



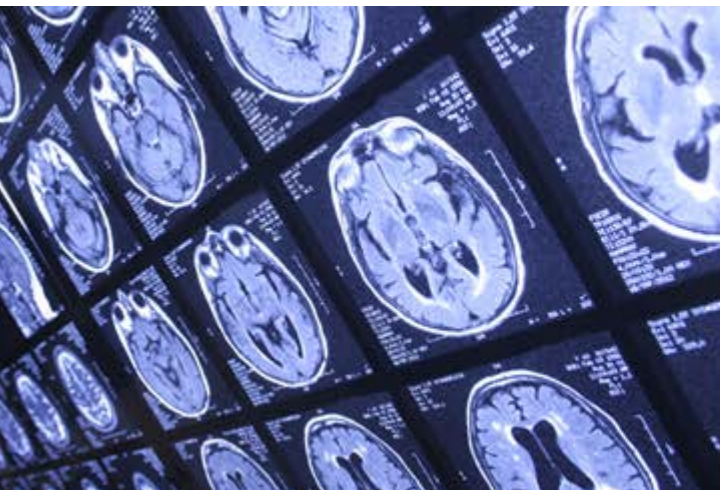
Medicines & Healthcare products
Regulatory Agency



MHRA
Regulating Medicines and Medical Devices

Inspection findings - Sterile Products

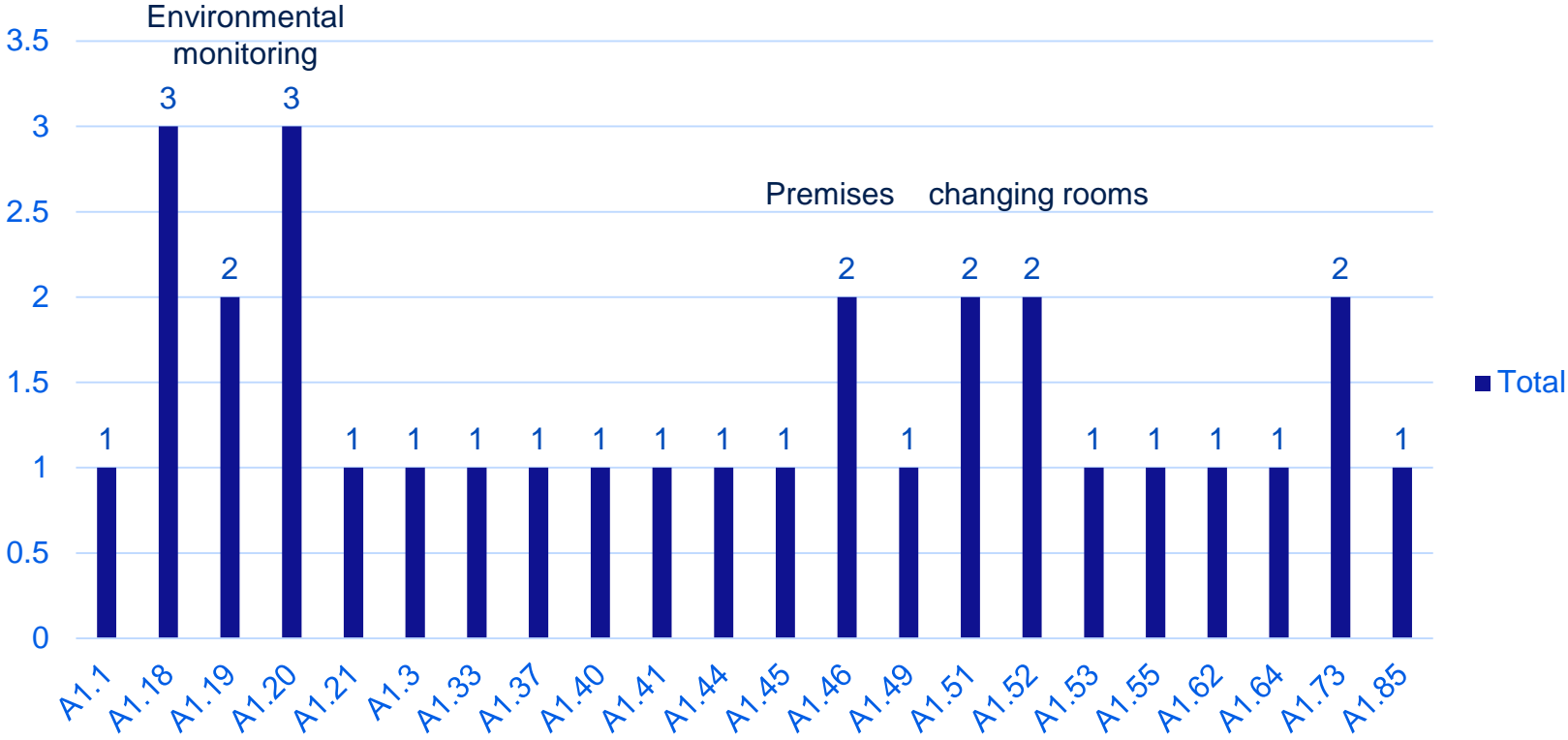
Tracy Moore, Expert GMDP Inspector
16 November 2019





MHRA 2018 Deficiency data

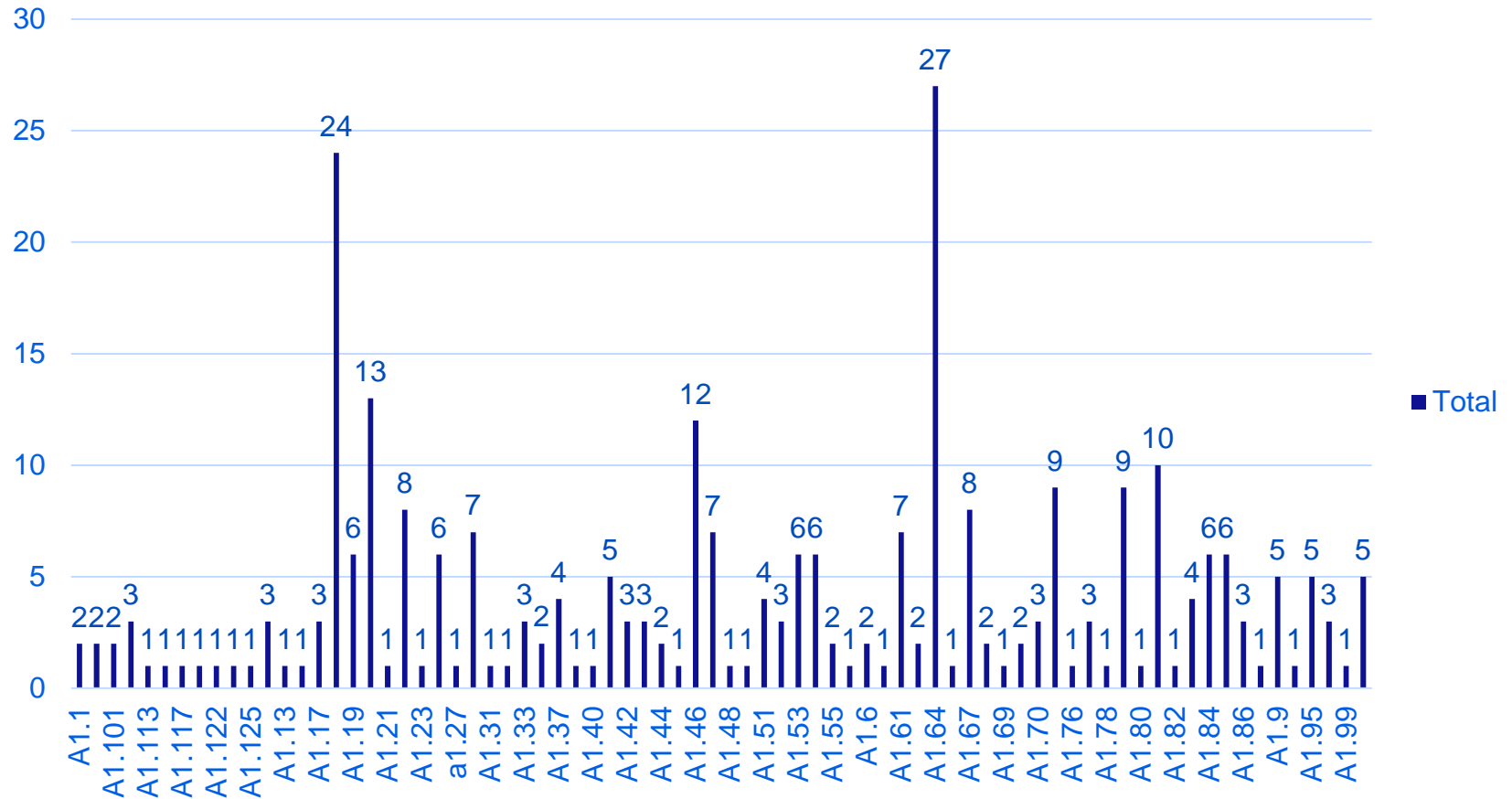
Total no. critical deficiencies raised by Annex 1 reference in 2018





MHRA 2018 Deficiency data

Total deficiencies with a critical or major finding



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



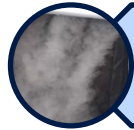
QRM



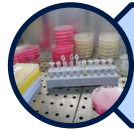
Aseptic process simulation (APS)



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

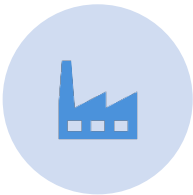
Deficiencies – Aseptic Process Simulations (APS)



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



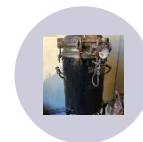
Occluded surfaces



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?

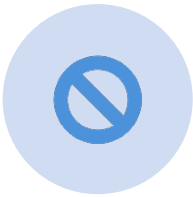


'Know' how replacement parts can be sterilised through if not in standard loading



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



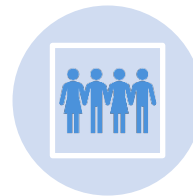
Lack of
understanding &
process knowledge



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 sterile 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



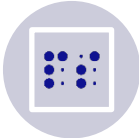
Remember - just one part of the overall picture



Deficiencies – Investigations - summary



Priority (or lack of)



Detail



Weak Investigations and assessments



Not proportionate



Not scientifically justified



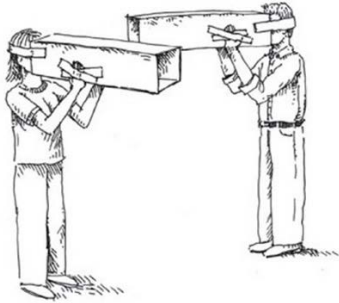
“Sat Nav Investigations”



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](#)

The screenshot shows a blog post on the MHRA Inspectorate website. The header includes the GOV.UK logo and the MHRA logo. The page title is 'VHP (Vapour Hydrogen Peroxide) Fragility'. The author is Andrew Hopkins, dated 20 April 2018. The post discusses the revision of Annex 1 of the EU and PIC/S GMPs for sterile medicinal products. It mentions that the author has been the chairperson for this revision and has engaged with stakeholders. The post also discusses the fragility of VHP and the challenges of sterilising direct and indirect contact parts. There are sections for 'Indirect product contact parts' and 'Direct contact parts'. The post concludes with a note on the issue of sterilisation. On the right side, there is a search bar, a 'Categories' dropdown menu, and a 'We are hiring' button. At the bottom, there are social media links for MHRA on Twitter, LinkedIn, and a company page.

© Crown copyright 2019

About copyright

All material created by the Medicines and Healthcare Products Regulatory Agency, including materials featured within these Medicines and Healthcare Products Regulatory Agency presentation notes and delegate pack, is subject to Crown copyright protection. We control the copyright to our work (which includes all information, database rights, logos and visual images), under a delegation of authority from the Controller of Her Majesty's Stationery Office (HMSO).

The Medicines and Healthcare Products Regulatory Agency authorises you to make one free copy, by downloading to printer or to electronic, magnetic or optical storage media, of these presentations for the purposes of private research, study and reference. Any other copy or use of Crown copyright materials featured on this site, in any form or medium is subject to the prior approval of the Medicines and Healthcare products Regulatory Agency.

Further information, including an application form for requests to reproduce our material can be found at **www.mhra.gov.uk/crowncopyright**

Material from other organisations

The permission to reproduce Crown copyright protected material does not extend to any material in this pack which is subject to a separate licence or is the copyright of a third party. Authorisation to reproduce such material must be obtained from the copyright holders concerned.