

LOGFILE Feature 04/2020 – Microbiological monitoring in non-sterile areas

7-9 Minuten

At our GMP Conference, the “GMP-BERATER Tage“, in October 2019 we presented a GMP dialogue on "Microbiological Monitoring in non-sterile areas". Questions on the topic were asked by participants and answered by GMP inspector Franz Schönfeld, PhD and microbiologist Frank Mertens, PhD in a lively discussion.

The GMP requirements for microbiological monitoring in the sterile production areas are laid down in several regulations. However, hardly anything is defined for non-sterile zones. How should microbiological monitoring be established there? How and how often do you check the air quality? Which methods are used? May rapid methods be used? Which limit values can be applied?

Is it useful to create a microbial library?

Microbiological monitoring and trending are increasingly replacing individual tests against limit values. Qualitative assessment is becoming increasingly important: Which microorganisms occur frequently? In what places? And where are the sources of entry?

From this point of view, it may well make sense to create a microbial library, even if this is not stipulated anywhere. However, one should only concentrate on conspicuous findings. This library can also be used for culture media testing (growth controls).

Another area of application is qualification: In the qualification of rooms and water installations, the microbial (initial) status is determined. However, changes can only be detected if the

microbial spectrum is known. Here too, a microbial library provides useful services.

What to do if monitoring reveals deviations, but the products are okay?

The permissible bacterial count for non-sterile products is specified in the pharmacopoeias. It is up to you to determine the appropriate environmental conditions with which the required microbial status of the product is reliably achieved. Since every product and every production facility is different, there are no generally applicable guidelines for this.

If monitoring reveals deviations that do not affect the microbial status of the finished product, the self-defined limit values are probably too strict. In practice, decision-makers often lack the necessary expertise in this area. Often too much of a good thing is then done out of misunderstood risk awareness.

In this case, the experts recommend evaluating the existing monitoring data and carrying out a risk analysis on the basis of the trend analysis, which has to be carried out regularly anyway. Based on this, a new concept can be developed in which limit values, sampling points and examination frequencies are defined or adapted on a risk-based basis.

The following applies to risk analysis:

- The severity is unchangeable (here: effect of the microbial infestation)
- The probability of occurrence can be reduced by preventive measures. This means here: the probability of microbial infestation can be reduced, e.g. incoming goods control of raw materials and appropriate personal hygiene.
- The probability of detection can be increased by monitoring.

The risk priority number (RPN) is the product of the three factors: severity, probability of occurrence and probability of detection.

If the probability of occurrence is reduced by (additional) preventive

measures, the scope of monitoring can be reduced.

As Dr Franz Schönfeld reported from his inspection practice, risk analysis, especially FMEA, is often not applied correctly in practice. For example, too little is asked about the objective of the measures (the objective is the microbial status in the product!). Moreover, too little attention is often paid to the real risks. For example, there is hardly any distinction between the production of liquid, semi-solid or solid pharmaceutical forms, but everything is dealt with according to the same scheme.

When should the sampling take place: in operation or at rest?

Here, too, the aim of the measures must be kept in mind, namely the microbial status of the finished product. In order to be able to assess whether this is negatively influenced by the microbial status of the production environment, sampling must be carried out in operation, i.e. during ongoing production.

Does personnel monitoring make sense for the production of cytostatic drugs using isolator technology?

In the production of active substances, the monitoring effort can be reduced compared to the production of medicinal products. The active substance is homogeneous and the samples are therefore representative. Contract givers often make excessive and unjustified demands - here too, a lack of microbiological expertise is often the reason.

Are overalls in class D required?

According to the experts, this requirement is excessive - at least in the European area. However, in other cultures and countries where daily showers are not part of the general understanding of hygiene, wearing overalls in class D can be useful.

Should clean room class D be used for the production of non-sterile products?

To use clean room class D with all its consequences regarding classification, qualification and monitoring for the production of non-sterile products is certainly too excessive. However, depending on the dosage form, it may be useful to define the monitoring parameters "based on class D". Competent risk management is also required here!

Does a product that is supposed to be spore-free have to be sterile at the same time?

This question can be clearly answered with "no": "spore-free" does not mean "sterile".

Is a certain methodology prescribed for the detection of specified microorganisms?

For environmental monitoring of non-sterile medicinal products, the methodology for the detection of specified microorganisms is not specified. Detective work is often called for, especially in problem cases. This is where professional competence is required - and with it the whole range of microbiological methods.

Conclusion:

- *The definition of parameters for microbiological monitoring in non-sterile production leaves a great deal of freedom to those responsible - and thus requires solid microbiological expertise. In practice, this is often not present, especially among decision-makers. The consequences are often too strict limit values, excessive sampling frequencies and unnecessarily many sampling points.*
- *Exaggerated requirements are also frequently made by contract givers. This also reflects the mixture of a lack of expertise and risk*

aversion.

- *On the other hand, there is a lack of understanding of risk when conducting risk analyses. Thus, the procedure is often "according to the book", whereby the actual risks, such as the type of pharmaceutical form manufactured, are not taken into account.*
- *In general, there is great uncertainty as to what is correct and how much is sufficient to ensure the microbial status of non-sterile medicinal products.*

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