MHRA Annual Deficiency Review Highlights Sterility Assurance Issues – Part 2

by Dr. Tim Sandle

6 min. reading time

Last week's LOGFILE (No. 36/2017) presented the first part of an in-depth examination of MHRA's 2016 findings regarding sterility assurance. Don't miss today's sequel that takes a closer look at the deficiencies relating to Chapter 4 - Quality Control and to Annex 1 of the EU GMP Guide.

Chapter 4 – Quality Control

Microbiology laboratories play an essential part in gathering the data needed to assess whether sterility assurance is in control. The 2016 MHRA highlighted three areas where microbiology laboratories were not up to the expected standard. The first one ties in with data integrity and it reads:

> *"The Microbiology laboratory did not have a microbiological plate reader with magnifying glass to ensure accurate colony counts."*

Accurate counting of agar plates is of great importance, especially with higher grades of cleanrooms (Grades A and B) where batch disposition rests on the environmental monitoring profile. Many microbial colonies can be hard to discern and the use of white light, the ability to capture microbial numbers and magnification are each important for this purpose.
The second area relates to chemical expiry. This crosses over with other quality control functions:

> *"There was no consideration of the chemical stability of the reagents when setting the shelf life for the opened chemicals."*

In a microbiology laboratory, this could relate to endotoxin test reagents or to culture media expiry.
The third area relates to the inadequacy of laboratory error investigations, which are often called out for a lack of detail. A specific MHRA finding relates to the ineffectiveness of preventative actions especially in the context of the same error recurring.

Annex 1 – Manufacture of Sterile Medicinal Products

Unsurprisingly, the major set of sterility assurance deficiencies relate to Annex 1, which is concerned with the manufacture of terminally sterilised and aseptically filled products. Here there are many deficiencies relating to risk of microbial contamination and failure to ensure sterility assurance. Some citations of interest are highlighted in this article.
The first relates to risk of fibres. This is an important consideration for sterile products since sterile products are required to be sterile, apyrogenic and free from visible particulates. The deficiency raised reads:

> *"Bags containing filling equipment (for example filling needles) were opened by tearing the bag which presented a risk of introducing fibres to the equipment/line and subsequently the product."*

The area of concern relates to the quality of the bags used to wrap equipment. With this, it is not only fibres that are a potential concern but also the loss of sterility. This can arise should the integrity of the wrapping be compromised, as is noted in a second finding:

> *"The innermost bag containing the stopper track was damaged prior to loading into the filling line which presented a risk of fibres being transferred to stoppers and subsequently the product."*

Ingress of microorganisms into the fluid path is a concern with aseptic processing. While aseptic connector technology has advanced with the introduction of sterile disposable technology, it remains that the number of aseptic connections made should be kept to a minimum. One MHRA deficiency infers that such a review did not take place:

> *"There was insufficient evidence documented to demonstrate that the number of aseptic connections after sterilisation had been minimised."*

Making aseptic connections involves close working from the operator. With this activity, as well as at other times when the aseptic barrier can be broken, regular and effective glove sanitisation from operators is an important step to avoid contamination transfer. Regular glove sanitisation is also important during changing procedures, as the MHRA note:

> *"There is no sanitisation of hands after each individual garment is touched and put on."*

While not sanitising hands is a contamination control weakness, not wearing gloves at all suggests a significant knowledge gap in relation to aseptic processing. For one company, the MHRA recorded:

> *"Sterile gloves were not being worn by the operator sanitising materials into the transfer hatch to the EU Grade B area."*

A second area relating to gowning concerns footwear, albeit for lower grade cleanrooms:

> *"Gowning procedures required operators to remove their shoes when entering Grade D and C areas. The nature of the foot coverings used would not prevent microbial contamination passing from the operator's feet onto the clean room floors."*

In the above example, it seems that overshoes were being worn rather than personnel being issued with dedicated and captive footwear. A further operator-related MHRA observation concerned aseptic processing where complete coverage of the operator is essential to reduce the transmission risk of microbe-carrying particles. The agency state:

"A gap between the hood and mask was seen for some operators resulting in exposed skin at the side of the face MHRA annual deficiency review continued GMP REVIEW 7 VOL.16 NO.2 JULY 2017 with the potential for product contamination especially when working in a LAF cabinet."

Summary

Reading and reviewing findings from regulatory inspections can help an organisation to develop best practices and to understand the current 'hot topics' in relation to regulatory inspections. Such reviews also allow an organisation to appreciate inspectorate trends. One such trend is the number of findings under the umbrella term 'sterility assurance'. Examining a selection of these, as this article has done, indicates that within the scope of sterility assurance personnel-related matters are the most common, especially in relation to gowning and disinfection. Sharing this information within the organisation and building it into contamination control awareness training or GMP refresher courses not only improves contamination control but it puts the organisation in a stronger position ahead of their next regulatory inspection.

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Sources:

[1] MHRA. MHRA GMP Inspection Deficiency Data Trend 2016.
London, UK: MHRA; 2016. Available at:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/609030/MHRA_GMP_Inspection_Deficiency_Data_Trend_2016.pdf
[2] Sandle T. Sterility, Sterilisation and Sterility Assurance for Pharmaceuticals: Technology, Validation and Current Regulations. Oxford, UK: Woodhead Publishing; 2013, pp. 1–5.

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