MHRA Annual Deficiency Review Highlights Sterility Assurance Issues – Part 1

by Dr. Tim Sandle

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 and assess the impact on their sites.
The latest MHRA GMP Inspection Deficiency Data Trend 2016 is notable for the number of findings under the umbrella term 'sterility assurance'. This is a new deficiency group so this article examines a selection of these findings.

Biological indicators

Warning letters issued by the US Food and Drug Administration are available for any person to review. Reviewing these letters is of interest both in relation to specific events and for signalling inspectorate trends. Information from European inspectors is harder to come by and has, until recently, been gleaned from occasional presentations made by inspectors at conferences.

For the past 3 years, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) has produced information summarising key inspectorate trends. With each successive year, the level of detail provided with the headline trends has been made more comprehensive. The most recent review (2016) [1] is notable for the appearance of 'sterility assurance' in the top ten key categories of inspectorate trends. Not only does this subject appear on the list for the first time, it occupies the number 2 spot. The top ten main categories for MHRA findings in 2016 are as follows.

1. Quality system
2. Sterility assurance
3. Production
4. Complaints and recall
5. Qualification/validation
6. Premises and equipment
7. Computerised systems
8. Personnel
9. Documentation
10. Quality control

It must stand that there have been 'sterility assurance' issues with the previous reviews and there is a strong possibility that these have been categorised in other ways. Nonetheless, the topic of

sterility assurance is being seen as something of sufficient importance to be given its own category and to be subsequently ranked second.

MHRA critical and major deficiencies

The MHRA list of major deficiencies has been taken from inspections of 242 UK-based manufacturers together with 82 inspections undertaken overseas. The top ten list covers "critical" and "major" deviations, as assessed by the agency, only.

The data trending presentation is different to 2015, with the aim of allowing readers to identify the following.

- The severity and frequency by the EU good manufacturing practice (GMP) references.
- The overall number of deficiencies by categories: Critical, Major, Other.
- The high-impact issues compared with high-frequency issues.

Across the board, many of the findings relate to Chapter 1 of the EU Guidelines to GMP, Section 1.4 Pharmaceutical Quality System, which refers to the pre-requisites for an appropriate pharmaceutical quality system; and Section 1.8 describing GMPs needed for the manufacture of medicinal products. In addition, there are also several observations in the handling of deviations and corrective and preventive action, plus product quality reviews.

Sterility assurance

Sterility assurance concerns the wider embracement of the aspects of GMP, which are designed to protect the product from contamination at all stages of manufacturing (from incoming raw materials through to finished products), and thus it forms an integral part of the quality assurance system. The term should not be confused with the 'Sterility Assurance Level' (SAL), which is used to assess terminal sterilisation processes (the probability of a single unit being non-sterile after a batch has been subjected to the sterilisation process) [2]. As to what constitutes 'sterility assurance' is open to debate but it extends to any areas of weakness that could lead to microorganisms being present where their presence is undesirable and which could lead to a product or patient risk.

MHRA findings relating to sterility assurance

The MHRA 2016 review covers each of the top ten categories and the review takes the form of a presentation. The purpose of this article is to consider the areas that fall under 'sterility assurance'. For this exercise, the examples are grouped under the appropriate sections of the EU Guidelines to GMP.

Chapter 1 – Pharmaceutical Quality System

Under Chapter 1 of the EU Guidelines to GMP are deficiencies relating to senior management oversight. These deficiencies include:

> *"There was no written procedure for the Quality Monthly Meetings attended by the departmental managers to review the effective implementation of the quality system."*

With this deficiency, it is important that information relating to contamination control risks are reviewed by all senior managers. Also falling under Chapter 1 are deficiencies relating to a lack

of monitoring of regulatory updates. Here, the trends noted include there being no mechanism to ensure that changes to regulatory requirements were captured and the impact to the site considered. The regulatory landscape moves at a fairly rapid rate and it is important that those with responsibilities for sterility assurance are aware of the changes. An example would be the recent change to the cleanroom classification standard ISO 14644.

Chapter 3 – Premises and Equipment

Maintaining premises in good order is important for addressing contamination control risks, as is keeping equipment in good order. This section of the guide also relates to best practices. One of the practices called out in the MHRA review is:

> *"A pool of liquid was observed in the corner of the formulation area corridor, indicating poor maintenance (leak) or poor cleaning (spill) practices."*

Water, being both a vector of microbial contamination and a growth source (at least for Gram-negative bacteria), presents a major contamination risk to corridors. Microbial growth can also be affected under conditions of high humidity and fluctuations to temperature. Assurance can be provided through continuous monitoring and having suitable alarm set-points. In contradiction to this, the MHRA reported:

> *"Temperatures and relative humidity were only captured twice per day throughout manufacturing as instantaneous measurements. No maximum/minimum data was available to provide assurance of temperature and relative humidity requirements at all times."*

Under equipment, concerns with isolators are featured, specifically relating to the efficacy of the sanitisation cycle. For isolator decontamination cycles to work, the gaseous agent needs to be able to penetrate all surfaces. In one example of a weak case, the MHRA record:

> *"The arrangement of gloves and components during hydrogen peroxide sanitisation created occluded surfaces e.g.*
>
> - *isolator gloves were creased*
> - *a bunch of plastic ties were pinned tightly together*
> - *isolator gloves lying against product bags*
> - *small equipment such as scissors and spoons were lying horizontally on metal racking."*

With the above example, this would prevent effective sanitisation of the items. Linked with isolators are clean air spaces in general. With both isolators and clean air devices the maintenance of the airflow is an essential feature of contamination control. Importantly not every area within the device is afforded the same degree of clean air protection. This is why the MHRA noted that in one company there were no diagrams that defined the positioning of components in the area to ensure that unidirectional airflow was maintained.

Also associated with premises is cleaning validation. This topic invariably features highly in relation to regulatory concerns and several examples are included in the MHRA review. These are

divided between absence of documented evidence for cleaning validation and occasions where hold times exceed the validated cleaning hold times.

Next week in part 2 of the article you'll learn about MHRA's findings related to Chapter 4 - Quality Control and to Annex 1.

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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.

The article was first published in gmp review Vol.16 No.2 July 2017 and is reprinted in our LOGFILE Newsletter by courtesy of gmp review.

