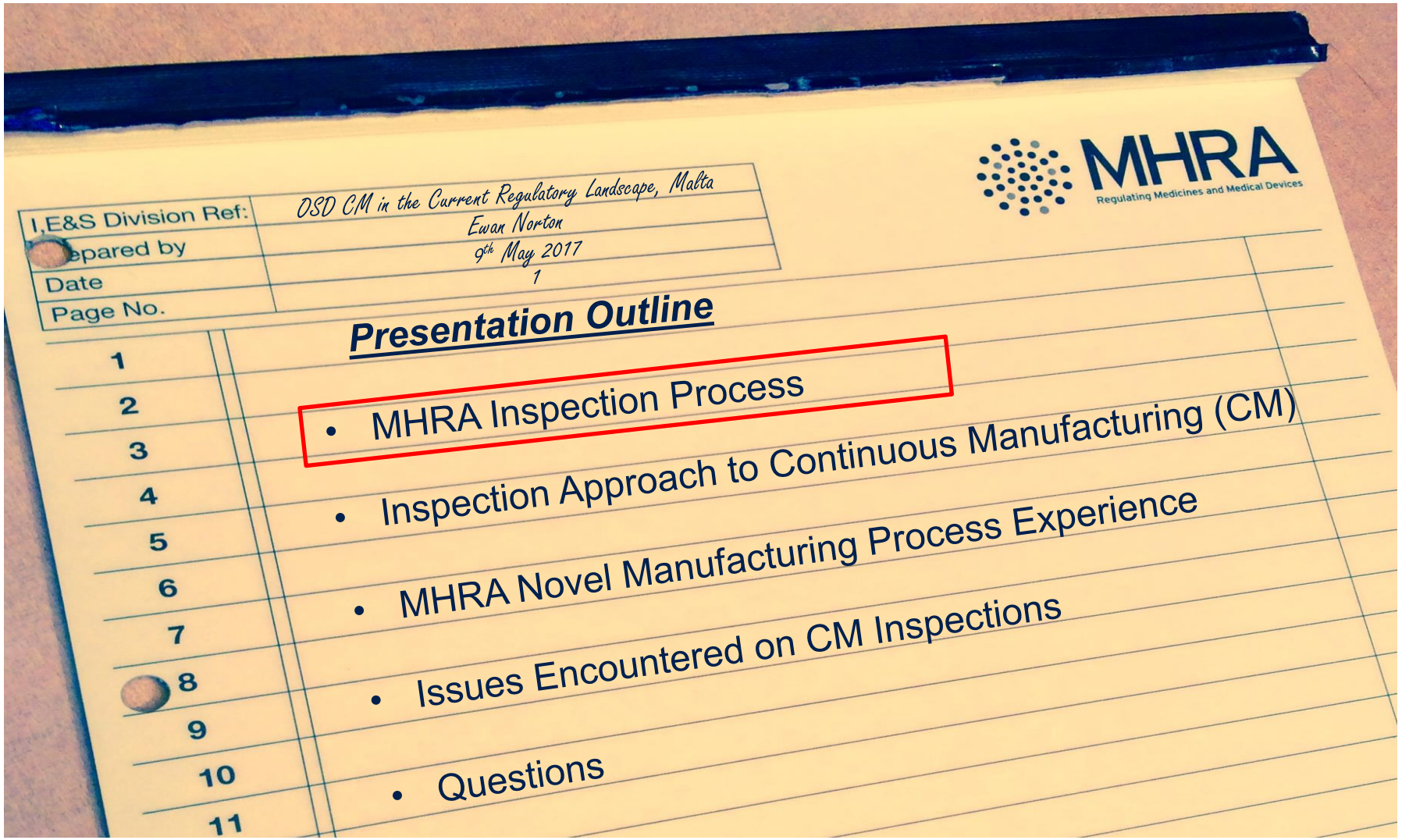
Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

MHRA Experience on ‘Early Adopter’ Continuous Manufacturing Inspections

Ewan Norton MHRA GMDP Inspector

OSD CM in the Current Regulatory Landscape, Malta, May 2017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OSD CM in the Current Regulatory Landscape, Malta
epared by
Ewan Norton
Date
9th May 2017
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MHRA
Regulating Medicines and Medical Devices
Presentation Outline
MHRA Inspection Process
Inspection Approach to Continuous Manufacturing (CM)
MHRA Novel Manufacturing Process Experience
Issues Encountered on CM Inspections
Questions

MHRA Inspection Process

- Inspection frequency & duration based on factors including;
  - site history
  - activities carried out
  - size of site,
  - number of personnel
  - risk rating relative to other companies

- Any deficiencies are referenced back to EU guidelines
  - drives consistency between inspectors
  - Interestingly, don’t need to wait for it to go wrong to be able to cite a deficiency.

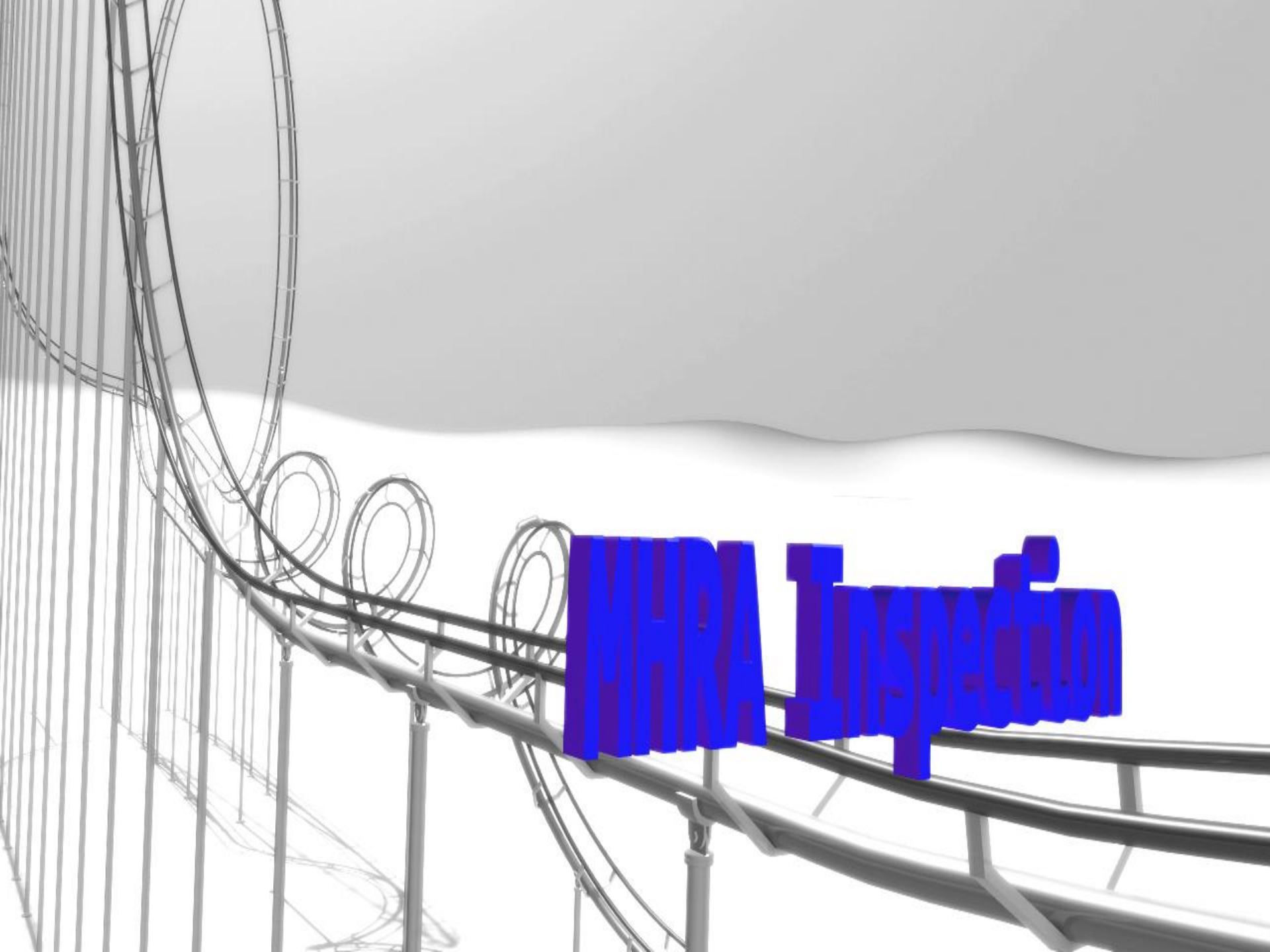
MHRA Inspection Process

- Assessors review the applications and confirm that the science is sound and supported by the data submitted.
  - If questions remain, can ask the inspector to check while on site

- Inspectors consider your Quality System and level of compliance
  - What you are ***actually doing***, what you are ***planning to do*** and is it ***written down*** somewhere
  - Look for what ***could*** **go wrong**, what ***has*** **gone wrong** and, how you propose to ***stop it*** **happening again**

MHRA Inspection Process

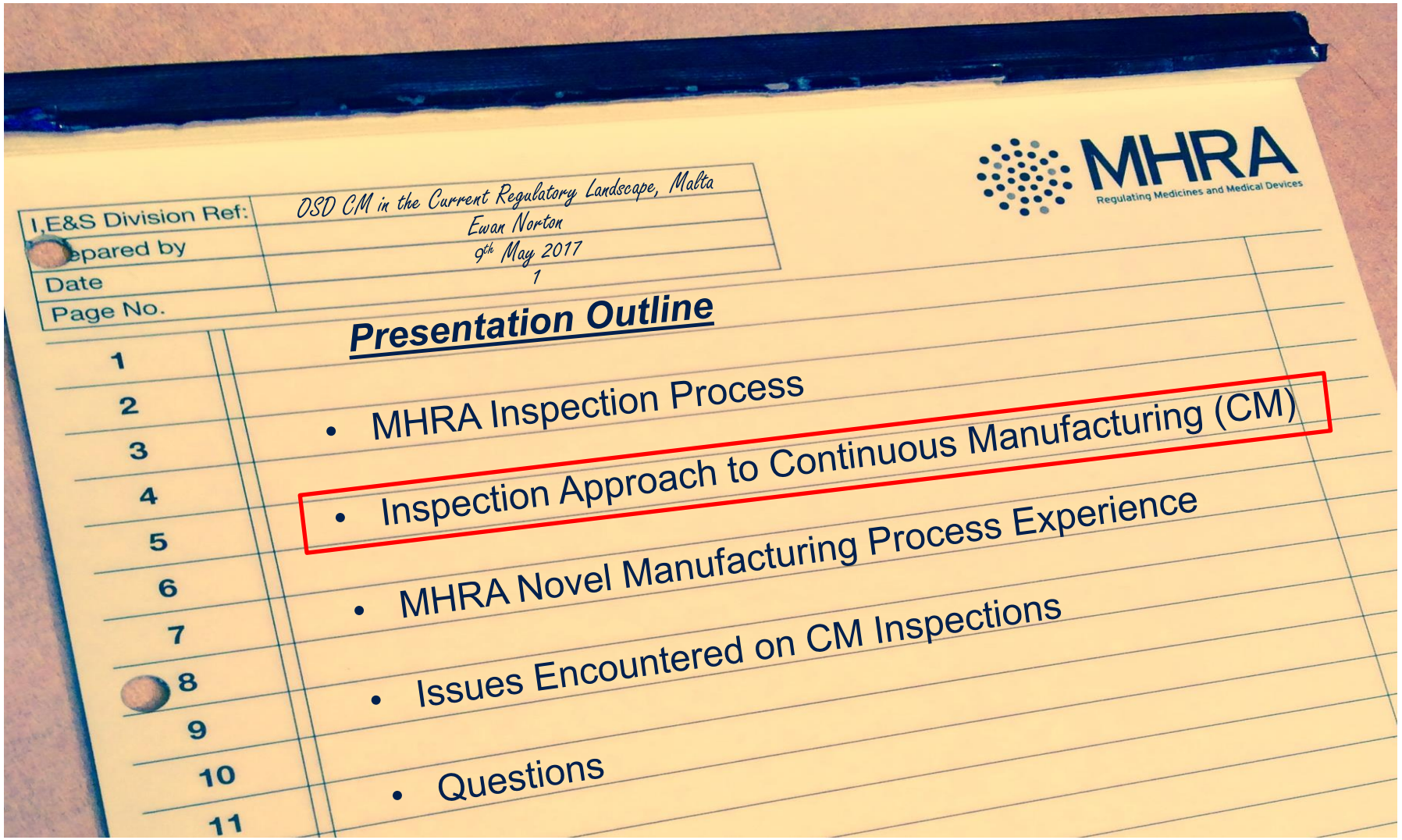
- Approximately equal times spent on documentation and on plant


MHRA Inspection

MHRA Inspection Process

- Sometimes an inspection can feel like a bit of a **rough ride**…

But there are ways to make it smoother…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Inspection Approach to CM

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Spot the Difference:

Inspection Approach to CM

Spot the Difference:

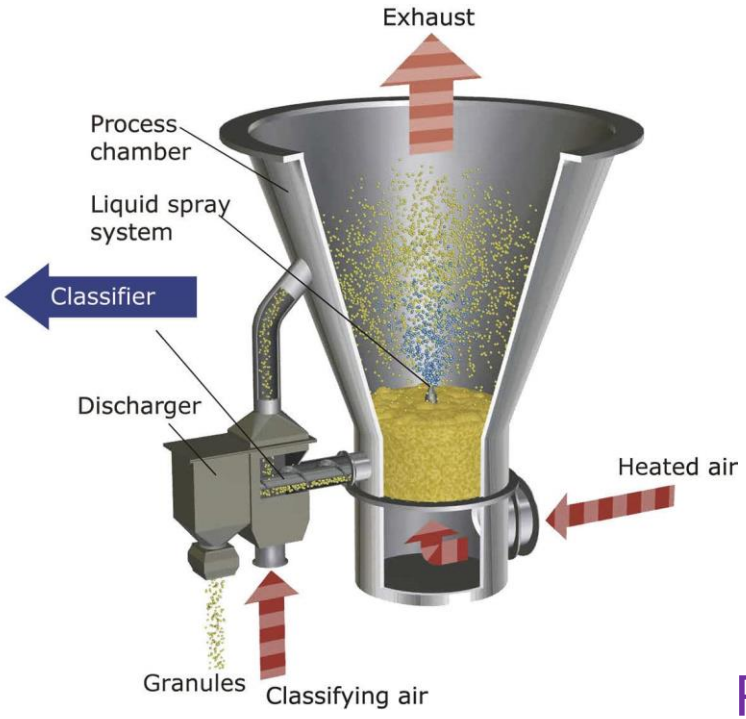
- Risk rating not influenced by Continuous vs Batch
- Inspection duration typically the same for both
- Physical time on plant during inspection not impacted by the type of process operated
- Still look at deviations to see what *has* gone wrong and what CAPA *were* implemented
- Assessor(s) may come with us on inspections
  - this will be the ‘norm’ until we (and you) have appropriate experience of potential pitfalls

Inspection Approach to CM

Approaches to cleaning

Computerised Systems

Equipment Set Up



Process Consistency

Calibration & Maintenance

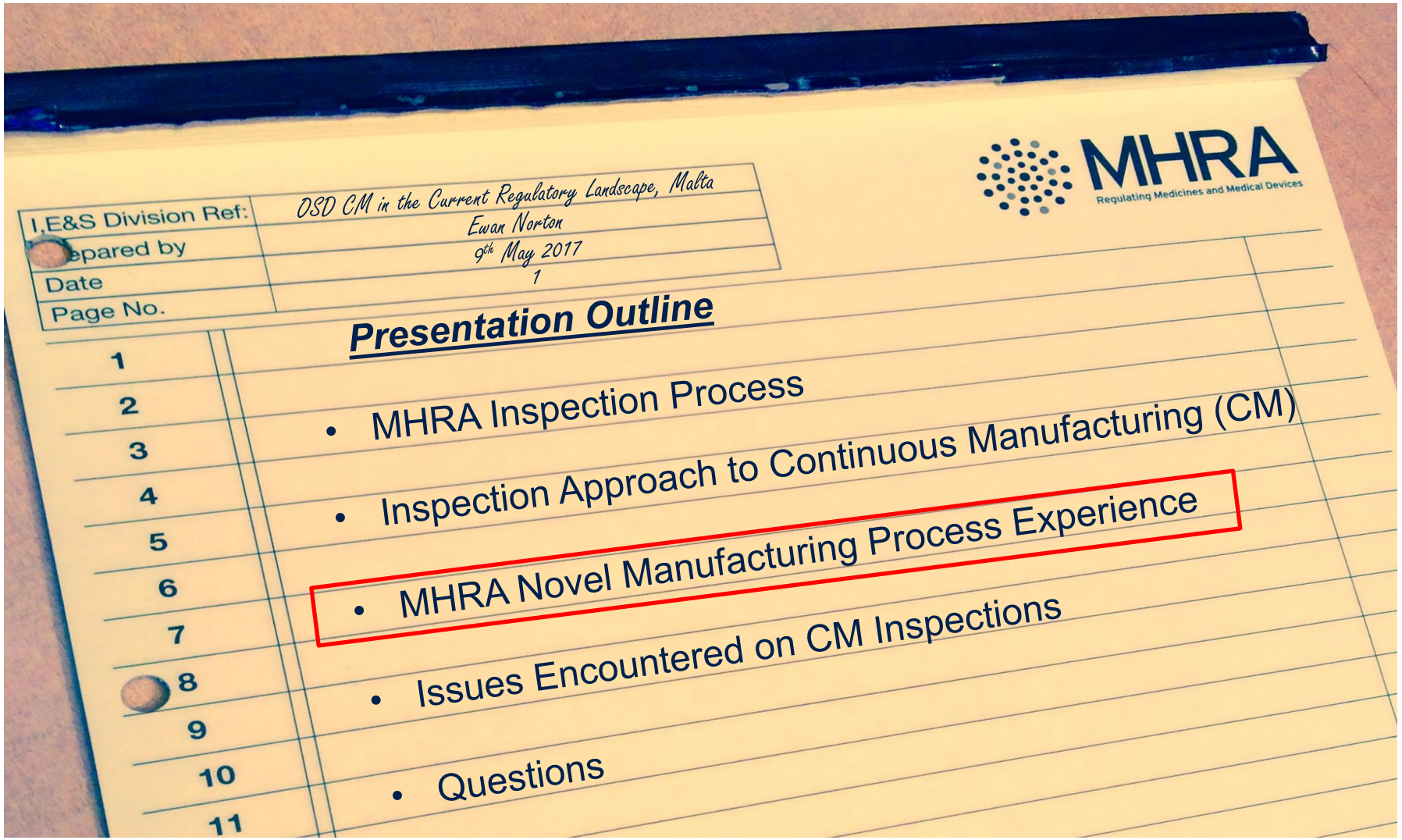
Control of Changes

Training of Operators

Deviations & CAPA

Residence Time Distribution

Rejection Mechanisms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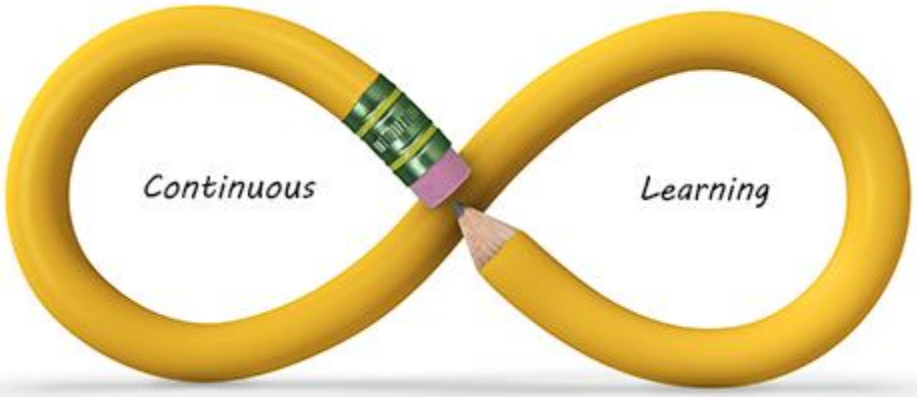
MHRA Novel Manufacturing Process Experience

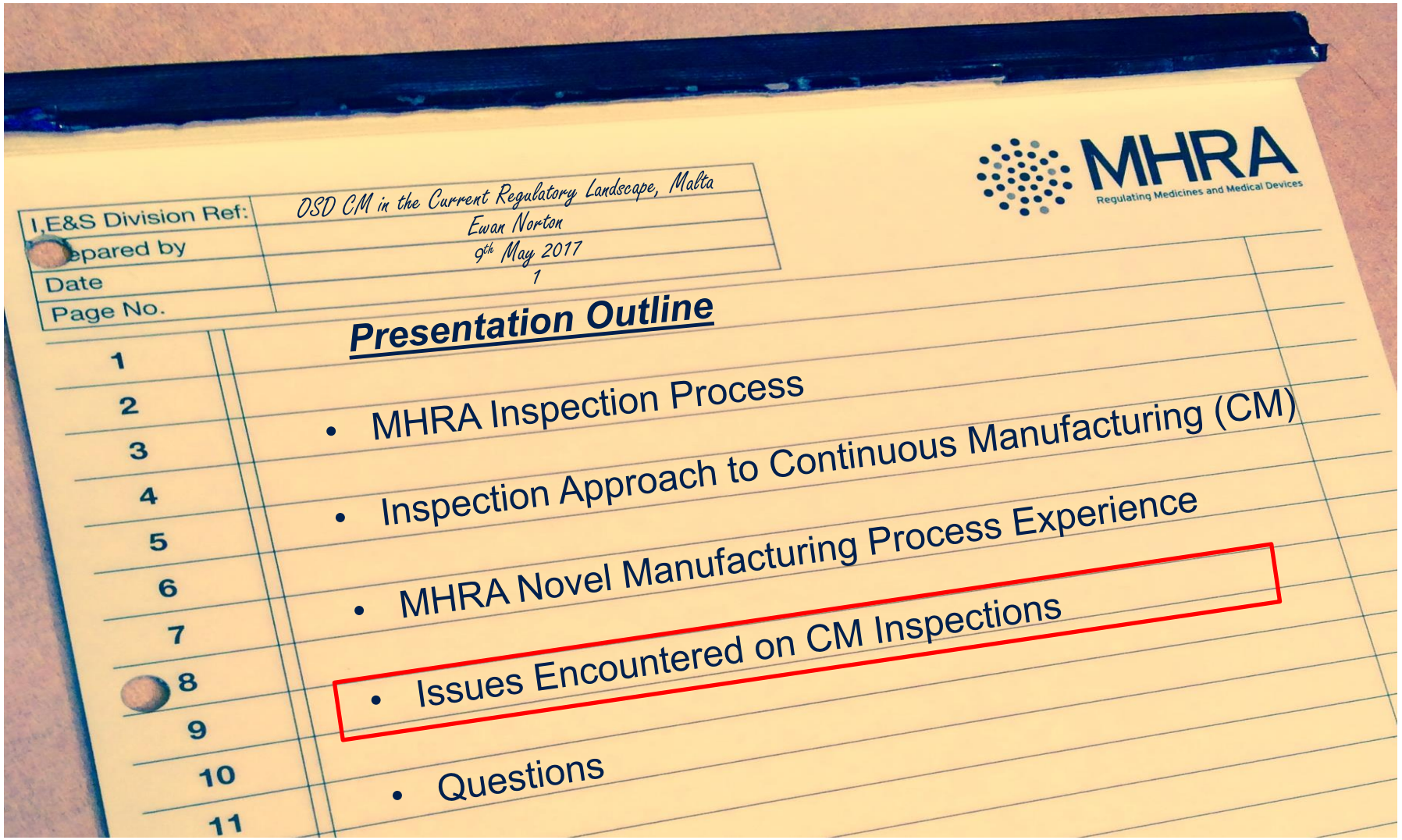
- The MHRA has an '**Innovation Office'**
  - Access to expert regulatory information, advice and guidance that helps the development of innovative medicines, medical devices or ***novel manufacturing processes***
  - Formed in 2012 in response to calls from academia, government and industry
  - **Free** expert regulatory information, advice and guidance
  - For organisations of all backgrounds and sizes, including Small to Medium Enterprises (SMEs) and also individuals

  - Search online for '*MHRA Innovation Office*' or email: **innovationoffice@mhra.gov.uk**

MHRA CM Experience

- Inspected Drug Product CM sites for pre-approval and for routine re-inspections
- We have inspected a number of API CM Sites
  - both API and Non-Standard API
- The experience is with a core group of inspectors
  - number is increasing
- Increasing our knowledge and experience in a number of ways

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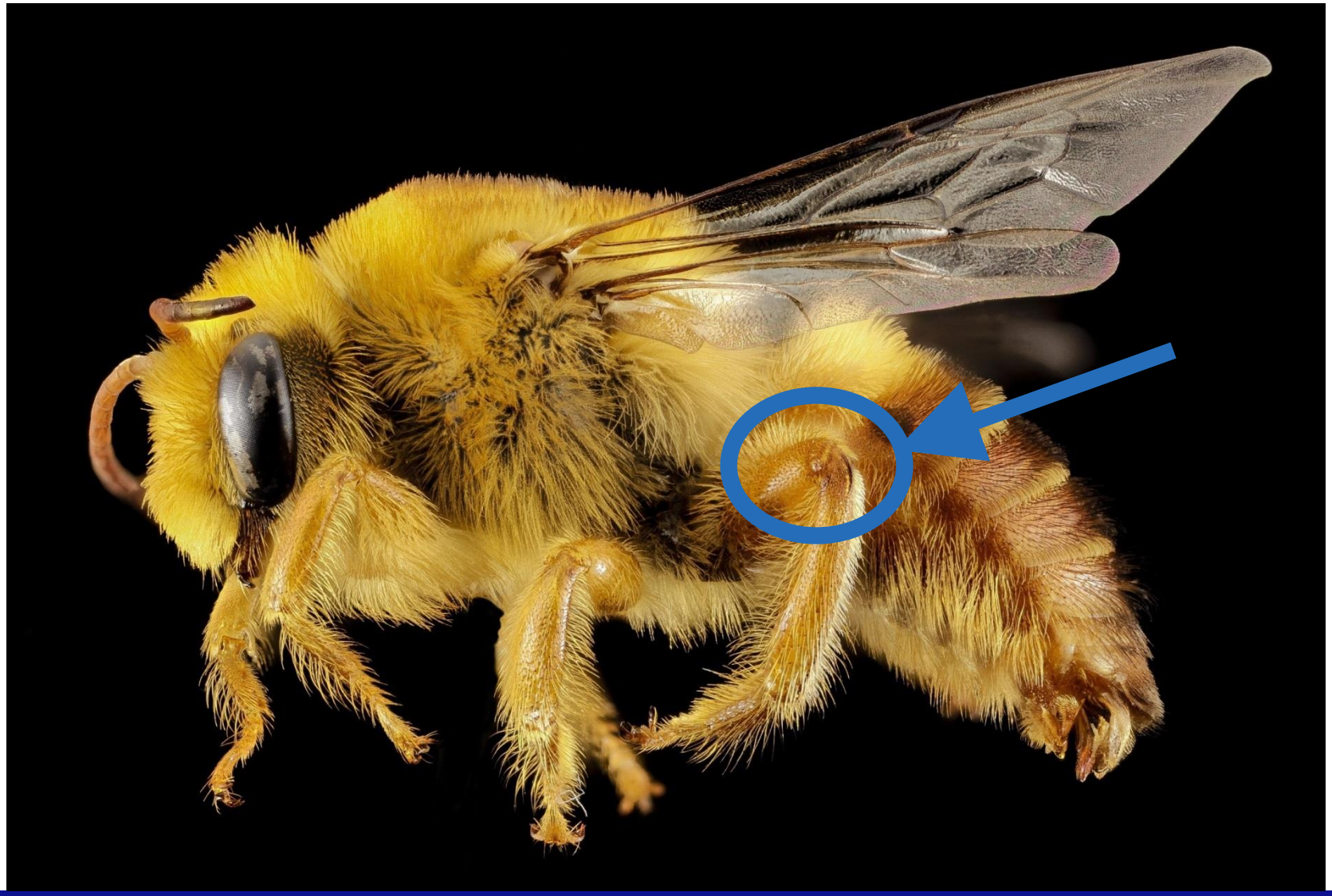
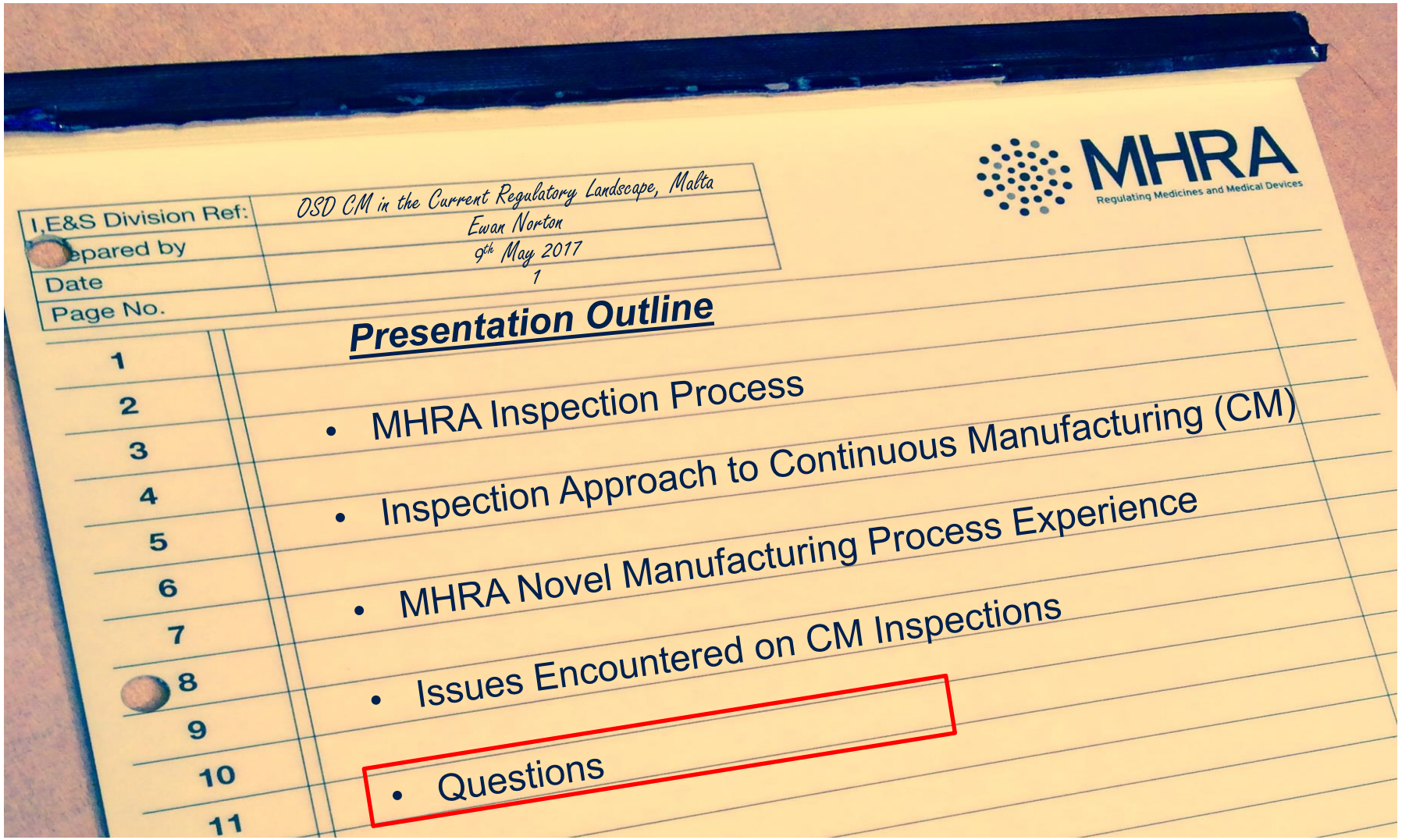


Issues Encountered on CM Inspections

- We have observed a (limited) number of issues in;
  - Process stability (high reject volumes)
  - Calibration
  - Equipment malfunction
  - In-Process Testing results
  - Residence Time Distribution not known
  - Cleaning
  - Switch away from Real Time Release Testing (RTRT)
  - **BIG DATA**

- Inspections currently infrequent enough that not yet able to define a set of ‘standard’ inspection issues for CM.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Questions from (*or for*) you…

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Grazzi