

More than a Filling

Remote microbiological monitoring on aseptic filling lines presents many challenges, but a variety of techniques and technologies are available to assist the manufacturer

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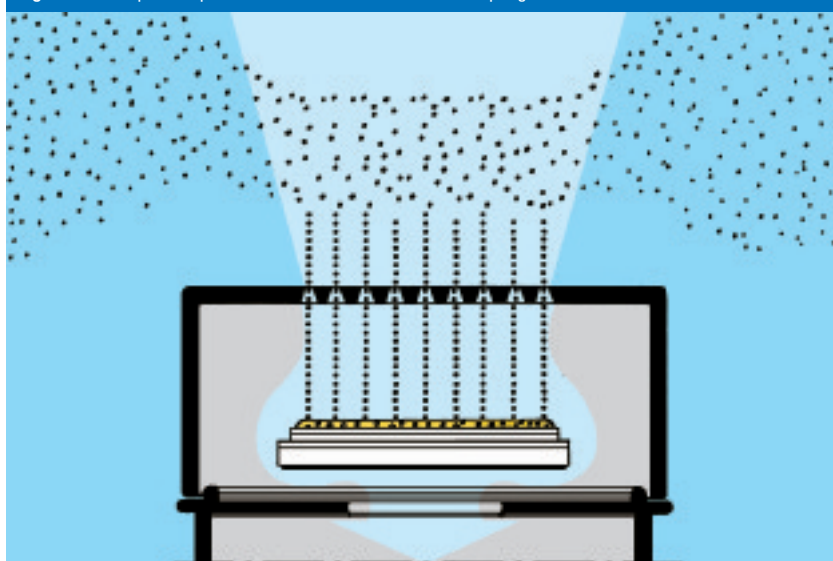
The microbiological safety of biologics, such as blood plasma products, is critical as they are largely administered intravenously and must be filled in a completely aseptic environment. This risk to patient safety can also be translated into a financial risk for the manufacturer. In the simplest example, if confidence in the sterility of a sterile medicine is less than absolute, the batch must be discarded or reprocessed with subsequent cost implications.

The use of isolator technology is becoming increasingly popular for aseptic production processes as an alternative to staffed clean rooms, since this removes the greatest microbiological risk factor – non-microbiologically sterile human contact. Subsequently, there is a regulatory expectation that the atmosphere and the internal surfaces of the isolator should be demonstrated as being completely sterile throughout the manufacturing or filling process. As a result, manufacturers of biologics need to ensure they can microbiologically monitor their Grade A manufacturing and filling environments in the safest, most efficient and effective ways possible.

Preventing Operator Contamination

Good Manufacturing Practice (GMP) for sterile medicinal products requires that all processes that present a risk to the finished product are carried out in controlled and appropriately classified environments. The classification requires compliance with limits for non-viable particle counts of more than 0.5µm and more than 5.0µm. The recommended

Figure 1: Multi-point impaction method for microbial air sampling



microbiological monitoring limit for Grade A manufacturing and filling of aseptic products is effectively zero colony forming units per cubic metre (1). Furthermore, when the filling operation is under unidirectional airflow, it is important that the monitoring point is at the same height.

The manufacture of blood plasma products provides an excellent example of the requirement for effective environmental monitoring for GMP quality control purposes. Aseptic filling of plasma products into individual vials following intermediate raw blood plasma processing stages involves many personnel, which can result in an increased risk of operator contamination and ensuing downtime with associated costs. As a result, it is essential to minimise direct human contact and unnecessary operator interventions when undertaking environmental monitoring.

Traditionally, environmental monitoring has been undertaken by fully gowned operators using microbial air samplers or administering settle plates at the point of fill. However, this requires an intervention into the filling line by opening isolator screening to enable access, resulting in downtime and risk of contamination. The installation of glove ports through isolator screens is an option that many companies are now adopting to address these issues. However, this means that operators no longer have direct access to the filling line; therefore a remote means of monitoring the filling environment is required. This need can be met by a remote air sampling system that can provide the necessary critical environmental monitoring data for quality control purposes prior to the batch release of final plasma products.

It is typically necessary to monitor at the beginning and end of a filling run at the

point of fill and also at other critical points, such as the vial in-feed area. Therefore, since requirements are often very specific, such as the need for remote air monitoring at the exact height of the point of fill of final product vials, it is ideal that a biologic manufacturer and air sampler provider can work closely together. This enables the development of bespoke remote air sampling systems which can maximise flexibility and control of critical environment monitoring programmes.

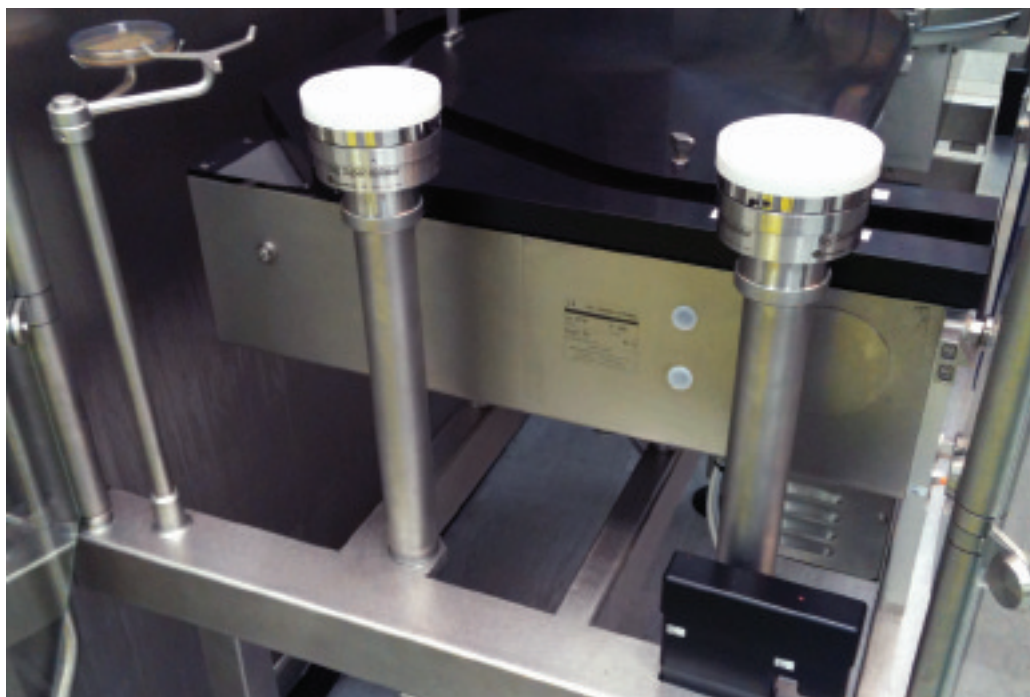


Figure 2: Remote control microbiological agar impaction isolator air samplers installed in filling line adjacent to settle plate holder at height of open vials.

How the Technology Works

Remote microbial air samplers work in the same way as standard handheld air samplers to ensure complete compatibility between background room and isolator monitoring programmes. Multi-point impaction or single stage sieve sampling techniques used by air samplers ensure statistically sound results, since they sample at a fixed rate (see Figure 1). Airborne particles are drawn through the sampling head and are impacted onto the agar media surface of a standard contact plate or petri dish. All agar plates utilised should be irradiated in sterile packaging for transfer into the isolator, either with H₂O₂ vapour surface sterilisation or spray and wipe transfer systems.

To ensure full compatibility with biologic or pharmaceutical manufacturing environments where disinfection systems such as vaporised hydrogen peroxide (VHP) are used, it is necessary that the remotely located sampling head, which is permanently situated within the Grade A environment, is stainless steel. This head should then be

connected through isolator screens, via a high quality pressure and vacuum rated connector to retain isolator integrity, to an external control unit and power source. This reduces the need for the sampler to be continually passed into the filling environment and minimises contamination risks.

It is also possible for multiple sampling heads to be attached to a single control unit to enable all required points to be monitored efficiently and cost-effectively during a filling run (see Figure 2). When using multiple sampling heads controlled by one control unit, it is also useful to be able to pre-programme individual sampling heads either to sample at set times or to be operator-

initiated at the sampling head. This external control unit therefore ensures that dedicated monitoring programmes can be readily established and controlled from outside the Grade A environment. Such programmes may include taking a single cubic metre sample at a critical time, or dividing this into fractions throughout the filling session.

Advantages of Remote Monitoring

In addition to flexibility, reliability and accuracy, another key requirement for a

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Figure 3: Remote control microbiological air samplers can be bespoke to each filling line

remote air sampling system is ease of use and speed of sampling. It is common to have two daily shifts of operating personnel in any given filling suite; consequently air samplers must be quick and easy to use by a number of different operators. Remote samplers can also dramatically reduce sampling errors, since if a sample is taken remotely, contamination is likely to be a genuine product issue rather than the operator inadvertently contaminating the sample. This subsequently cuts down on the time and cost associated with such errors.

Quality Media Are Vital

A further key factor to be considered for effective remote monitoring is the quality of the contact plate contained within the air sampler. A false positive in either the sterility test or critical environmental monitoring has the potential to cause the loss of a batch, as well as an expensive

and time consuming investigation of the cause and a corrective action programme. This means that confidence in the culture media used in the production and sterility testing areas is also critical. As a result, regulators have increasingly raised their stringent conformance demands on the level of quality of culture media and service delivered by suppliers. For example, detailed certificates of analysis and sterility are now a standard requirement. In addition, the sterility of packaging, in part delivered by gamma irradiation of triple wrapped agar plates, is now considered essential to eliminate the risk of extremely costly false positives.

Conclusion

Since microbiological quality results are at the forefront of final batch release of biologic

medicines, such as blood plasma products, the effective microbial monitoring of the Grade A manufacturing and filling environments is crucial to guarantee their safety. Biologic manufacturers require rigorous microbial air sampling techniques that can minimise contamination risk in Grade A filling environments, such as isolators. Bespoke designed remote air samplers are now increasingly ensuring minimal sampling errors and are maintaining environmental integrity during critical environment monitoring programmes for quality control purposes prior to batch release (see Figure 3).

Reference

1. EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products, http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex1_en.pdf

About the Author



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