Macedonian pharmaceutical bulletin, 68 (Suppl 1) 173 - 174 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.082
Short communication

Trending environmental monitoring data, analysis and data management for non-sterile pharmaceutical manufacturing

Hristina Sekuloska*, Apostol Todorovski, Marina Petreska

Quality Control Department, Bionika Pharmaceuticals, str. Skupi 57, 1000 Skopje, North Macedonia

Introduction

Environmental monitoring (EM) is a required, essential component of current good manufacturing practices (cGMP). The purpose of environmental monitoring is to assess the cleanliness of pharmaceutical (sterile and nonsterile) manufacturing environments, as well as to determine if the manufacturing facility is in a state of microbial control. Environmental monitoring includes the collection of data relating to the numbers of microorganisms present in surface samples (contact plates or swabs), non – viable particles, microorganisms in air samples (active sampling with air samplers and passive sampling with settle plates), personnel monitoring and microorganism identification. EM data should be studied for trends. EM trends examine data over time to look for changes or movements in a general direction.

Data from the environmental monitoring trending is important and can be performed for many reasons including: regulatory compliance, ensuring a state of control of the facility, to ensure that an efficient environmental monitoring program is established, to determine the effectiveness of cleaning and providing an assurance that the sanitization procedures is working as expected, also the ability to be proactive before a problem gets out of hand, identifying sources of microbiological contamination, establishing alert and action levels, to determine any problem and ensuring a state of control of the facility (Booth, 2021; Sutton, 2015).

The aim of this paper is to show trending of EM data collected from microbial monitoring of air, surfaces and particle monitoring in grade D cleanroom areas, analyzing data, setting action and alert limits, interpreting the overall monitoring process behavior (EudraLex GMP guideline).

Materials and methods

Microbial monitoring of air in cleanrooms

Volumetric air sampling for regular testing and monitoring of air in grade D cleanrooms is performed with RCS® High Flow Touch Microbial Air Sampler and Tryptic soy agar (TSA) strips are used, which after the air sampling are inserted in the appropriate casing and thus incubated. Incubation of agar strips is performed for 3 days at 24°C (to encourage the growth of yeasts and molds) and an additional two days at 35°C (conditions for the growth of mesophilic bacteria).

Surfaces sampling

Sampling for regular check of microbiological purity of the surfaces in grade D cleanrooms is carried out using contact convex Tryptic soy agar (TSA) plates with neutralizers. Sampling is performed by applying the plate on the inspection point and holding it for 10 seconds with gentle pressure. The incubation period of the agar plates is for 3 days at 24°C (to encourage the growth of yeasts and molds) and an additional two days at 35°C (conditions for the growth of mesophilic bacteria).

Particle count monitoring

Particle sampling in grade D areas is carried out with portable laser particle counter type HANDHELD 3013 (for particles ≥ 0.5 and 5 μm), with a suitable sample flow rate (at least 28 liters per minute).

Data analysis and data management

*hristina.sekuloska@bionikapharm.com

Three-sigma limits (3-sigma limits) is a statistical calculation that refers to data within three standard deviations from a mean. Sigma is a statistical measurement of variability, showing how much variation exists from a statistical average.Three-sigma limits are used to set up the upper and lower control limits in statistical quality control charts. With this statistical approach of data trending we get the following statistically significant parameters:

Control charts, also known as Shewhart control charts, determine if there is a controlled or uncontrolled variation in a process. *Alert Level* is an established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follows-up the potential problem. Alert levels are always lower than Action Levels. *Action Level* is an established microbial or airborne particle level that, when exceeded, should trigger immediate intervention, including root cause investigation, an assessment of the potential impact to product and requirements for corrective and preventive actions.

Using this method for statistical data trending, the tracking of Alert Level and Action Level is performed in a given time period.

Results and discussion

By using 3 sigma approach data collected from regular testing of cleanrooms in a time period from seven years (from 2014 to 2021) was statistically analyzed, charted, action and alert levels were set and trend was detected. The frequency of monitoring and the number of testing locations is based on a documented risk assessment. The number of sampling locations and their positioning for particle count concentration is done according to principles described in ISO 14644-1, current version.

During the regular checks, alert levels and action levels from the data collections were compared and annual comparisons are made between each year. Trend analysis data are presented in tabular form and graphically with control charts, taking in consideration results from regular testing of microbial air quality and surfaces as well as particle concentration in grade D cleanroom areas. In order to obtain control charts, that determine the results that would go beyond the trend limits, by implementing a 3 - sigma statistical approach the mean value was obtained from all results for each individual parameter.

To set the trend range, the calculation of the standard deviation (s) was done. The trend range was determined by setting an upper control limit (UCL) and a lower control limit (LCL). The upper control limit (UCL) is set three-sigma levels above the mean, and the lower control limit (LCL) is set at three sigma levels below the mean.

According to the trend analysis of data from regular testing of air quality (in terms of microbial cleanliness purity and particle counts) and microbiological cleanliness of surfaces, in grade D cleanroom areas, obtained results are well within trend and within the acceptance criteria.

Conclusion

From the above presented results and discussion it can be concluded that all results from regular environmental monitoring of grade D cleanroom areas in terms of microbial contamination (in air samples and surfaces), as well as total particle count concentration, are within trend limits and no adverse trend is observed in the mentioned seven year time period. Sufficient data should be available to determine alert and action limits by 3-sigma formula. These limits for EM should be calculated with minimum one year data because results vary in different seasons of the year. According the trend analysis, the results stay within the acceptance criteria, i.e. they do not pass the UCL and LCL, that demonstrates the appropriateness of the performance of the Heating-ventilating air conditioning system (HVAC system), design of premises, the efficiency and proper implementation of the cleaning and disinfection procedures and assurance that Contamination Control Strategy (CCS) is implemented across the facility, as well as it confirms the good personnel behavior using the protective gowning in controlled manufacturing areas.

References

Booth, C.M., 2021. An Introduction to trending in Environmental Monitoring Programs. Available at: https://www.outsourcedpharma.com/doc/an-introduction-to-trending-in-environmental-monitoring-programs-0001 (Last assessed: 18.04.2022)

EU GMP Annex 1 Revision: Manufacture of Sterile Products (Draft). Rev 12. 396-397, 420. Feb 20, 2020 Available at: https://ec.europa.eu/health/system/files/2020-02/2020_annex1ps_sterile_medicinal_products_en_0.pdf (Last assessed: 18.04.2022)

ISO 14644-1, Cleanrooms and associated controlled environments, classification of air cleanliness by particle concentration, 2015

Sutton, S., 2015. Trending in the Environmental Monitoring Program. Available at: https://www.americanpharmaceuticalreview.com/Featured-Articles/179364-Trending-in-the-Environmental-Monitoring-Program/ (Last assessed: 18.04.2022)