GMP risk based environmental control and process monitoring for aseptic processing

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Abstract

Manufacture of sterile medicinal and therapeutic products requires an approach following risk based initiatives and Good Manufacturing Practice (GMP). Quality Risk Management (QRM) is a principle regulatory requirement based on designing the process properly, understanding where the weaknesses are, proceeding to explore those weaknesses and applying appropriate control measures (technical and organisational) to reduce risks to low and manageable levels.

In principle this is relatively straight forward; understand the process, including critical quality attributes (CQAs), and by doing so understand the risks to product quality and patient safety in sterile product manufacturing. With risks understood control measures and deviation detection can be applied.

As straight forward as these principles seem, firms find difficulty to meet risk based GMP expectations with tangible process solutions. This article considers some principles of risk based environmental control and monitoring to help apply risk control measures and environmental monitoring methods that meet best practice requirements.

Overview of challenges

Control measures should deliver risk mitigate to acceptable levels, recognising all risks cannot be avoided but can be managed. There are difficulties however setting control measures because new product types – including new biological products – have unique processing challenges (fig. 1) with increasing requirements for cross contamination control, and new technologies for manufacturing and environmental monitoring e. g. single use/disposable systems and Rapid Micro Methods (RMM).

Contamination and cross contamination control starts with good process design and today it is better to engineer solutions which do not allow an operator to do something you do not want them to do. Facilities should be moving away from designs where operator failure and human error is a high risk.

Sterile medicinal and therapeutic product efficacy is increased by use of biological 'delivery systems' including antibodies and viral vectors. In addition some conjugate products use a biological delivery system for targeted delivery of a toxic component for oncology treatment. Such products require aseptic processing as they typically cannot be terminally sterilised (in the final product container).

Aseptic processing to meet today’s regulatory requirements apply the measure of contamination risk control with use of separation barrier technology [1], isolators, and Restricted Access Barrier Systems (RABS). Where cross contamination control is required this often means a form of containment is required and this has led to the increased specification of isolators over RABS. To manage cross contamination it is important a product stays within a set process zone boundary with control of material en-
try and exit to the process zone and it is possible to decontaminate up to the boundary avoiding un-cleanable mechanical spaces or dead legs in design.

Three types of aseptic processing have developed based on different product types (fig. 1):

- **Aseptic processing of sterile medicines that are non-hazardous e.g. pharmaceuticals or non-pathogenic biologic products that require protection from contamination in manufacturing/filling.**

- **Aseptic: Toxic processing of sterile medicines including cyto-toxics that require product protection and operator protection (and possibly cross contamination) control measures.**

- **Aseptic: bio-hazard processing (including biologics, live viruses) that require product protection, operator protection and cross contamination control.**

As product profiles change there is more consideration to the challenges of processing smaller batches with different aseptic processing needs [2] leading to multiple products in the same facility and a greater emphasis on cross contamination control.

In processing of bio-products there is a transition through ‘Closed system processing’ where the product or starting components are inside a closed system e.g. fermenter, reactor etc. into ‘Open system processing’ where the product is openly exposed to the ISO 14644-1, ISO 5/VDI 2083-3 processing environment e.g. during filling open containers. ISO 5/EU-A to ISO 8/EU-C environmental grades are specified in EU Good Manufacturing Practice (GMP) Annex 1 combining requirements of total particulate, at reference particle sizes of 0.5 micron and 5.0 micron, and not to exceed microbiological levels, reported as Colony Forming Units (CFUs).

Although there are still contamination risks in closed system processing, at aseptic connections, sampling interventions and product transfers there is a significant contamination risk escalation in open system processing.

Surrounding environments of closed systems require some level of bioburden control and associated monitoring with a much greater extent of environmental control and monitoring applied as risks escalate when products are open to the ISO 5 environment.

The ISO 5 processing environments where sterile products are exposed require a high level of control, monitoring and data trending to provide assurance that the ongoing state of control is as specified and meets required regulatory compliance.

Good process design requires a balance between technical and organisational control measures (fig. 2) to meet requirements of specific product quality, efficacy and patient safety. The approach to sterile product manufacturing should be set out in a control strategy [3] which forms part of GMP requirements.

A key part of process design is the extent and balance between open systems processing and closed system processing.

The more sterile products are processed in the open format the higher the risks of exposure to contamination. Closed systems may include single use disposable bags, product lines and connections that are assembled as a sterile system.

Requirements in GMP increasingly have to be balanced with containment to provide operator safety and/or cross contamination control.

Biological safety level (BSL) containment is typically for pathogens where operator and environmental protection is paramount.

Often negative pressure enclosures with once through air changes are specified but such control measures do not fully support patient safety requirements in aseptic processing as...
in-leakage can compromise sterile products and patient safety.

In addition uni-directional airflow is a key GMP control attribute in ISO 5 environments and this is not fully consistent with requirements of once through airflow for controlled areas.

Pharmaceutical containment has to be interpreted with GMP compliance so sterile product quality and patient safety are not compromised. The Pharmaceutical and Health-care Sciences Society (PHSS) details a containment hierarchy in the Bio-contamination typical monograph 20 [4] that facilitates balancing containment and GMP.

Process design also has to take account of capacity/product throughput, available resources and return of investment to ensure the process solution is sustainable.

Technical and organisational control measures will change to meet different aseptic processing types.

Table 1 indicates the types of technical and organisational measures that should be considered in contamination and cross contamination control.

### Aseptic filling of non-hazardous products – principle requirements

- Aseptic processing in barrier technology, including isolators and RABS, providing ISO 5 controlled environments with integrated risk based environmental monitoring systems and data trending systems.
- Cleanroom background environment to isolator barrier ISO 8 (best practice) for 'open processing' of pharmaceutical products. Cleanroom background environment for RABS ISO 7/EU-B. Filling zone positive pressure to surround.
- Isolator/RABS air-handling system configured for part recirculation and fresh air exchange.
- For isolators secure closed material transfer devices are required for transfer of process and monitoring materials into the ISO 5 process zone, including transfer of environmental monitoring plates. For RABS the transfer points across the barrier may use aerodynamic protection to prevent the RABS ISO 5 zone becoming contaminated in transfer of sterilised items.
- Isolators typically employ gaseous disinfection with vapourised hydrogen peroxide (vH₂O₂). RABS are typically manually disinfected with all product contact parts sterilised out of place, transferred to the barrier and aseptically assembled into place.
- Ready to Use (RTU): pre-sterilised product containers (vials, syringes or cartridges) may enter the ISO 5 filling zone via de-bagger/No-Touch-Transfer systems (NTT) [5]: using a combination of pressure differentials and aerodynamic protection contamination control measures. Such technology can replace other methods that require a decontamination step of the outer surfaces of the container 'tubs', e.g. ebeam.

### Table 1

<table>
<thead>
<tr>
<th>Technical control measures</th>
<th>Organisational control measures</th>
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<tr>
<td>Zoning of controlled areas and pressure differential regimes; 1) product protection, 2) preventing cross contamination.</td>
<td>Dedicated facilities. Dedicated equipment (full or part). Gowning strategy including use of Personnel Protective Equipment (PPE).</td>
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<tr>
<td>Airflow; product protection/containment. Barrier technology to separate operators from process/products: barrier leak integrity.</td>
<td>Shared equipment with cleaning/decontamination between product types and/or batches. Outsourcing/supply chain management.</td>
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<tr>
<td>Single use disposable systems. Closed material transfers, e.g. Rapid Transfer Port (RTP) alpha/beta Material transfers with decontamination step e.g. Vaporised Hydrogen Peroxide (VHP). Decontamination processes: cleaning, sterilisation, surface sterilisation, disinfection, chemical decontamination.</td>
<td>Campaigning of products e.g. seasonal with cleaning/decontamination between campaigns. Aseptic/sterile holds for batch production. Fast turnaround (short down time). Disaster/major deviation recovery planning.</td>
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### Aseptic filling of toxic (cytotoxic) products – principle requirements

- As containment is required aseptic processing in barrier isolator technology is specified providing ISO 5 controlled environments with integrated risk based environmental monitoring systems.
• Cleanroom – isolator background environment: ISO 8 for ‘open processing’ of pharmaceutical products. Filling zone positive pressure to surround but less positive than any additional adjacent ISO 5 isolator modules to provide a containment measure.
• At container exit from the isolator an ‘active’ mouse-hole may be required: a contain air discharge and prevent isolator air mixing with the surrounding environment.
• An external surface product container washer/decontamination system may be required to prevent contamination spread into the downstream areas.
• Cleanroom HVAC configured for part recirculation and fresh air exchange. Terminal High Efficiency Particulate Air Filter (HEPA) filters required at the room air supply and (depending on risks) at the barrier wall exhaust.
• Isolator air-handling system configured for part recirculation and air exchange: Air supply can be taken from surrounding environment or dedicated Air Handling Unit (AHU) and vent discharge must be ducted to outside via double HEPA filtration with safe change bag-in/bag-out filters on primary containment boundary.
• Secure ‘closed’ material transfer devices required for all process support materials (including environmental monitoring) entering and leaving the ISO 5 processing zone.
• RTU: pre-sterilised containers may enter the ISO 5 filling environment via de-bagger/NTT device together with additional isolator modules (each side of fill zone) to provide a high pressure barrier so air flows into ISO 5 and into additional isolator module (without mixing).
• Cleaning-in-Place (CIP) systems required for barrier/equipment surfaces that become contaminated during processing with waste control measures applied for all contaminated waste.
• Gaseous Vaporised Hydrogen Peroxide (VHP) surface decontamination used for isolator barrier, non-contact machine surfaces, surface sterilisation of stopper bowls/guides, packaging difficult to manually disinfect.

Aseptic filling of bio-hazard products (including biologics/live viruses) – principle requirements
• Aseptic processing in barrier isolator technology provides containment together with ISO 5 con-
trolled environments with integrated risk based environmental monitoring systems.
- Cleanroom background environment to Isolator barrier: ISO 8 for 'open processing' of pharmaceutical products: best practice cGMP.
- Cleanroom HVAC configured for once through air exchange with terminal HEPA filters at Cleanroom barrier air supply and double Exhaust filters with primary exhaust barrier filter of ULPA grade, considering Biological safety (BSL) requirements. There is a requirement to balance containment with current Good Manufacturing Practice (cGMP) without compromise to patient safety or product quality.
- Isolator air-handling system configured for part recirculation and air exchange to meet ISO 5 requirements for aseptic processing, in the case of aseptic filling biological safety cabinets would not be considered good practice.
- Secure 'closed' material transfer devices required for all process support materials entering and leaving the ISO 5 process zone.
- Isolator air supply can be taken supply from surrounding environment (or dedicated AHU) and vent discharge ducted to outside via double Ultra Low Penetration Air Filter (ULPA)/HEPA filtration: safe change bag-in/bag-out filters on primary containment boundary filters. Clean-decontamination in-place systems provided for primary containment boundary of isolator and enclosed equipment.
- RTU: pre-sterilised containers may enter the ISO 5 filling environment via de-bagger/NTT device together with additional isolator modules (each side of fill zone) to provide a high pressure barrier so air flows into ISO 5 and isolator buffer zone (without mixing).
- Gaseous VHP surface decontamination to be used for isolator barrier, non-contact machine surfaces, surface sterilisation of stopper bowls/guides and packaging difficult to manually disinfect. Gaseous VHP may also be specified for environmental viral clearance if required.

**Risk based environmental classification and monitoring – overview**

In principle environmental control is classified by 'total particulate' levels at two reference particle sizes in Europe of 0.5 micron and 5.0 micron and only 0.5 micron for US Food and Drug Administration (FDA) requirements together with monitoring CFU microbiological levels to not exceed levels/limits set out in EU GMP Annex 1 and FDA guidance to industry for aseptic processing.

For classification total particulate levels are defined for a one cubic metre sample at each challenge location. Not to exceed CFU levels are set for each zone class (ISO 5–8) with the active air (volumetric) measure of one cubic metre and settle/contact plate’s colonies per plate. ISO 14644-1/2 indicates the amount of minimum sample locations based on unit area.

For monitoring in pharmaceutical facilities for total particulate inside ISO 5 zones continuous monitoring is required and to maintain a better picture of environmental status data is processed over one cubic foot sample sizes with continuous run charts that consider a ‘rolling’ one cubic metre of results.

Microbiological monitoring has known limitations in both recovery and sample size considering the small proportion of actual air-volume processed or surface area sampled of the controlled zone and associated equipment [5]. To provide a fuller picture of contamination control status trend data from sample programs is required.

Trend metrics may include: incidence rates above alert and action levels in an Environmental Monitoring (EM) program, incidences of Out Of Specification (OOS) deviations e. g. recurring alarms indicating the process does not have robust control and Out Of Trend (OOT) deviations.

There is a necessity to monitor Critical Control Parameters (CPPs) and detect with appropriate response to deviations.

In the clean air environments of ISO 5 inside isolator barriers it is highly unlikely there is homogeneous distribution of contamination such that a single sample location will represent generally the contamination status of the zone.

Typically uni-directional down-flow 'first-air' is protective providing a clean column of air that is delivered via HEPA filters with the first contact of the air being the critical surfaces e. g. product containers and product (fig. 3). In monitoring it is important to detect any compromise of the ‘first-air’ that would put critical surfaces or products at risk of contamination.

Risk based sample locations are discussed in literature and in specific terms. This means sample locations...
take consideration from possible generation/sources of contamination and the pathway from the source to at risk locations e. g. open product containers or filled product.

**Positioning settle plates**
To define risk based sample locations a review of the process flows is required together with any potential intervention into the barrier system, inherent or corrective. There also has to be an assessment of air movements and possibility of carrying a contamination source to a point at risk e. g. exposed product or open container before filling.

Such assessment of air moments requires smoke studies that may include visualisation studies or a combination of smoke as a particle challenge and particle counter to monitor particle movements. Such studies are essential when verifying positioning of settle plates.

Settle plate positioning can be considered in two ways: 1) position plate in a possible pathway between an activity (operators entering gloves during aseptic processing) or 2) monitor the air flow that has passed over a critical surface then over the plate. A good example would be a feeder bowl where a plate cannot be positioned inside the bowl during processing but the airflow that exits/overspills from the bowl can be monitored via a settle plate.

**Active air sampling**
Active air sampling is required at the commencement of set-up for production operations to provide evidence the starting conditions were compliant. Depending on the length of the production period it may also be useful to undertake active air sampling during processing and at shift or day ends so no extended periods of operation are at risk of non-compliant monitoring data that would require investigation if later found to deviate outside specified or regulatory levels.

Active air samplers need to monitor at risk locations at positions of activity inside isolators as a result of operator glove access. Additional active air sampling may be specified during media fills to assess such operator interactions (although they are under barrier conditions). End of shift/campaign active air sampling is expected in all cases to verify continued state of control.

Recovery efficiency of active air samplers is defined by a D50 value [4].

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<th>Table 2</th>
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<td><strong>Combined EM programs that deliver process monitoring.</strong></td>
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<td><strong>EM sampling plan Qualification stage</strong></td>
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<tr>
<td>Characterisation at start-up and classification at rest (Operation Qualification – OQ).</td>
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<tr>
<td>Performance Qualification (PQ) in establishing environmental control: process simulation/media fills</td>
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<tr>
<td><strong>Routine EM in operation risk based sampling locations:</strong> environmental monitoring results and deviation incidence rates trended</td>
</tr>
<tr>
<td><strong>End of batch/campaign EM:</strong> environmental monitoring including surface sampling (trended)</td>
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**Joining Forces in Containment Solutions.**
Contact plates, finger prints (dabs) and swabs

Surface sampling is something that is completed at the end of a batch/campaign as generally the sampling process contaminates surfaces with growth media and is difficult to recover (unacceptable risk) during processing. Swabs are used on complex surface shapes that are not suitable to surface plate sampling.

In isolators it is typically acceptable to only sample finger prints for gloves that have been used in production. In aseptic filling the swabbing of needles at the end of batch production is considered good practice.

If in-process surface sampling is required, defined by risk assessment, growth media contact plates are replaced by non-contaminating swabs that have been qualified for recovery at least equal to that of contact plates.

Risk based EM sampling plans – example

Sampling plans and associated setting of sample locations are required through different qualification and product stages (table 2).

There may be more sample locations in characterisation and classification to fully assess a controlled area but when it comes to routine monitoring sampling should be reduced to key risk areas as the process of sampling can in fact develop into a risk in its own right so ‘over sampling’ has more risk than benefit.

The combination of data from all environmental monitoring programs forms environmental control process monitoring.

Setting sample locations

A full review of process flows and associated risks of contamination of critical points is required to set sampling positions as ‘risk based’. Clear diagrams (fig. 4) are needed of sample locations categorised by sample method/type. Such diagrams should indicate the path open product containers take and where operators interact with the barrier system, including the isolator surrounding environment where operators are present. Actual location of samples is as much about height the sample is taken as a plan view on diagrams to provide detection of contamination.

The ISO 7 barrier surrounding environment needs monitoring to understand the extent of bioburden that is challenging the barrier. With measurable CFU in these environments it is possible to be proactive if contamination levels increase before the ISO 5 areas are potentially contaminated hence avoiding very difficult root cause investigations.

Figure 4: EM sample locations.
Perspective on use of RMM in risk based EM

RMM technology is without doubt the future for monitoring systems in isolators but it is still at the development and evaluation stage. Not only is it of great advantage to record and respond to monitoring data in real time to improve contamination risk control and management but also the technology is intervention free without the need to access the monitored zone with growth media plates, which in itself can be a risk.

Differentiation between non-biological fluorescing materials and actual bio-counts is a current area of development to manage the issue of ‘over reporting’ contamination with false counts and the issue where batch records and regulatory compliance are compromised by incompatible data. Full RMM implementation will require technical developments but also there will need to be regulatory recognition of the too very different data forms of bio-counts, as electronic data and CFUs derived from classification growth based methods. The revision of EU GMP Annex 1 is not expected to endorse real time rapid micro methods for ISO 5 filling zones as yet the technology is not considered mature enough.

Summary

Risk based initiatives improve patient safety and product quality but the potential is only realised with implementation of good process design practical control measures that combine to meet requirements for processing different product types and methods of aseptic processing. It comes down to a fundamental understanding of the product and processing type and risk control measures, technical and organisational, applied with sound science and good practice.

Trend metrics provide a more complete picture on the status of contamination control in the manufacturing environments but today drug producers also have to consider cross contamination control measures that are often a combination or equipment and facility design that together provide a process solution.

Environmental monitoring trend data is only as good as the sampling locations, plans and programs and it is essential monitoring locations take a risk based perspective. In the clean environments of isolators it is important to consider process flows, operator and machine interactions which have the potential as a contamination source and deviation event.

Isolators are not a complete barrier to all combination so risk based control and monitoring is a pre-requisite to provide the necessary assurance of sterility that sterile products are not compromised during aseptic manufacturing.

References