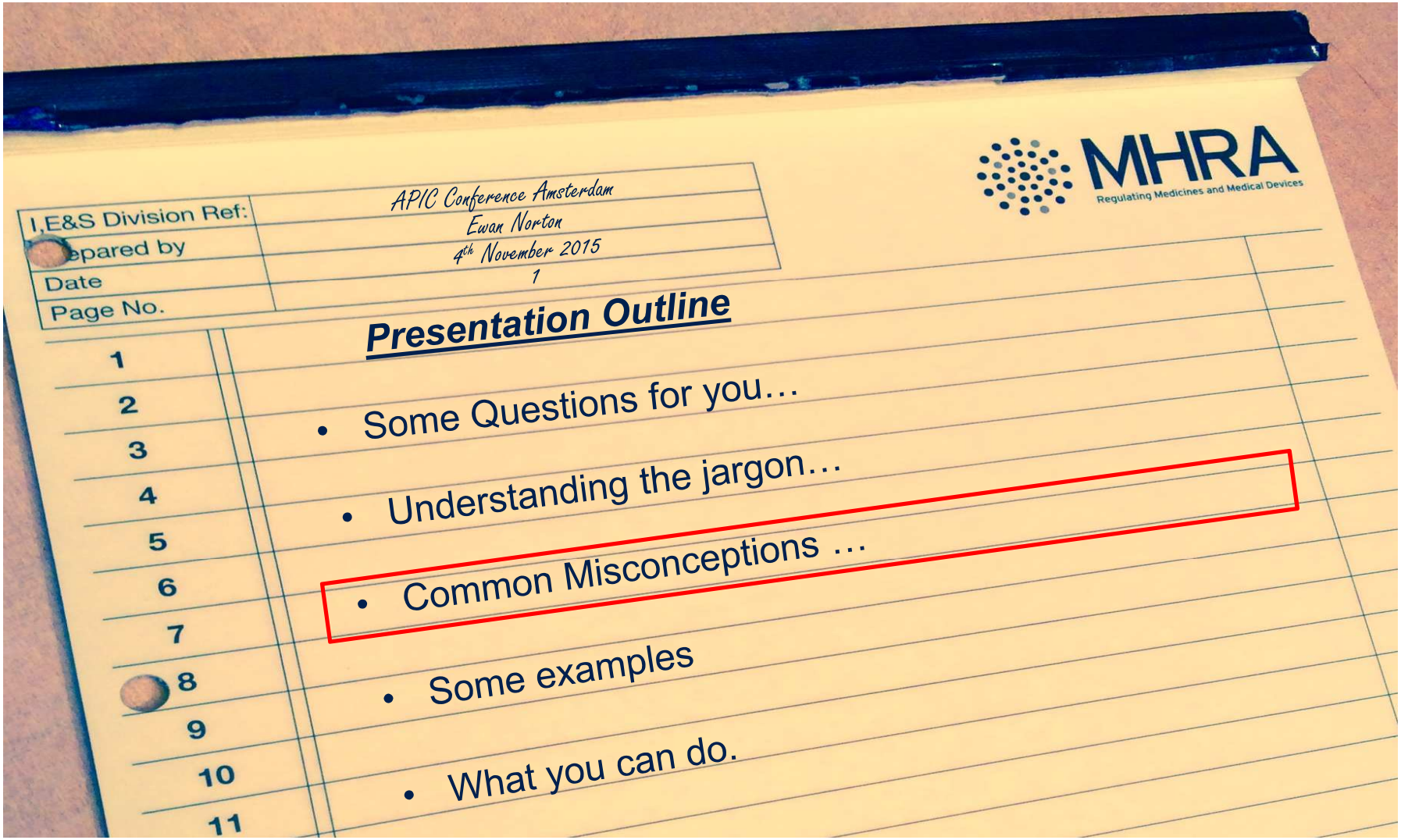
GMP Example:

Data (purple) = **3.5**

Metadata, giving context and meaning, (Dark Red):

Sodium Chloride batch 4826, **3.5**mg. E. Norton 01 Nov 2015

Without metadata, the data has no meaning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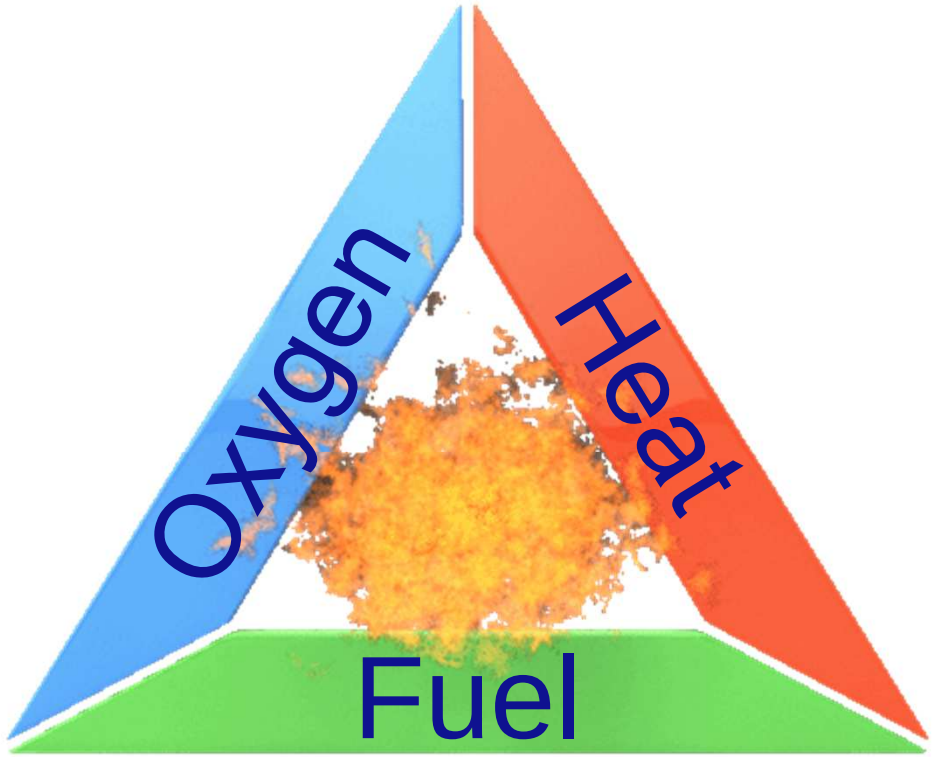
Some Common Misconceptions…

- I’d never do anything like that, nor would anyone I know…
- You only find data integrity issues in QC Labs…
- We’re okay as we have got a validated Chromatography Data System with a built in audit trail...
- This sort of thing only happens in Asia…

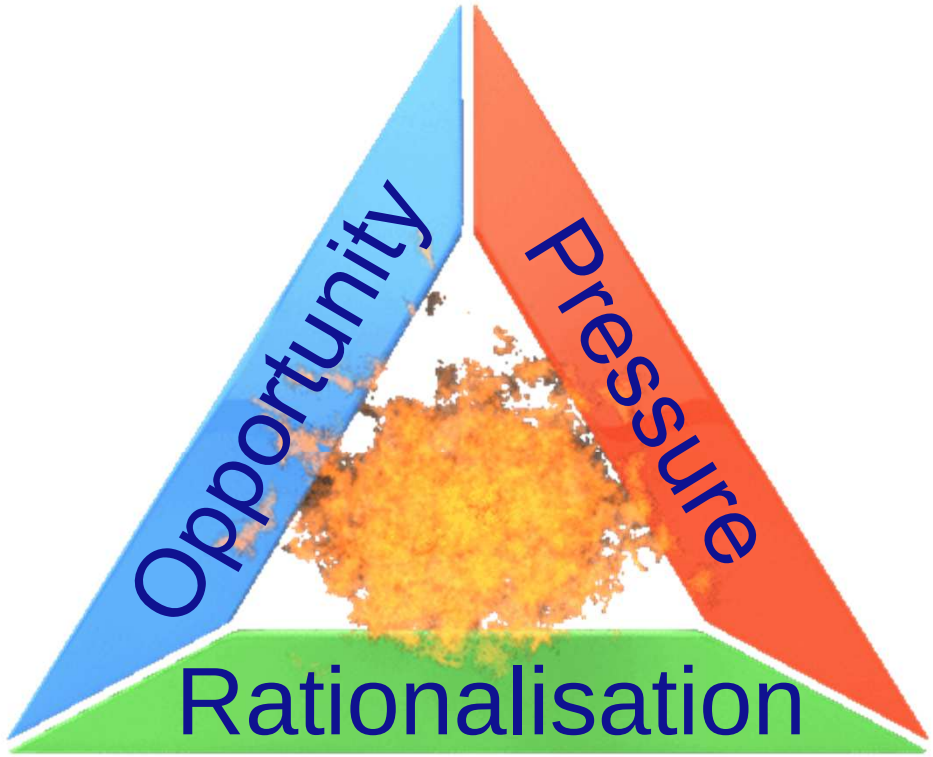
Misconceptions: I’d never do anything like that, nor would anyone I know!

- We received training at the MHRA in Data Integrity (DI) and we were advised that;
  - Most DI issues encountered are not deliberate!
  - Once you get above a certain number of people in a company you **will** find DI issues.
  - The motivation for people to *deliberately* commit DI fraud *can* be understood...

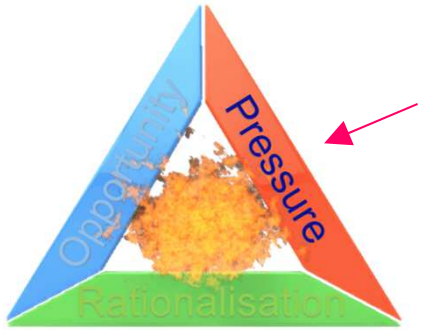
Fire Triangle



Cressey Triangle

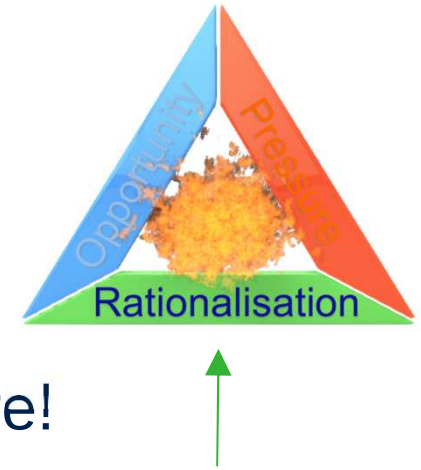


Cressey Triangle



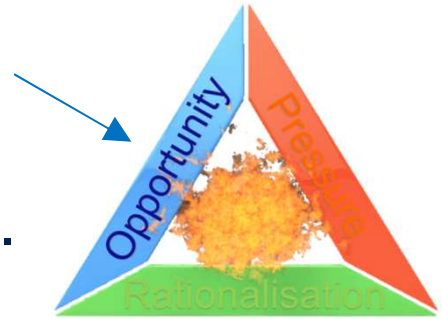
- I have a huge amount of work to do and I can't keep up…
- My boss does not like bad news and he already thinks I'm not very good…
- I have made a number of simple mistakes recently..
- I have just bought a new house and have kids at college…

Cressey Triangle



- It won’t make any difference!
- The results have always been okay before!
- I’ve probably just made a simple mistake!
- If I have to do this again we’ll miss the deadline!
- I could get sacked if I admit to that simple mistake!
- My wife would divorce me if I lost my job now!

Cressey Triangle



- Paper based system with poor controls.
- Electronic system but nobody checks the raw data.
- There’s a loophole in the system.
- User rights not appropriate.
- There’s no printout on the balances.
- Can change the time on the computer.
- The master copies are available.

Misconceptions: You only find data integrity issues in QC labs…

- You can find Data Integrity issues in all areas of organisations.

However…

- QC Labs do present a significant risk due to the volume of data generated.
- QC Sub Contract Labs often used;
  - Level of oversight often falls below that applied internally.
  - Only audited once every two to three years.
  - Only get printout of results.

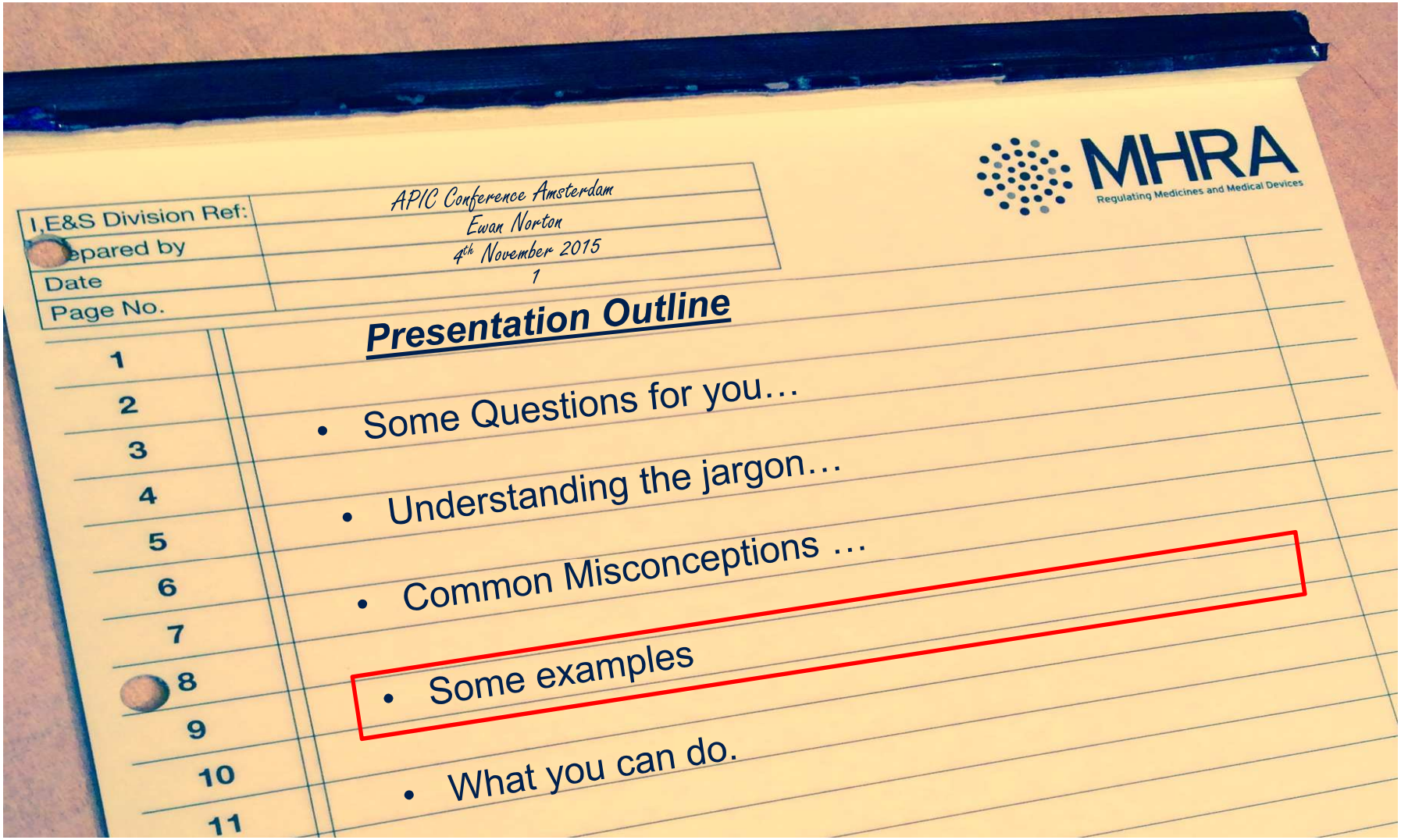
Misconceptions: We're okay as we have a validated CDS with an audit trail…

- People assume that having an Audit Trail on a Chromatography Data System (CDS) makes them bomb proof.
  - But if you never look at it you won't see what's really going on…
- Reliance on paper output from complex validated electronic systems with no checking of the primary or meta data…
- Lab Supervisors or senior analysts having Admin rights for CDS.
  - But who is policing this…?

Misconceptions: Only happens in Asia…

- There are ***cultural*** differences in Asia that mean that there is the *potential* to see data integrity issues involving more people;
  - Not the done thing to highlight an error by your boss.
  - Always saying ‘Yes’ when asked to do something.
  - Being easily replaceable if you do not do what is expected of you.

- Note: we <u>do</u> see examples in Europe where multiple people are involved.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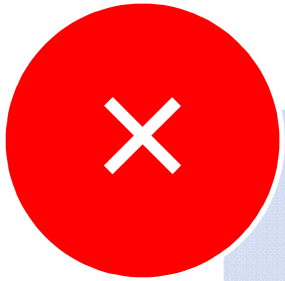
Example 1

Issues involving many people with ***no*** intent to mislead…

- Batch records being rewritten upon completion of batch to make them neater.
  - Original batch records were retained.
  - No changes had been made to content.
  - This activity had become custom and practice at the site.



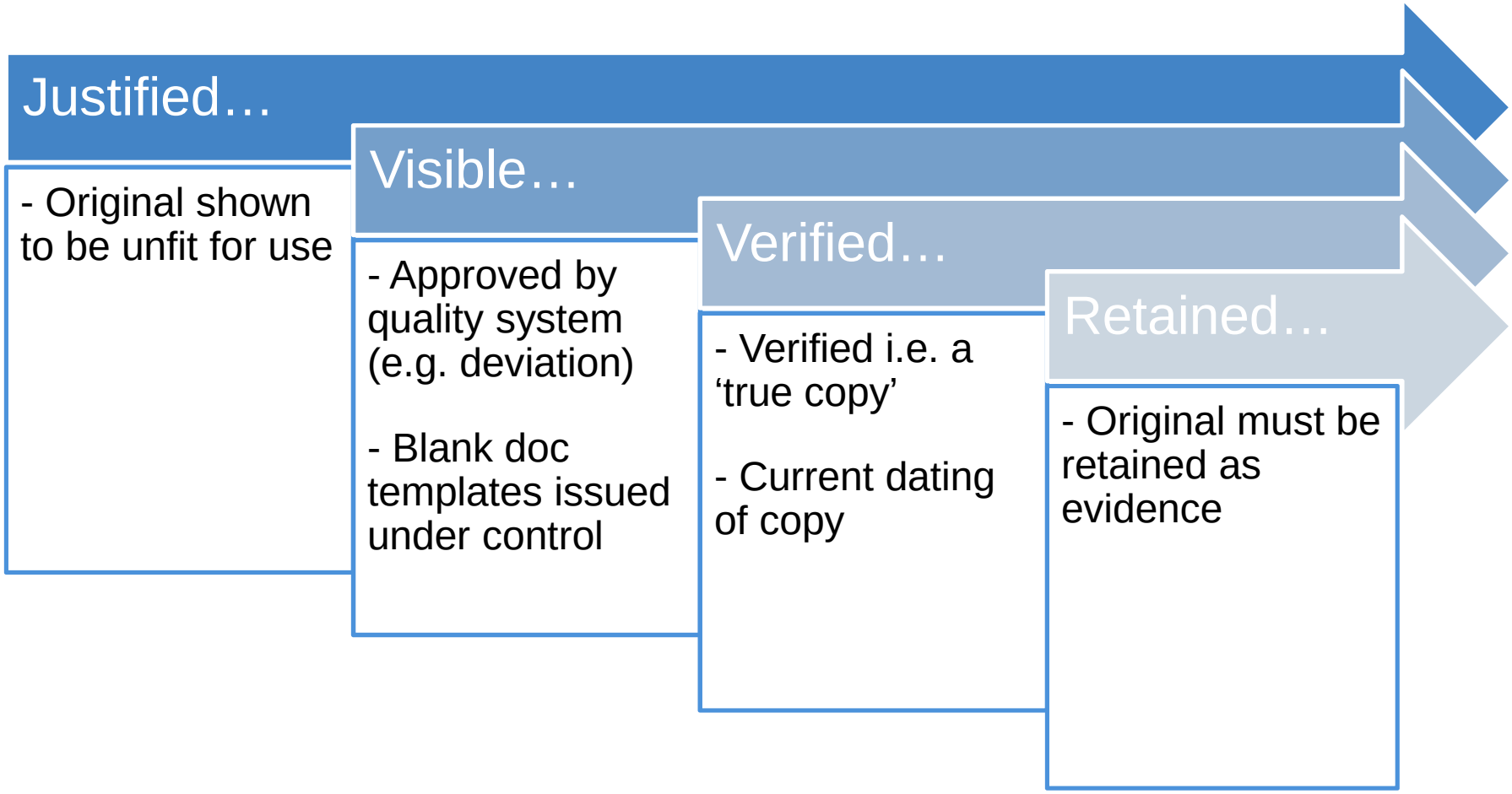
- Undesirable data
- Minor damage
- ‘Tidying’ documents

- Unusable original
- Major damage / spillage
- Uncorrectable entry error

Can you ever justify recreating documents?

Yes, on rare occasions.

Recreating documents in a way that avoids DI issues:



Issues involving many people with ***no*** intent to mislead…

- Trial injections were being carried out on HPLCs/GCs and not reported in main data.
  - Trial injections of system was the batch to be tested.
  - Trial injections were not deleted but were not easy to find.
  - No records were kept of who carried out the testing or the sample preparation.

- Not our initial reaction, but after significant effort it was concluded that this was not a deliberate attempt to mislead.

Example 2

Issue with one Individual intent on misleading

- Person was working on pre-clinical trial analysis for a contract organisation for several major pharma companies.
- Had been ‘selectively’ reporting data for 6 years.
- Some results obtained would have failed if they had been reported in full and accurately.
- Took a huge investigation to determine the impact.

2013

Scientist jailed for falsifying drug test results

A scientist who faked research data for experimental anti-cancer drugs has been jailed for three months for falsifying test results.

had been selectively reporting research data since 2003

, has become the first person in the UK to be jailed under scientific safety laws.

was working at the Edinburgh branch of US pharmaceutical firm : in 2009 when he came up with the scam.

If it had been successful, cancer patients who took the drug could have been harmed, the court was told.

Edinburgh Sheriff Court heard how had manipulated the results of an experiment so it was deemed successful when it had actually failed.

Issue with one Individual intent on misleading (continued)

- No financial benefit out of his actions.

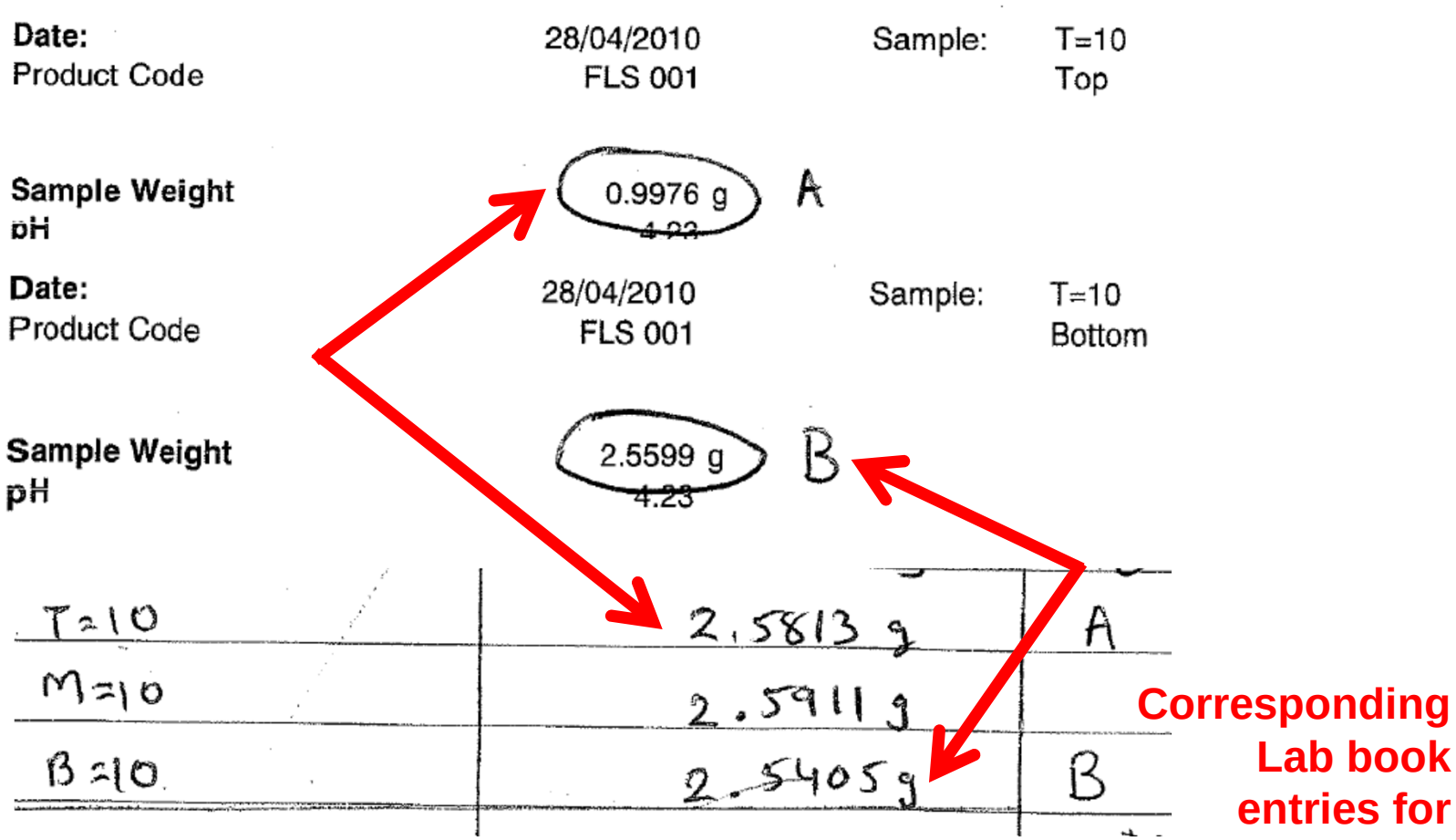
- Defence solicitor stated ‘*he had been under a lot of **pressure** at the time and had been having trouble with his personal life*’.

- It was confirmed that the issues were limited to a single person and the management of the company were not implicated.

Example 3

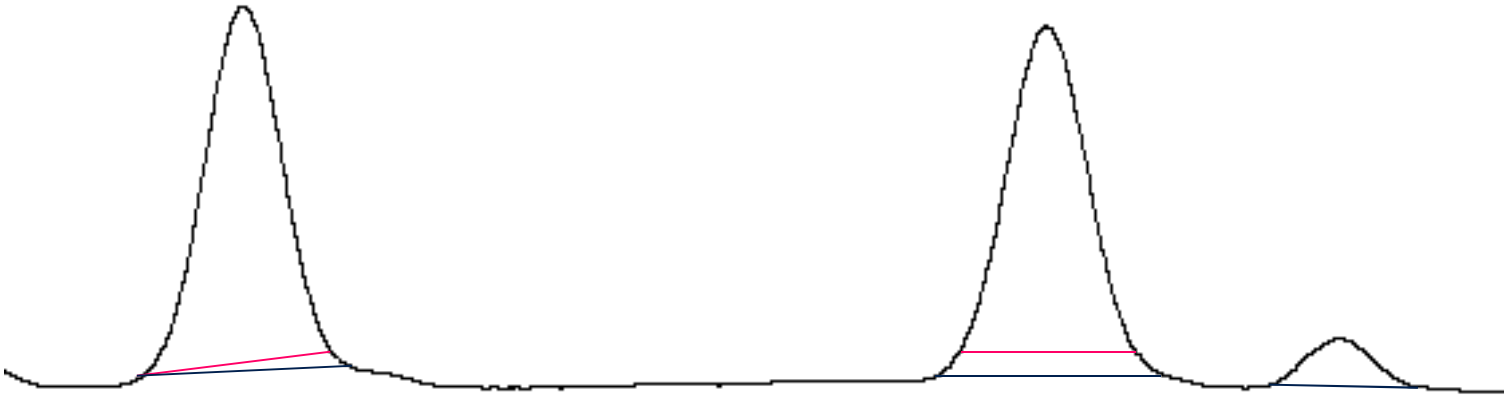
Why do we need to check the data?

Excel spreadsheet used to calculate assay:



Corresponding Lab book entries for sample weights:

Why do we need to check the data?



Why do we need to check the data?

Sample name	Acquisition Time	Filename
Acet.@250 REP 1	17:13:19	090811-003.rst
Acet.@250 REP 2	17:17:10	090811-004.rst
Acet.@250 REP 5	17:28:19	090811-007.rst
Acet.@250 REP 5	17:34:07	090811-007-20150311-173718.rst
Acet.@250 REP 6	17:37:58	090811-008.rst
Acet.@250 inj acc	17:41:58	090811-009.rst

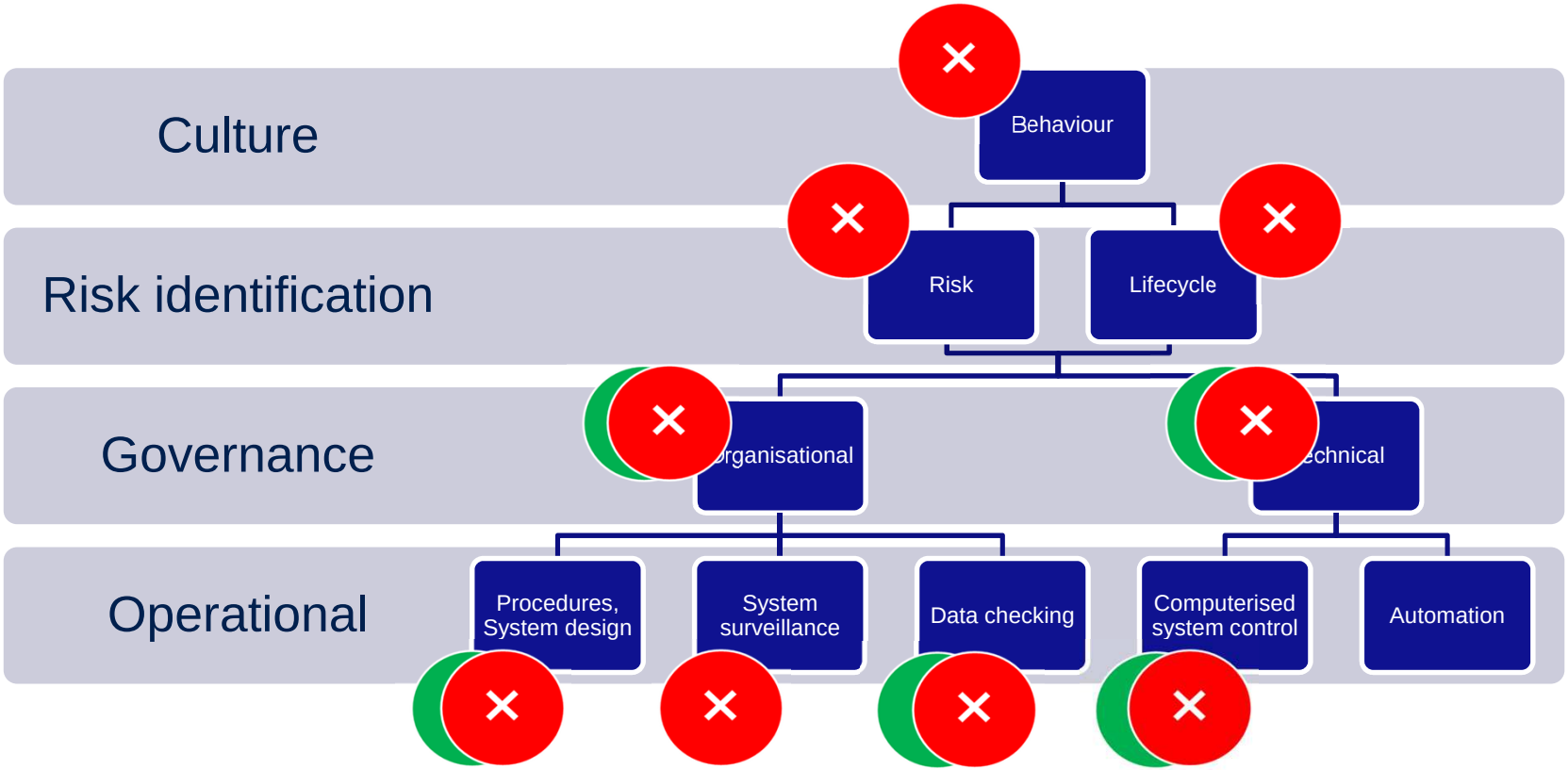
Where are REP 3 and REP 4? We have an 11 minute gap and the .005 & .006 datafiles are missing.

Why has REP 5 been re-injected?

Why does the 6th injection have a different sample name?

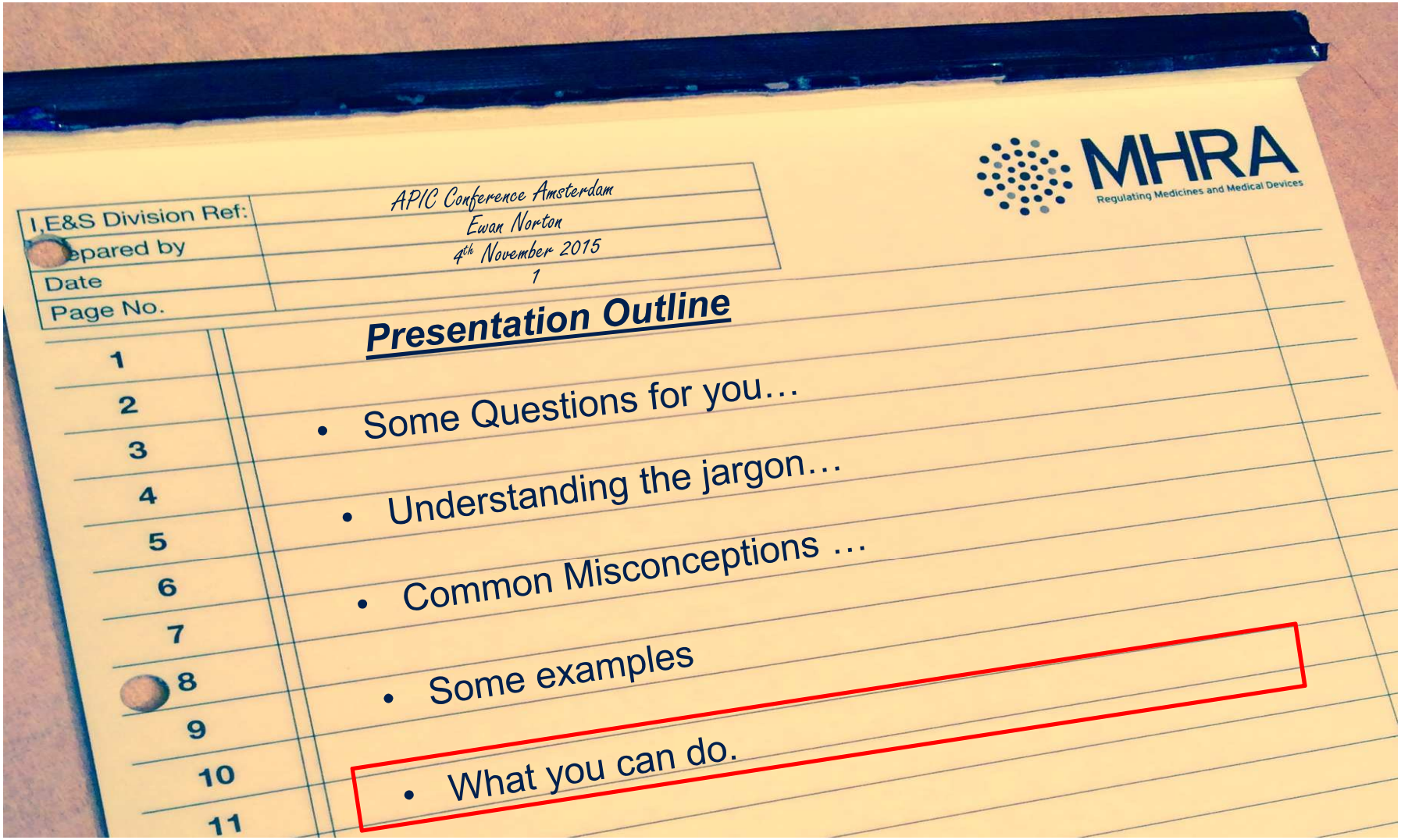
Example 4

Issue involving multiple individuals with intent to mislead



Example 5

Data Integrity Issue in USA & Europe involving multiple Individuals…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What can you do?

- ✓ Develop a Data Governance Policy for your company/site.
- ✓ Make your systems provide a barrier to Data Integrity issues
  - '*Prevention is better than Cure*'.
- ✓ Train your staff in the risks of Data Integrity issues (both intentional and unintentional).
- ✓ Carry out a periodic Data Integrity orientated self-inspection of your systems.
- ✓ Treat your contract companies the same way you treat your own organisation.

What can you do?

- ✓ Implement a procedure which describes the process for the review and approval of data, including raw data.
  - Data review must also include relevant metadata, including audit trails.
  - Data review must be documented.
- ✓ Do not be heavy handed with your staff.
- ✓ Look at the published MHRA documents on data integrity (links on the next slide).
- ✓ Read Annex 11 - has different (additional) requirements to 21CFR Part 11.

What can you do?

Read these Guidance Documents available online...

MHRA Detailed Guidance on Data Integrity:

https://www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions

MHRA Short Blogs on Data Integrity:

https://mhrainspectorate.blog.gov.uk/2015/06/25/good-manufacturing-practice-gmp-data-integrity-a-new-look-at-an-old-topic-part-1/

https://mhrainspectorate.blog.gov.uk/2015/07/14/good-manufacturing-practice-gmp-data-integrity-a-new-look-at-an-old-topic-part-2/

WHO Draft Guidance Document

http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15-624_16092015.pdf

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Any Questions ?