ENVIRONMENTAL MONITORING PROCESSES AND VALIDATION

How to create the ideal EM Program for your business

Cherwell
LABORATORIES

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Introduction

Environmental monitoring (EM) procedures and protocols are a fact of everyday life for any organisation that uses aseptic processes in their manufacturing.

Being able to prove the cleanliness of any environment in which medicines, or other substances destined for human contact are produced, is of course paramount. The EU Good Manufacturing Practice (GMP) Annex 1 and similar international guidelines exist to ensure that the highest standards in patient safety are met. These form the basis for stringent guidelines to which all businesses using aseptic environments can now comply. They also represent a move towards establishing a recognised global standard. The EU GMP Annex 1, for example, will also be adopted by both the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the World Health Organisation (WHO).

Yet while the intent of these regulatory guides is clear, a common complaint is that they can appear both excessively prescriptive and open to interpretation. Indeed, they are ultimately intended to be used across many pharma and medical manufacturing sectors, so they do need to be comprehensive.

The sheer volume of new content in the much-revised GMP Annex 1 alone does present a challenge for businesses wanting to comply; only to feel overwhelmed by the choices they have to make in order to determine the right path for them.

So how can an organisation determine its best EM plan to ensure compliance that also fits with their business model and budget? What looks like best practice for one business can quickly become too time-consuming, expensive and personnel-intensive to be viable for another. How can an organisation ensure the highest standards of patient safety without embarking on an unnecessarily arduous and complicated journey?

Taking a focused, practical approach to applying the guidance directly to the specific characteristics and requirements of your business, will help you achieve and maintain quality risk assessment on your particular processes and methods. With pragmatic application, the process of achieving compliance can also help your teams understand why and justify how EM requirements are met.

In this eBook, we aim to offer a consultative guide to the most business-efficient EM measures organisations can take to comply with the EU GMP Annex 1, and practical steps you can take to create the ideal EM process for your specific business needs.

First: A note on compliance and why it matters

Since it was first introduced in 1989, the EU GMP Annex 1 – Manufacture of Sterile Medicinal Products – has been through several revisions.

Each time, the impact of change is felt across many sectors within the pharmaceutical industry: drug and medical device manufacturers, sterile medicinal product manufacturers, advanced therapies and hospital pharmacy aseptic services.

While it can seem daunting for individual businesses to keep up with these changes, Annex 1 must also keep up with new technologies, procedures and quality risk management within the cleanroom.

It was created to remove any lingering potential risks to patient safety and move towards a recognised global standard. The ultimate intention is to offer a comprehensive guide to support the manufacture of sterile medicinal products in a very broad sense.

Of course, even in sterile medicinal product manufacturing, the terms ‘sterile’ and ‘aseptic’ are not the same thing. Sterility, for these purposes, is defined as a state: ‘free from living germs or viable microorganisms that have the potential to reproduce. Aseptic in this context, describes a process: that by which sterilised materials should be handled in a controlled environment designed to maintain microbial contamination at levels known to present minimal risk.

A compliant sterile state and aseptic processes can only be achieved using an appropriate combination of environmental monitoring methods in a validated procedure. The GMP offers best practise guidelines to help relevant organisations ensure their sterile environments are maintained by using proven methods that are universally recognised as effective.

Ultimately the EU GMP Annex 1 guidelines and principles aim to be useful in their broadest sense, meaning they can be applied to any sterile environment or any environment where the control of microbial, particulate and pyrogen contamination is necessary.

The case a few years ago, of contaminated medicine originating from the NECC pharmacy in Massachusetts USA, showed the world how tragic the outcomes can be if an aseptic processing environment is compromised. Meningitis killed 64 people and injured 800 more after they received medicine contaminated with fungal spores. Two NECC executives are now serving time in federal prison and, unsurprisingly, the compounding pharmacy has been shut down. This case was the result of many counts of cleanroom negligence and illustrates vividly the full impact of poor EM.

How we are moving towards a global standard

With a definite emphasis on quality risk management, ongoing revisions of both the EU GMP Annex 1 and other international standards collectively aim to create singular, up to date documentation. This could then also be opened up to other industries outside pharmaceutical manufacturing that use aseptic processes.

Sterile manufacturing technology has developed and advanced a great deal and it is recognised that the guidelines surrounding certain processes in these areas must be addressed regularly in order to keep up.

Annex 1 now considers single use technologies, quality risk management being applied where it has not been applied before, such as in the use of compressed gases in pharmaceutical manufacturing, aseptic operator qualifications, process water systems and other critical utilities, plus cleaning validation for surfaces in cleanrooms and closed manufacturing systems.

While GMP Annex 1 is the official European Union guideline, the issues it tackles are universal. Both viable and non-viable monitoring are addressed. Notably, for non-viable EM there has been a change from ISO 14644 parts 1 and 2 1999 to the 2015 version. The latest revisions specifically address what this change means and advise on implications.

Microbiological methods of monitoring are now addressed specifically, with recommendations for how to apply them. While advice is now offered about best practices for EM, including continuous monitoring during filling operations. Furthermore, it advises on how to approach data and the expectation to speciate isolates from grade A and grade B areas.

Further areas detailed in the latest EU guidelines include:

- Pharmaceutical Quality System (PQS) – specific requirements of the PQS when applied to sterile medicinal products
- Personnel – requirements for the specific training, knowledge and skills and the qualification of personnel
- Premises – guidance regarding the design needs of the facility and also guidance on the qualification of premises including how to use barrier technology
- Equipment – guidance on the design and operation of equipment
- Utilities – guidance regarding special requirements of utilities such as water, air and vacuum
- Production and specific technologies - approaches taken with regards to aseptic and terminal sterilisation processes and different technologies lyophilisation and blow fill seal (BFS) where specific requirements may be required. Approaches to sterilisation of products equipment and packaging components
- Viable and non-viable environmental and process monitoring: Ongoing routine monitoring with regards to the setting of alert limits and reviewing trend data, plus guidance on the requirements of aseptic process simulation.

Achieving compliance for your EM processes and program

As we mentioned in the introduction, taking a practical, bespoke approach to compliance will help you achieve the best results for your business.

To make sure you fully understand the level of compliance your business requires, it is important to first lay good foundations. To help with this, we have broken down preparation into four steps.

1. EM Audit

Regardless of how your business operates and in which sector it falls, there are some general best practice notes that all organisations relying on aseptic processes should observe.

Start with a full EM audit.

- What methods are you currently using?
- Why?
- What sort of data are you gathering?
- How are you using that data to inform your compliance protocol?

For total compliance with the latest guidelines, your entire manufacturing facility, including your equipment and your process design, must qualify against, be optimised for, and validated according to Annex 11 and Annex 15 of EU GMP. In addition, general chapters such as chapter 5 on the prevention of cross-contamination in production, apply to all medicines. Therefore, principles of Annex 1 can be applied to non-sterile products as well.

Appropriate technologies that prevent risk and contamination must be implemented so control measures are in place for protection of the product. These measures must safeguard against potential risks of contamination from external sources of particulate and microbial contamination, such as outsourced materials, personnel and your surrounding environment.

2. Understand the Utilities chapter

Take time to fully understand the latest documentation on ‘Utilities’ as this must be closely followed. This chapter outlines the required equipment and other materials that will come into contact with your product that may directly or indirectly influence it. It looks into your water systems, the steam used for sterilisation activities as well as compressed gas, vacuum and cooling systems.

The EU GMP Annex 1 makes a specific call to a better and more holistic contamination control strategy. It is expected that you document this strategy formally, so every effort made to minimise the risk of contamination is reflected and can be presented if necessary. There's an expectation of manufacturers making significant changes that allow for visual inspections. It also underpins that it is mandatory to have HEPA/ULPA filtration in all classified areas of your operation.

It is important to note that Annex 1 does not stand alone as an independent EU document but instead, directly applies to the PIC/S (Pharmaceutical Inspection Co-operation Scheme) guidelines. It outlines expectations of all personnel which align with PIC/S document PE 009-11 'Manufacture of sterile Medicinal Products'. The personnel or responsible person referred to in the PIC/S document PE 009-11 or 'QP' will need to adhere to the same stringent guidelines laid out for the personnel in Annex 1.

3. Pull your current EM program apart and analyse every element

How comprehensive is your current EM program? Make a detailed report of all monitoring of the following including method, frequency and the last time any changes were made:

- Nonviable particulates
- Airborne viable
- Pressure differentials
- Temperature and humidity
- Direction of air flow
- Surface microbial contaminants on personnel and equipment, work tables, floors and walls.

The data collected from this program should be used to provide insight into the aseptic condition of critical areas of your operations.

- The control of your manufacturing facility and operations
- Short-term and long-term evaluation processes
- How well your detection system works to alert you if microbial and particulate matter gain access into your operation
- Your training and regular behaviour of your operators and employees
- Your standard operating procedure (SOP)
- Any differential pressure issues in your facility and the indicators of your HVAC and HEPA systems
- The organisms recovered in your facility
- This insight must be used when evaluating possible changes in your control mechanisms in your facility

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4. Research active and passive EM options

Your EM program should be geared around your particular business needs, size and sector. The simple truth is that there are many elements you can use to create an EM program that both ensures your compliance and fits your budget. For best results, you should create a program with various active and passive elements.

Consider all areas of your operations and how you will monitor:

- Surfaces: contact plates and swabs
- Personnel protective gear: gloves, face masks, hair coverings and garments
- Compressed gases: provisions for sampling gases plus all components of their containers
- Air: actively, using samplers that can be used throughout your site and passively, using settle plates

You should also understand the full specifications and implications of any materials or equipment that could compromise the microbiological quality of your product. And finally, fully document all disinfection and sanitisation processes implemented throughout your operation.

For further guidance and advice on EM programs and methods, you can also contact the Medicines and Healthcare products Regulatory Agency (MHRA).

Examples of best practice environmental monitoring programs

Once you've completed the steps outlined above, it's time to plan your new, compliant EM program so that it fits your specific requirements.

For the results you need, it's critical to take a bespoke, holistic approach because one size does not fit all. In this section, we take a look at two examples of best practice that we hope will help you formulate a plan that addresses the levels of compliance you require in your industry and also fits in with your business model.

EM best practice for industrial pharma – large and mid-scale

The GMP was originally designed to protect patients who may come into contact with products created by the mid-scale to large industrial pharma industry, so for organisations operating in this sector full compliance is imperative.

Airborne particulates, temperature and humidity should be monitored constantly using regularly calibrated equipment while passive EM methods should also be used where appropriate.

For this sector, contamination prevention is critical. Once contamination has occurred, the consequences can be devastating to both patients and the manufacturer so it must be avoided at all costs.

Industrial pharmaceutical manufacturing processes can include non-sterile, aseptic fill products or employ a terminal sterilisation. If non-sterile or aseptically filled products are contaminated it will inevitably result in a loss of activity of the pharmaceutical product or it will negatively impact patient safety.

In the manufacture of commercial drugs or commercially used chemicals, the products themselves are sensitive. Defined limits and constant analysis are paramount to identifying challenges and monitoring the environment.

A real understanding of how the upstream and downstream manufacturing activities interact must be identified for the appropriate EM strategy to be created. Ultimately, you must employ a risk-based approach. Any proposed process must incorporate external factors such media validation and supplier

certification and internal factors such as equipment calibration and multiple sampling methods.

You need to feel confident in every area of your environmental monitoring that all culture media has been manufactured in a strictly controlled environment and tested thoroughly and that all active air samplers are sampling defined air volumes.

Regular reviews of your EM program are also very important in ensuring your processes are providing the data you need. Finally, be ready for new legislation. In the pharmaceutical industry, regulations are likely to only get tighter.

EM process must address the following challenges:

- A large manufacturing area with a high number of sample points
- A risk assessment must be performed to inform sampling regime
- Multiple methods of sample capture –settle plates, regular schedule for surface sampling plus air samplers specific to the area they are monitoring
- Very specific equipment such as a high-volume sampler or an integrated solution may be required

EM best practice for commercial scale hospitals and aseptic compounders

Commercial scale hospitals and aseptic compounders are under similar levels of scrutiny as large scale pharma. The main difference for this sector is size of operation and budget but they still have the same obligation to avoid harm to patients.

NHS hospital trusts are feeling increasing pressure to maintain the highest performance levels with minimal funding and increasing patient numbers. Aseptic compounders face all the regulation of large-scale pharmaceutical operations yet may require space and cost saving solutions.

In commercial hospitals and aseptic compounders speed is also a factor, with quick and easy production of medications or parenteral fluids considered a priority, to produce IV bags and infusion bags for antibiotics for instance.

In these environments, areas requiring EM are those used in aseptic manufacture; those where there is any close interaction between human operator, equipment and product and those where any product is passed to staff who will take it for patient use.

Be ready for new legislation. In the pharmaceutical industry, regulations are likely to only get tighter.

The elements of an EM program for these environments must include surface sampling, air sampling and personnel sampling in all these areas. In an aseptic compounding facility, each separate compounding location must be closely monitored.

Any locations where sterile products are stored must also be carefully monitored because these products tend to have a shorter shelf life. Finally, due to potentially close patient vicinity, these environments can be subject not only to GMP compliance and industry regulations, but also in the USA to the Patient Safety Act.

For facilities where short shelf-life products are manufactured, there is an increased need to demonstrate that the environment is continuously and consistently well controlled. Individual session EM results are often not available at the crucial moment before a batch is administered to a patient, offering a disjointed evidence trail at best and potentially unnoticed contaminations at worst.

EM process must address the following challenges:

- Typically working in more confined space, e.g. isolator cabinets, LAF / UDAF cabinets
- Multi-station monitoring that can deliver consistent results
- High turnaround, quick processes that require flexible and reliable monitoring solutions
- Program may require specific equipment such as hand-held air samplers

Conclusion

Your EM program must cover all necessary areas within your facility and provide data and information that can direct and motivate appropriate measures to counter any risk.

Achieving compliance doesn't have to mean major headaches for your business, as long as you're clear about what compliance means for your manufacturing facility.

You will need a combination of EM solutions tailored to your needs to meet the latest guidelines, but this does not have to mean a significant investment. Achieving the perfect combination for your business can be very cost-effective if you're clear about what you need and why.

Once you have found your ideal EM program, validate your processes and document them. This protocol is too important to allow it to be anything but a firm plan that all relevant operatives understand. Your GMP compliance is only as strong as your weakest link so educating all parties involved in your aseptic processes is as vital as the air sampling methods you choose.

Finally, examine your EM validation processes every year. Legislation will almost certainly change over time, your business model could also change and new sampling products and techniques will likely become available. Only by regularly reviewing your processes will you ensure compliance and continue to source the best EM suppliers for your needs.

About Cherwell Laboratories

THE ENVIRONMENTAL MONITORING PROCESSES AND VALIDATION GUIDE

Cherwell Laboratories, located in Bicester, Oxfordshire in the UK, is a family run manufacturer of prepared microbiological media and supplier of environmental monitoring equipment. We supply to the UK, Ireland and a number of western and central European countries, primarily to aseptic manufacturing sectors, such as pharmaceuticals and medical devices.

We are unique to many of our larger competitors in that we are able to offer bespoke solutions to match customer needs. This not only applies to our range of prepared media but also for the air sampling equipment and EM accessories we specialise in.

We never dreamt when we founded Cherwell in 1971, as a veterinary diagnostic laboratory, that we would transition in the industry to be the company we are today. It was in the late 80s that the veterinary lab closed, but we retained the microbiology facility and turned our focus to the marketing of Redipor prepared media and developing sales of EM samplers into the pharma sector.

Since the early 80's, we have been the UK distributor for the SAS range of air samplers. Recognised across the industry, many of the leading pharma companies across the world use the distinctive yellow SAS as the cornerstone of their EM programs. During the 30 plus years of selling SAS we have tweaked and created bespoke solutions for individual clients. More recently Cherwell has added to its capabilities with the addition of the ImpactAir slit to agar sampler to meet the needs in critical environments.

With over thirty years insight and experience with environmental monitoring applications, we have intricate insight and expertise that ensures we continually deliver high calibre products and services to our many clients.

If you would like to explore our product range in greater detail, you are welcome to do so **here.**

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