Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Inspection findings - Sterile Products

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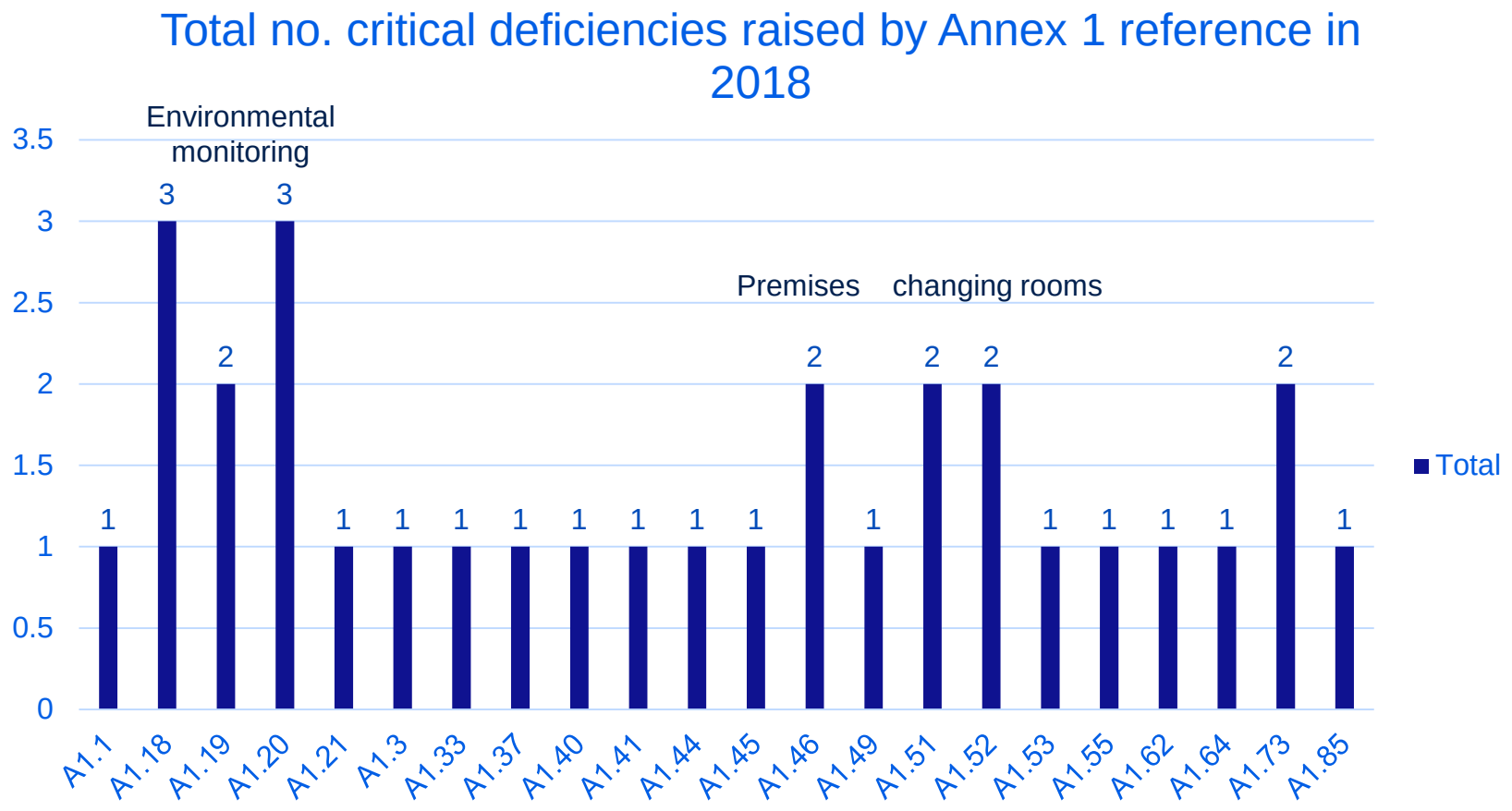
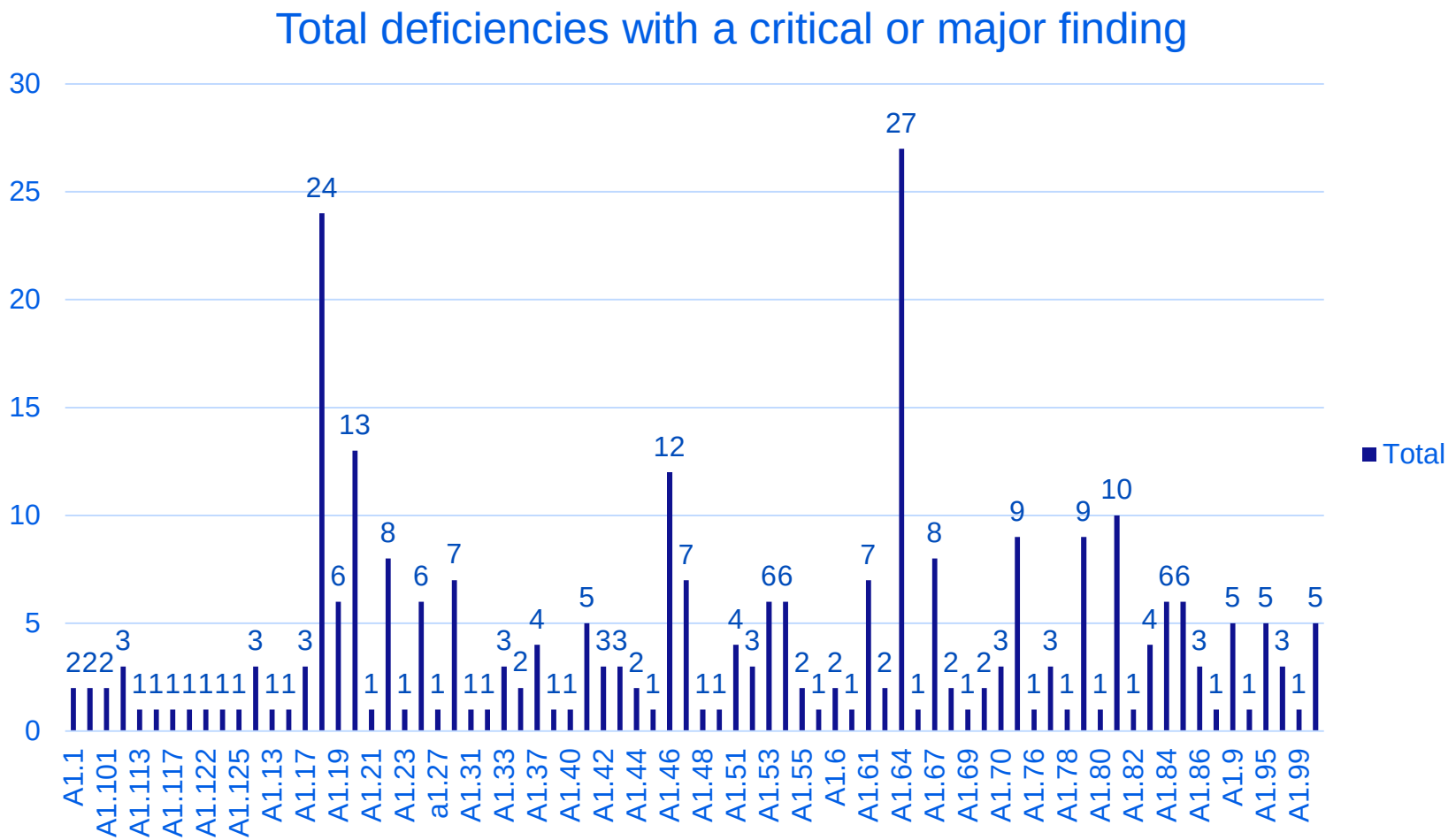
16 November 2019

MHRA
Regulating Medicines and Medical Devices

MHRA 2018 Deficiency data



MHRA 2018 Deficiency data



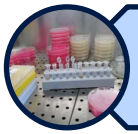
High number of deficiencies >3 yrs associated with or high risk deficiencies identified concerning:

QRM

Aseptic process simulation (APS)

Lack of sterilisation

Smoke visualisation studies

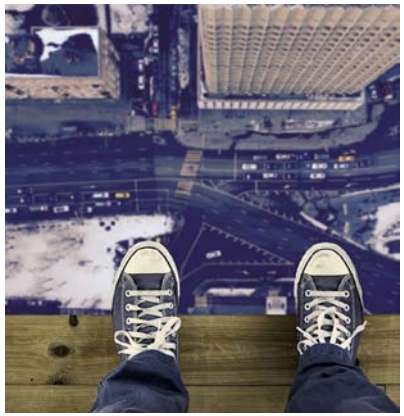


Environmental monitoring

Investigations

Deficiencies - QRM

- Starting by justifying current practice
- Blindly following RPN Scoring
- “Current Control Measures are adequate”
- “Nothing’s ever gone wrong”
- Lack of knowledge / experience in the area



Inspection points - QRM

What should you be doing?

- Assess the risk
- Compare the current controls
- Add any additional controls
- Performed by people that understand the process(es)
- Part of the PQS
- Defined Review Strategy

Deficiencies – Aseptic Process Simulations (APS)

- Process is not actually represented
- Interventions not performed
- Aborted and invalidated runs
- Not appropriately documented
- 
  Validating bad practice
- Contaminated units not properly investigated

Deficiencies – Aseptic Process Simulations (APS)

Manufacturing process not represented:

Duration of fill in hours

Over rejection of units

Not all routine interventions performed

Interventions performed differently

Interventions not documented appropriately

Inappropriate ‘interventions’ included (e.g. from isolated events)

‘Validating’ bad practice

APS not appropriately designed

No plan of what APS is to simulate

Insufficient quantities produced

Hybrids of processes

Not all required staff scheduled

Trainees used as ‘not a product’

Change in process not considered

Performed during ‘shut down’

No consideration how to inspect the finished units

Deficiencies – Aseptic Process Simulations (APS)

Not investigated properly:

Especially 1 in greater than 10,000

Records not sufficiently detailed

Risk assessments poor (all EM generally ok therefore all product ok)

Do not justify event brackets (only impacts one batch because……..)

Not all relevant product held/rejected

Aborted and invalidated APS:

Invalidated too late

Aborted fills when there is evidence that routine manufacturing would (and has) continued in the same circumstances

No definition in procedure

No deviation raised to explain and justify.

Inspection points - APS

What should you be doing?

- Ensure reflect actual process – detail
- Design the process & review
- Interventions need to be related to batches
- Not to validate bad practice
- If they fail need to react quickly and appropriately
- Need to investigate and document properly

Deficiencies – Lack of Sterilisation

- Indirect product contact items into Grade A environment
- Direct product contact items into Grade A environment!
- Poor cycle design
- Not qualifying all loads
- Worst case loads
- Occluded surfaces
- Wet loads

- Lack of understanding

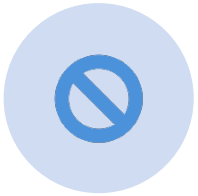
- Equipment not capable

Inspection points – Lack of Sterilisation

What should you be doing?

- Indirect and direct contact parts need robust sterilisation process
- Ensure each of the processes meets the requirements of Annex 1
- Talking! Requires good and frequent communication – engineers – operators – validation - quality unit
- Review: Does every item have its own ‘way in’ to Grade A if needed?
- ‘Know’ how replacement parts can sterilised through if not in standard loading
- Know the process as Inspectors DO inspect in detail!

Deficiencies – Smoke visualisation studies

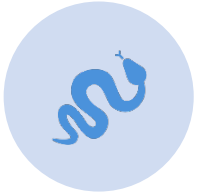


No clear boundary of A/B

Procedures not clearly written and followed

Lack of understanding & process knowledge

Outsourcing controls



Unable to demonstrate airflow

Issues not assessed for impact

Deficiencies – Smoke visualisation studies

The 'in operation' monitoring of Grade A was deficient in that;
The maintenance of laminarity as viewed on recorded smoke studies were deficient as evidenced by;
For fill line [redacted] There was no documented or physical Grade A / B interface to support where the laminarity was required to be maintained to (confirmation of clean zone segregation). The recording did not demonstrate that the airflow was free from turbulence or disruption in the grade A area, that there were no dead zones or that there was no ingress from the surrounding grade B area which the report [redacted] stated that the recording demonstrated.
For fill line [redacted]: During the static [redacted] study, smoke was seen to rise upwards on the left-hand side and the camera footage was not sufficiently focused in this area to demonstrate where the smoke rose up to (i.e. entering A or remaining in B – confirmation of clean zone segregation). In general some of the footage viewed did not have smoke generation in the correct area to demonstrate what the footage hopes to achieve and the camera angles on occasions did not capture the actual smoke footage. The site should review all smoke study supporting [redacted] to ensure this data can be relied upon.

Inspection points – Smoke visualisation studies

What should you be doing?

- Need to demonstrate the airflows within the critical zones
- Recorded by video/ filmed……in a way that this can be seen clearly
- ‘Team’ reviewed & assessed for impact
- Correct & mitigate
- Should include common interventions
- Should show airflows between Grades
- Documented in a report (approved)

Deficiencies – Environmental Monitoring

- Monitoring not well designed
- Results not reported in a timely manner
- Results not reacted to
- Results impact not properly assessed
- Investigations poor and lack detail
- Trending not performed or poorly performed
- Staff not using common sense
- Knowledge of microbiology in steriles environment
- The wrong people – who investigates?
- Data Integrity!

Deficiencies – Environmental monitoring

Rationale

Often seeing weak or deficient rationales for EM

Needs to be appropriate to the product(s) and risk

Local Isolates?

Should consider, placement, methods and frequency

Documented (and approved)

Input from a microbiologist with production personnel

Data

Needs to be reliable – followed original assessment?

Lack of reaction to results – or reaction only to some results…

Results not reported in a timely manner

Inadequate (use of) trending

Lack of knowledge / experience

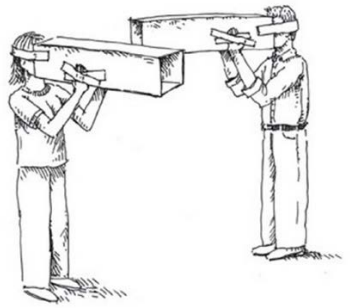
Inspection points – Environmental monitoring

What should you be doing?

- Design the monitoring to give the results that are there!
- Procedures written so operators can follow
- Have team help design programme & validate
- Control of outsourcing – media, technicians, access all areas?
- Don’t underplay the importance of an effective monitoring programme
- Act on results
- Investigate in timely manner
- QC won’t give assurance of contamination or lack of
- Remember - just one part of the overall picture

Deficiencies – Investigations - summary

- Priority (or lack of)
- Detail
- Weak Investigations and assessments
- Not proportionate
- Not scientifically justified
- “Sat Nav Investigations”
- No CAPA, learnings or trends
- The wrong people investigate



Further reading

- Blogs issued by MHRA
- VHP posted in April 2018

  https://mhrainspectorate.blog.gov.uk/2018/04/20/vhp-vapour-hydrogen-peroxide-fragility/
- PHSS guidance note 1 published
- 2018 MHRA Deficiency data available in Excel format

https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

► feedback-from-gmp-inspections

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