Environmental Monitoring in Aseptic Manufacturing

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PEER REVIEW

Abstract
Environmental monitoring is critical to ensuring microbiological and particulate purity in pharmaceutical manufacturing, particularly for sterile and aseptically produced products. Cleanrooms classified by ISO standards provide controlled environments tailored to product risk levels. Contamination sources include personnel, environment, raw materials, and processes, necessitating robust monitoring to verify control effectiveness. Conventional methods such as settle plates and active air sampling remain standard, but rapid microbiological methods (RMM) employing biofluorescent particle counters (BFPC) offer real-time data and early contamination detection. Despite challenges in correlating traditional colony-forming units (CFU) with new autofluorescent units (AFU), RMM align with evolving regulatory guidance (e.g., Annex 1) and promise improved contamination control, reduced operator intervention, and expedited batch release, signalling a paradigm shift in environmental monitoring strategies.

Keywords
Annex 1 | Contamination Control Strategy | Biofluorescence | Isolator | Rapid Microbiological Methods

Purpose and value of environmental monitoring

The product safety of drugs and medical devices has always been the top priority throughout the entire life cycle of pharmaceutical products. For this reason, strict requirements are imposed – adapted to the method of administration (e.g., topical, oral, parenteral) – with regards to microbiological and particulate purity. This inevitably means that, from a microbiological point of view, qualified cleanrooms are necessary for the manufacture of sterile or microbiologically critical dosage forms [1]. These cleanliness zones are designed and operated in such a way that they meet defined physical and microbiological requirements when monitored [2]. The highest requirements apply to the manufacture of products that are required to be sterile. Compared to the manufacturing of non-sterile products, sterile production poses the greatest challenges by far and can therefore rightly be described as the premier league [3]. In this premier league, the manufacture of pharmaceuticals that cannot be terminally sterilized but must be produced aseptically takes the top spot in terms of the challenges posed. In order to effectively prevent the entry of living and non-living particles into these products, production takes place in cleanrooms of class A or ISO 5 according to ISO 14644-1. The strictest regulations apply to this cleanroom class, which means that only a very small number of non-living particles and no microorganisms whatsoever are permitted. For other less critical products (e.g., oral dosage forms), lower cleanroom classes are sufficient for manufacturing, where the requirements for the occurrence of microorganisms and the presence of non-living particles are significantly lower. The lower the cleanroom class, the more non-living and living particles are tolerated.

Microbiological and particulate contaminants can enter the pharmaceutical product from the environment in various ways and then contaminate it. A very good and clear description, which includes a wide range of different sources of contamination, can be found, for example, in the US Pharmacopeia [4]. The most important sources of contamination mentioned here are personnel, the environment (air, surfaces, water), raw materials, auxiliary materials and the manufacturing processes themselves. These sources of contamination must be kept under control. Environmental monitoring is used to check whether the measures taken to achieve this are effective. Monitoring cleanrooms is therefore an important part of the overall contamination control strategy [2].

An environmental monitoring program should be established and documented. The purpose of the environmental monitoring program is to [5]:

Provide assurance that cleanrooms and air handling units continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements.

Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.

Environmental monitoring should support root cause analysis when contamination occurs and help to ensure that the cause can be eliminated. The results of the identification of microbiological contaminants can then be used to deduce the natural habitat of the microorganism and, in a further step, to determine where the actual source of contamination is to be found. At least, this approach is recommended for most groups of microorganisms. However, when *Bacillus sp.* occurs, this procedure becomes extremely complicated, as these microorganisms are ubiquitous, making it very difficult to narrow down the source of contamination.

Trending the monitoring data allows early detection of any negative trends developing in the cleanroom, which can then be counteracted in due time. It is recommended that the trending contains all measured sampling points. The great advantage of trending is that slow, gradual changes in the microbial and particulate status of the cleanroom can be detected at an early stage, whereas in routine monitoring these remain under the radar because they are still below the threshold of warning and action values. According to Annex 1, section 10.10., trend data generated for classified areas should be reviewed as part of product batch certification/release.

Regulatory requirements

Numerous guidelines describe in detail the handling of environmental monitoring [6,7] and the limit values specified for the corresponding cleanroom classes [8]. The latest key regulatory requirements for environmental monitoring can be derived in particular from Annex 1 to the EC GMP guidelines (2022) [9]. Some of the requirements mentioned there are particularly noteworthy:

Total particles

- *"9.14 A total particle monitoring program should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state."*
- *"9.16 For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly."*

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Figure 1: Automatic settle plate changer (source: MBV).

"9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 µm) and with a suitable sample flow rate (at least 28 litres [1 ft³] per minute) so that all interventions, transient events and any system deterioration is captured. [...]"

Viable particles

- *"9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation."*
- *"9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. [...]"*
- *"9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring [...] "*
- *"9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available."*
- *"9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated [...]"*

Rapid/Alternative methods

- *"2.1 [...]The use of appropriate technologies ([...], rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product."*
- *"9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product [...]"*
- *"10.10 [...] For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid/alternative methods."*

Common methods for environmental control

In order to prove that a cleanroom complies with the relevant class, the specified limit values must be adhered to for both viable and non-viable particles. Various methods are available for this purpose, the most commonly used are briefly described below.

It should always be borne in mind that the values obtained for monitoring are not absolute values, but merely a snapshot of the actual condition of the cleanroom [10,11]. Depending on the method used, it should also be taken into account that there may be considerable measurement inaccuracies, e.g., due to the sampling itself. In general, surface monitoring has been found to recover <50 % [6], even when used with relatively high inoculum levels on standardized coupons. In actual production environments where organisms are stressed to varying degrees, recovery rates may be lower. In addition, sampling can only detect microorganisms for which the environmental conditions during incubation are actually suitable. For example, the incubation conditions would have to be adjusted for the detection of microaerophilic/anaerobic microorganisms. With the incubation conditions specified for aerobic monitoring, it will not be possible to detect the above mentioned microorganisms. By selecting the appropriate culture media and incubation conditions, the operator thus limits the spectrum of microorganisms that can be detected. In many respects, USP <1116> is correct when it states that a negative result in microbiological hygiene monitoring does not necessarily mean that there were no microorganisms in the tested environment. If no microorganisms were detected, this does not mean that none were present, so it can be assumed that there are a corresponding number of unreported cases. From a microbiological perspective, blinders are being put on here, as the focus is on a fairly limited spectrum of microorganisms, but at the same time, this small spectrum is being searched for with a magnifying glass. This makes sense,

as the regulatory requirements are fully met, but it does not hurt to be aware of this.

1. Determination of microbiological contamination in air
There are 2 basic methods available for determining the microbial count in air with different levels of significance: passive and active air sampling.

1.1 Passive air sampling (qualitative method)
In passive air monitoring, standard agar plates (90 mm tryptic soybean agar, TSA) are used as settle plates for a defined period of up to a maximum of 4 h, which has to be validated and is demanded by Annex 1 (4.31) [5] and USP<1116> [6]. To do this, the lid of the plates is removed and the plates are then left open. Microorganisms that fall onto the plate during sampling can grow during subsequent incubation and can then be counted as colonies on the agar plate. The result is purely qualitative and can be expressed as: germ count per plate (without specifying the amount of air sampled, as this is not known). The probability of a microorganism falling onto a settle plate and not next to it is correspondingly low. It is therefore reasonable to assume that when microorganisms are detected on a settle plate, the number of germs in the environment must be correspondingly high in order for a germ to be detected on the agar plate at all. The significance of passive air monitoring is correspondingly low. Settle plates are very well suited for all sampling points where the plates can be positioned well and used during the process without further interaction. To eliminate the need for operator intervention every 4 h – but still be able to continue sampling the same location during monitoring – automatic settle plate changers are available on the market (fig. 1). Without operator intervention and without risk for secondary contamination, microbiological monitoring of the air can thus be carried out automatically and continuously over a longer period of time.

1.2. Active air sampling (quantitative method)
The most common method for active air monitoring is based on the impaction principle. A specified amount of air (e.g., 1 000 L) is aspirated through a lid with holes or slits, it is accelerated and undergoes a rapid lateral change of direction; this causes suspended particles to impact onto the detection surface due to their mass inertia (fig. 2). This provides a quantitative result that indicates the germ count per defined volume.

Different manufacturers of active air sampling devices achieve slightly different d_{50} values. The d_{50} value (cut-off size) of an air sampler describes its physical collection or separation efficiency. It is defined as the aerodynamic equivalent particle diameter at which 50 % of airborne particles are collected on the agar surface, while the remaining 50 % pass through the airstream. The lower the d_{50} value, the better the physical sampling efficiency. According to EN 17141, a d_{50} value below 2 µm, which is exactly the range

Figure 2: Active air sampling (source: MBV).

in which microorganisms are found, is considered appropriate for an air sampler. Larger particles are then detected in almost complete numbers on the agar plates. As described in Annex 1, section 9.29, supporting data for the recovery efficiency of the chosen sampling methods should be available. The user is thereby requested to also obtain data from the equipment manufacturer.

2. Determining the microbiological contamination of surfaces
To test regular or flat surfaces, contact plates are predominantly used, and less often swabs.

2.1. Contact plates
To perform a contact plate test, agar plates with a nutrient medium are used, whose agar surface is higher than the edge of the plate. A contact plate is a very simple method for determining the bacterial count on surfaces that are accessible and flat and – very importantly – can be easily cleaned after the contact plate has been taken, as nutrient medium residue remains at the site of the contact.

2.2. Swabs
The use of swabs is recommended if the area to be sampled is difficult to access, uneven or very small, for example

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Requirement	Frequency	Implementation	Remark
monitoring in grade A, for the full duration of critical processing	continuous	settle plates (duration/ plate is max. 4 h)	-
active air sampling	at pre-defined time intervals (i.e. acc. to USP <1116> once per shift)	Active air sampler using agar plates: 1 000 L in 10 min. with a flow rate of 100 L/min.	-

Table 1: Conventional option for environmental monitoring.

Requirement	Frequency	Implementation	Remark
monitoring in grade A, for the full duration of critical processing	continuous	active air sampler will not require 10 min for 1000 L, but instead draws the air onto the agar plate over an extended period of time. Often 1 000 L are still sampled for the reporting colony forming units (CFU)/ m^3. However, the time frame of the sampling is extended.	option to eliminate settle plates or use less
active air sampling			option to eliminate active air sampling of 1 000 L at predefined time intervals

Table 2: Advanced option for environmental monitoring.

swabs are used to sample filling needles post filling operation. The quantitative significance of swabs depends in particular on whether all microorganisms can be removed and released after sampling so that they can then be detected as individual colonies after being applied to an agar plate. After swabbing the sample is transferred either on solid (quantitative result) or liquid nutrient medium (qualitative result).

Non-viable particles

Particle counters are used to determine non-viable particles. These actively draw in the prescribed volume of air (at least 28 L/min) and then indicate the corresponding values for particles >5 µm and >0.5 µm.

Different Strategies for implementation in daily routine

The regulatory requirements described above can be implemented using various strategies. Each user can decide for themselves which strategy to choose, whether to continue with conservative processes or to pursue alternative, progressive, or completely new approaches. This is less relevant for surface sampling, where there have been no significant optimizations in recent years, but the situation is quite different for the monitoring of air. Three options for air monitoring are described below: a conventional, an advanced, and a future-oriented option.

Conventional option

To meet the Annex 1 requirement for continuous monitoring in cleanroom class A, settle plates can be used. The settle plates are replaced with new ones after a maximum of 4 h so that the growth properties are not lost due to the agar plates drying out. Short interruptions in continuous monitoring due to plate changes are acceptable. Regulatory requirements stipulate that active air sampling must also be carried out at predefined times with the usual sampling volume of 1 000 L (tab. 1).

Advanced option

Some manufacturers of devices for active air sampling have launched models that sample with a lower air flow rate than the standard tested 1 000 L per 10 min. With a reduced air flow, the time required to measure a given volume is extended. This makes it possible to meet the requirement for continuous monitoring while conducting active air sampling. Once the required amount of air has been sampled, a new active air sampling with reduced flow is started. There is a wide range of models available on the market, with flow rates of 25, 50, or 100 (standard) L/min being the most common, and even single-use systems are available. The benefit of this implementation option is that extended active air monitoring increases the time where the process is controlled with a quantitative method (tab. 2).

Future-oriented option

Devices based on alternative and/or rapid microbiological methods (RMM) are significantly more future-oriented and, with the appropriate practical experience, can provide real-time information on the microbiological contamination of the sampled air (tab. 3). The devices currently available on the market contain particle counters that can indicate the number of particles by size using known methods. In addition, the number of microorganisms present in the sampled volume is also indicated, using the biofluorescence method. The laser integrated into the measuring device detects particles which fluoresce, if they are of biological origin and thus contain endogenous

fluorophores (e.g., amino acids, proteins, NAD[P]H, flavins). The laser radiation is absorbed by the particle and re-emitted with a longer wavelength [12].

The rapid method using biofluorescence presents the pharmaceutical industry with the challenge of accepting a new unit of measurement, moving away from the classic CFU and instead dealing with auto fluorescent units (AFU). This requires a significant shift in mindset. The pharmaceutical industry and their microbiologists have been accustomed to dealing with and evaluating CFU for decades, and Annex 1 also provides a clear definition of this term:

> *"A microbiological term that describes a single detectable colony that originates from one or more microorganisms" [13].*

However, a critical examination of this unit of measurement, which has been in use for over 125 years, reveals that it is more of an estimate than a precise specification [14,15]. Microbiology is known for not being one of the exact sciences (for example, a factor of 2 is used in the evaluation of many analysis results) and for dealing confidently with uncertainties. A logarithmic approach is more meaningful than a consideration of absolute measured values.

The use of AFU once again presents the pharmaceutical industry with the challenge that this unit covers a significantly wider range of particles that are of biological origin but include not only viable and culturable particles but also non-viable particles (physically damaged cells, viables but non-culturables) [16]. The consequence of this is that the number of particles measured is significantly higher than is the case with conventional measurement. The pharmaceutical industry has already had a similar experience when, a few years ago, a change was made to the Reasoners agar (R2A) culture medium for microbiological testing of water. Here, too, the change in culture medium suddenly led to conspicuous findings in perfectly functioning systems, because in addition to microorganisms that grew well, microorganisms were now also detected that were not detectable with the previously used culture medium. It was necessary to learn how to classify and evaluate the new, more realistic values in a meaningful way. This is exactly what is needed again this time. It is perfectly clear that it will not be possible to make a reliable statement about the correlation between CFU and AFU, as there is no separation within the AFUs into culturable and non-culturable particles. The significance of the new AFU values still needs to be defined.

In any case, it is crystal clear that the future belongs to rapid methods. Annex 1 in particular, explicitly points out in many text passages that the use of rapid methods should be considered (e.g., 2.1, 2.5, 9.28). It is therefore not only a good idea, but rather a strong expectation to look into rapid methods and consider their use. The following section therefore describes the use of a biofluorescent particle counter (BFPC) using the example of the Rapid-C+ from Plair.

Figure 3: Rapid-C+ as an example for a BFPC (source: MBV).

Requirement	Frequency	Implementation	Remark
Monitoring in grade A, for the full duration of critical processing	Continuous	RMM; combination of continuous particle measurement and continuous active air sampling	Option to eliminate settle plates
Active air sampling			Option to eliminate active air sampling of 1 000 L at predefined time intervals

Table 3: Future-oriented option for environmental monitoring.

Practical example: Use of a BFPC for environmental monitoring in aseptic areas

With a special BFPC like the Rapid-C+ (fig. 3), a single device can be used to perform several environmental monitoring

measurements in aseptic areas in parallel, continuously, in real time and with exactly the same air:

- *Total particle counts*
  Determination of the number of particles in the size range of 0.5 µm to100 µm.
- *Viable particle counts*
  Microbial air monitoring with a BFPC providing instant result in case of presence of viable particles.
- *CFU counts*
  Active air sampling on agar plates. The same particles as mentioned above are sampled on traditional agar media using a removable aseptic container holding an agar plate under a sieve.

Continuous air sampling with the presented BFPC eliminates the need for settle plates if these were used to meet the requirement for continuous monitoring. It also eliminates the need for active air sampling of 1 000 L at specific times, as the active air sampling is already performed by the device itself.

An unbeatable advantage lies in the fact that the same sample of air is used to collect the air for total and viable particle and germ count determination. In aseptically critical areas, space is usually very limited, therefore it is a great advantage to be able to measure multiple parameters simultaneously using the same sampling probe/measurement position.

The device draws in 5 L of air per min. This has the advantage that continuous measurement can be carried out for more than 4 h without impairing the growth properties of the agar plate used due to moisture loss caused by the air flow. The only disadvantage, however, is that the Annex 1 requirement for a test air volume of at least 28 L/min for continuous particle measurement is not met, and therefore an additional particle counter must currently be installed or there is also a paradigm shift here, and the measurement of 5 L instead of 28 L is regulatorily accepted, provided that the equivalence of both methods is demonstrated.

Significance of the measurement data collected

The measurement data obtained with the aforementioned device and continuously collected from environmental monitoring allow the following conclusions to be drawn:

- *Total particle counts*
  Continuous measurement allows an increase in the number of particles to be detected early and in real time. Root cause analysis can then be started and CAPA measures initiated very quickly.
- *Viable particle counts*
  The measurement data obtained with the BFPC allows changes in the number of particles in the room air to be quickly detected. Viable particles and, included therein, potential microbiological contamination can thus be detected in real time. Here, too, a root cause analysis can be started and CAPA measures initiated. An immediate measure could be to separate individual manufactured samples in which increased particle concentrations have been detected. These samples can then be evaluated separately and any influence on the entire batch can be ruled out.
- *CFU counts*
  The results of active air sampling on agar plates are only available after the incubation period, i.e., with a delay of almost 1 week. However, they are then reported in the usual unit of CFU. According to Annex 1, microorganisms detected during monitoring when limit values are exceeded must be identified, which requires growth on a nutrient medium. The agar plate cannot therefore be dispensed with.

This results in 2 scenarios for how the rapid method can be used in pharmaceutical manufacturing:

- *Scenario 1:*
  When using a BFPC in a manufacturing isolator, a potential microbial contamination of particles can be detected earlier, which also allows for a correspondingly rapid response (e.g., separation of samples). If no findings with elevated viable particle counts occur, it can be assumed at an early stage that the detection of microbial growth on the agar plates will also be negative. Ultimately, however, the evaluation of the agar plates at the end of the incubation period is decisive, i.e., the specific CFUs represent the true values and are ultimately decisive for the evaluation of the batch produced. Only what has grown on the agar plate counts and can be identified.
  The aforementioned BFPC device thus serves as an early warning system, but the decisive factor is the detection of microbial growth on an agar plate, which is the conventional method.
- *Scenario 2:*
  There is a shift in mindset and AFUs are used for evaluation instead of CFUs. In this case, corresponding risk-based limit values must be redefined. The agar plate located in the aforementioned BFPC device then serves only for the purpose of identifying grown colonies.

Scenario 1 is well suited for gaining initial experience because comparative data can be collected. Starting with scenario 1 and later switching to scenario 2 can therefore make sense in order to successfully implement a RMM in a risk-based and well-founded manner. The Rapid-C$^+$ can be implemented in both conventional isolators with gloves and in gloveless isolators. Especially in gloveless isolators where the focus is already on innovation and automation the implementation of an RMM brings advantages. The device presented can be built under the base plate of the isolator and exchange of the nutrient medium in the autoclavable holder can be performed by the manufacturing personnel without intervention into the isolator grade A environment (fig. 4).

Figure 4: Gloveless isolator "robocell" with integrated Rapid-C⁺ (source: SKAN and MBV).

Following successful comparability studies all nutrient media plates needed for active and passive air monitoring could be eliminated from the isolator.

Conclusion

The strategy for environmental monitoring should be selected on a case-by-case basis and thus adapted to the specific situation on site. Regulatory requirements can be implemented in various ways, allowing for a high degree of flexibility. For example, the conventional use of settle plates in combination with active air sampling is still common for continuous monitoring. However, Annex 1 also contains several references to the fact that the use of rapid methods should be examined and considered. In terms of a CCS that is as comprehensive as possible, the use of real-time monitoring solutions offers decisive advantages:

- simpler/better root cause analysis
- prevents future incidents
- allows immediate response to excursions
- direct feedback
- continuous monitoring
- reduce the need for interventions (sampling and handling)
- lower risk of contamination (caused by operator); intervention free in grade A
- faster batch release (when no viable particles are detected)
- reduced downtime (no stoppage due to plate change)

The arguments mentioned are strong, and Annex 1 provides additional impetus, so it can be assumed that microbiological real-time monitoring will gain considerable momentum.

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