Biological contamination events in isolators: Requirements and expectations

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Bio-contamination found in critical zones within processing environments can affect the whole process and sterility of the final products, potentially putting patients at risk. This can lead to significant financial costs and impact operational resources. This white paper examines the regulatory environment around processing in a GMP and hospital pharmacy environment and looks at the importance of root cause investigation into biological contamination.

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Biological contamination management requires a formal process of root cause analysis (RCA), microbiological identification (at species level) and correction and preventative action (CAPA) to avoid reoccurrence. Root causes of why the biological contamination is present are not always easy to identify as they are often the result of complex environmental interactions. The outcome of a root cause investigation would be expected to identify at least the most probable cause if the actual cause cannot to be fully identified. Investigations and CAPA implementation can be time consuming and interfere with production operations. Failure to understand why the loss of control occurred can lead to in-depth QA/regulatory scrutiny thereby significantly increasing the QA work load.

There are clear regulatory expectations for the total particulate and microbiological control levels (GMP Annex 1) in aseptic processing and aseptic preparation environments. Different processes have different levels of risk relating to bio-contamination. For example, there are more risks where sterile medicinal products or ingredients are opened and exposed in a Grade A/ISO 5 aseptic process environment than those that where closed containers of sterile products and closed transfers are used in the same class of environment. In 'closed systems' the risks are at the sterile interfaces and aseptic connections.

Currently the microbiological control requirements and expectations are the same for both total particulate and microbiological control levels risk classes.

Combining Quality Risk Management (QRM) initiatives with process knowledge can help to identify potential contamination risk areas. A more assured process, having better control and deviation detection, can then be applied to mitigate these risks.

Microbiological sampling technologies and monitoring techniques together with sterility testing have limitations. Zero recorded bio-contamination results may not be the full picture of the contamination control status in the environment or product batch due to limitations of detection.

It is important to learn from bio-contamination events and apply the learning to improve assurance of bio-contamination control in any isolator system or critical zone.

Microbiological control requirements and expectations

The EU Grade A/ISO 5 critical zones of isolators have a microbiological control requirement of <1cfu as specified in 'GMP Annex 1 / FDA – Guide to Industry: Sterile drug products produced by Aseptic processing'. Less than one colony forming unit is effectively zero detected bio-contamination and deviation in control. This means that the detection of bio-contamination is a significant event and needs appropriate investigation.

Isolators using gaseous disinfection processes with an appropriate pre-cleaning step (typically using the bench mark bio-decontamination process - hydrogen peroxide vapour) routinely perform to the zero cfu detected bio-contamination requirement.

Isolators using manual spray and wipe disinfection typically do not routinely perform to zero detected microbiological contamination, Here the risks of impact on sterile product quality, efficacy and ultimately patient safety (risk of infection) need special consideration.

In UK hospital aseptic preparation services, licensed pharmacies are regulated by the MHRA. The reference and regulatory expectation is compliance to EU GMP Annex 1 for Grade A zones.

Within unlicensed, section 10, UK hospital pharmacy units (i.e. those exempt from the licensing requirements of the Medicines Act), reference is taken to the guidance on quality assurance of aseptic preparation services. Here it clearly lays out the requirements that qualify exemption as:

1. The preparation is done by or under supervision of a pharmacist, who takes full responsibility for the quality of the product.
2. The preparation system is a closed system e.g. closed transfers between containers of solutions with the exception of an ampoule where one withdrawal can be made.
3. Licensed sterile medicinal products are used as ingredients or the ingredients are manufactured sterile in licensed facilities.
4. Products will be allocated a shelf life of no more than one week. The shelf life should be supported by stability data.
5. All activities should be in accordance with the defined NHS guidelines.

The microbiological control in unlicensed / section 10 facilities and in compliance to the Quality assurance guideline still makes reference to EU GMP and requirements of the tables specified in Annex 1. NB. the current table version of GMP Annex 1 in the 2012 issue of the Quality assurance guide is out of date as Annex 1 has been updated.

In the USA hospital pharmacy aseptic units are covered under USP<797> which takes reference to ISO standards for process environments. Here ISO 5 covers the direct preparation area for aseptic processing or preparation.

ISO 5 is classified with total particulate levels considering only 0.5µm. These levels closely compare to EU Grade A (actually ISO 4.8 = EU GMP Grade A).

The USP<797> makes reference to USP<1116> for microbiological control requirements. Within USP<1116> microbiological control takes more reference to incidence rates of bio-contamination and not absolute cfu levels due to the limitations of sampling technology. However expectations for isolator environments are still high with not more than 0.1% of contaminated samples in an environmental monitoring program considered acceptable.

Also currently under revision is ISO 14698. This is concerned with biological contamination classification and monitoring in controlled areas. ISO 14698 (currently valid in 2012 is a poor standard not fully applied) will be the counterpart to USP <1116> in Europe.

Between Europe and the USA there is still debate about the amount of 'acceptable' cfu microbiological contamination in any one sample or zone (isolator) where monitoring takes place. This is a result of sampling limitations and the inherent microbiological variations. There is also a difference as to how useful monitoring settle plates are. Here the USA puts far more emphasis on active air sampling.

Even with inherent poor recovery of bio-contamination in sampling technologies, it is still considered in Europe that

a 1cfu bio-contamination event may indicate a deviation in control that needs investigation.

More and more research into microbiological monitoring technologies verifies how poor the recovery of bio-contamination may be. Comparison studies with new instantaneous microbiological detection (IMD) systems indicate wide levels of recovery and further challenge characterisation of contamination levels in controlled environments.

There are viable but non-culturable (VBNC) microorganisms together with objectionable and acceptable microorganisms (if a product has a preservative). All of these make up the bio-contamination community and microbiological profile.

Quality risk management provides the opportunity to interpret and direct risk mitigation against bio-contamination. In the first instance however the principles of Quality by Design (QbD) apply, being that quality, and bio-contamination control, can be designed into a process with process knowledge, risk understanding and risk mitigation features or procedures.

It is not possible to test into compliance (repeat tests until one passes) with any true quality assurance in a process. Using QbD principles significantly contributes towards bio-contamination free or compliant results in routine environmental monitoring and sterility testing.

Having process knowledge, applying good design and process control together with sensors and monitors that detect changes in control state of quality critical attributes, mean investigations into root causes of a bio-contamination event, if they occur, become far more scientific than a random search process.

Although there is not a regulatory requirement for continuous particle monitoring in sterility testing or aseptic services isolators, the trend is towards installation as a risk management tool.

By detection and alarms based on movement in total particle count monitoring, trends during 'real time' monitoring, sterility tests or aseptic preparations may be suspended. This has the benefit of not putting the test or preparation under further risk until the cause identified. Trend results do have to take care of peaks in particle loads during sterile packaging removal but there are expected clean up rates that should return readings to the control state.

Summary

In summary, if isolator or controlled barrier separation technology equipment is fully integrated as operational modules (with an effective and robust bio-decontamination process together with monitoring technology that detects deviation in critical quality attributes) then risk management is substantially improved.

Importantly, such systems could not restrict process times or process transfers or not be excessively expensive to limit access to the technology. Such equipment and processes would fully support QbD and would make a significant contribution to quality risk management with a focus on patient needs and safety.

Fully integrated and operational barrier separation technology systems would be easier to validate and service (with one service provider).

Simplicity of use where there is less reliance on operator procedure (which can lead to potential error) is also an important concept and requirement. More and more automation supports function design and operation to improve process control, report deviations and manage risks.

The reduction in bio-contamination events reduces a significant burden on the necessary root cause investigations and corrective and preventative actions but the main benefit of course is the reduction in risks to patients.

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